Max-Planck-Institut
für Kohlenforschung

technische universität
dortmund

Studien zu Chagosensine:

Totalsynthese der postulierten Struktur

&

Synthetische Arbeiten zur stereochemischen Strukturaufklärung

Dissertation

zur Erlangung des akademischen Grades
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M. Sc. Marc Heinrich

geboren am 01.05.1990
in Freiburg im Breisgau

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Die vorliegende Arbeit entstand unter der Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Oktober 2015 bis November 2019 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits in folgendem Beitrag veröffentlicht:

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Die praktischen Arbeiten erfolgten in enger Zusammenarbeit mit Dr. John J. Murphy, Dr. Marina K. Ilg, Dr. Aurélien Letort Dr. Jakub Flasz, Dr. Dragoş-Adrian Roşca und Samira Speicher. Zur NMR-spektroskopischen Strukturaufklärung wurden alle Verbindungen, welche in tabellarischer Form zugeordnet wurden, von Petra Philipps aus der NMR-Abteilung des Max-Planck-Instituts für Kohlenforschung unabhängig kontrolliert und bestätigt. Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesen Mitarbeitern alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle vermerkt.

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„Fragen wir deshalb nicht zuerst, was nicht geht oder was schon immer so war.

Fragen wir zuerst, was geht, und suchen wir nach dem,

was noch nie so gemacht wurde.“

„So let us not ask first what is wrong or what has always been.

Let us first ask what is possible and look for something

that has never been done before.“

(Dr. Angela D. Merkel)

Studien zu Chagosensine: Totalsynthese der postulierten Struktur und synthetische Arbeiten zur stereochemischen Strukturaufklärung

Ausgehend von den vorangegangenen synthetischen Studien innerhalb der Arbeitsgruppe beinhaltet diese Doktorarbeit die erste Totalsynthese der vermeintlichen Struktur von Chagosensine. Nach Widerlegung der postulierten Struktur sollten sieben weitere Diastereomere zur Aufklärung der korrekten Stereochemie führen, wobei jedoch keine der synthetisierten Verbindungen dem Naturstoff entspricht.

Eingebettet in einen 16-gliedrigen Makrozyklus besitzt das faszinierende Polyketid neben den zwei *trans*-konfigurierte THF-Ringen ein einzigartiges Strukturmotiv, das *Z,Z*-konfigurierte 2-Chlor-1,3-dien, dessen Aufbau das Herzstück der zugrundeliegenden Retrosynthese darstellte. Zusätzlich zur strukturellen Bestätigung der komplexen molekularen Architektur mit insgesamt 11 Stereozentren sollte eine robuste Totalsynthese ausreichende Mengen an Naturstoff und weiteren Analoga zur Testung der biologischen Aktivität zugänglich machen.

In der Anfangsphase war der Fokus der Totalsynthese auf den Aufbau des 16-gliedrigen Kernzyklus gerichtet. Dabei konnte der gespannte Zyklus weder mittels der ringschließender Alken- noch Alkin-Metathese in ausreichenden Mengen geschlossen werden, weshalb eine Makrolaktonisierung favorisiert wurde. Mittels einer neuartigen Palladium-katalysierten Kreuzkupplung konnten die beiden Fragmente konvergent und regioselektiv vereinigt werden. Ein Kupfer-vermittelter Zinn-Chlor-Austausch vervollständigte die erste stereoselektive Darstellung des hervorstechenden Strukturmerkmals von Chagosensine. Nach Darstellung der *seco*-Säure gelang der erstmalige Aufbau des gespannten 16-gliedrigen Makrozyklus durch Laktonisierung unter extremen Mukaiyama Bedingungen. Trotz der ersten erfolgreichen Darstellung des Kernzyklus von Chagosensine offenbarte dieser Syntheseweg eine niedrige Gesamtausbaute in Verbindung mit einer vermeintlich unselektiven Einführung der fehlenden Seitenkette, weshalb eine neue Route geplant wurde.

Hierbei sollte die Einbringung des kompletten nördlichen Fragmentes in die zuvor entwickelten Schlüsselschritte die erste Totalsynthese dieses faszinierenden Naturstoffes ermöglichen. Zwar konnte aufbauend auf den bisherigen Syntheseweg die gesamte nördliche Untereinheit hergestellt werden, jedoch bereitete die *trans*-Hydrometallierung mit der darauffolgenden Defunktionalisierung unüberwindbare Schwierigkeiten. Deshalb wurde ein neuer Darstellungsweg ausgehend von (−)-Citronellal entwickelt, welcher den kompletten Aufbau des Nordfragments in lediglich 15 Schritten mit einer Gesamtausbeute von 7.6% ermöglichte.

Unter den optimierten Reaktionsbedingungen für die chemoselektive Kreuzkupplung und den anschließenden Einbau des Chlorsubstituenten wurde das Herzstück von Chagosensine in guten Ausbeuten und unter vollständiger Stereokontrolle dargestellt. Jedoch gelang die gewünschte

Differenzierung einer diolhaltigen *seco*-Säure nicht, sondern ein 13-gliedrigen Zyklus wurde unerwarteterweise geschlossen. Allerdings ermöglichte die Schützung der zuvor reaktiven Hydroxygruppe die gewünschte Makrolaktonisierung zum 16-gliedrigen Ring in 40% Ausbeute unter extremen Yamaguchi Bedingungen. Nach vollständiger Entschützung mit anschließender Pinnick-Oxidation erwies sich der so erhaltene vermeintliche Naturstoff als höchst instabil, weshalb eine zusätzliche Derivatisierung zum entsprechenden Methylester durchgeführt wurde. Bedauerlicherweise offenbarte der Vergleich der ^{1}H und ^{13}C-NMR Spektren mit den Literaturdaten die eindeutige Fehlinterpretation der zugrundeliegenden Stereochemie des marinen Naturstoffes durch das Isolationsteam, was im finalen Teil dieser Doktorarbeit umfangreiche Arbeiten mit dem Ziel der stereochemischen Strukturaufklärung von Chagosensine zur Folge hatte.

Nach Identifizierung von fünf Stereozentren mit fraglicher stereochemischer Bestimmung wurde eine stereodivergente Darstellung von sieben Diastereomeren unter Beibehaltung der entwickelten Funktionalisierungen der Endstufen geplant. In Bezug auf die zweite Permutation des Nordteils wurde der bestehende Syntheseweg in einem Punkt weitreichend verändert, was schließlich die Einführung aller weiterer Stereozentren gestattete. Im Gegensatz zum modularen Darstellungsweg des isomeren Nordfragments, erbrachte erst die komplette Neuausrichtung der Südroute eine skalierbare Herstellung aller vier Fragmente mit sich.

Basierend auf der neuartigen Kreuzkupplungsmethode wurde eine Verbindungsbibliothek bestehend aus acht Diastereomeren erschaffen. Im weiteren Verlauf wurden durch Adaption der verlässlichen Schlüsselschritte die restlichen sieben *seco*-Säuren im Parallelsynthese Verfahren hergestellt. Beim anschließenden Ringschluss zeigte sich nun eine unvermeidliche Substratabhängigkeit, was die Ausbeuten zwischen 11% und 72% schwanken ließ. Die etablierte Schlusssequenz ermöglichte zwar die Isolation der vermeintlichen Stereoisomere des Naturstoffes, jedoch erwiesen sich die Analoga als äußerst instabil. Entweder wurde die Öffnung des Makrolaktons durch das methanolhaltige NMR-Lösungsmittelgemisch ausgelöst, oder der 16-gliedrige Ring erweiterte sich zum stabilen 18-gliedrigen Makrozyklus. Mit den Literaturdaten stimmen weder die Datensätze der stabilen Derivate noch die ^{1}H-Spektren der Gemische mit instabilen Verbindungen überein. Zusätzlich zu den detaillierten NMR-spektroskopischen Diskrepanzen konnten weitere tiefgreifende Unstimmigkeiten mit dem Isolationspaper aufgedeckt werden, welche in Kombination mit dem Fehlen der Originalspektren die Strukturaufklärung von Chagosensine zu einem unmöglichen Unterfangen machen.

Chagosensine: Total Synthesis of Putative Structure and Efforts towards Stereochemical Revision

Based on the initial studies in the Fürstner group, the herein reported synthetic efforts mark the first total synthesis of putative chagosensine. After proving the mis-assignment of the natural product by the isolation team, we embarked on the synthetic endeavor for structural elucidation of the natural product by synthesizing seven additional diastereoisomers.

Embedded in a 16-membered macrocycle, the intriguing polyketide possesses two *trans*-configured THF-rings and a unique *Z,Z*-configured 2-chloro-1,3-diene. In addition to the structural confirmation of the complex molecular architecture inhabiting a total of 11 stereogenic centers, a concise and scalable synthesis was planned in order to provide sufficient quantities of the natural product as well as analogues for biological profiling.

In the initial period of the synthetic endeavor we focused on furnishing the 16-membered macrocyclic core. Hence, neither a ring-closing alkene nor alkyne metathesis was able to forge the strained ring in sufficient quantities, which prompted us to pursue a macrolactonization approach. A novel palladium-catalyzed cross coupling assembled the two fragments in a highly convergent and regioselective manner. Subsequent chloro-destannylation completed the first stereoselective introduction of the most salient feature of chagosensine. After liberating the *seco*-acid, the ring closure of the strained 16-membered macrocycle was accomplished by lactonization under forcing Mukaiyama conditions for the first time. Despite the successful synthesis of the core cycle of chagosensine, the synthetic route suffered from a low overall yield in combination with a putative unselective introduction of the missing side chain, which led to a revised synthetic route.

By maintaining the established key transformations, the implementation of the entire northern fragment was envisioned to enable the first total synthesis of this fascinating natural product. Despite the successful synthesis of the complete northern fragment based on the previous fragment synthesis the *trans*-hydrometalation followed by protodemetalation raised unsurmountable difficulties. Therefore the revised, second-generation synthesis of the complete northern part commenced with (−)-citronellal as the ultimate surrogate for the side chain, finally affording the northern fragment in a remarkable overall yield of 7.6% over 15 steps.

Subjecting the complete northern fragment to the optimized reaction conditions for the site-selective Stille cross coupling and subsequent chloro-destannylation, the unique *Z,Z*-chlorodiene was introduced in high yield as a single isomer. Undesirable differentiation of a diol-containing *seco*-acid resulted in the exclusive formation of the highly strained 13-membered macrocycle. However, protection group management enabled the ring closure to the desired 16-membered macrolactone in 40% yield under forcing Yamaguchi lactonization conditions. Global deprotection and subsequent Pinnick oxidation liberated the putative natural product, which surprisingly proved

to be highly unstable. Derivatization to the methyl ester afforded a stable compound, enabling comparison with the derivatized natural product. Unfortunately, this methyl ester mismatched with the isolated methyl ester, displaying major discrepancies in ^{1}H- and ^{13}C-NMR along the entire carbon skeleton. After unambiguously proving the stereochemical mis-assignment by the isolation team, the final stage of this thesis aimed for the elucidation of the correct stereochemistry of chagosensine.

After identifying structural subunits with questionable stereochemical assignment, the stereodivergent synthesis of seven putative diastereomers was planned by maintaining the elaborated late-stage functionalizations. In regard of the second northern fragment, the previous route was adjusted in a single transformation paving the way for installing all other stereogenic centers. In contrast to the modular synthesis of the isomeric northern fragment, the scalable synthesis of the four southern fragments required a new route.

Based on the newly developed cross coupling protocol, a compound library of eight diastereoisomers was generated from the two northern fragments in combination with the four southern fragments. Following the reliable sequence, the synthesis of the additional seven *seco*-acids was accomplished by parallel synthesis. During the ring closure, the isolated yield ranged from 11% to 72% due to inevitable substrate dependency. Although the final synthetic protocol enabled the isolation of all stereoisomers, the putative natural products were highly fragile. Treatment with the methanolic NMR solvent mixture either induced ring expansion by intramolecular transesterification to the stable 18-membered macrocycle or opened the macrolactone at ambient temperature. Neither the data sets of the stable derivatives nor the ^{1}H-NMR spectra of the mixtures with unstable diastereomers are matching with the literature data. In addition to the tremendous NMR-spectroscopic deviations, further deep-seated discrepancies with the isolation paper could be revealed, which in combination with the unavailability of the original spectra make the structural revision of chagosensine an impossible task.

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Chagosensine

Total Synthesis of Putative Structure

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Efforts towards Stereochemical Revision

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1 Introduction

1.1 A Personal Account on the Self-Perception of Total Synthesis

1.1.1 Total Synthesis – the Age of Accessibility

The beginning of total synthesis can be essentially traced back to the synthesis of urea by F. Wöhler in 1828, marking the origin of organic chemistry by disproving the existence of a *vis vitalis*.[1] Alongside its long-lasting history, the exciting field of total synthesis has been under constant debate within the chemical community.[2] Lacking of spectroscopic and analytical methods in the 19th century, the synthesis of natural products was the only method for structure determination. As steady improvements in spectroscopy advanced, Sir R. Robinson declared in 1936: "We have travelled far since 1828 and the interest attached to `total synthesis´ has disappeared".[3] Despite its everlasting purpose for ultimate structural confirmation,[4] the major aspects of total synthesis shifted towards the inherent aesthetic appeal of the synthetic route. R. B. Woodward described the art of synthesis as: "The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men… The unique challenge which chemical synthesis provides for the creative imagination and the skilled hands ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both".[5] The single total synthesis of vitamin B_{12} by R. B. Woodward and A. Eschenmoser *et. al.* is considered as a milestone in organic chemistry exclusively following an academic purpose.[6] Awarding E. J. Corey with the Nobel Prize in Chemistry in 1990 "for his development of the theory and methodology of organic synthesis" marks an important landmark and a turning point in the history of synthetic chemistry.

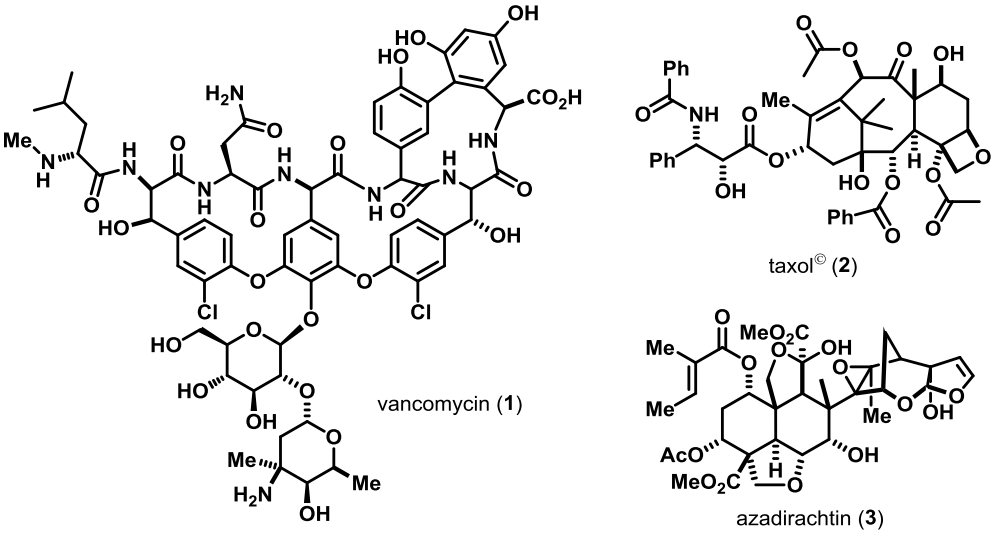


Figure 1.1. Structures of natural product, which total synthesis was initiated in the 1990s.

Regarding the total synthesis of vancomycin[7] (**1**) and taxol[8] (**2**) (Figure 1.1) as well as the work on palytoxin by Y. Kishi *et. al.*,[9] the chemical community experienced the synthesis of complex natural products as a "meaningless race to the summit that is often won by brute force" (P. Ball).[2d] After achieving the first total synthesis of the natural insecticide azadirachtin (**3**),[10] S. V. Ley shared his opinion on this 22 years enduring synthetic endeavor: "I don't have to be first; the elegance of the approach is what interests me".[11]

1.1.2 Focusing on the Economies of Synthesis – the Age of Scalability

By rather concentrating on the synthetic approach than the feasibility of accessing a large and complicated target, a countermovement within the synthetic community evolved, which focused on selectivity and efficiency of the applied methods.[12] Reporting the stereoselective synthesis of all L-hexoses by iterative asymmetric epoxidation of allylic alcohols, the value of reagent-controlled asymmetric catalysis was highlighted by Sharpless and Masamune in 1990.[13] As a pioneer in the field of asymmetric catalysis, B. M. Trost phrased the term "atom economy" in 1991, which emphasizes the importance of chemo-, regio-, diastereo- and enantioselectivity.[14] Within the decade a new era of transition metal-catalyzed transformations emerged, which were implemented in target-orientated synthesis facilitating natural product synthesis to result in an unmet efficiency.[15] The persistent and innovative developments of novel methodologies have revealed new shortcuts for a given retrosynthetic approach or have established new disconnection strategies. Serving as the ultimate proving ground, the synthetic feasibility of a newly developed transformation has been tested in target-oriented synthesis, showcasing unexpected limitations in functional group compatibility or selectivity. Otherwise, the unsolved problems in natural product synthesis have encouraged the development of novel methodologies and thereby consistently pushing the frontiers of organic synthesis. A. Fürstner summarized this obvious codependency as: "Methodological work and total synthesis are therefore nothing but two sides of the same precious coin and cross-fertilize each other."[16]

Despite concentrating on the quality of a route by evaluating its synthetic efficiency, the latest generation of natural product synthesis has emphasized on its practicality in terms of scalability and reproducibility.[17] In order to provide the final target in decent quantities for advanced biological profiling, the contemporary view of total synthesis adapts a more process character. By declaring the 21st century to the "age of scalability", P. S. Baran puts an effort in combining the criteria of atom economy with a high quantitative throughput.[18] Numerous efforts in scaling the efficiency of a total synthesis have been introduced concerning step count,[19] protection-group-free synthesis[20] or redox economy.[21]

Constant improvements in synthetic organic chemistry have enhanced the cooperative effects with numerous scientific areas like medicinal chemistry or material science. “Synthesis is a discipline that is central to all areas of chemistry” (W. R. Roush).[2c] In particular, the exciting field of total synthesis is a never-ending inspiration creating avalanches in neighboring fields.

1.1.3 Functional-Orientated Synthesis

Despite the constant improvements in synthetic chemistry, the shear structural complexity of a natural product might prevent its utility for medicinal chemistry (blue area in Figure 1.2). The biological activity usually emanates from a certain amount of functional groups localized in specific areas of the molecular architecture, which are required for the specific compound-target interaction. While maintaining the function of the natural product, the unnecessary groups can be removed, resulting in a simplified analogue with a shorter synthetic route (green area in Figure 1.2).[22]

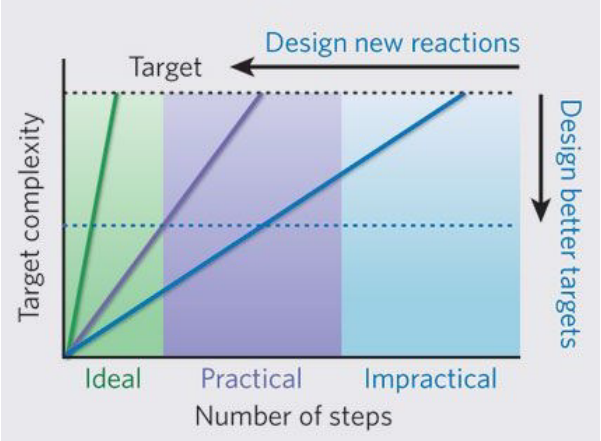


Figure 1.2. Simplified chart for the discrimination of ideal (green), practical (purple) and impractical (blue) total synthesis by correlating the synthetic utility with the structural complexity of a target compound.[23]

Contemplating on the sheer function of the target compound, P. A. Wender has emphasized on a functional-orientated synthesis by designing simplified natural-product-derived analogues.[23-24] By combining computational three-dimensional modeling with organic synthesis, the disconnection strategies have aimed at identifying the necessary biological subunit and accessing the designed targets under the premises of step and atom economy.

However, investigations in structure-activity-relationship (SAR) and biological profiling can only be conducted with sufficient quantities of compound. Hence, the common approach for accessing natural-product-derived analogues follows three options: engineering the biosynthetic gene clusters, a semisynthetic derivatization, or a diverted total synthesis.[16,25] The reprogramming of natural biosynthetic pathways of non-ribosomal peptide synthetases (NRPs)[26] and polyketide synthases (PKSs)[27] generated successfully analogues of peptides, polyketides and hybrids. However, the modified analogues are still limited to the building block scaffold of the engineered NRPs and PKSs.

As a second option, the semisynthesis commences with the actual natural product demanding its availability in significant amounts. In regard of the simplification of the parent structure, the defunctionalization must be able to differentiate between the present functional groups in order to achieve decent levels of chemoselectivity. Otherwise, introduction of further functionalities to the parent carbon skeleton are limited to the selectivity of the applied method, which is commonly highly substrate-dependent.[28] Therefore, the intrigue complexity of the naturally ocurring precursor can limit its utility in target-oriented synthesis of other natural products.[29] Finally, the third option, a diverted synthetic approach, can access a big variety of analogues depending on the stage of diversification *en route* to the final target,[30] which also enable the study of structure-activity relationships (SAR).[16,31]

Isolated in 1968 by G. R. Pettit, the family of bryostatins exhibits a wide range of novel biological activities due to the binding affinity to protein kinases C (PKCs).[32] The total step count of the initial total syntheses ranged from 79 to 89.[33] By applying newly developed transformations, the recently published routes towards different members of the bryostatin family advanced to a diminished step count of maximum 63 steps.[34] Achieving a scalable synthesis of bryostatin 1 (**4**) in only 29 total steps (19 steps for the longest linear sequence (LLS)),[35] the Wender group provided sufficient quantities for further biological testing, showing its hidden potentials as a latency reversing agent for HIV[36] and the treatment for Alzheimer.[37]

In regard of its diversification and especially simplification, the first generation of analogues, the so called “bryologs” (**5**), were synthesized in 30 steps and exhibited a binding affinity to PKCs comparable to the parent natural product (Figure 1.3).[38] By retaining the putative pharmacophore in the southern domain, further modifications in the second generation of bryologs resulted in constant improvement in pharmacokinetics and pharmacodynamics, while successively decreasing the number of required chemical transformations.[39]

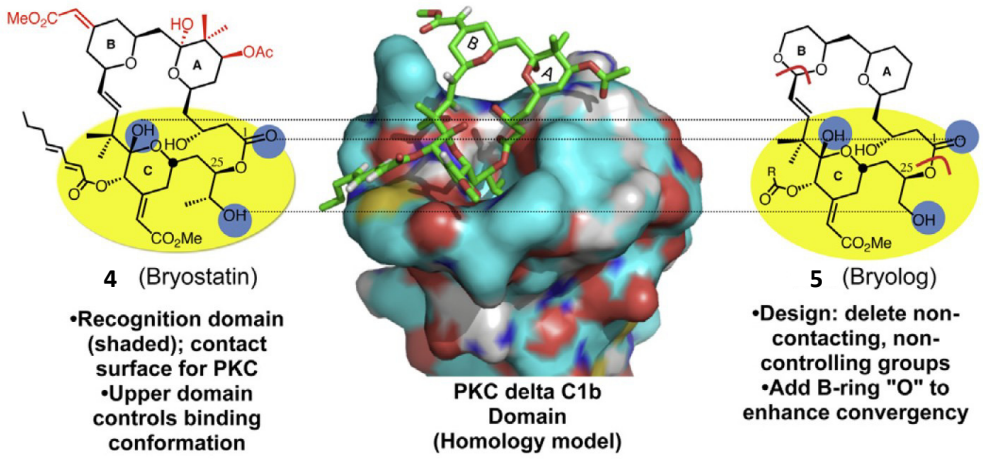


Figure 1.3. Identification of the binding domain by testing the structure-activity-relationship of bryostatin 1 (**4**) and designing natural-product-derived analogues **5** with simplified structural complexity.[40]

In conclusion, on the one hand, the advances in the field of methodology development are shortening the overall step count of total synthesis leading to a more feasible application of the targeted compounds in medicinal chemistry. On the other hand, investigations in the biological function of natural product can simplify the molecular architecture significantly. While maintaining the desired ligand to target binding interaction, the function-orientated analogue is more accessible than the parent natural product.

1.1.4 An outdated Reinvention of Synthetic Chemistry?

Currently, the essential dual nature of total synthesis as craftsmanship and art is endangered by the robo-chemist.[41] Forecasting the replacement of the experienced chemists by a small, but growing community, the automated processes might revolutionize the fields or organic synthesis and drug discovery.[42] By conducting iterative Suzuki cross coupling of commercialized building blocks, M. Burke has introduced a "3D printer", which "essentially will print out the needed small molecule from a computer".[43] In this perspective, the redundancy of synthetic organic chemist is not limited to the operational aspects of conducting an experiment, but also in improving the reaction conditions and designing the underlying retrosynthesis.[44] Computational retrosynthetic approaches[45] in combination with artificial intelligence (AI) algorithm[46] crusade against the guild of synthetic chemist, declaring total synthesis a moribund field.[47] Moreover, the field of total synthesis could be replaced by synthetic biology.[48] "One can imagine producing nearly any organic molecule – even those that are not produced naturally – in an engineered microorganism" (J. Keasling).[49] As a matter of fact, synthetic biology and AI will undoubtedly have a tremendous impact on natural product synthesis. So, after experiencing a "glorious past"[50] is natural product synthesis facing an inconvenient truth and heading towards its inevitable extinction?

For chemical industry, skilled organic chemists are head-hunted, as their translational capabilities can be applied in numerous fields such as agricultural and medicinal chemistry or material science. Hence, limiting the purpose of total synthesis to satisfying the demand of educated and trained employees is too shorthanded.[2h] The total synthesis of a complex natural product is the ultimate challenge for many synthetic organic chemists. While encountering numerous pitfalls *en route* to the final target, the creativity and the thought process for managing these problems are incomprehensible for society and even for the majority of the scientific community. Similar to art, its aesthetic nature in combination with its hybrid character as an intellectual craftsmanship explain the encountered inaccessibility and the obliging prejudices against total synthesis. "The agreement that complex synthesis, by itself, is beautiful is doubtless true, but also dangerous… And, unfortunately, the beauty of Organic Synthesis is not something, that most non-synthetic-chemists can understand" (G. Whitesides).[2g] By shining some light on its undoubtful beauty, the herein reported synthetic

endeavor towards chagosensine bears witness for the everlasting purpose of natural product total synthesis.

1.2 The Role of Macrocycles in Small Drug Discovery

In medicinal chemistry, natural products and their analogues have an enormous impact on the living conditions of countless patients around the world. On average, 33% of all annually approved drugs originate from natural products.[51] How is it possible that complex molecular architectures accessible by a multistep synthesis or gained from limited natural resources play such an undeniable importance in drug discovery?

The molecular complexity of synthetic drugs is restrained by the used guidelines for oral bioavailability such as the Lipinski's rule-of-five.[52] By avoiding sp^3-hybridized carbons, stereogenic centers and complicated ring systems, the molecular diversity of the drug candidate is diminished, resulting in an overall decrease in finding new hits.[53]

In contrast, the intricate molecular architectures of natural products violate most of the common rules for "druggability" and still exhibit bioavailability.[54] The advantageous properties of natural-product-derived drug candidates can be summarized as: higher molecular weight, lower hydrophilicity, fewer rotatable bindings, fewer aromatic substituents and an intrigue three-dimensional structure.[55] Especially, macrocyclic drugs are seen as valuable targets for reaching in the *terra incognita* of the chemical space.[56] Based on their conformational pre-organization, the binding of 12-membered and higher ordered ring systems to the desired target are occurring with a diminished entropic loss. Macrocycles are represented in 3% of all natural products. A common feature is the spatial organization of functional domains within the carbon skeleton (Figure 1.4).[57]

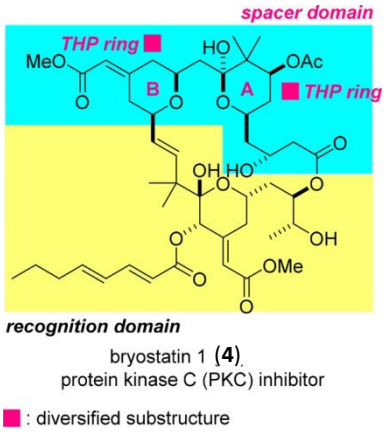


Figure 1.4. Structure of bryostatin 1 (**4**) divided into spacer and recognition domain. Substructures derivatized in Wender's SAR studies indicated in pink.[25]

Regarding the above mentioned bryostatin 1 (**4**), the macrolactone can be divided into two domains based on their function upon binding to the target. The crucial recognition derives from the

interaction of three functional groups within the binding domain (also see Figure 1.3, blue functional groups). Located in the opposite region of the carbon framework, a nonpolar subunit represents the modulator or spacer domain, which can be altered without affecting the parent binding affinity.[56b] Due to the low conformational flexibility of the macrocycle, the spacer region provides the required pre-organization of the three-dimensional architecture for binding of the recognition domain. Thus, the removal of functional groups in the spacer domain does not affect the overall binding affinity of the simplified analogues, which can be seen in bryolog **5** (see Figure 1.3).[38] From an evolutionary standpoint, this common, intrinsic polarity might have proven to be advantageous in the chemical battle of microbes and could serve as a promising template for the concept of *de novo* synthesis of macrocyclic drugs.[58]

1.3 Marine Natural Products – Cornucopia of Structural Diversity

1.3.1 Sponges – the Most Prolific Source of Bioactive Secondary Metabolites

By occupying more than 70% of the earth's surface, the world's oceans contain about 500.000 estimated species. The marine sponges, algae, microbes, tunicates and other species are producing a gigantic cornucopia of more than 15.000 marine natural products.[59]

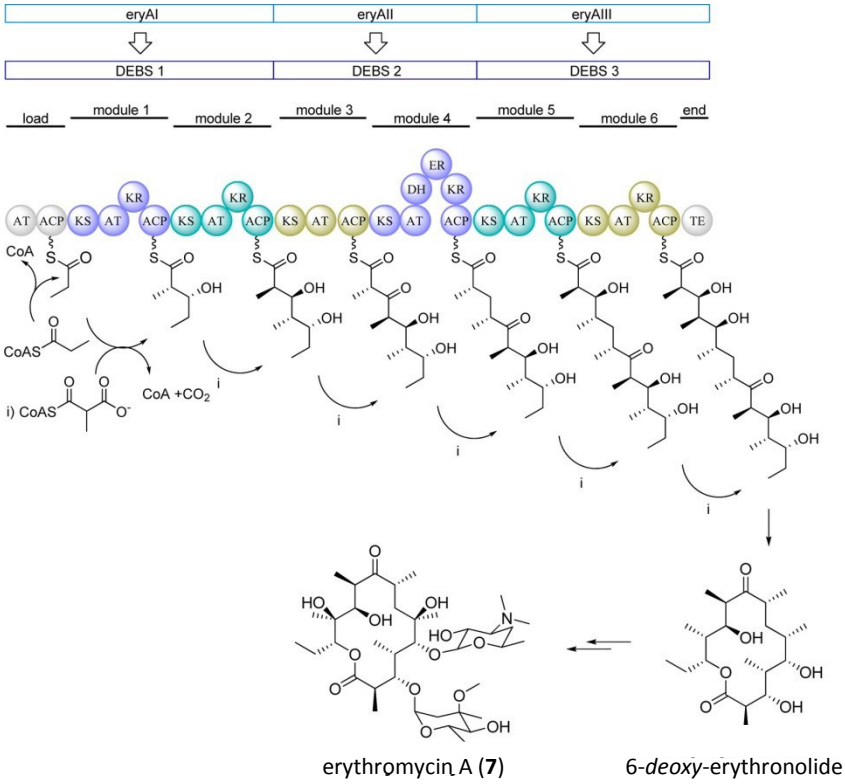
Since one billion years, sponges as the simplest multicellular organisms have evolved to approximately 8000 described species.[60] With about 40% of the volume, diverse microbial communities are living in symbiosis with their host.[61] By inhabiting 10^{10} bacteria per gram of sponge wet weight, sponges are providing the perfect breeding ground and thus are described as "microbial fermenters".[62] In respect to the discovery of bioactive compounds with potential pharmaceutical application, marine sponges are ranked as the most prolific source of bioactive secondary metabolites.[63] As agents of chemical warfare between microbes, the secondary metabolites are assumed to provide their host with an evolutionary advantage.[64] Concerning the potential of macrocyclic systems as new drug candidates, their specific ligand-target interaction causes high hit rates on pharmacologically important targets.[65]

However, the natural resources are usually only capable of affording sufficient amounts for the structural determination and the preliminary biological testing of the natural product. The artificial harvesting of sponges in aquacultures[66] as well as the engineering of polyketide synthases (PKSs)[67] are evolving, but still provide no adequate alternative to total synthesis.

1.3.2 The Biosynthetic Pathway of Polyketides

Despite the outlined structural diversity of polyketides, their biosynthetic origin roots in the same class of enzymes, the large multi-functional polyketide synthases (PKSs).[68] Based on iterative Claisen

condensations of a thioester with acetate and propionate building blocks, the polyketide is produced by different domains within the PKS (Scheme 1.1). Further manipulations of the growing chain are exemplary introduced by ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER). The sequence usually ends with the thioesterase (TE) domain facilitating the challenging ring closure to the depicted final macrolactone **6**.



Scheme 1.1. Domain arrangement of erythromycin synthase and the subsequent functionalization of **6**.[69]

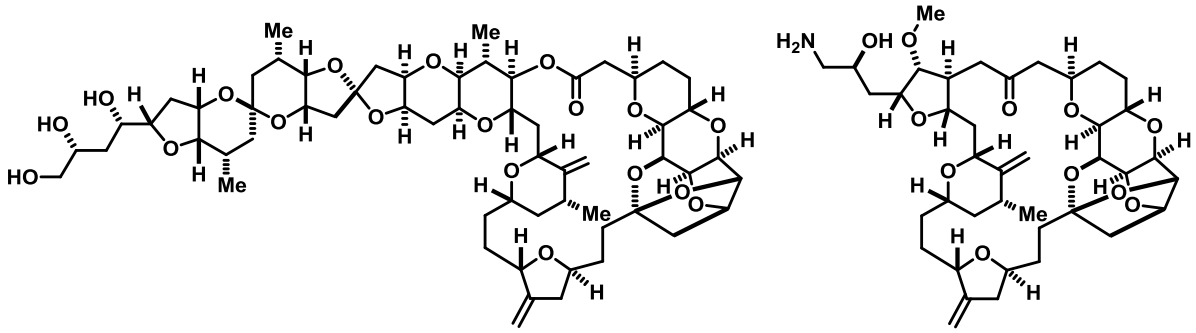
Subsequent functionalization of the parent carbon skeleton increases the structural complexity. Regarding the biological synthesis of erythromycin A (**7**), the additional oxidation and introduction of the sugar moieties actually results in the observed biological activity. The different opportunities in oxidizing the carbon framework can set the stage for major changes in the connectivity. For example peroxidases or alkene mono-oxygenesases (AMOs) can introduce epoxides, which upon subsequent intramolecular nucleophilic attack can generate cyclic ethers such as tetrahydropyrans and tetrahydrofurans.

1.3.3 Tetrahydrofuran-Containing Macrolides

Due to their striking biological activities, the class of THF-containing polyketides from marine origin exhibit a marvelous molecular architecture attracting numerous synthetic groups in the past decades.[69]

1.3.3.1 Complex Macrolides as Commercial Drugs

Initially isolated from the marine sponge *Halichondria okadai Kadota* by D. Uemura in 1986,[70] halichondrin B (**8**) showed high cytotoxicity against melanomas and leukemia (Figure 1.5).[71] Attempting to harvest the sponge *Lissidendoryx* for providing meaningful quantities for advanced pharmaceutical tests, one ton of the sponge afforded a disappointing quantity of 300 mg of the natural product. Despite this unpleasing harvest, the first total synthesis in 1992 by the Y. Kishi group required a humongous step count of 90 transformations in total.[72] However, testing of advanced intermediates for biological activity, the eastern part was found to be the crucial recognition domain,[73] which is able to bind to the $\alpha\beta$-tubulin-heterodimer and hereby inhibits the cell growth of cancer cell lines.[74] Further structural optimization led to the simplified analogue eribulin (**9**), which is an approved drug for metastatic breast cancer and advanced liposarcoma.[75] By constantly improving its synthetic route, the drug Havalen© is currently synthesized in 62 overall steps.[76]



halichondrin B (**8**) eribulin, Havalen© (**9**)

Figure 1.5. Structure of the halichondrin B (**8**) and its commercialized analogue eribulin (**9**).

Despite the toxicity of chromium dichloride, the iterative usage of asymmetric NHK reaction enabled the selective synthesis of this important drug, even on an industrial scale.[77] Regardless of the tremendous synthetic efforts, the drug is commercialized by Eisai Co., Ltd. in 2016 for 148 Million € in sales.[78] After highlighting the already existing impact of complex natural-product-based drugs within the drug portfolio, more natural products will emerge as promising drug candidates for challenging pharmaceutical targets in the future .[79]

1.3.3.2 Halogen-Containing Macrolides – Biosynthesis and Bioactivity

The unique marine environment also enables the synthesis of chemical structures unprecedented in terrestrial organisms. Based on the high concentration of chloride (19.000 mg/kg) and bromide (65 mg/kg) in the oceans, covalently bound halogen atoms are incorporated in 15-20% of all marine natural products. In particular, chloro substituted derivatives represent more than half of the 5000 known halogenated natural products.[80]

In most cases, aromatic or olefinic systems are substituted with chlorines.[81] In regard of their biosynthetic pathway, the chloroperoxidases (CPO) were originally assumed to catalyze the introduction of chlorines. Possessing an iron or a vanadium center, CPOs are generating hypohalous acids from hydrogen peroxide and chloride, which are known to add unselectively to double bonds. As the formation of chlorohydrins or alkenyl chlorides under naturally existing reaction conditions was not observed, the postulated importance of CPOs was disproven. In contrast, the flavin-depending halogenases were found to facilitate the epoxidation of a double bond as well as the subsequent attack of a chloride in a highly selective fashion.[82]

Concerning their biological activity, the influence of chlorine substituents can be quite substantial.[83] Listed as an essential medicine by the WHO, the most prominent member of chlorinated natural products, vancomycin (**1**), displays no antibacterial properties upon removing the chloro substituents on the two aromatic rings (see Figure 1.1).[84] By inducing a specific conformation of the parent macrocycle, the halogens lock the essential conformation of the adjacent peptidic cycle required for binding to the bacterial enzyme.[85] Further beneficial physicochemical properties can be attributed to the electrophilicity of chlorine, which remotely influences neighboring functional groups and suppresses oxidative degradation of the carbon framework. Despite engaging in hydrogen bonding or London dispersion forces for additional non-covalent interactions, the halogen-containing drugs are more lipophilic, which is also important for their pharmacokinetic and –dynamic properties.

1.4 Total Synthesis of Haterumalide

1.4.1 Isolation of the Haterumalide and Biselide Family

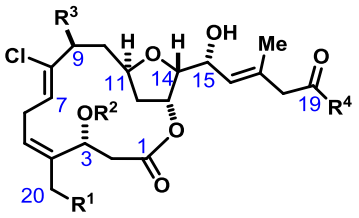
Due to the structural similarity to chagosensine, the family of haterumalides and biselides will be discussed in the following chapters (Table 1.1).[86] Initially isolated as haterumalide NA from Okinawan sponge *Ircinia* by D. Uemura *et. al.*,[87] the identical natural product was later isolated from bacterial sources such as *Serratia marcescens,*[88] *Serratia plymuthica*[89] and *Serratia liquefaciens.*[90] Moreover, the isolation of close relatives from the Okinawan ascidian *Didermnidae sp*., the biselide family,[91] highlights the existence of similar biosynthetic pathways in different host organisms. Haterumalide NA showed strong toxicity (LD_{50} = 0.6 µg/mL) against brine shrimp, while esterification of the carboxylate or oxidation at C20 in the biselide series decreased the acute toxicity (LD_{99} = 50 µg/mL).[91b]

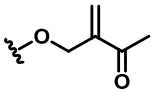
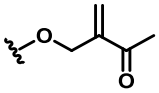
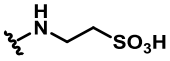
Except for linear biselide E,[92] all the representatives of this family have an allylic alcohol in the side chain and a 14-membered macrolactone in common. The macrocyclic framework features a skipped *Z*-chlorodiene and a *trans*-configured THF-ring in the northern part. Within the haterumalide family, the different members have either an ester or a carboxylic acid present in the side chain.

Furthermore, haterumalide NC and ND possess another chiral allylic alcohol at C9 embedded in the macrocyclic framework.

Despite the similar array of functional groups, the majority of the biselide family members exhibit a merely higher oxidized carbon skeleton in that they incorporate a primary allylic alcohol at C20 in the southern part. According to the described structural permutations in the closely related haterumalide family, the different biselides differ by the carboxyl group at C19 present in the side chain.

Table 1.1 Structures of haterumalides[87,93] and biselides[91].



natural product	R^1	R^2	R^3	R^4
haterumalide NA	H	Ac	H	OH
haterumalide NB	H	Ac	H	OBu
haterumalide NC	H	Ac	OH	OBu
haterumalide ND	H	Ac	OH	OH
haterumalide NE	H	H	H	OH
haterumalide B	H	Ac	H	
biselide A	OAc	Ac	H	OH
biselide B	OAc	Ac	H	
biselide C	OH	Ac	H	OH
biselide D	H	Ac	H	

1.4.2 Total Synthesis of Haterumalide NA

1.4.2.1 Original Stereochemical Assignment and Structural Revision

Haterumalide NA (**10**) and its methyl ester exhibit high cytotoxicity against a variety of cancer cell lines such as leukemia (P338), human colon cancer (DLD-1) and breast cancer (BT-20).[87-88] However, the potential as a pharmaceutical lead is diminished, as acute toxicity in mice (LD_{99} = 0.24 g/kg) and towards brine shrimp (LD_{50} = 0.6 µg/mL) as well as a low bioactivity against for mammary cell line (IC_{50} = 0.6 µg/mL) was observed after extensive biological testing.[91b,94]

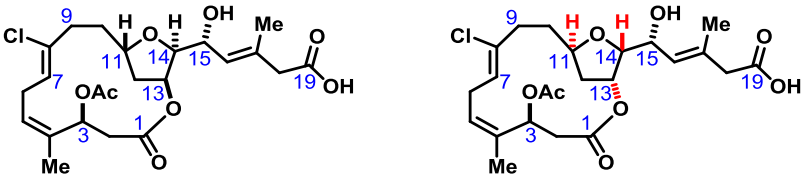


Figure 1.6. Putative (**10a**) and revised (**10b**) structure of haterumalide NA.

In 2003, the first total synthesis by H. Kigoshi *et. al.* proved the mis-assignment of haterumalide NA by the isolation team (Figure 1.6).[95] Regarding the putative structure **10a**, the determination of the absolute configuration of the allylic alcohol at C15 by Mosher ester analysis prompted the Uemura group to assign the absolute stereochemistry of the adjacent THF-ring based on the *J*-coupling constant.[87] According to the Karplus equation, a big coupling constant ($J_{14–15}$ = 8.7 Hz) correlates with an *anti*-relationship between C14 and C15, resulting in the structural assignment of the putative structure **10a** (Figure 1.7).[96] However, based on the conformational flexibility of the 5-membered ring and the adjacent side chain, the revised stereochemistry in **10b** can exhibit the same *anti-periplanar* conformation as depicted in Figure 1.7.[95] Therefore, the outlined correlation between flexible ring systems and adjacent side chains is misleading and can result in a mis-assigned stereochemical structure.

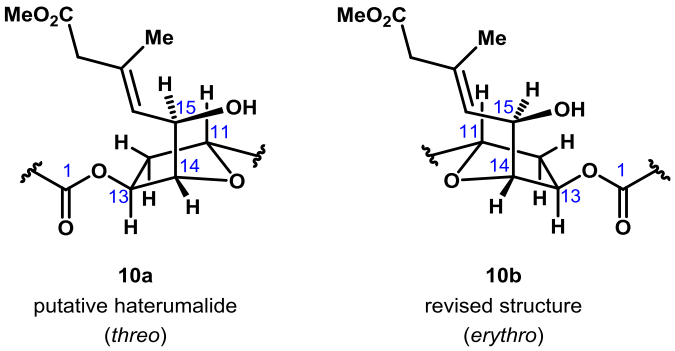


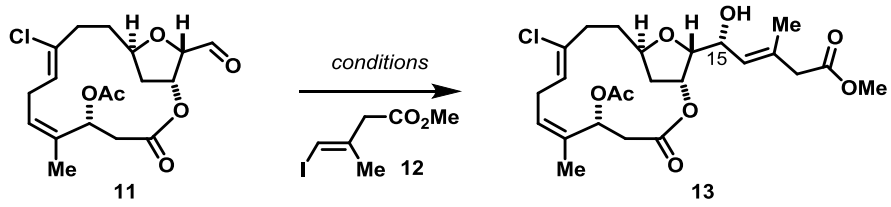
Figure 1.7. Conformational model of the northern THF-ring in putative (**10a**) and revised (**10b**) structure of haterumalide NA.[95]

1.4.2.2 Introduction of the Side Chain by NHK Addition

In the NHK coupling reaction of aldehyde **11** with alkenyl iodide **12**, the stereochemical outcome provided putative haterumalide NA (**10a**) as the minor diastereomer (1:11 dr). Fortunately, comparison of the major diastereomer with the NMR-spectra of the isolation team, matched with the spectroscopic data, albeit showing the opposite optical activity in the CD spectra (*ent*-**10b**). The high substrate dependency of the intermolecular NHK addition derives from the chiral oxygen-bridged ring, facilitating a Felkin-Anh transition state. In general, the addition products of *α*-alkoxy aldehydes afford *anti*-diols predominantly.[97] Intrigued by the high selectivity of the

chromium-mediated coupling, all subsequent total syntheses added the side chain under slightly modified NHK reaction conditions (Table 1.2).

Table 1.2. NHK reaction conditions applied in the total synthesis of methyl ester haterumalide NA (**13**).[98]



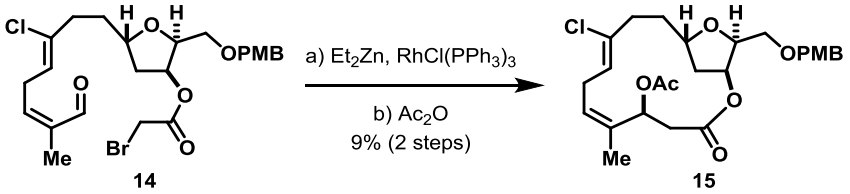
entry	conditions	yield	*dr* (C15)
1[95]	80 eq. **12**, 170 eq. $CrCl_2$ (1% $NiCl_2$)	57% (2 steps)	11:1
2[99]	30 eq. **12**, 90 eq. $CrCl_2$ (1% $NiCl_2$)	30% (2 steps)	n.r.
3[100]	n.r.	50% (2 steps)	10:1
4[101]	6 eq. **12**, 18.8 eq. $CrCl_2$ (1% $NiCl_2$)	49%	n.r.

n.r. = not reported

The first total synthesis used 80 equivalents of coupling partner **12** and 170 equivalents of toxic $CrCl_2$ containing 1 mol% of $NiCl_2$ in DMSO as the solvent (entry 1). Subsequent decrease of the amount of alkenyl iodide **12** and chromium dichloride in the successional total syntheses achieved similar yields with comparable diastereoselectivity (entry 2-4, Table 1.2).

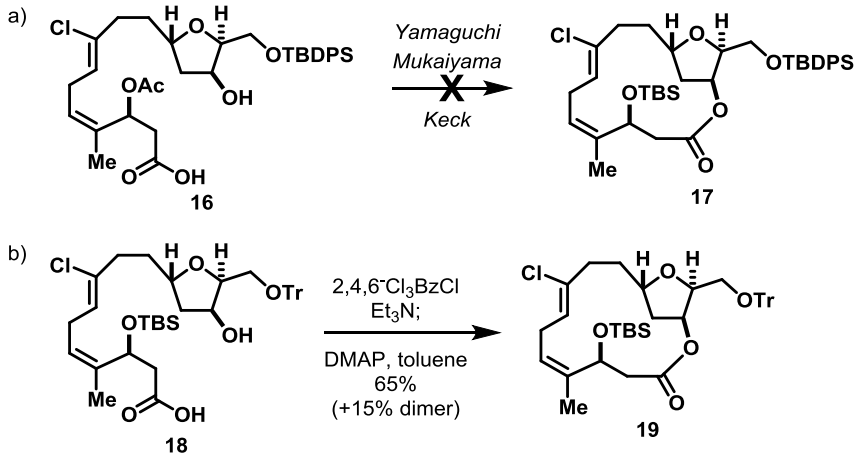
1.4.2.3 Ring Closure Approaches

Focusing on the different retrosynthetic approaches towards the macrocyclic core structure of haterumalide, the first total synthesis by H. Kigoshi *et. al.* applied an intramolecular, ring-closing Reformatzky reaction of α,β-unsaturated aldehyde **14**, affording the 14-membered macrocycle **15** in low yield (Scheme 1.2).[95]



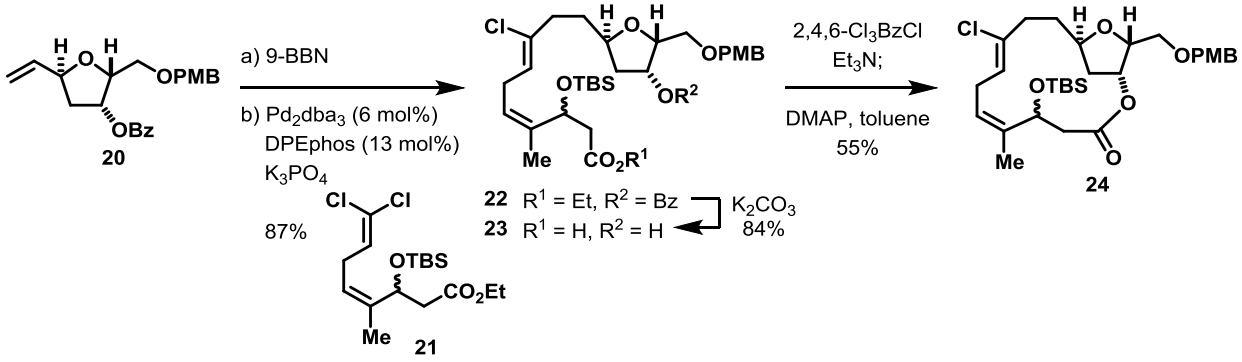
Scheme 1.2. First successful ring closure of **15** by Reformatzky reaction.[95]

Whereas initial macrolactonization attempts towards **17** were met with failure by the H. Kigoshi group (Scheme 1.3a),[95] the B. Snider group managed to cyclize the *seco*-acid **18** by changing the protection groups in the precursor (Scheme 1.3b).[99] Addition of the preformed mixed Yamaguchi anhydride derived from **18** to a solution of DMAP in toluene at ambient temperature provided the macrolactone **19** in 65% yield as well as 15% of the corresponding lactide.



Scheme 1.3. a) Attempted macrolactonization by Kigoshi.[95] b) Successful ring closure of **19** under Yamaguchi conditions.[99]

Later total syntheses mainly followed up with a macrolactonization approach for ring closure, only differing in the protection group strategy.[100,102] Highlighting the potential of transition metal-catalyzed cross coupling for stereoselective carbon-carbon bond formation, E. Roulland *et. al.* introduced the *Z*-alkenyl chloride subunit in **22** by a novel site-selective sp^2-sp^3 Suzuki cross coupling of dichloroalkene **21** with the corresponding boron adduct of **20** (Scheme 1.4).[102a] Subsequent saponification of **22** liberated the *seco*-acid **23**, which was subjected to the reported Yamaguchi macrolactonization forging the 14-membered macrocycle **24** in good yield.

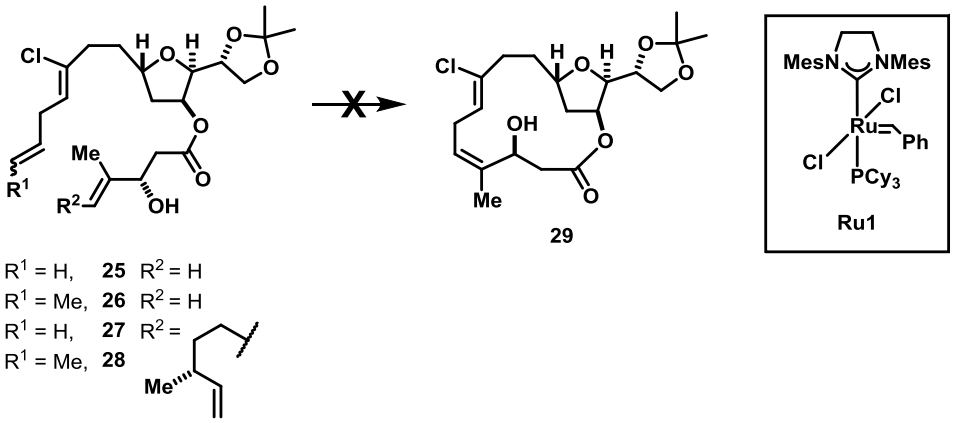


Scheme 1.4. Palladium-catalyzed site-selective Suzuki reaction of **21** and subsequent Yamaguchi macrolactonization.[102a]

By applying bulky bidentate ligands such as Xanthphos and DPEphos with bite angles of 111° and 102°, respectively, the cross coupled adducts are assembled in high yields.[103] A consecutive cross coupling of the generated alkenyl chloride also gives access to stereodefined trisubstituted alkenes, which are a common motif in numerous natural products.[104]

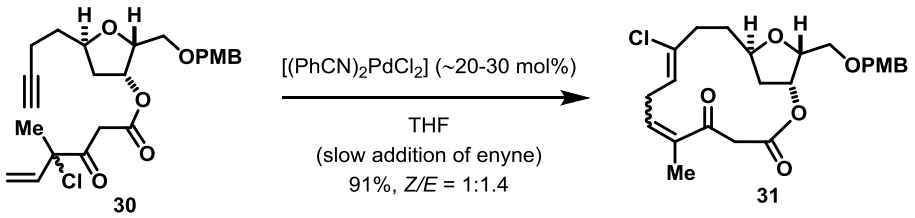
The T. Hoye group envisioned to forge the 14-membered macrocycle of haterumalide NA (**10b**) by relay ring-closing metathesis (RRCM) (Scheme 1.5).[105] The introduction of a relay tether offers the unique opportunity to introduce an active ruthenium alkenylidene species on a less reactive alkene. This implementation was found to be crucial on a model substrate, enabling the RRCM initiation via an electron-deficient β-ketoalkylidene or an allylidene complex, which have been inert under the regular conditions for ring-closing metathesis (RCM).[106] Subjecting the RRCM precursors **27** or **28** to

the optimized reaction conditions with Grubbs second-generation catalyst (**Ru1**) resulted in truncation of the relay tether to the terminal olefins **25** and **26**, respectively (Scheme 1.5), but failed to afford **29**.[101,107] Further synthetic efforts in the RCM approach by the R. Britton group[108] with precursors, which are lacking of the THF-ring, support the assessment by T. R. Hoye that the unsuccessful ring closure can be seen "as evidence for strain in the bridged bicycle of haterumalide NA".



Scheme 1.5. Attempted RCM (**25** and **26**) and RRCM (**27** and **28**) towards macrocycle **29**.[101]

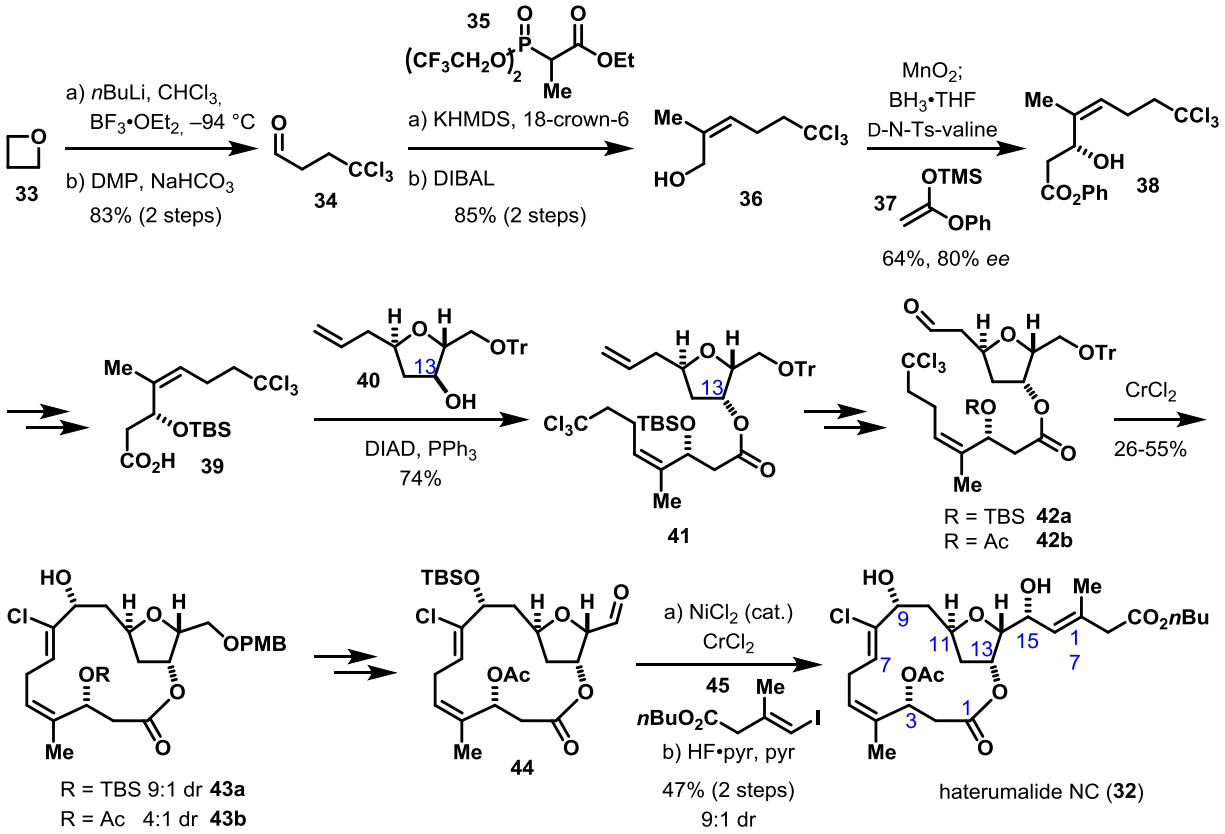
The T. Hoye group revised their retrosynthetic plan by applying an intramolecular Pd-catalyzed Kaneda chloroallylation of **30**. The skipped chlorodiene **31** was isolated in good yield with high regioselectivity, albeit with a low *E/Z*-ratio in the enone subunit (Scheme 1.6).[101]



Scheme 1.6. Intramolecular chlorocarbonylation for the ring closure of **30**.[101]

1.4.3 Total Synthesis of Haterumalide NC

Taking advantage of the allylic alcohol at C9 in haterumalide NC (**32**), the B. Borhan group established a ring-closing NHK reaction, furnishing the 14-membered macrocycle and the *Z*-chloroalkene simultaneously under Falck conditions (Scheme 1.7).[109]



Scheme 1.7. Total synthesis of haterumalide NC (**32**) by the B. Borhan group.[109]

Commencing with the addition of lithium trichloromethanide under Lewis acidic condition, the oxetane (**33**) was opened and the resulting alcohol was then oxidized with DMP. Treatment of aldehyde **34** under Still-Gennari conditions afforded the trisubstituted olefin in high yield with exclusive *Z*-selectivity.[110] After redox manipulations, the *α,β*-unsaturated aldehyde of **36** was subjected to an asymmetric Mukaiyama aldol reaction with **37**, affording allylic alcohol **38** in 64% yield with 80% *ee*. Additional protection group management completed the synthesis of the southern fragment **39**. Esterification of the northern fragment **40** deriving from 2-deoxy-D-ribose under Mitsunobu conditions established the correct stereochemistry of the THF-ring at C13 in **41**. By exchanging the protection group at C3, the aldehydes **42a** and **42b** were synthesized in order to evaluate the importance of sterical bias during the intramolecular NHK reaction.

The chromium-mediated ring closure of the 14-membered macrolactone provided the allylic alcohols **43a** and **43b** in a remarkable diastereoselectivity of 9:1 and 4:1, respectively. Lacking of neighboring functionalities for stereoinduction, the striking facial selectivity of the intramolecular addition must derive from a pre-organization of the linear precursors. In agreement with the prior syntheses of

haterumalide NA (see Section 1.4.2.2), the following intermolecular NHK addition of alkenyl iodide **45** to aldehyde **44** gave the corresponding allylic alcohol in 52% yield with 9:1 dr. Liberation of the alcohol completed the first total synthesis of haterumalide NC (**32**) in 16 steps as the longest linear sequence with an overall yield of 6.2%. Aiming for a divergent total synthesis approach,[111] the defunctionalization of the allylic alcohol **43a** at C9 under Barton-McCombie conditions[112] also accomplished the formal synthesis of haterumalide NA (**10b**).

1.5 Asymmetric Synthesis of *E*-Allyl Alcohols

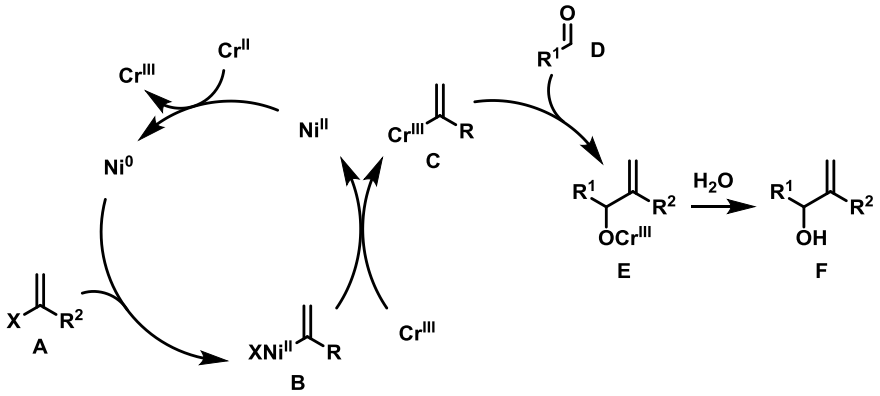
Formation of chiral allylic alcohols has been an objective of numerous synthetic methods.[113] However, the majority of asymmetric additions to aldehydes are intolerant to a variety of functional groups or are lacking of an acceptable level of stereoselectivity.[114]

1.5.1 The Nozaki-Hiyama-Kishi (NHK) Reaction

The broad functional group tolerance in both coupling partners as well as the pronounced chemoselectivity of organochromium intermediates for adding to electrophilic aldehydes renders the NHK reaction an indispensable tool for total synthesis.[98,115] In contrast to other organometallic reagents, the organochromium species have a strongly covalent C–Cr character, tolerating protic functional groups and acidic positions.

1.5.1.1 Mechanism of NHK Reaction

In aprotic solvents, allyl and benzyl halides are smoothly converted to the corresponding allyl- and benzylchromium reagents. However, alkenyl or aryl halides display no reactivity on treatment with chromium dichloride of high purity. The Y. Kishi group[116] and the H. Nozaki group[117] discovered that nickel chloride in catalytical amounts is necessary in order to facilitate the oxidative addition (Scheme 1.8).



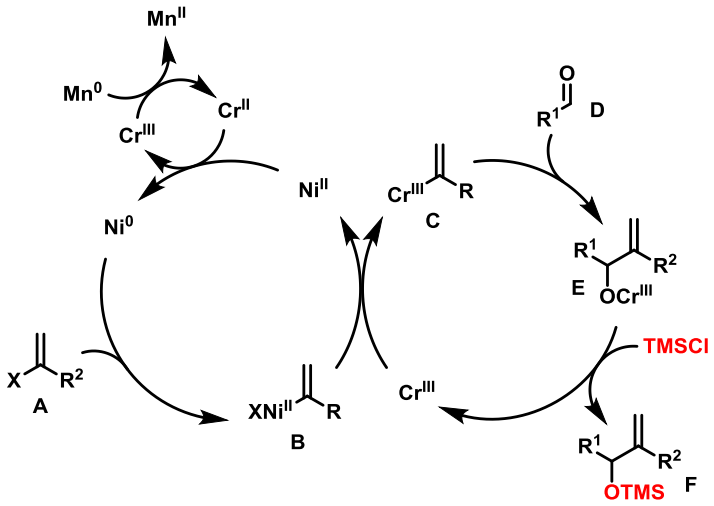
Scheme 1.8. Importance of catalytic amounts of nickel in the mechanism of NHK coupling with alkenyl halides.

In the presence of a low-valent Ni(0) or Ni(I)-species, the aryl or alkenyl halide **A** undergoes an oxidative addition to the alkenylnickel(II) **B**, which were found to degrade via dimerization.[118]

Mechanistic studies of NHK reactions by A. Berkessel *et. al.* showed the importance of $CrCl_2$ in suppressing this degradation pathway by an uncertain reaction mode.[118] Subsequent transmetalation to chromium generates the oxophilic alkenylchromium intermediate **C**. In order to close the catalytic cycle, the excess of Cr(II) (4-16 equiv.) enables regeneration of the low valent Ni(0) or Ni(I)-species from the liberated Ni(II) complex. In the presence of aldehyde **D**, the alkenylchromium **C** adds preferentially by a Felkin-Anh transition state.[97] Formation of the strong Cr–O-bond in **E** is highly exergonic, often used to facilitate the ring closure of highly strained cycles and medium-sized rings.[119] Subsequent hydrolysis of the chromium oxide **E** liberates the desired allylic alcohol **F** upon aqueous work-up.

1.5.1.2 Catalytic NHK Reaction

Despite the synthetic utility of organochromium reagents, the toxicity of chromium salts is considered a major disadvantage of the NHK reaction. In order to decrease the amount of $CrCl_2$, the introduction of inexpensive, non-toxic manganese as the terminal reductant by A. Fürstner *et. al.* led to the discovery of the catalytic variant of the NHK coupling.[120] Hence, cyclic voltammetry showed the catalytic role of $CrCl_3$ for the generation of low valent nickel species (Scheme 1.9), which is not directly reduced by the reducing manganese powder.[118]



Scheme 1.9. Mechanism of Nozaki-Hiyama-Kishi reaction in catalytic amounts of $CrCl_3$.[115]

This primary catalytic cycle is accompanied by another secondary cycle of chromium responsible for adding the alkenyl substituent to the aldehyde **D**. The Cr-mediated NHK reaction is terminated by the formation of the strong chromium(III) alkoxide **E** representing the thermodynamic sink. In order to liberate the Cr(III), the cleavage of the Cr-O-bond with a dissociation energy of 461 kJ mol^{-1} is realized by adding TMSCl, generating the hydrolysable silyl ether **F**.[121] Alternatively, the usage of Cp_2ZrCl_2 as a dissociating agent was shown to be more effective than TMSCl.[122]

1.5.1.3 Asymmetric NHK Reaction

Based on the discovery of the catalytic NHK reaction by the A. Fürstner group, the stage was set for the development of an enantioselective variant.[123] The first results in enantioselective allylation by P. G. Cozzi *et. al.* used commercially available salen ligand **46** (Figure 1.8).[124] Further modifications of the parent diamine **47** by the A. Berkessel group increased the enantioselectivity to more than 90% *ee*.[125] Besides the established C_2-symmetric ligands, Y. Kishi *et. al.* introduced sulfonamides **48** displaying very high enantio- and diastereoselectivity. Highlighting their potential as the ligand of choice, the Y. Kishi group achieved a highly selective total synthesis of the eastern part of halichondrin B (**8**) by consecutive asymmetric NHK reactions.[72e] Despite the broad synthetic utility of the Kishi ligands, the overall high catalyst loading is the major disadvantage of this asymmetric addition protocol. Taking advantage of a heterobimetallic catalyst, the new ligand system is coordinating to chromium and nickel simultaneously, enabling a catalytic transformation below a catalyst loading of 2 mol%.[126] In regard of the diastereoselective addition to α-stereogenic aldehydes, the chiral ligands can either improve the selectivity or override the natural substrate-control to a certain extend.[72e,127]

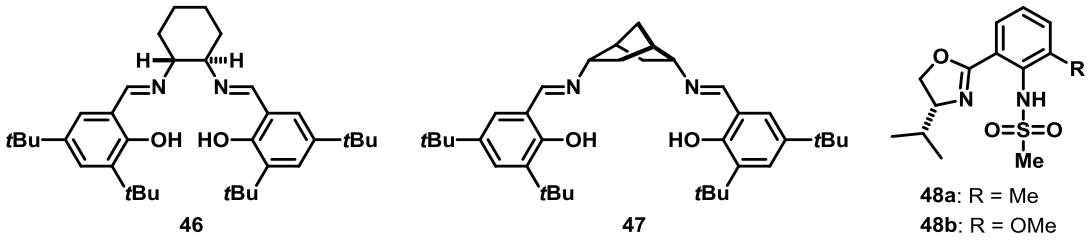
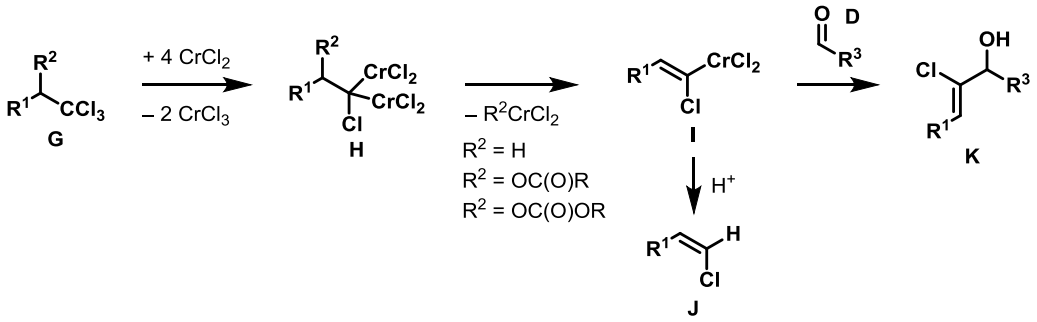


Figure 1.8. Common ligands applied in asymmetric NHK reactions.

1.5.1.4 Falck-modified NHK for the Stereoselective Synthesis of Alkenyl Chlorides

Regarding the additions of chloroalkenes to aldehydes, the straightforward transmetalation of 1,1-dichloroalkenes suffers from a marginal yield of 4% under the regular NHK conditions.[128] Formally introducing trichloro-substituted alkyl chains as the ultimate precursor, the Falck group managed to add alkenyl chlorides to aldehydes in good yield with exclusive *Z*-selectivity (Scheme 1.10).[129] Acting as a single electron reductant, the required four equivalents of $CrCl_2$ enable the oxidative addition to trichloromethylalkane **G** to generate the 1-chloro-1,1-bischromium alkane **H**.[130] Based on the fundamental *syn*-selectivity of β-hydride elimination, the α-chloroalkenylidene chromium(III) carbenoid **I** is liberated in a stereoselective fashion due to the steric clash between the two chromium(III) substituents and the neighboring alkylchain R^1 in **H**.



Scheme 1.10. Mechanism for *Z*-selective generation alkenyl chlorides **J** and **K**.

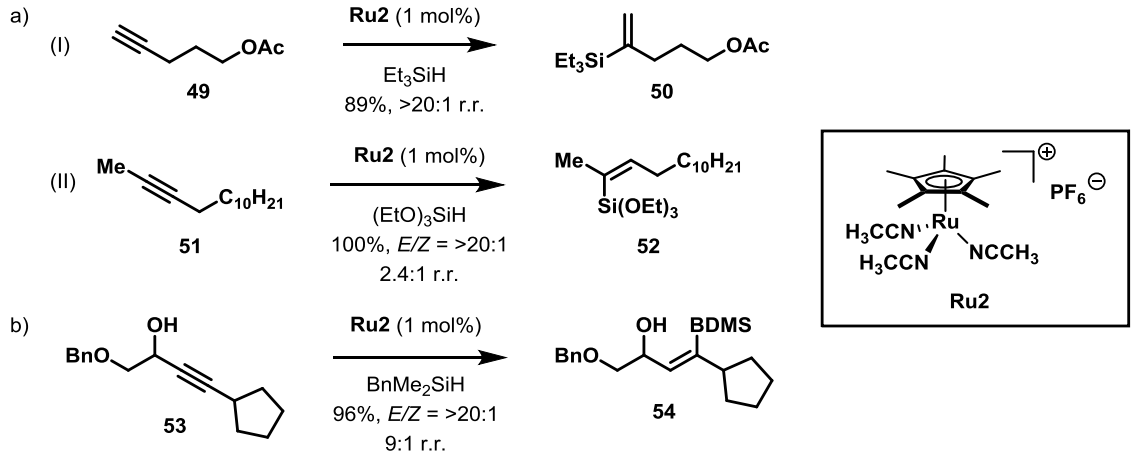
Alternatively, the stereoselective synthesis of **I** can be also achieved by β-elimination of the corresponding carbonates (R^2 = OC(O)OR) and esters (R^2 = OC(O)R) in **H**.[128,131] Taking advantage of the exclusive *E*-selectivity, the aqueous work-up of **I** gives access to *Z*-alkenyl chlorides **J**, which are valuable coupling partners in palladium-catalyzed cross coupling.[132] However, with a stereodefined α-chloroalkenylchromium reagent **I** in hand, the addition to aldehyde **D** occurs under stereoretention of the trisubstituted olefin, providing chlorine substituted allyl alcohol **K** as a single *Z*-isomer. According to the high substrate-dependency encountered in regular NHK reactions (see Section 1.5.2.2), the discrimination of the *Re*- or *Si*-face of the carbonyl group is dictated by the stereoinduction of aldehyde **D**. [129a]

1.5.2 A novel Surrogate for NHK Reactions - The *trans*-Reduction of Propargyl Alcohols

Facing a dominant substrate-control in the NHK reaction, the asymmetric alkynylation of aldehydes and the subsequent *trans*-reduction represent an adequate alternative in the stereoselective synthesis of *E*-allyl alcohols. In general, the diastereoselective synthesis of propargyl alcohols was found to be reagent-controlled, even in mismatched cases.[133] Due to its broad synthetic utility, the Carreira alkynylation enables the stereoselective addition of alkynes to aldehydes on advanced intermediates in total synthesis under mild reaction conditions.[134] Formation of the *E*-alkene was limited to the *trans*-selective reduction of propargyl alcohols by metal hydrides such as $LiAlH_4$ or Red-Al,[135] whereas milder alternatives are basically missing.[136] Excluding radical processes involving transition metal-catalyzed hydrogen atom transfer (HAT)[137] and successive isomerization of the initial addition adduct,[138] all metal-catalyzed hydrogenation and hydrofunctionalization reactions are fundamentally *Z*-selective.[139] After the oxidative addition of hydrogen or H–E-bonds, the migratory insertion of the coordinating π-bond of the substrate into the resulting metal hydride is under frontier orbital control.[140]

1.5.2.1 *trans*-Hydrosilylation of Alkynes

Overcoming the limitations of suprafacial *cis*-selective hydrometalation of internal alkynes, the recent development in catalyst design advanced the field of organometallic chemistry by facilitating an unorthodox *trans*-selective hydrofunctionalization.[141] The discovery of the ruthenium-catalyzed *trans*-selective hydrosilylation of internal alkynes by the B. M. Trost group initiated a new era of *trans*-hydroelementation of alkynes in methodology development and natural product synthesis (Scheme 1.11a).[142] Despite the recent efforts in understanding the mechanism of this intriguing transformation,[143] the exact mechanism of the concerted or stepwise addition[144] and the differences to the *E*-selective Chalk-Harrod mechanism[145] remain uncertain.

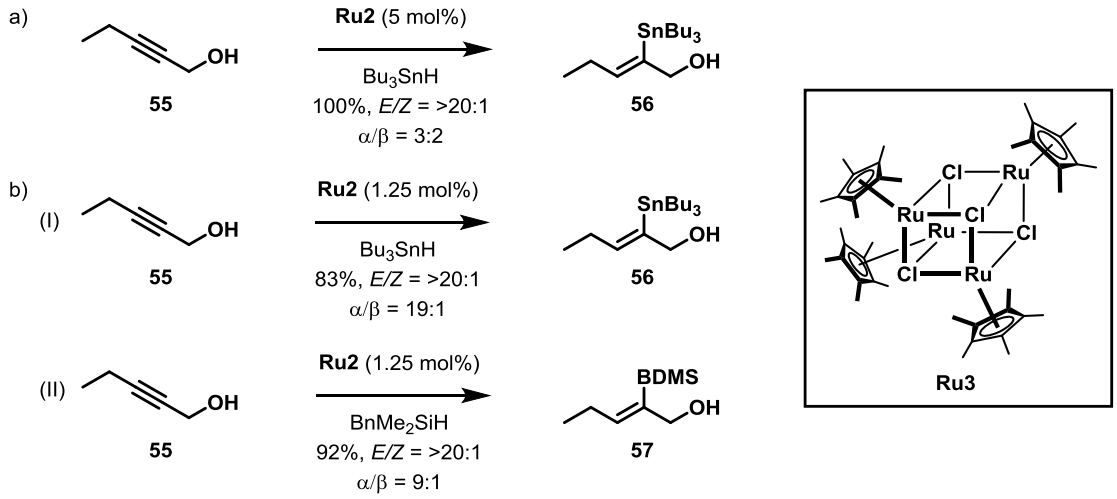


Scheme 1.11. a) Initial reports on the *trans*-hydrosilylation. b) Regioselective *trans*-hydrosilylation of propargyl alcohols.

Despite its profound stereo- and chemoselectivity, the regioselectivity of the ruthenium-catalyzed hydrosilylation is highly substrate dependent (Scheme 1.11). Whereas terminal alkyne **49** give the branched product **50** (Scheme 1.11a(I)), the internal unbiased alkyne **51** exhibited a minor regioselectivity in favor of alkenylsilane **52** (Scheme 1.11b(I)).[142a] In contrast, good levels of regioselectivity are obtained by subjecting unprotected propargyl alcohol **53** to the optimized reaction conditions (Scheme 1.11b).[142b] Adding predominantly to the distal position in alkenylsilane **54**, the selective downstream functionalization of propargyl alcohols was initiated. Based on the original synthetic studies by T. Takeda *et. al.*,[146] the B. M. Trost group employed alkenylsilanes in Hiyama-Denmark type cross couplings[147] or converted them to ketones,[142b] α-hydoxyketones[148] and *E*-olefins.[149] Applying the two-step sequence comprising of *trans*-hydrosilylation and protodesilylation on advanced intermediates in total syntheses highlights its potential for the late-stage introduction of chiral allylic alcohols.[134b,150] Nevertheless, the treatment of advanced intermediates with fluoride sources is met with limited functional group compatibility, causing the cleavage of important silyl-containing protection groups.

1.5.2.2 *trans*-Hydrostannylation of Propargyl Alcohols

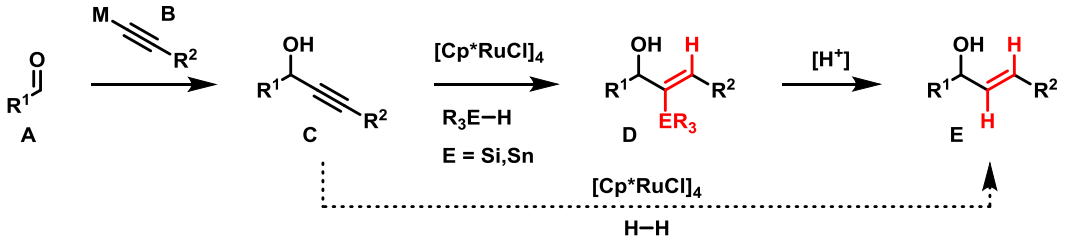
In contrast to the alkenylsilanes, a stannane-containing surrogate could be functionalized more easily and exhibit a much higher functional group tolerance upon derivatization.[151] This synthetic downstream potential was initially dampened by the low selectivity of the *trans*-hydrostannylation of propargyl alcohol **55** under the previous reaction conditions (Scheme 1.12a).



Scheme 1.12. a) *Trans*-hydrostannylation with **Ru2**. b) *Trans*-hydrostannylation and *trans*-hydrosilylation with **Ru3**.

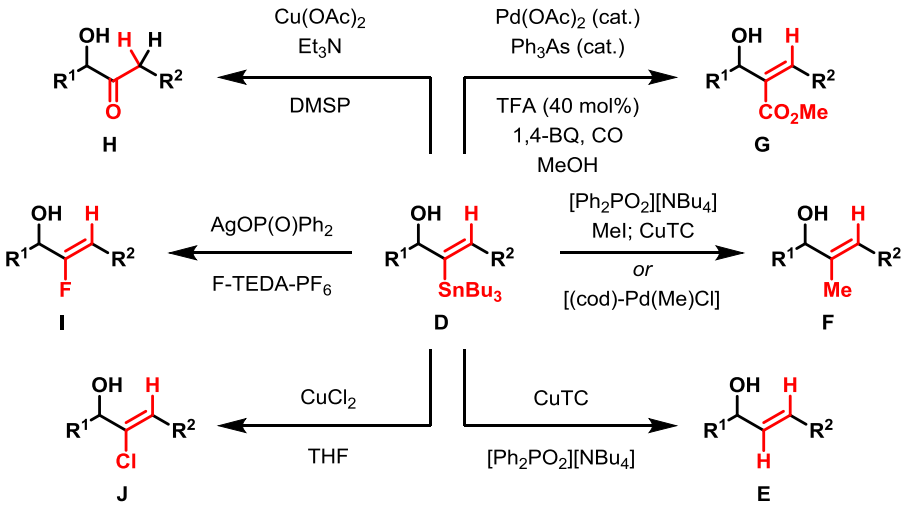
After extensive catalyst screening, the cationic ruthenium catalyst **Ru2** was replaced by the chloride-containing ruthenium catalyst **Ru3**, which provides the *trans*-adduct **56** as a single regioisomer (Scheme 1.12b).[152] Using the same catalyst, the selectivity of the *trans*-hydrosilylation was inverted, affording the proximal alkenylsilane **57** as well (see Scheme 1.11). This profound regiocontrol can be traced back to a hydrogen bonding between the chloride ligand and the free hydroxy group.[153] Furthermore, the A. Fürstner group showed, that internal alkynes containing hydroxy groups in close proximity could be differentiated from competing unsaturated motifs lacking of hydrogen-bond donors.[154]

Taking advantage of the high selectivity of *trans*-hydrofunctionalization with **Ru3**, the novel sequence initiated by asymmetric alkynylation of aldehyde **A** would allow discriminating the unprotected, chiral propargyl alcohol **C** from other alkyne moieties present in a given substrate. Subsequent addition of either silane or stannane sets the stage for the final protodemetalation of **D**, affording the desired allyl alcohol **E** in high levels of regio-, chemo- and stereoselectivity (Scheme 1.13).[141b,155] Despite the broad functional group tolerance and its synthetic utility in total synthesis, the *trans*-additions to sterically encumbered alkynes[156] or those lacking of proximal functional groups with hydrogen-donor abilities[157] are unfeasible for this ruthenium-catalyzed transformation. Thus, the total syntheses of callyspongiolide[158] and rhizoxin D[159] had to be revised.



Scheme 1.13. Alternative approach to *E*-allyl alcohols **E** by asymmetric alkynylation and two-step *trans*-reduction.

Regarding the subsequent derivatization of the generated alkenylstannanes **D**, this mild addition protocol enables the introduction of various motifs.[154,160] Despite the synthesis of the desired *E*-alkenes **E** by protodestannylation,[141b,155] the versatile downstream functionalization of hydrostannylated propargyl alcohols **D** is enabled by the well-established organotin chemistry (Scheme 1.14).[151a] [151b]

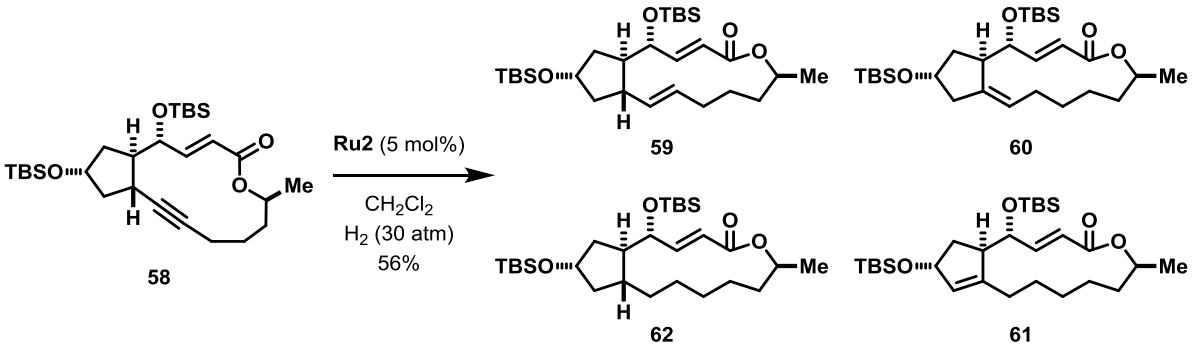


Scheme 1.14. Late-stage diversification of alkenylstannane **D** for diverted total synthesis.[141c]

Besides the successful formations of C–C-bonds by methylation[161] to **F** or Stille carbonylative cross coupling (**G**),[162] the introduction of heteroatoms such as ketone **H**,[163] chlorides[160,164] **I** and fluorides[165] **J** were accomplished, rendering ruthenium-catalyzed *trans*-hydrostannylation a suitable methodology for the late-stage diversification of advanced intermediates.

1.5.2.3 *trans*-Hydrogenation of Alkynes

Concerning the direct *trans*-reduction of alkynes (see Scheme 1.13),[166] its application to the total synthesis of brefeldin A[167] displayed the major disadvantages of the catalytic hydrogenation by causing double-bond isomerization (**60** and **61**, 20%) and overreduction (**62**, <5%) (Scheme 1.15).



Scheme 1.15. *Trans*-hydrogenation applied in the total synthesis of brefeldin A.[167]

Mechanistic studies featuring X-ray crystal structure analysis, solid-state and solution NMR as well as DFT calculations displayed a highly complicated reaction pattern emanating from a ruthenium carbene after *gem*-dihydrogenation.[168] Further synthetic utilization of this *in situ* formed carbene led to intramolecular reductive cyclopropanation and metathesis of enynes.[169] Despite the recent efforts in understanding the mechanism of the ruthenium-catalyzed *trans*-reduction, the undesired side reactions cannot be suppressed entirely, limiting the synthetic utility of this transformation for advanced substrates.

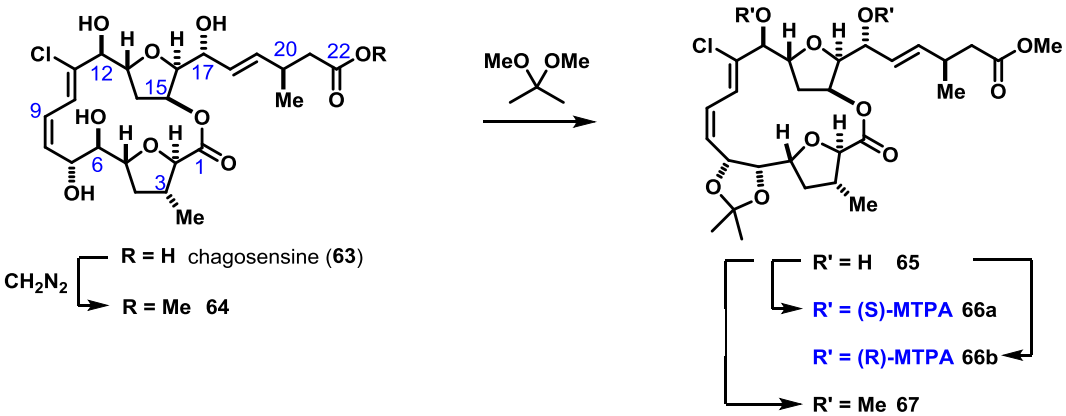
2 Total Synthesis of the Putative Structure of Chagosensine

2.1 Isolation and Stereochemical Assignment of Chagosensine

Chagosensine (**63**) was isolated from the Red Sea sponge *Leucetta chagosensis* obtained at the Aqaba Gulf in Israel (Picture 2.1).[170] The marine macrolide was obtained from 800 g (wet weight) in 0.0029% yield. Despite the substantial amount of 24 mg of isolated natural product no biological profiling was conducted and the entire material was used for structural elucidation by derivatization.

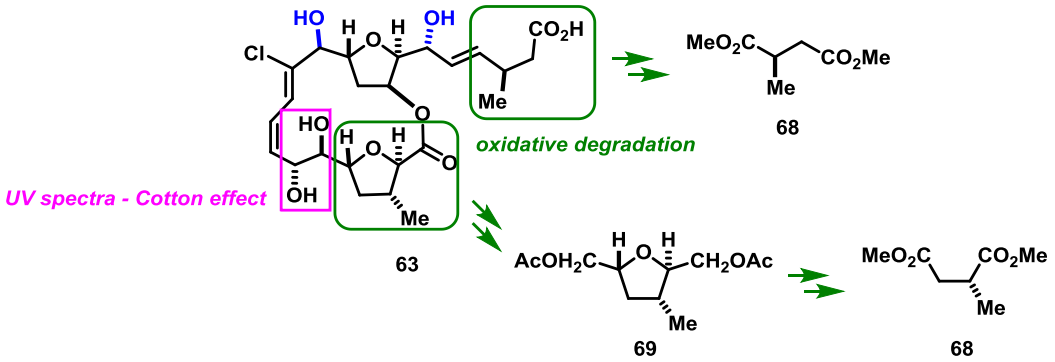
Picture 2.1. *Leucetta chagosensis*, Red Sea sponge containing chagosensine (**63**).[80b]

The intricate structure of chagosensine possesses a total of 11 stereogenic centers, comprising of two tertiary carbons and nine secondary alcohols. The highly oxygenated carbon framework is decorated with two *trans*-configured THF-rings and a unique *Z,Z*-chlorodiene embedded in the 16-membered macrolactone, which to date is unprecedented among natural products. Besides this distinguishable unsaturated moiety, an additional olefinic entity is present in the side chain as an allylic alcohol. After NMR analysis based on two-dimensional experiments such as HSQC, HMBC and NOESY, the connectivity and the relative stereochemistry of the two THF-rings were elucidated by the isolation team.[170]



Scheme 2.1. Derivatization of chagosensine (**63**) for stereochemical assignment.[170]

For the assignment of the absolute stereochemistry, the derivatization by the isolation team commenced with esterification of the carboxylic acid **63** to methyl ester **64** (Scheme 2.1). After acetonide-protection of the 6,7-diol in the southern part, the two stereocenters of the remaining allylic alcohols in **65** were assigned by Mosher ester analysis (**66a** and **66b**). In analogy to the structural assignment of haterumalide NA (see Section 1.4.2.1),[87] the absolute stereochemistry of the northern THF-ring was assigned by analysis of *J*-coupling values with the adjacent side chain. A high *J*-value of 7.7 Hz between the allylic alcohol at H17 and H16 embedded in the THF-ring was correlated with a *trans*-relationship.[170] Concerning the stereochemical assignment of the two tertiary stereogenic centers at C3 and C20, oxidative degradation of the carbon framework led to **68**, which was compared with the commercially available compounds by GC using a chiral stationary phase (Scheme 2.2).



Scheme 2.2. Methods applied for stereochemical assignment of chagosensine.[170]

Regarding the 6,7-diol in proximity to the southern THF-ring, the respective acetonide **67** was deprotected and treated with *p*-methoxycinnamoyl chloride, installing two additional chromophores at C6 and C7 in **70** for exciton coupled circular dichroism (ECCD) analysis (Figure 2.1c).[171] Based on the exciton chirality rule, the absolute orientation of the interacting chromophores can be assigned.[172] Upon electronical excitation, the electric dipole transition on one chromophore is interacting with an neighboring chromophore, which results in an exciton splitting of the locally excited states. This splitting is manifested in a redshifted and blueshifted Cotton effect with

oppositely signed Δε in the CD spectra. The turning point of this bisignate CD either occurs from a positive long wavelength Cotton effect to a negative short wavelength Cotton effect, representing a positive exciton chirality, which is depicted at λ = 289 nm in Figure 2.1a, or the opposite negative exciton chirality occurring at λ = 324 nm in Figure 2.1a. When the induced electronic dipoles in **70** are excited at higher wavelengths (λ = 324 nm), the counter-clockwise arrangement of the two chromophores along the C6−C7 trajectory visualized in Figure 2.1b induces a negative chirality in the CD spectrum. In combination with the high *J*-value (J_{6-7} = 10.0 Hz), the isolation team concluded that the 6,7-diol must be (*R,R*)-configured (Figure 2.1c).

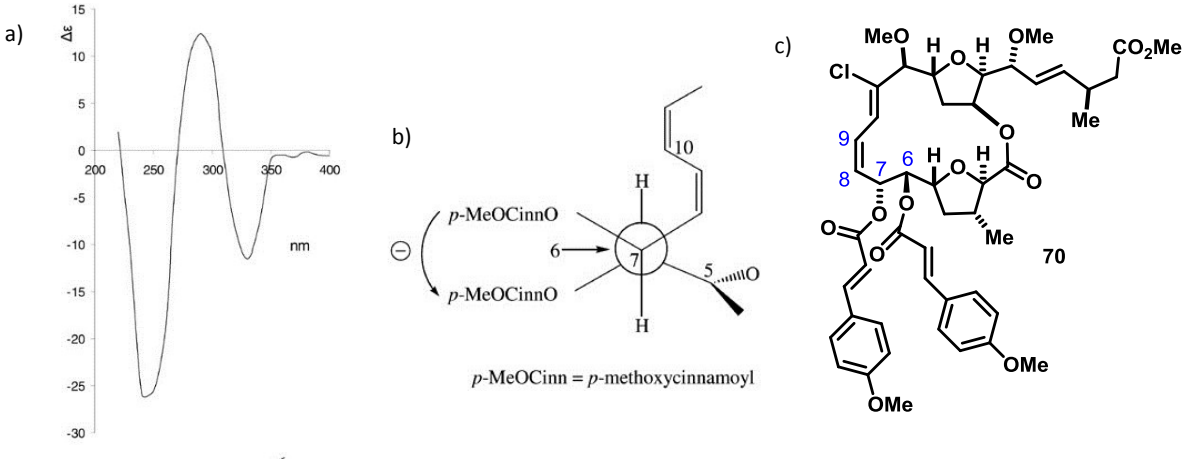


Figure 2.1. CD analysis of the Cotton effect for the stereochemical assignment of 6,7-diol by ECCD. a) CD spectra of **70**. b) Postulated conformational orientation of the chromophores correlating with a negative EDM. c) Structure of **70** with two chromophores.[170]

The closest relatives of chagosensine (**63**) are the members of the haterumalide (**10**) and biselide families (see Section 1.4). While **10** has a *skipped* rather than a conjugated chlorodiene unit, the original stereochemical assignment of the northern THF-ring and the adjacent allylic alcohol of **63** and **10a** are matching (Figure 2.2). However, after stereochemical revision of haterumalide NA (**10b**) by total synthesis, the tetrahydrofuran moieties are ostensibly enantiomeric, whereas the absolute configurations of the neighboring hydroxylated chiral center remain identical. The consequences of this structural revision from an *anti*- in **10a** to a *syn*-relationship in **10b** for the stereochemical assignment of chagosensine will be discussed in Section 3.1. Further stereochemical correspondence can be found in isolaulimalide (**71**) and amphidinolide C (**72**) and F. While the relative and absolute configuration of the northern THF-ring matches with **71**, the southern structural features of **72** including the THF-ring and the neighboring *anti* 1,2-diol are identical with those in **63** (Figure 2.2).

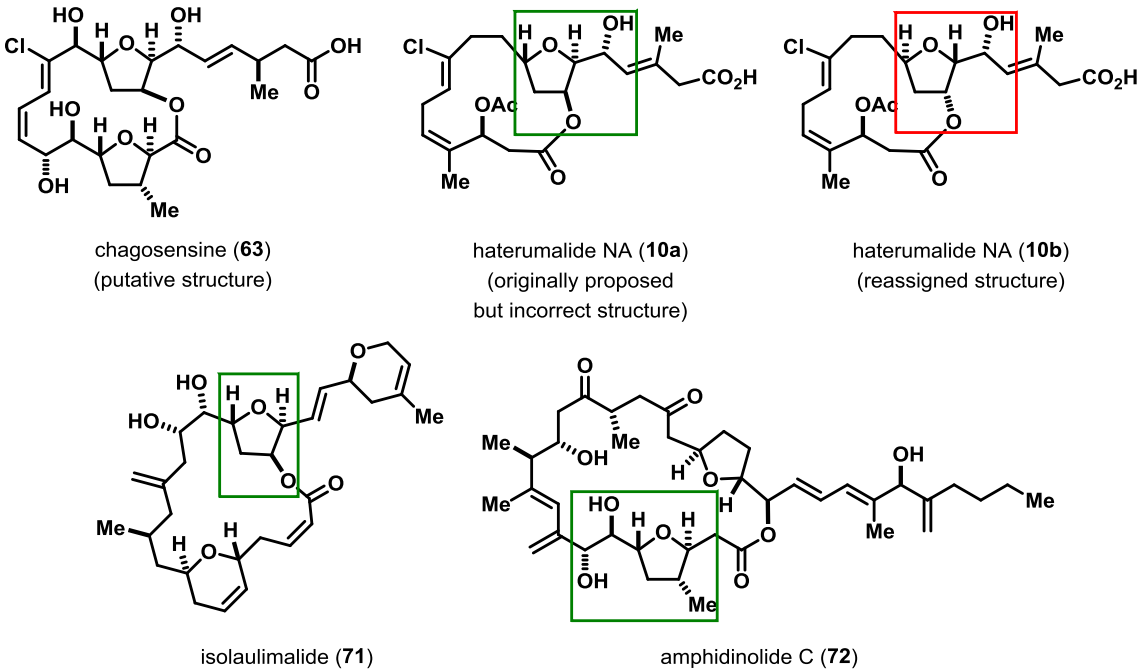


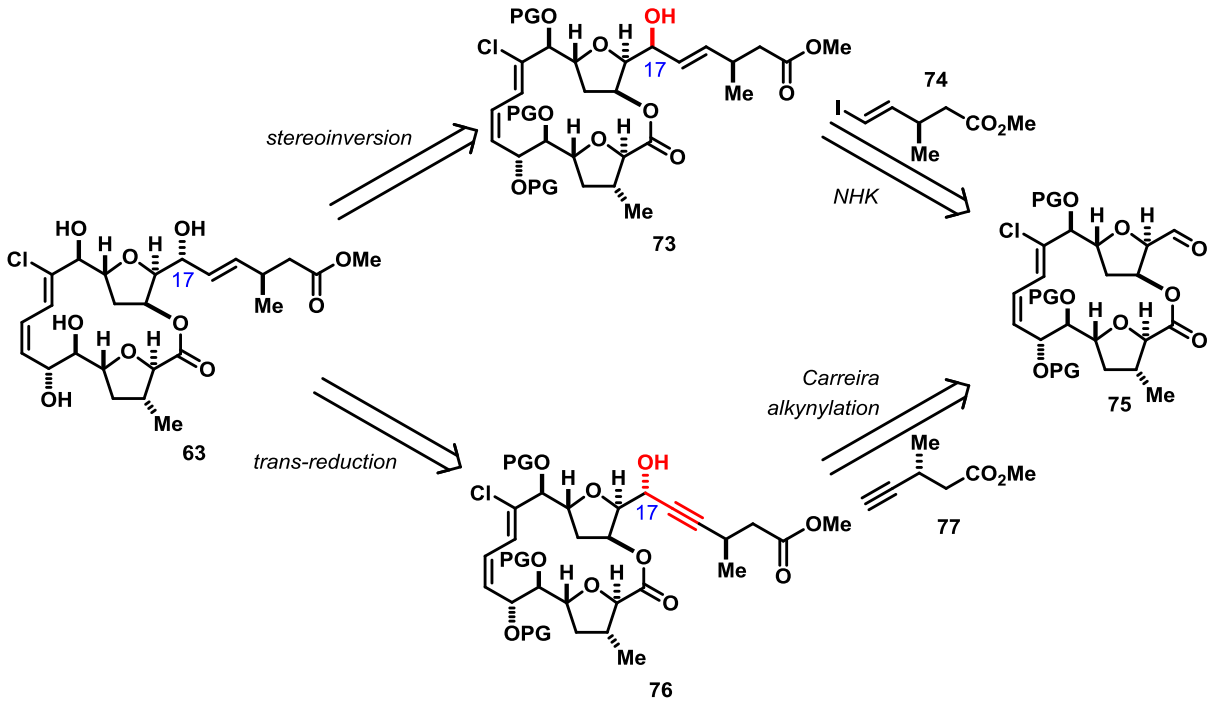
Figure 2.2. Structural similarities of **63** with other THF-containing macrolides.

Despite these structural similarities and the recent achievements in accessing these natural products (see Section 1.4), the encouraging profile of chagosensine in terms of complicated molecular architecture and the favorable biological properties of chlorine-containing small molecules (see Section 1.3.3.2) has remained surprisingly unappreciated. Neither a total synthesis nor a fragment synthesis had been reported, although a considerable amount of methodological paper had referred to this intriguing polyketide.[173] This largely disproportional level of attention might be related to the untested biological activity of **63** or the arguably much higher synthetic challenge posed by this target.[170]

2.2 Initial Retrosynthetic Analysis

2.2.1 Introduction of Side Chain to the Macrocyclic Core

The biggest challenge for the retrosynthesis of chagosensine lies in the unique *Z,Z*-chlorodiene embedded in the 16-membered macrolactone. Thus, the first retrosynthetic disassembly of **63** separated the side chain from the cyclic core structure, leading back to aldehyde **75** in Scheme 2.3. Two different approaches were considered for introducing the side chain to **75**. Based on the total syntheses of haterumalide NA (see Section 1.4.2.2), the intermolecular NHK reaction of alkenyl iodide **74** was assumed to afford the undesired allylic alcohol at C17 in **73**, which would imply a treacherous stereochemical inversion as a late-stage transformation. Alternatively, by taking advantage of the reagent-controlled addition of alkyne **77** to **75** under Carreira conditions,[134c,d] the desired stereochemistry at C17 in **76** would be set beforehand. Subsequent *trans*-reduction of **76** should give access to the *E*-olefin in **63** and thereby highlight the utility of the newly developed methodology as a late-stage transformation (see Section 1.5.2).

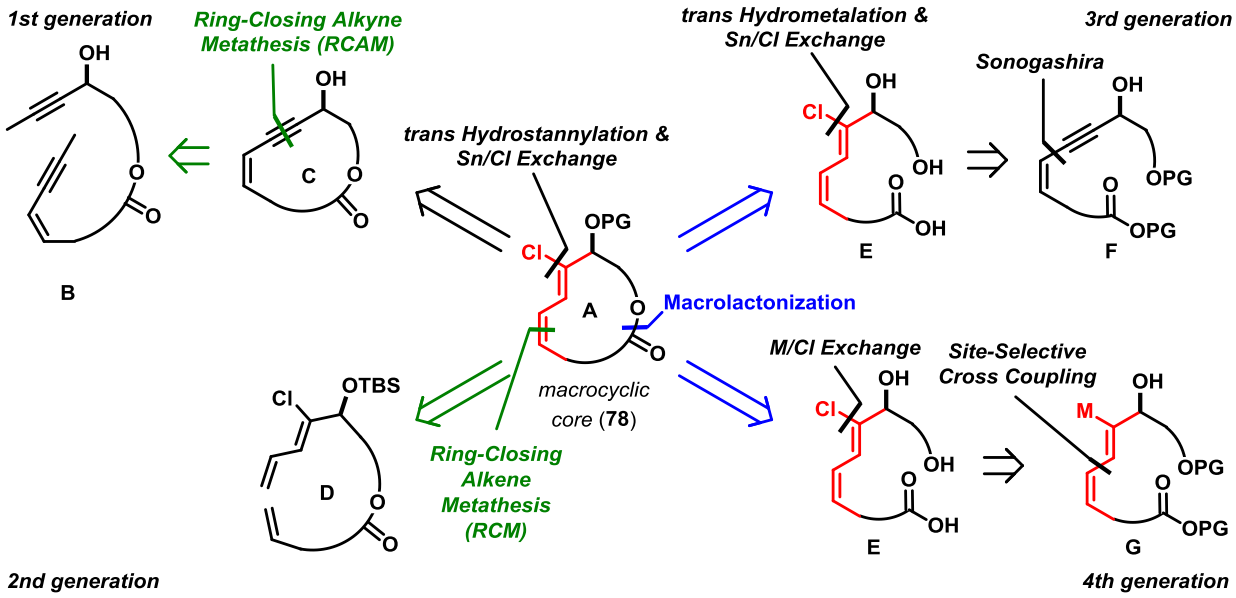


Scheme 2.3. Retrosynthetic analysis for the late-stage introduction of the side chain **74** via NHK addition and presumable stereoinversion at C17 in **73** or asymmetric alkynylation with **77** and *trans*-reduction of **76**.[174]

2.2.2 Four Retrosynthetic Strategies for Accessing the Macrocyclic Core 78

After outlining the different scenarios for introducing the side chain, the structural features of the macrocyclic core were dismantled retrosynthetically. Hence, two main strategies were considered for forging the strained macrocyclic core **78** (Scheme 2.4). Targeting the diene entity of chagosensine for ring closure, we envisioned that either alkyne or alkene metathesis could afford the 16-membered

ring **A** and provide a promising entry point for the stereoselective formation of the chlorodiene. Otherwise, the introduction of the unique *Z,Z*-chlorodiene and the subsequent macrolactonization would facilitate the ring closure of a highly strained macrocycle.



Scheme 2.4. Retrosynthetic analysis towards macrocyclic core **78** by RCAM, RCM and macrolactonization. M = metal or metalloid.

Initially aiming for the ring-closing alkyne metathesis (RCAM) of **B**,[175] the first-generation synthesis was envisioned to access the macrocyclic enyne **C**, setting the stage for the hydroxy-directed *trans*-hydrostannylation followed by chloro-destannylation (see Section 1.5.2.2). The second approach intended to furnish the macrocycle and chlorodiene simultaneously by a ring-closing diene alkene metathesis (RCM) of **D**. Hence, the pre-installed *Z*-chlorodiene would serve as a "protecting group" masking the internal alkene and thereby prevent truncation during metathesis.

By separating ring closure from installing the unsaturated subunit, the macrolactonization of *seco*-acid **E** was envisaged to provide the highly strained macrocycle **78**.[176] The two fragments could be assembled by palladium-catalyzed cross coupling in a highly convergent fashion, rendering a versatile tool for the stereoselective synthesis of dienes and polyenes in total synthesis.[177] Hence, the cross coupling approach was divided into a C_{sp}–C_{sp^2}-bond formation in **F** and a C_{sp^2}–C_{sp^2}-bond formation in **G** originating from a similar fragment synthesis. Regarding the third generation synthesis, the forging of the enyne by Sonogashira cross coupling would set the stage for the regioselective *trans*-hydrostannylation of propargyl alcohol **F** followed by a subsequent chloro-destannylation. Otherwise, the chlorine substituent in **E** could be introduced by a chloro-demetalation of dienylmetal or dienylmetalloid **G**, which was traced back to a C_{sp^2}–C_{sp^2}-cross coupling approach. Despite the spare examples for the stereoselective synthesis of **G**, we were confident that a site-selective palladium-catalyzed methodology could be developed. Subjecting the

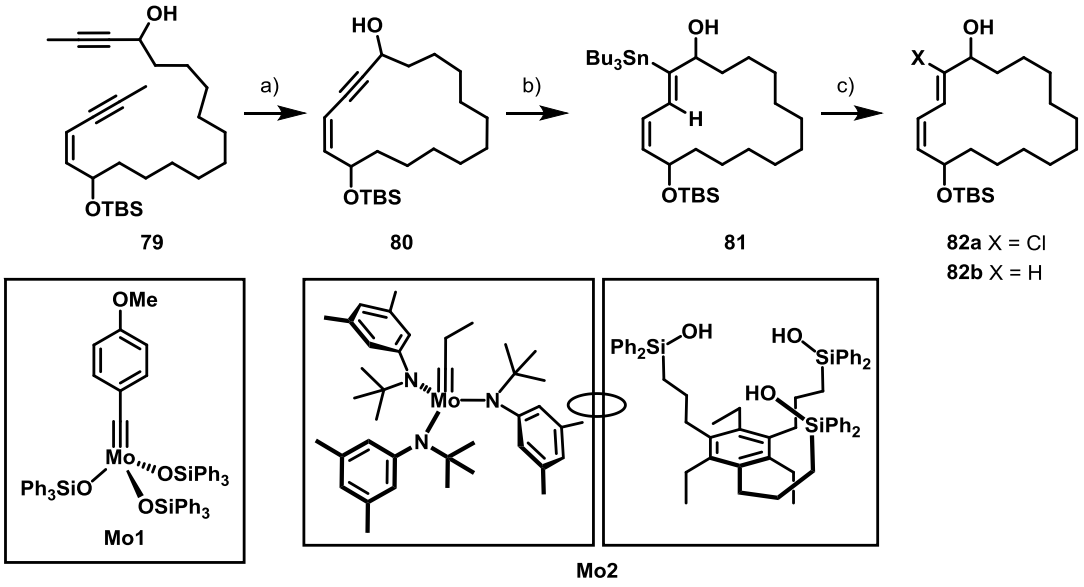
seco-acid **E** from the two cross coupling strategies to macrolactonization conditions, the furnished macrocyclic core **78** should ultimately lead to the first total synthesis of chagosensine (**63**) by the previously described late-stage introduction of the missing side chain (see Scheme 2.3).

This detailed plan of action addresses the synthetic difficulties encountered during the four-generation enduring synthetic studies towards macrocyclic core **78**, thereby offering an unprecedented evaluation of the different elaborated transformations by a challenging natural product synthesis.

2.3 RCAM Approach (1st Generation Synthesis)[174]

Remark: The following route was investigated by Dr. M. K. Ilg and Dr. J. Flasz.

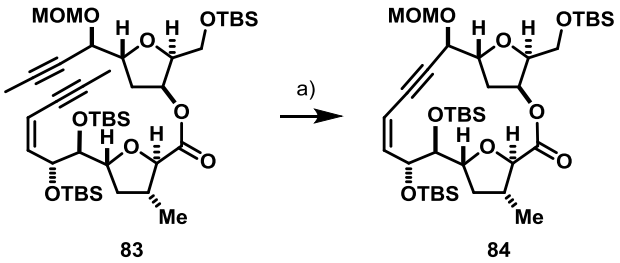
The initial investigations conducted by M. K. Ilg tested the feasibility of a key sequence comprised of RCAM, regioselective *trans*-hydrostannylation and chloro-destannylation on a model substrate (Scheme 2.5). During the ring closure of diyne **79**, the 16-membered macrocycle **80** flanked by two potential leaving groups could be furnished by the newest generation of molybdenum-based alkyne metathesis catalyst **Mo2**, whereas its predecessor **Mo1** oligomerized the precursor **79**.[178]



Scheme 2.5. Testing the outlined key sequence on model substrate **79**. Reactions and conditions: a) **Mo2** (20 mol%), 5 Å molecular sieves, toluene, reflux, 90%; b) *n*Bu_3SnH, $[Cp^*RuCl]_4$ (18 mol%), CH_2Cl_2, 79%; c) $CuCl_2$, THF, 67% (**82a**), 6% (**82b**).[174]

Subjecting enyne **80** to the optimized reaction conditions for the ruthenium-catalyzed *trans*-hydrostannylation, dienylstannane **81** was obtained in 79% yield as a single isomer. Applying the copper-mediated chloro-destannylation, *Z,Z*-chlorodiene **82a** was isolated with stereoretention of the trisubstituted olefin along with minor quantities of protodestannylated diene **82b**.[164,179]

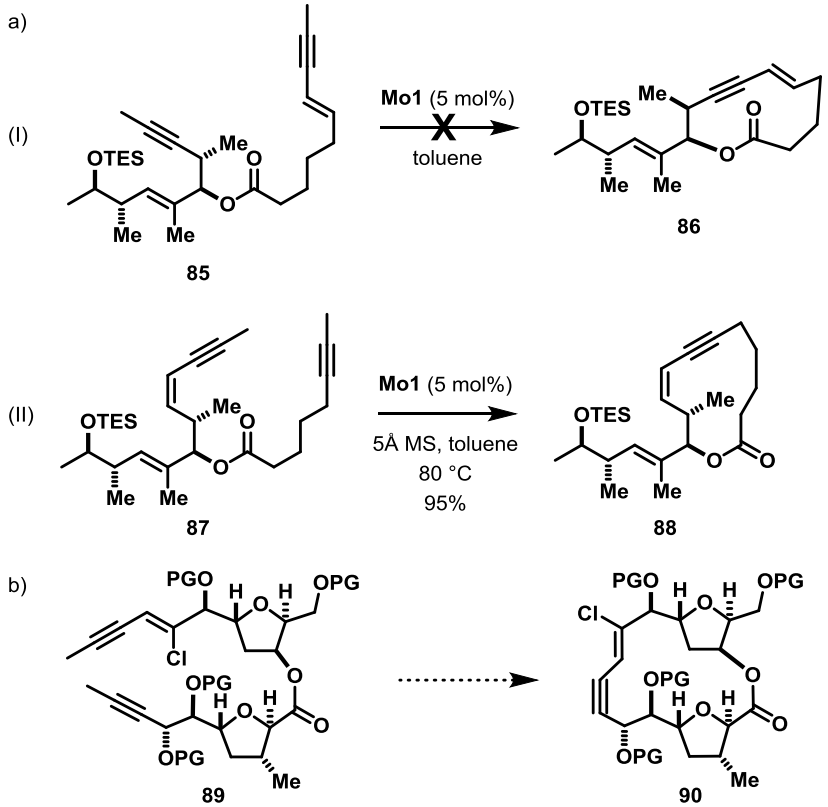
With these promising results in hand, M. K. Ilg and J. Flasz focused on the synthesis of the macrocycle **78**. After esterification of a variety of southern and northern fragments differing in the protection group settings, the different precursors were subjected to RCAM conditions using the molybdenum-based catalysts **Mo1** or **Mo2**. In agreement with the previous results obtained on the model substrate (Scheme 2.5), **Mo2** furnished the macrocycle **84** exclusively by using the visualized array of protection groups, albeit in marginal yield of 15% (Scheme 2.6).



83 84

Scheme 2.6. Fruitful RCAM attempt with MOM-protected propargyl alcohol **83**. Reactions and conditions: a) **Mo2** (20 mol%), 5 Å molecular sieves, toluene (0.001 M), reflux, 15%.[174]

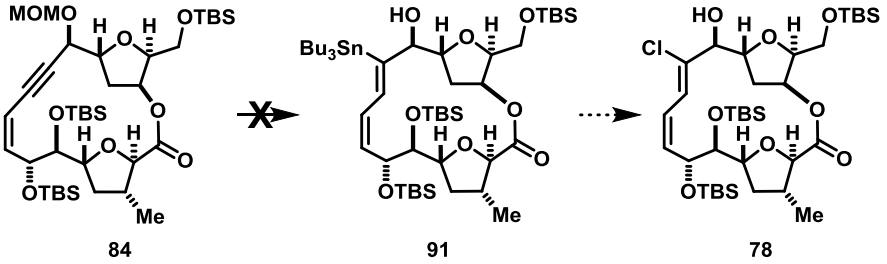
Although the successful formation of the strained 1,3-enynes was achieved, the low yield prompted us to question the structural predisposition of the applied precursor (Scheme 2.7). In reminiscence of the total synthesis of lactimidomycin, enyne **85** under **Mo1** catalysis resulted in the formation of dimers and oligomers (Scheme 2.7a(I)).[150c] Under identical conditions the isomeric compound **87** was cyclized to the macrolactone **88** in excellent yield (Scheme 2.7a(II)). Switching the predisposition in a revised RCAM approach (Scheme 2.7b), the ring closure of chloro enyne **89** was assumed to be even less feasible due to increased ring strain of macrocycle **90**.



85 86 87 88 89 90

Scheme 2.7. Substrate-dependency of RCAM in the total synthesis of lactimidomycin.[150c]

The thermodynamic aspects play an important role for the successful ring closure by RCAM. Despite the entropic driving force of metathesis by expelling a volatile alkyne, the approximately isenthalpic process cannot compensate for the generation of considerable ring strain. If ring closure is kinetically and thermodynamically inhibited, the molybdenum alkylidyne is resting in proximity to Lewis-labile functional group, which likely enhances the rate of catalyst decomposition.[178,180]



Scheme 2.8. Unsuccessful MOM-deprotection and failed *trans*-hydrofunctionalization of **84**.

With minor quantities of cyclic enyne **84** in hand, the liberation of the propargyl alcohol was unsuccessful by the common methods for cleaving MOM-ethers (Scheme 2.8).[174] Therefore, the direct *trans*-hydrostannylation on enyne **84** was investigated but failed. Mechanistic studies concerning the substrate scope of the ruthenium-catalyzed addition displayed a remarkable dependence on hydrogen bond donation in close proximity to the unsaturated moiety (see Section 1.5.2.2).[153] Employing precursors lacking of a free hydroxy groups in the *trans*-hydrostannylation, the ruthenium-catalyst coordinates solely to the enyne entity without facilitating the addition to the corresponding dienylstannane.[154] In agreement with the mechanistic studies, the unavailability of a free hydroxy groups prevents acetal **84** from engaging in the *trans*-hydrostannylation. Due to the unsuccessful cleavage of the MOM group, the RCAM approach was considered to be a dead end, which prompted us to investigate the RCM approach as the second-generation synthesis towards macrocycle **78**.

2.4 RCM Approach (2nd Generation Synthesis)

The second approach towards the 16-membered macrocyclic core was anticipated to highlight the utility of ring-closing alkene metathesis (RCM) for the synthesis of challenging 1,3-dienes. On the one hand, the direct access of the *Z,Z*-chlorodiene by RCM could benefit from a lower ring strain in the 16-membered macrocycle. On the other hand, the synthesis of the corresponding dienylic precursor maintains the difficulties of introducing a chlorodiene entity in a stereoselective fashion.

2.4.1 RCM – a Versatile Tool in Organic Synthesis

2.4.1.1 Introduction to RCM

Awarding Y. Chauvin,[181] R. H. Grubbs[182] and R. R. Schrock[183] with the Nobel prize "for the development of the metathesis method in organic synthesis" in 2005, RCM as one of the most important C–C-bond formation has been implemented as the key ring-closing transformation in numerous total syntheses.[184] In regard of the forged ring sizes, RCM facilitates the formation of normal ($5 \leq x \leq 7$) cycles, whereas the ring closure of large ($x \geq 12$) and especially medium-sized rings ($8 \leq x < 12$) were found to be highly substrate dependent. Despite the role of pre-organization of the applied precursors,[185] the steric and electronic properties of the reactive sites as well as the sheer presence of polar functional groups in the carbon framework were shown to be crucial for a successful ring closure.[186] Acting as a relay for the reactive intermediate, the ligation of polar functional groups (esters, ketones, ether etc.) within the scaffold was found to facilitate the RCM of 12-membered macrocycles.

Concerning the thermodynamic aspects of RCM as an inherently reversible process, the driving force of this essentially isodesmic reaction emanates largely from increasing entropy by liberating ethylene gas. Thereby suffering from dimerization and oligomerization in RCM, the ring-chain equilibrium can be influenced by the substrate and the applied reaction conditions.[187]

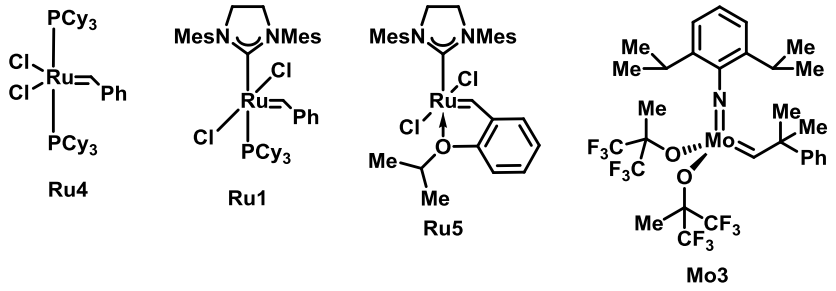


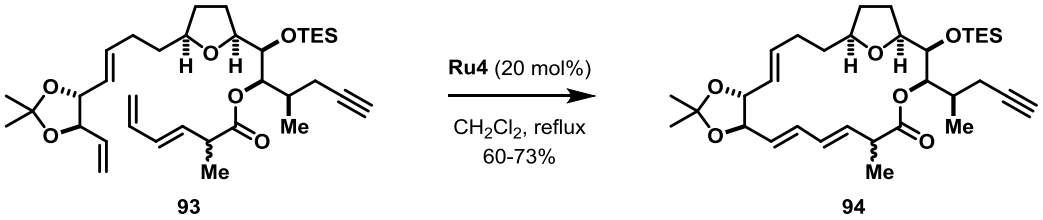
Figure 2.3. Common Ru-based and Mo-based alkylidene complexes used in RCM.

Initially introduced by R. H. Grubbs[188] *et. al.* and R. R. Schrock *et. al.*,[189] the catalyst of choice for RCM are either ruthenium[190] or molybdenum[191] based alkylidene complexes (Figure 2.3). Due to the diminished Lewis acidity of ruthenium, the various Grubbs catalysts exhibit a broad functional

group tolerance, including unprotected alcohols, aldehydes and free carboxylic acids. Furthermore, Ru-based catalysts display a pronounced reactivity towards terminal olefins, which makes them advantageous in the selective RCM of diene-containing precursors.

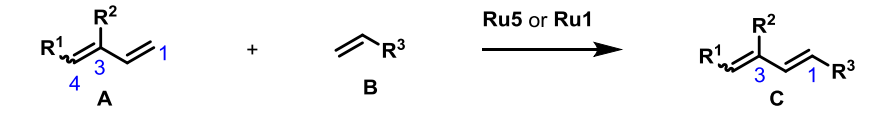
2.4.1.2 Alkene Diene Ring-Closing Metathesis

As a polyenic scaffold is present in a lot of macrocyclic natural products, a synthetic entry by metathesis has been investigated by numerous research groups.[192] Regarding the synthesis of the simplest polyene, the introduction of 1,3-dienes requires a high regioselectivity of the catalyst towards the terminal unsaturated moiety. For example, the ene-diene ring closure of **93** in the total synthesis of amphidinolide E by W. r. Roush *et. al.* highlights the selectivity of the 1st generation Grubbs catalyst (**Ru4**) for terminal unsaturated moieties (Scheme 2.9).[193]



Scheme 2.9. Fruitful RCM of diene **94** towards the synthesis of amphidinolide E with first-generation Grubbs catalyst.[193]

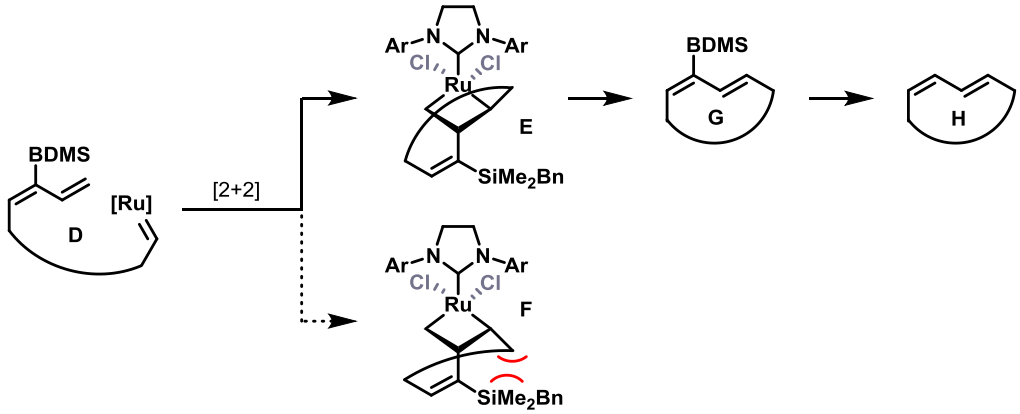
However, if the catalyst engages with the internal alkene, the truncation to the olefinic macrocycle under liberation of butadiene is observed as the major product as demonstrated in an attempted RCM towards etnangien.[194] Suffering from difficult separation of the isomers and a diminished yield, the correlation between ring size and regioselectivity was investigated, providing inconclusive results.[195] Therefore, the synthetic efforts in suppressing truncation have focused on substrate design in either the alkene or the diene entity. In cross metathesis (CM), the introduction of methyl[196] or alkyl[197] substituents at the 3-position of terminal dienes **A** resulted in the chemo- and stereoselective formation of *E*-dienes **C** (Scheme 2.10). This strategy was also successfully applied in RCM, furnishing the macrocycles of nannocystin A[198] and plecomacrolides.[199]



Scheme 2.10. Alkyl substituted dienes **A** for the chemo- and *E*-selective formation of 1,3-dienes **C**.

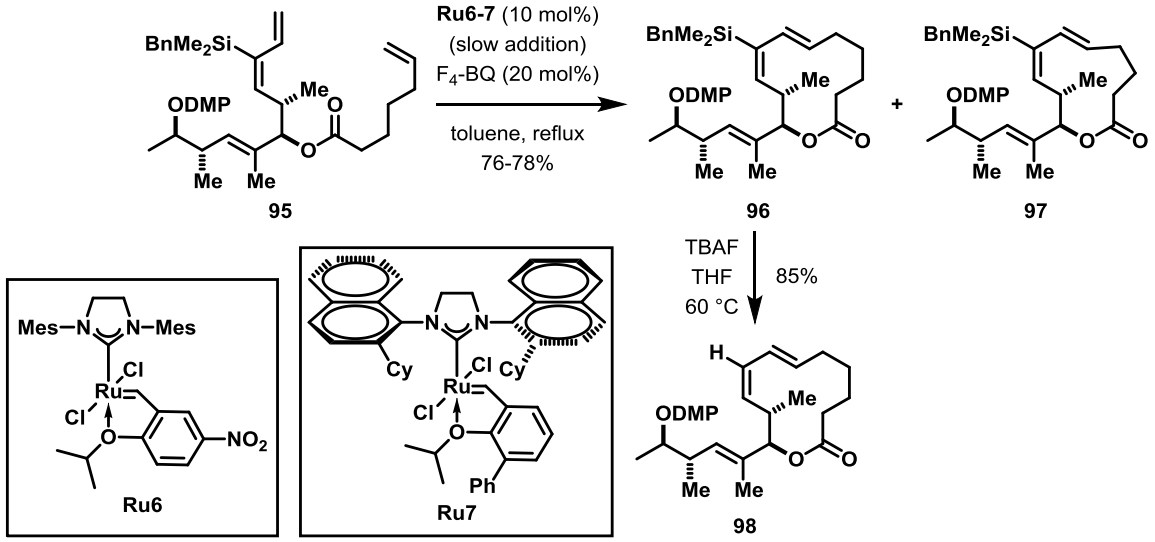
In order to access unsubstituted 1,3-dienes **H** in a regio- and stereoselective fashion, A. Fürstner *et. al.* exchanged the alkyl substituent with a removable silyl group **D**, serving as a "protecting group" for electron-rich dienes in RCM (Scheme 2.11).[200] In agreement with the stereoselectivity of alkyl substituted dienes, the silyl derivatives enabled the synthesis of the *E*-isomer **G**. After regioselective [2+2] cycloaddition of **D**, the directing effect of silyl and alkyl groups can be rationalized by a steric

clash between the alkyl substituent in metallacyclobutane **F**, whereas **E** is thermodynamically more favorable. Subsequent cycloreversion of **E** provides the *E*,*E*-configured 2-silyl-1,3-diene **G**. The subsequent stereoretentive protodesilylating of **G** liberates the desired *Z*,*E*-configured 1,3-diene **H**.



Scheme 2.11. Clarification of stereodirecting effect of silyl substituent by steric clash in metallacyclobutane **C**. [200]

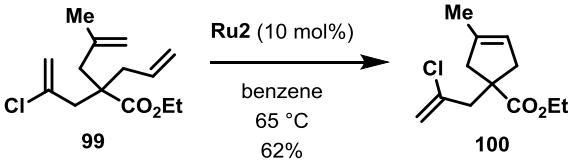
Applying the silyl-protected ene-diene RCM in the total synthesis of lactimidomycin, an inseparable mixture of desired dienylsilane **96** and the C_1-truncated diene **97** was obtained (Scheme 2.12). Due to the slow rate of ring closure, the parent terminal alkene is permanently exposed to metathesis conditions, which upon catalyst decomposition causes olefin isomerization. Switching from the Grela[201] catalyst **Ru6** to the Dorta[202] catalyst **Ru7**, the more steric encumbered NHC ligand suppressed the alkene isomerization and provided diene **96** in good yield with high stereoselectivity. Treatment of **96** with TBAF completed the synthesis of diene **98**. Notably, the silyl-stereodirecting effect is not limited to dienes and has also been applied for the *Z*-selective synthesis of alkenes in RCM.[203]



Scheme 2.12. Optimized reaction conditions for the silyl-stereodirected ene-diene RCM towards lactimidomycin.[200]

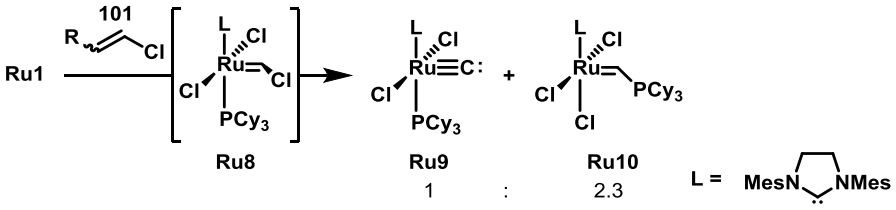
2.4.1.3 **Halogen-Substituted Alkenes in Metathesis Reactions**

Besides tuning the steric bias for achieving selectivity in metathesis reactions, additional work has focused on changing the electronic properties of the diene. Preliminary results by J. Cossy *et. al.* displayed a pronounced reactivity of $\alpha,\beta,\gamma,\delta$-unsaturated esters and amides to react with alkenes in the γ,δ-position, albeit in low yields.[204] Further reduction of electron density in the α,β-double bond with bromines enhanced the chemo- and stereoselectivity as well as the yield of the desired *E*-diene.[197] Despite the initial assumption that alkenyl halides are inert in cross metathesis,[205] Weinreb *et. al.* reported the first RCM of alkenyl chorides, furnishing 5- to 7-membered rings.[206] However, the electronic preferences of the ruthenium catalyst for engaging with the more electron-rich alkenylic moieties can be seen in model substrate **99** (Scheme 2.13).[207] While the electron-deficient chloroalkene does not participate in the RCM with **Ru2**, the electron-rich disubstituted alkene undergoes metathesis to liberate the trisubstituted olefin **100**.



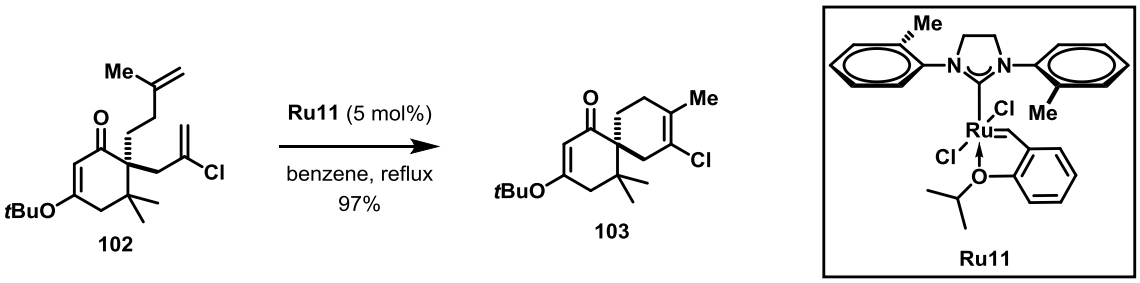
Scheme 2.13. Intramolecular differentiation between alkenyl chloride and trisubstituted alkene in RCM.[207]

Mechanistic studies concerning the fate of the ruthenium–monohalomethylidene moiety by J. Kampf *et. al.* revealed the instantaneous formation of a terminal carbide **Ru9** and a phosphoniomethylidene complex **Ru10** in a 1:2-3 ration upon treatment of Grubbs second-generation catalyst **Ru1** with alkenyl chloride **101** (Scheme 2.14).[208]



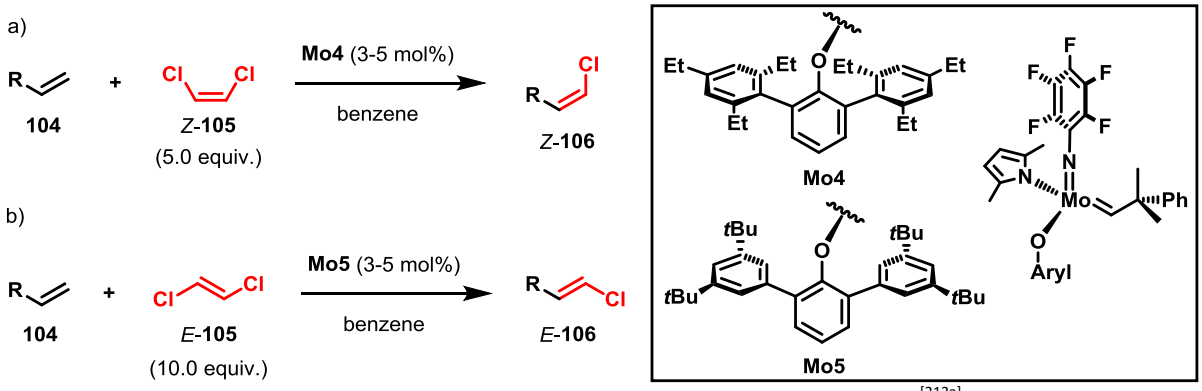
Scheme 2.14. Faith of chloromethylidene species **Ru8** in the presence of phosphine ligands.[208]

In the presence of phosphine-free ruthenium-based catalysts such as the Hoveyda-Grubbs catalyst (**Ru5**) an excess of alkenyl chloride **101** forms a chloride-bridged heterodimer, which upon dissociation engages in cross metathesis with electron-rich alkenes.[209] Despite the limited substrate scope, the forging of a tetrasubstituted chloroalkene **103** in the total synthesis of elatol[210] was accomplished by treatment of chloroalkene **102** with catalytic amounts of a slimmer Ru-based catalyst **Ru11** (Scheme 2.15).[211]



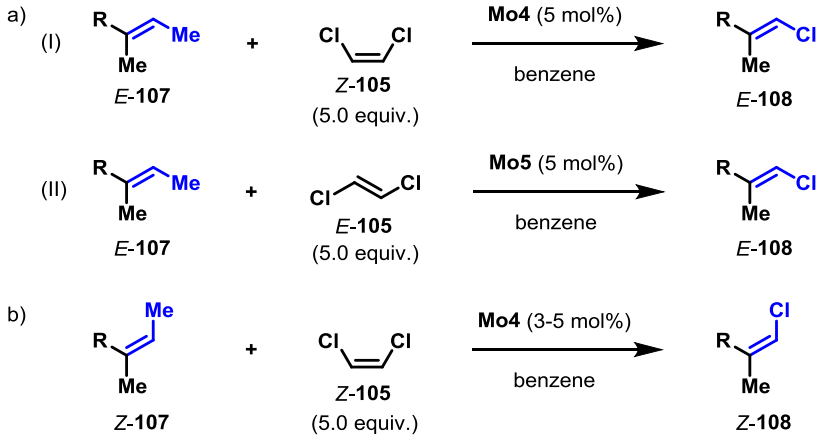
Scheme 2.15. Engaging of chloroalkene **102** in RCM towards elatol by Stewart catalyst **Ru11**.[210]

In contrast to the Ru-based catalyst, recent developments by A. Hoveyda and R. Schrock *et. al.* highlight the potential of Mo-based catalysts for CM of alkenyl halides (Scheme 2.15 and 2.16). Applying either *Z*-**105** or *E*-**105** in CM of terminal alkenes **104**, the catalysts **Mo4** or **Mo5** are able to transfer the stereochemistry of the substrate to the forged C–C-double bond of alkene *Z*-**105** or *E*-**106**, respectively (Scheme 2.16).[212]



Scheme 2.16. a) **Mo4**-catalyzed stereoretentive CM with *Z*-**105** and terminal alkene **104**.[212a] b) **Mo5**-catalyzed stereoretentive CM with *E*-**105** and terminal alkene **104**.[212b]

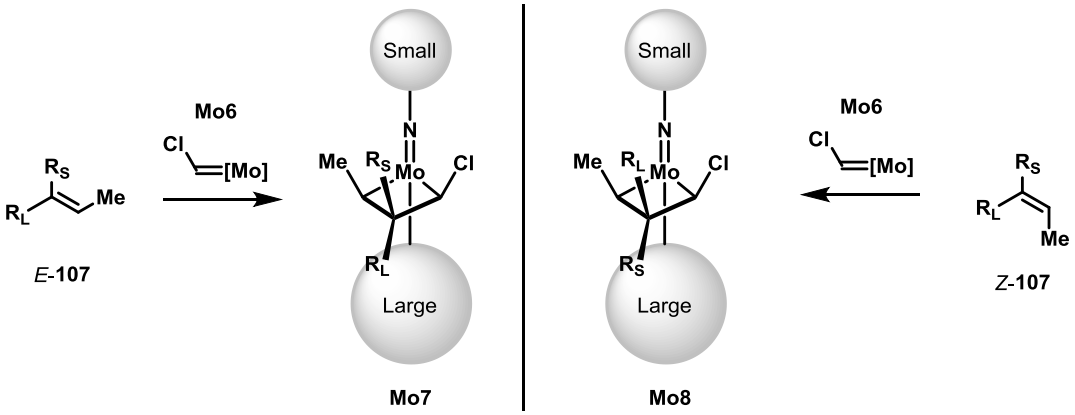
Reversing the stereochemical predisposition to the employed olefin, the *E/Z*-stereochemistry of the trisubstituted alkene **107** dictates the *E/Z*-selectivity in the resulting halogen-substituted olefins **108**, disregarding the applied stereochemistry of the 1,2-dichloroethene (**105**) (Scheme 2.17).[213]



Scheme 2.17. Mo-catalyzed stereoretentive CM of trisubstituted alkenes.[213]

The initial formation of the chloro alkenylidene species (**Mo6**) as the reactive intermediate could be proven by X-ray crystal structure analysis of the corresponding bipyridine adduct.[214] The

E/Z-selectivity is determined by the preferential arrangement of the substituent within the metallacyclobutane. In case of **Mo4** for *Z*-**105** or **Mo5** for *E*-**105**, the stereochemical transposition of the more substituted olefin can be rationalized by directing the substituent of the less substituted olefin to the same side in the metallacyclobutane (Scheme 2.18).[213]

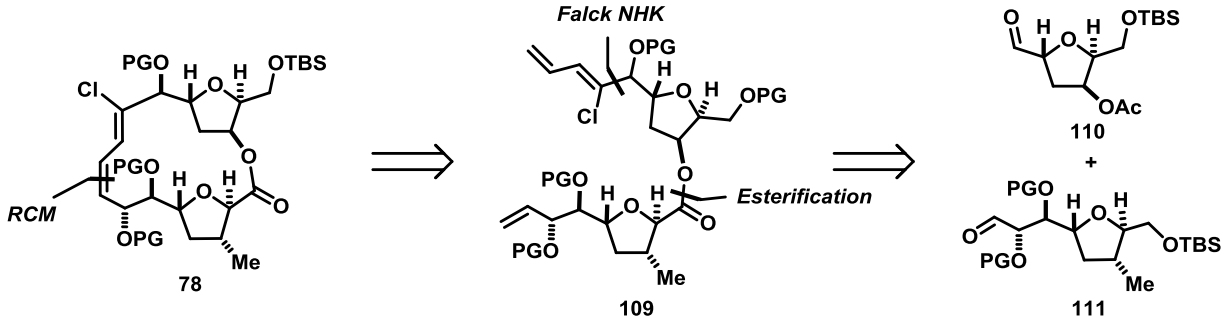


Scheme 2.18. Arrangement of the substituents in the metallacyclobutanes for transposing the introduced *E/Z*-stereochemistry in the trisubstituted chloroalkenes.[213]

In stereoretentive[215] as well as stereoselective[216] metathesis, the discrimination of the substituents within the metallacyclobutane is essential for obtaining high levels of *E/Z*-selectivity.

2.4.2 Retrosynthetic Analysis

The concept of site-selective RCM with electron-deficient dienes prompted us to investigate its feasibility in the stereoselective synthesis of the unique *Z,Z*-chlorodiene in chagosensine. Serving as an inherent "protecting group", the less reactive alkenyl chloride should facilitate the ring closure at the terminal position. Concerning the stereochemical outcome, the influence of a single chloro substituent at this specific position on a diene has not been investigated yet. Disregarding the directing effect of alkyl and silyl substituents on different positions on the diene (see Section 2.4.1.2), the rigidity of the macrocycle was believed to prevent the formation of the *E*-isomer. In the retrosynthetic perspective, the esterification of the northern fragment with the southern fragment was envisioned to set the stage for the RCM of **109**, forging the 16-membered macrocycle **78** (Scheme 2.19). Introduction of the chlorodiene moiety should be possible by a stereoselective Falck-modified NHK addition to aldehyde **110** (see Section 1.5.1.4), deriving from the former synthesis of the northern THF-ring developed by J. Flasz.[217] The synthesis of the southern alkene should start with the olefination of aldehyde **111**, emanating from the fragment synthesis established by M. K. Ilg.[174] Due to the importance of the fragment synthesis for this Ph.D. thesis, the synthetic efforts will be discussed briefly.



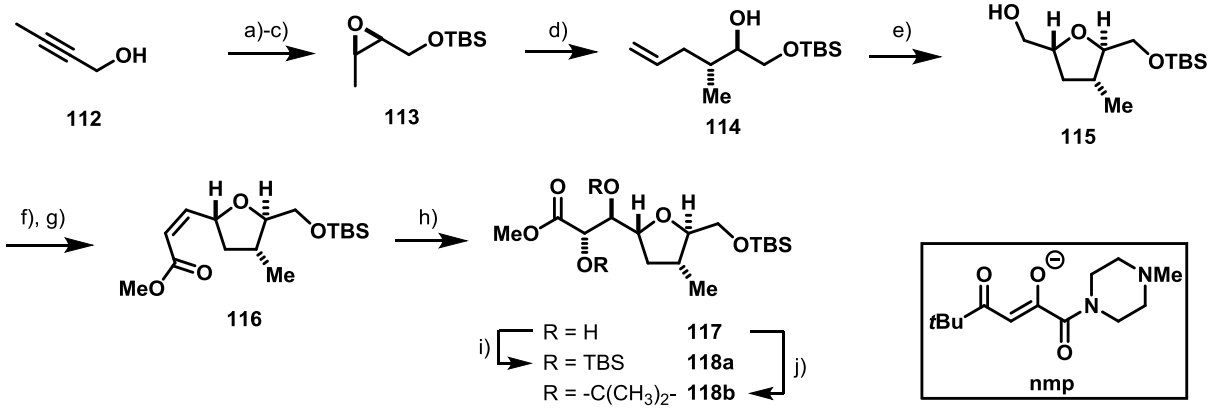
Scheme 2.19 Retrosynthetic plan towards macrocyclic core **78** by RCM of **109**.

2.4.3 Synthesis of the Southern Fragments

Remark: The following synthesis was conducted in close collaboration with Dr. M. K. Ilg and S. Speicher.

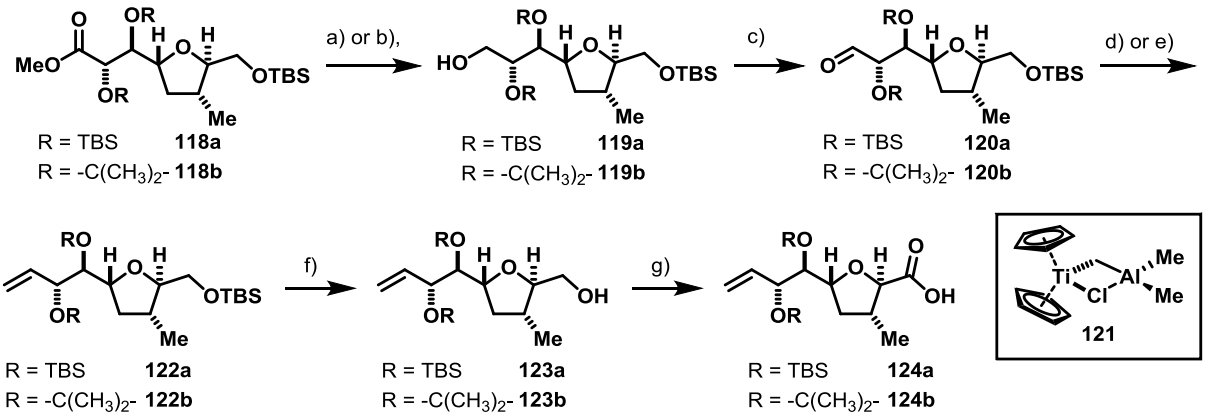
Given the structural similarities of the southern fragment of chagosensine with amphidinolide C (**72**) and F (Figure 2.2),[218] the retrosynthetic approach towards aldehyde **111** was inspired by a former fragment synthesis by the B. L. Pagenkopf group.[219] Emphasizing on the *trans*-selective formation of THF-rings[220] by an oxidative cobalt-catalyzed Mukaiyama oxidation,[221] B. L. Pagenkopf *et. al.* introduced a new ligand,[222] which allows for easier separation of the catalyst from polar compounds.

According to the literature-reported sequence, the synthesis of the southern fragment commenced with the *Z*-selective reduction of 2-butynol (**112**) and subsequent asymmetric Sharpless epoxidation of the corresponding allyl alcohol (Scheme 2.20). After TBS-protection, the epoxide **113** was treated with allyl magnesium bromide under copper catalysis.[223] With alcohol **114** in hand, the modified oxidative Mukaiyama cyclization provided the desired *trans* THF-ring **115** in high yield with exclusive diastereoselectivity. In agreement with the original results obtained by B. L. Pagenkopf, the sequence comprising of a modified Parikh-Doering oxidation,[224] Still-Gennari olefination[110] and Sharpless dihydroxylation of α,β-unsaturated ester **116** gave *anti*-diol **117** of which the stereochemistry was already assured by the B. L. Pagenkopf group.[219]



Scheme 2.20. Synthesis of TBS ether **118a** and acetonide **118b**. Reagents and conditions: a) H_2 (1 atm), Pd/$BaSO_4$ (5 mol%), quinoline (10 mol%), MeOH, 65%; b) *t*BuOOH, Ti(O*i*Pr)$_4$ (5 mol%), (+)-DET (6 mol%), CH_2Cl_2, −20 °C, 74% (90% *ee*); c) TBSCl, imidazole, DMAP (5 mol%), CH_2Cl_2, 0 °C → RT, 96%; d) allylmagnesium chloride, CuI (15 mol%), THF, –25 °C, r.r. = 10:1, 77% (pure regioisomer); e) Co(nmp)$_2$ (10 mol%), *t*BuOOH (10 mol%), *i*PrOH, O_2 (1 atm), 55 °C, 79% (>20:1 dr); f) [SO_3·pyridine], (*i*Pr)$_2$NEt, DMSO, CH_2Cl_2, −25 °C; g) $(F_3CCH_2O)_2CH_2COOMe$, KHMDS, 18-crown-6, THF, –78 °C → RT, *Z*/*E* = 12:1, 63% (of pure *Z*-**116** over 2 steps); h) K_2OsO_4 (6 mol%), $(DHQD)_2PYR$ (3 mol%), $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O, 0 °C, dr = 5:1, 67% of pure isomer, 11% of **117c**; i) TBSOTf, 2,6-lutidine, DMAP (20 mol%), CH_2Cl_2, 0 °C → RT, 86%; j) 2,2-dimethoxypropane, *p*TsOH (5 mol%), 89%.

In consideration of a possible impact of the protecting groups on the diol **117** during ring closure, the silyl ether **118a** and acetonide **118b** were synthesized in order to provide two southern fragments with different steric demand. Focusing on the synthesis of TBS-containing fragment **123a** (Scheme 2.21), the reduction of ester **118a** with Dibal-H resulted in overreduction to alcohol **119a**. Oxidation to aldehyde **120a** under the modified Parikh-Doering conditions set the stage for Wittig olefination of **120a** providing olefin **122a** in low yield. Switching to the more reactive Tebbe reagent (**121**) gave **122a** in an improved yield of 78%.[225] Applying conditions introduced by D. P. Curran in the total synthesis of (−)-dictyostatin,[226] the primary alcohol **123a** was liberated in presence of the other silyl protecting groups. Subsequent oxidation of **123a** with catalytic amounts of TEMPO in aqueous acetonitrile afforded the carboxylic acids **124a**.[227]



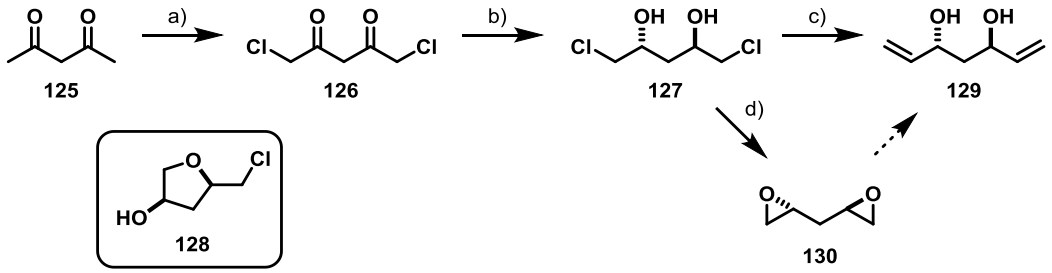
Scheme 2.21. Synthesis of bis-TBS ether and acetonide containing southern fragment for RCM approach. Reactions and conditions: a) Dibal-H, toluene, −78 °C, 98% (**119a**), 53% (**119b**); b) $LiAlH_4$, THF, 0 °C, 95% (**119b**); c) [SO_3·pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, –25 °C, 94% (**120a**), 84% (**120b**); d) methyltriphenylphosphonium bromide, NaHMDS, THF, 0 °C → RT, 27% (**121a**), 66% (**121b**); e) **121**, THF, 0 °C, 68% (**122a**), 66% (**122b**); f) HF·pyridine, pyridine, THF, 74% (**123a**), 84% (**123b**); g) TEMPO (30 mol%), BAIB, aq. MeCN, 51% (**124a**), quant. (**124b**).

Based on this route the synthesis of acetonide **124b** was further improved by minor adjustments (Scheme 2.21). By exchanging the reducing agent from Dibal-H (a) to $LiAlH_4$ (b) as well as changing the aqueous work-up of the modified Piancatelli oxidation (g), the sequence gave **124b** in 4.7% yield over 14 steps.

2.4.4 Synthesis of the Northern Fragments and Fragment Assembly

Remark: The following synthesis was planned by Dr. J. Flasz and improved in collaboration with Dr. J. J. Murphy, Dr. A. Letort, Dr. M. K. Ilg and S. Speicher.

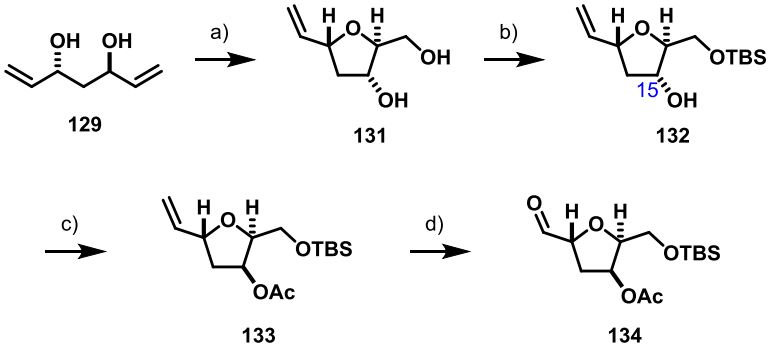
The synthesis of the northern fragment originates from the RCAM approach, which was initially investigated by J. Flasz (Scheme 2.22).[217] Following an organic synthesis procedure, acetylacetone underwent a double Claisen condensation with chloroacetyl chloride to generate α,α'-dichloro acetylacetonide (**126**).[228] The asymmetric Noyori reduction of **126** afforded the C_2-symmetric diol **127** in decent yield (54%) at elevated temperature with good enantio- (97% *ee*) and diastereoselectivity (>20:1 dr). Under the applied reaction conditions, diol **127** underwent an intramolecular nucleophilic substitution (S_Ni) generating THF-ring **128** as the major byproduct at elevated temperature. According to the literature procedure using a tenfold excess of sulfur ylide, the bisallyl alcohol **129** was obtained in variable yields ranging from 14-68%.[229] The formation of THF-ring **128** by an intramolecular attack under the basic reaction conditions was identified as the major side reaction. Considering a two-step approach towards bisallyl alcohol **129**, diol **127** was treated with potassium hydroxide in diethyl ether giving the literature-known bisepoxide **130** in quantitative yield.[228] Surprisingly, any attempts for the literature-known opening of **130** failed and the starting material was recovered.[229a]



Scheme 2.22. Synthesis of bisallyl alcohol **129**. Reagents and conditions: a) (i) $AlCl_3$, $ClCH_2COCl$, $PhNO_2$, $(CH_2Cl)_2$, 65 °C, 8 h; (ii) sat. aq. $Cu(OAc)_2$; (iii) H_2SO_4 (10%), Et_2O, 23%; b) $[RuCl_2((S)\text{-BINAP})]_2{\cdot}Et_3N$ (0.1 mol%), H_2 (62 bar), 70 °C, **127**/**128** = 6:1, dr = 20:1, 54% (pure isomer, 97% *ee*); c) Me_3SI, *n*BuLi, THF, –40 °C to RT, **129**/**128** = 9:1 (crude ^{1}H NMR), 68% (pure diol **129**). d) KOH, Et_2O, 0 °C → RT, 99%.

Disregarding the encountered problems with the literature-known synthesis, the C_2-symmetric diol **129** represents a valuable precursor for total synthesis. Previous work has focused on its "pseudo" C_2-desymmetrization, which has been achieved by different catalytic methods including tethered[229a,230] and mono-protected[229b] metathesis, allylic substitution[231] and palladium-catalyzed oxycarbonylation.[232] By applying the cobalt-catalyzed oxidative Mukaiyama cyclization, a new opportunity of breaking the C_2-symmetry in **129** is highlighted in this route towards the northern aldehyde **134** (Scheme 2.23).

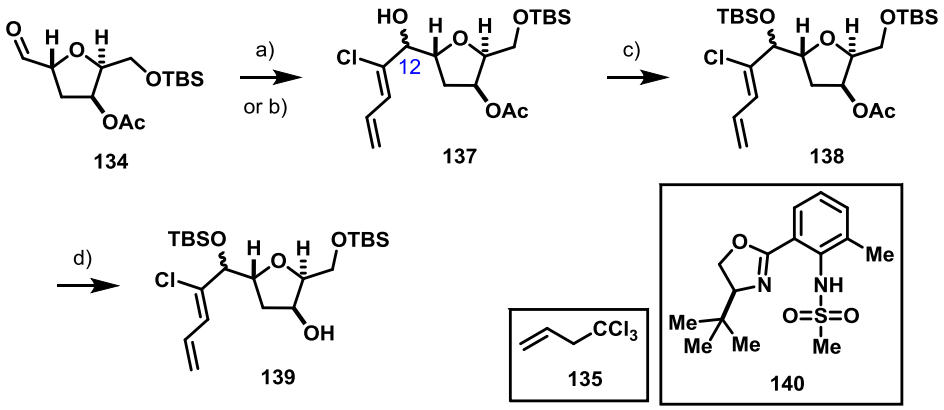
Subjecting diol **129** to the optimized reaction conditions with $Co(nmp)_2$, the *trans*-configured THF-ring **131** was forged in good yield with excellent diastereoselectivity. After mono protection of **131**, the C15-stereocenter of alcohol **132** was inverted by using acetic acid, which is a rather unusual coupling partner in Mitsunobu inversions.[233] Regarding the mandatory protonation of the diazo compound DEAD or DIAD (pKa < 11), acetic acid (pKa = 4.75) had been sugessted to be unsuitable for achieving complete activation.[234] After ozonolysis of **133**, the aldehyde **134** was obtained in 86% yield.



Scheme 2.23. Synthesis of NHK precursor **134** by pseudo desymmetrization of diol **129**. Reagents and conditions: a) $Co(nmp)_2$ (10 mol%), *t*BuOOH (10 mol%), *i*PrOH, O_2 (1 atm), 55 °C, dr = >20:1, 78% (pure diastereomer); b) TBSCl, Et_3N, DMAP (cat.), CH_2Cl_2, 81%; c) PPh_3, DIAD, toluene, 0 °C; AcOH, 0 °C → RT, 89%; d) O_3, CH_2Cl_2, –78 °C; PPh_3, –78 °C → RT, 86%.

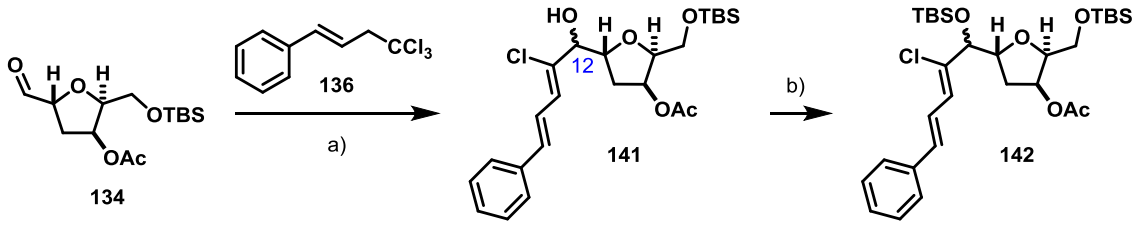
The required trichloromethyl-containing coupling partner **135**[235] and **136**[131b] for the Falck-modified NHK addition (see Section 1.5.1.4) were synthesized according to literature procedures. Using the necessary fourfold excess of chromium dichloride, the desired terminal *Z*-chlorodiene **137** was

generated in 79% yield by adding allyl trichloromethyl (**135**) to **134** (Scheme 2.24). The crude diastereomeric mixture was subsequently protected due to instability of allyl alcohol **137**. The following saponification of **138** gave the epimeric alcohols (*R*)-**139** and (*S*)-**139** as stable and separable diastereomers, albeit in low yields.



Scheme 2.24. Falck-modified NHK coupling of **134** with **135**. Reactions and conditions: a) $CrCl_2$, **135**, THF, dr = 1.9:1, 51% (mixture of diastereomers); b) $CrCl_2$, **140** (35 mol%), **135**, THF, 45% (mixture of diastereomers, dr = 2.5:1); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, dr = 2.4:1, 43% (mixture of diastereomers); d) K_2CO_3, MeOH, 39% (of pure (*R*)-**139**), 14% (of pure (*S*)-**139**).

Based on the general facial selectivity of NHK addition in favoring the Felkin-Anh product (see Section 1.5.1.3), the major diastereomer was assumed to be the undesired epimer (*R*)-**139**. As no efforts towards an asymmetric variant on the Falck modification of the NHK reaction have been described in the literature, the chiral ligand **140** was used in catalytic quantities (35 mol%) regardless of the existing background reaction. The selectivity could only be slightly enhanced to a 2.5:1 ratio, even though it is supposedly the "matched case".

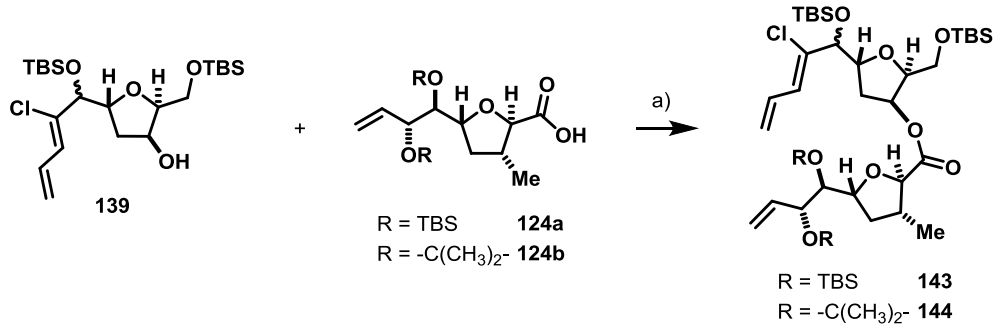


Scheme 2.25. Falck-modified NHK with styrene derivative **136** for enhanced stability in adduct **142**. Reactions and conditions: a) $CrCl_2$, **136**, THF, dr = 2.6:1, 52% (mixture of diastereomers); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 28% (of pure (*R*)-**142** over 2 steps), 11% (of pure (*S*)-**142** over 2 steps).

Less decomposition was anticipated by capping the terminal position with an aryl substituted (Scheme 2.25). Thus, **134** was coupled with styrene derivative **136** under Falck conditions, affording alcohol **141** as an inseparable mixture of diastereomers. Because of the instability of NHK adduct **141**, the crude mixture was treated with TBSOTf to give the bissilyl ethers (*R*)-**142** and (*S*)-**142** as separable and stable epimers. Despite the increased stability of styrene **136,** the introduction of the

diene motif still suffered from a very low yield, which made this particular substrate no adequate alternative.

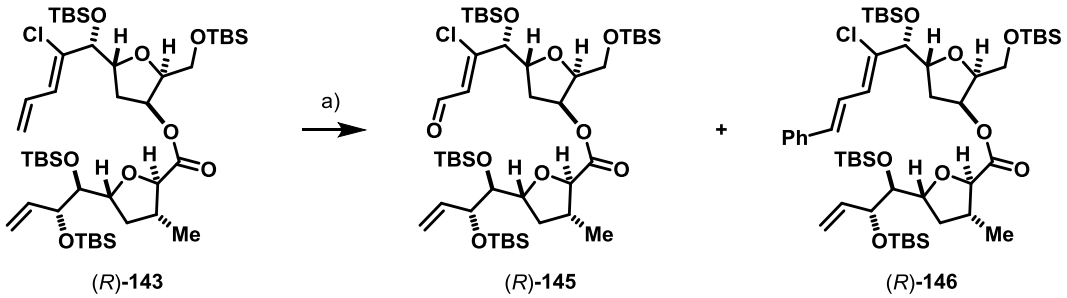
With the two diastereomeric northern fragments (*R*)-**139** and (*S*)-**139** and the two southern fragments **124a** and **124b** in hand, the fragment assembly by Yamaguchi esterification was investigated. Combining carboxylic acid **124a** with both alcohols (*R*)-**139** and (*S*)-**139** resulted in low yields, ranging from 25-31% (Scheme 2.26). In contrast, subjecting acetonide-containing carboxylic acid **124b** to the same reaction conditions with coupling partner (*S*)-**139**, the ester (*S*)-**144** was isolated in 61% yield.



Scheme 2.26. Yamaguchi esterification of diastereomeric alcohols (*R/S*)-**139** with southern fragments **124a** and **124b**. Reactions and conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 25% ((*R*)-**143**), 31% ((*R*)-**144)**, 61% ((*S*)-**144**).

2.4.5 Synthetic Studies in RCM towards Macrocyclic Core 78

After treatment of (*R*)-**143** with Grubbs first-generation catalyst (**Ru4**), no reactivity of the metathesizing alkenes could be detected by HPLC-MS analysis. Switching to the NHC-containing catalysts, Grubbs second-generation catalyst (**Ru1**) engaged with the diene subunit by generating aldehyde (*R*)-**145** and styrene derivative (*R*)-**146** in low quantities (Scheme 2.27).



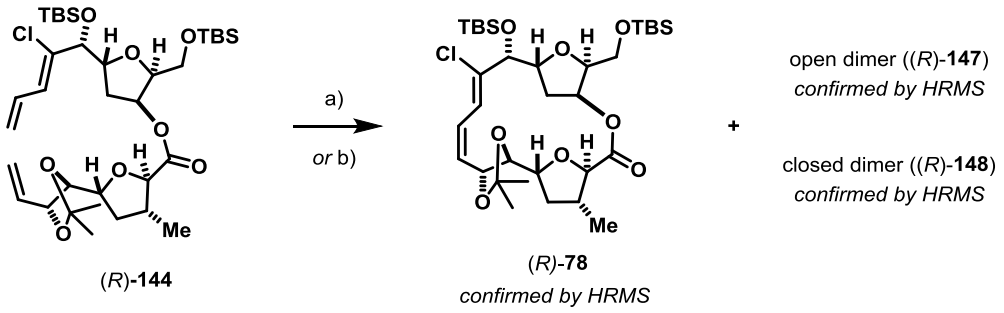
Scheme 2.27. RCM result with (*R*)-**143**. Reactions and conditions: a) **Ru2** (40 mol%), toluene, reflux, (*R*)-**145** (ca. 10%), (*R*)-**146** (ca. 15%).

The formal oxidation of the diene to the α,β-unsaturated aldehyde (*R*)-**145** likely derives from the formation of a η^1-alkenylcarbene ruthenium complex, which upon aqueous work-up reacts with water.[236] The same puzzling aldehyde formation had been already observed in the ene-diene RCM approach towards the total synthesis of the A ring of halichomycin under similar reaction

conditions.[237] Besides the oxidative cleavage of the terminal alkene in (*R*)-**145**, a phenyl substituent was incorporated in (*R*)-**146**, which originated from the precatalyst **Ru1**. Neither changing the solvent nor increasing the temperature had an effect on the outcome. Applying an atmosphere of ethylene diminished the amount of (*R*)-**143** by consuming the *in situ* generated styrene. In the presence of phosphine-free Hoveyda-Grubbs catalyst (**Ru5**) no metathesis reaction was observed, whereas catalytic amounts of the Schrock catalyst (**Mo3**) decomposed the starting material into unidentified products. In conclusion, **Ru1** seemed to be superior in terms of functional group tolerance, but did not engage with the southern alkene moiety. Contemplating the envisioned protecting effect of internal alkenyl chloride, the northern diene moiety participated in the metathesis reaction exclusively with the terminal alkene, displaying no truncated side products in the crude mixture. Nevertheless, the ring closure failed, presumably due to the steric bulk of the silyl protecting groups of the southern counterpart and/or the ring strain.

Switching to the acetonide (*R*)-**144**, the RCM reaction showed reactivity at both ends of the precursor for the first time (Scheme 2.28). Unfortunately, neither the Mo-based Schrock catalyst (**Mo3**), nor a variety of different Ru-based catalyst could give access to the desired macrocycle. The majority of the applied catalysts still did not engage in the metathesis reaction and the starting material (*R*)-**144** could be recovered. For those catalysts that engaged with the substrate, an array of decomposition products could be identified by NMR and MS analysis, including oligomers, α,β-unsaturated aldehydes and styrene incorporation at both ends. As reducing the steric bias near the terminal alkene proved to be beneficial, the high functional group density of (*R*)-**144** could increase the chances for deactivation of the reactive carbene species by coordination. Hence, the mere ligation of the carbene species by neighboring groups were found to coordinatively saturate the reactive intermediate, preventing further reactivity towards other alkenes.[238] The pre-complexation with titanium isopropoxide[239] might exhibit a templating effect,[185] which could bring the reactive alkenes in close proximity by encapsulating the substrate.[240] However, in the presence of stoichiometric amounts of the Lewis acid no reactivity was observed with Grubbs first-generation catalyst (**Ru4**).

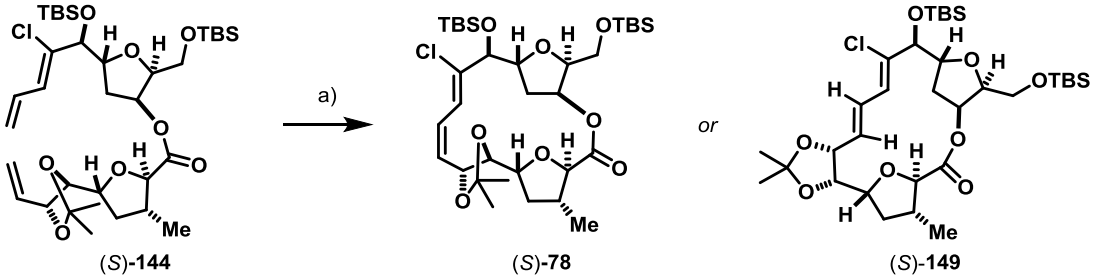
Another common decomposition pathway in metathesis is alkene isomerization,[241] which can be suppressed by adding either phenol[242] or tetrafluoroquinone.[243] Sequestering the *in situ* generated ruthenium hydride species, the reaction conditions with the beneficial additives suppressed the formation of the outlined side products but showed no signs of successful ring closure. Applying an atmosphere of ethylene, the oligomerization of the starting material (*R*)-**144** was facilitated, indicating an thermodynamically unfavorable ring closure towards the desired 16-membered macrocycle (*R*)-**78**.[244]



Scheme 2.28. Optimized conditions for RCM of (*R*)-**144** confirming the synthesis of simplified macrocycle (*R*)-**78**, open dimer (*R*)-**147** and closed dimer (*R*)-**147** by HRMS analysis. Reactions and conditions: a) **Ru1** (40 mol%), tetrafluorobenzoquinone (80 mol%), octafluorotoluene, 115 °C, (*R*)-**147** and (*R*)-**148** (traces); b) **Ru7** (40 mol%), %), tetrafluorobenzoquinone (80 mol%), octafluorotoluene, 115 °C, (*R*)-**78** (traces), (*R*)-**147** and (*R*)-**148** (traces).

When conducting the reaction in fluorinated solvents with Grubbs second-generation catalyst (**Ru2**), the open and closed dimer ((*R*)-**147** and (*R*)-**148**) were generated in trace amounts as an unseparable mixture for the first time, as indicated by HRMS analysis (Scheme 2.28).[245] Using the reaction conditions reported by D. Gallenkamp with **Ru7** in perfluorinated toluene, the formation of the desired product along with closed and open dimers were detected by HRMS analysis, albeit the obtained quantities were insufficient for NMR analysis.

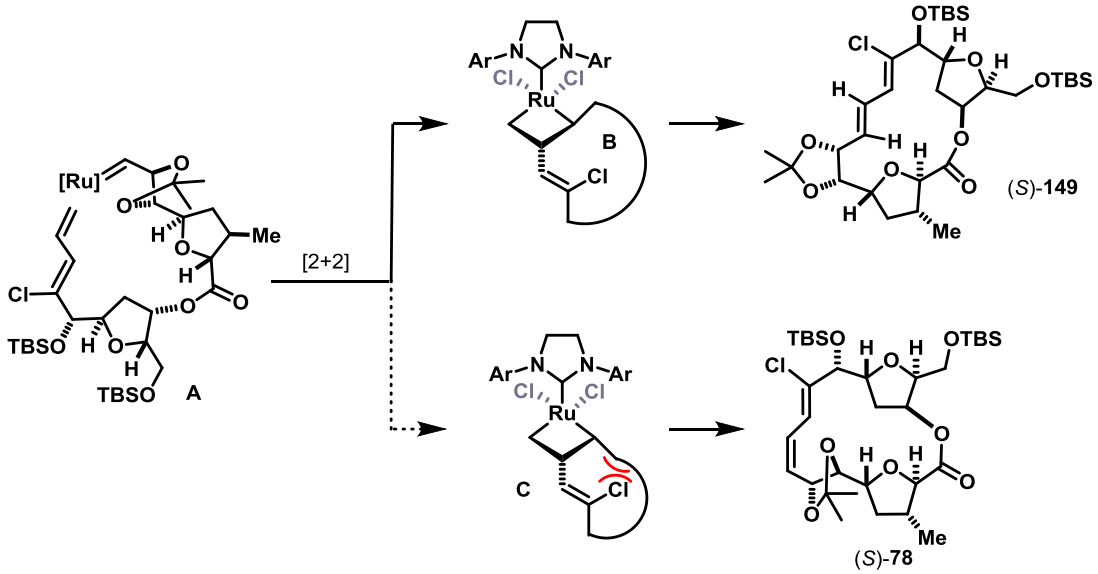
Lacking spectroscopic evidence for the proposed structure of the detected macrocycles, we turned our attention to the RCM of the presumably desired epimer (*S*)-**144**. Adapting the reaction conditions used for (*R*)-**78**, the ring closure towards (*S*)-**78** could be detected in traces and the molecular weight was confirmed by HRMS (Scheme 2.29). After preparative HPLC separation, the quantities of the presumable macrocycle (*S*)-**78** were insufficient for NMR analysis and its structure could not be confirmed.



Scheme 2.29. Optimized conditions for RCM of epimer (*S*)-**144** confirming the synthesis of macrocyclic core (*S*)-**78** by HRMS. Reactions and conditions: a) **Ru7** (80 mol%), tetrafluorobenzoquinone (80 mol%), octafluorotoluene, 115 °C, **78** (traces).

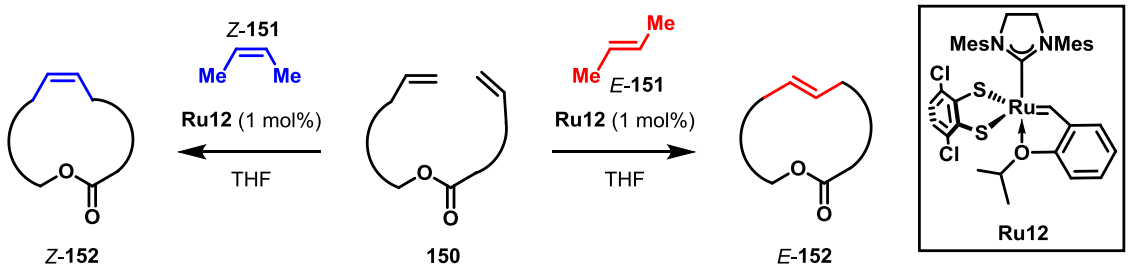
After eventually accomplishing the synthesis of compound **78** by the fourth-generation synthesis (see Section 2.5.2), comparison of the final macrocycle **78** with an analytic sample of metathesis product (*S*)-**78** by HPLC analysis displayed a discrepancy in the retention of more than 7 min. This significant deviation prompted us to postulate the formation of the *E*-isomer (*S*)-**149** during RCM (Scheme 2.30). In agreement with the observed stereoselectivity of silyl- and alkyl-substituted dienes (see Section 2.4.1.2), the steric clash between the chloro substituent and the cyclic alkyl chain in

metallacyclobutane **C** is likely to inhibit the formation of *Z,Z*-diene (*S*)-**78**. After intramolecular [2+2]-cycloaddition of **A**, the chlorine-directing effect facilitates the cycloreversion to the more strained *Z,E*-configured diene (*S*)-**149** by adapting a *trans*-configuration of the two alkyl substituents in metallacyclobutane **B**. Nevertheless, as the ultimate proof by NMR analysis is missing, no further speculations about the reaction outcome are made.



Scheme 2.30. Rationalization of mis-matching retention time of (*S*)-**78** and (*S*)-**149** in HPLC analysis by facilitating *E*-alkene formation during RCM of (*S*)-**144.**

Instead, a new strategy for challenging RCM and its advantageous will be discussed briefly. Based on the literature-known decomposition pathways of ruthenium methylidene complexes[246] and the corresponding ruthenacyclobutane,[246g,247] the avoidance of terminal alkenes as starting materials should significantly enhance the lifetime of the catalyst.[248] In combination with a stereoretentive transformation (see Section 2.4.1.3), the additional synthetic efforts for introducing 1,2-disubstituted alkenes are advantageous by maintaining the pre-installed *E/Z*-isomerism.[215] The recently developed dithiolate catalysts **Ru12** enable the stereochemical transposition of the applied precursor.[249] However, the synthesis of the surrogate might not be feasible or would be accompanied with an undesirable multistep synthesis of the 1,2-disubstituted alkene. Therefore, the group of A. Hoveyda circumvented this synthetic inconvenience by applying an atmosphere of 2-butene (**151**) during RCM (Scheme 2.31).[250] Due to the rapid capping of the terminal olefin **150**, the life-time of the active catalyst and its functional group tolerance is increased significantly. Furthermore, the *in situ* methylene capping strategy also facilitates the stereoselective synthesis of *Z*- or *E*-isomer **152** by utilizing *cis*-butene (*Z*-**151**) or *trans*-butene (*E*-**151**), respectively.

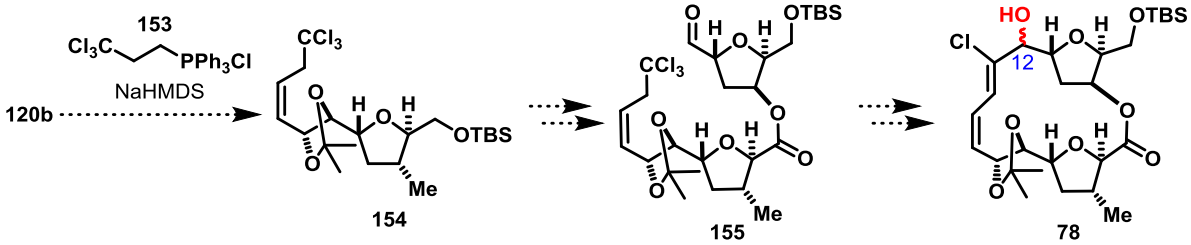


Scheme 2.31. *In situ* capping of terminal alkenes **150** for the stereoselective RCM.[250]

In case of the metathesis approach towards chagosensine, future work could focus on applying the recently developed conditions for stereoretentive RCM in combination with alkenyl chloride as an inherent "protecting group". Nevertheless, this promising RCM attempt was not tested on the total synthesis of chagosensine because of the encountered high ring strain.

2.4.6 Outlook on an Intramolecular NHK Approach

In consideration of the total synthesis of haterumalide NC by B. Borhan *et. al.* (see Section 1.4.3), the strong exothermic Cr-O bond formation would countervail the ring strain during an intramolecular NHK reaction (Scheme 2.32). In order to introduce the required trichloromethyl subunit, P. Fuchs *et. al.* designed a novel phosphonium salt **153**, which would react with aldehyde **154** in a *Z*-selective fashion.[251] The treatment of aldehyde **155** with $CrCl_2$ under Falck conditions for NHK reactions (see Section 1.5.1.4) should preserve the *Z*-configuration of the pre-installed olefin in **78**.[130]



Scheme 2.32. Outlined strategy for an intramolecular NHK attempt.

However, the introduced configuration at C12 is expected to be the incorrect epimer, which is based on the preferred Felkin-Anh transition state of NHK reactions (see Section 2.4.2). The general facial selectivity could only be overruled by a predominant substrate-control. Facing a questionable diastereoselectivity in the chromium-mediated addition, the subsequent establishment of the correct stereocenter would correlate with a complicated manipulation of an advanced intermediated bearing a chlorine substituent in proximity. Functionalization of this entity is rarely precedented in the literature and could presumably interfere with well-established diastereoselective transformations concerning reactivity and stereoinduction. Therefore, this alternative approach was not pursued and a revised synthetic approach using palladium-catalyzed cross coupling was developed.

2.5 Macrolactonization and Cross Coupling Attempts

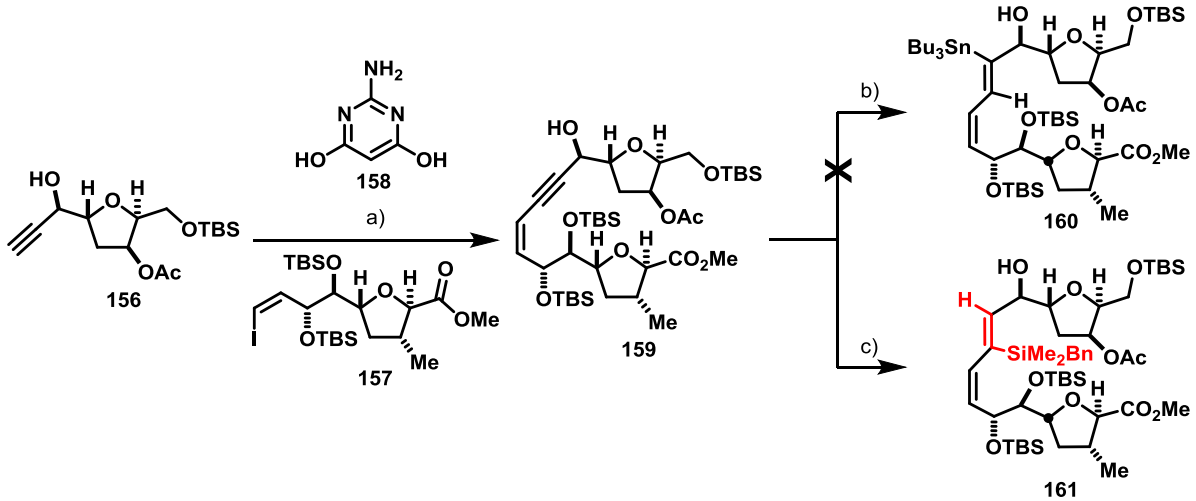
The unfruitful metathesis attempts prompted us to install the challenging *Z,Z*-chlorodiene beforehand. Based on the established and scalable route, the two fragments should be assembled by palladium-catalyzed cross coupling, giving access to the dienyl moiety in a highly convergent manner. After introduction of the chlorine substituent, the 16-membered macrocycle was envisioned to be furnished by macrolactonization. Because the *in situ* formed mixed anhydride is a highly energetic intermediate, the gained ester resonance energy could compensate the considerable ring strain.

2.5.1 Sonogashira Coupling and *trans*-Hydrometalation (3rd Generation Synthesis)[174]

Remark: The synthetic efforts for introducing the chlorodiene by Sonogashira cross coupling and subsequent Ru-catalyzed trans-hydrometalation were conducted by Dr. M. K. Ilg. The mechanistic studies were performed by Dr. D.-A. Rosca.

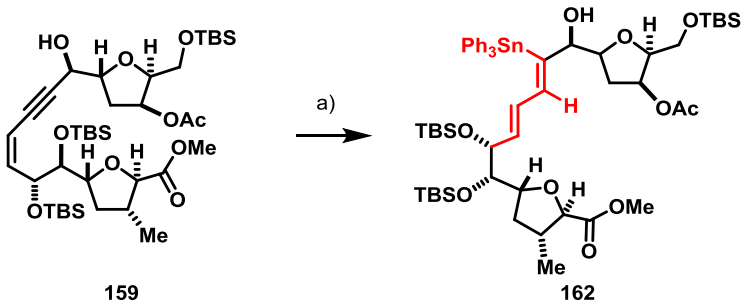
2.5.1.1 Fragments Assembly and failed *trans*-Hydrometalation

Focusing on carbon-carbon bond formations facilitated by palladium-catalyzed cross coupling, the preliminary approach designed by M. K. Ilg intended to retain the key sequence comprised of *trans*-hydrometalation and subsequent chloro-destannylation for installing the dienyl chloride (see Scheme 2.4). Hence, a copper-free Sonogashira coupling of alkyne **156** and alkenyl iodide **157** was employed to assemble the two fragments, albeit in surprisingly low yield. To this end, usage of the pyrimidine ligand **158** proved to be beneficial, but afforded enyne **159** in only 36% (Scheme 2.31).[252]



Scheme 2.33. Fragment assembly by Sonogashira cross coupling and attempted *trans*-hydrometalation on enyne **159**. Reactions and conditions: a) $Pd(OAc)_2$ (10 mol%), **159** (20 mol%), Cs_2CO_3, DMF, 0 °C, 36% (51% brsm); b) $[Cp^*RuCl]_4$ (75 mol%, [Ru] = 300 mol%), Bu_3SnH, CH_2Cl_2, 0%; c) $[Cp^*RuCl]_4$ (75 mol%, [Ru] = 300 mol%), $BnMe_2SiH$, CH_2Cl_2, 25%.[174]

Despite the successful *trans*-hydrostannylation on model substrate **80** (see Section 2.5), enyne **159** refused to undergo the addition with formation of **160**, even with super stoichiometric amounts of $[Cp^*RuCl]_4$ (**Ru3**). In contrast, hydrosilylation of **159** afforded silyl diene **161** by a *trans*-addition, albeit as the undesired, distal regioisomer. In both cases, the hydroxy group obviously fails to direct **Ru3**. Moreover, it should be noted that the *trans*-hydrostannylation under free radical conditions turned out to be no alternative to the ruthenium-catalyzed addition. Although addition to enyne **159** was successful in providing the desired dienylstannane in 58% yield with high stereoselectivity, the atom-transfer radical addition (ATRA) caused isomerization of the *Z*-alkenylic moiety, resulting in the *Z,E*-configured 2-stannyl-1,3-diene **162** (Scheme 2.34).[253]

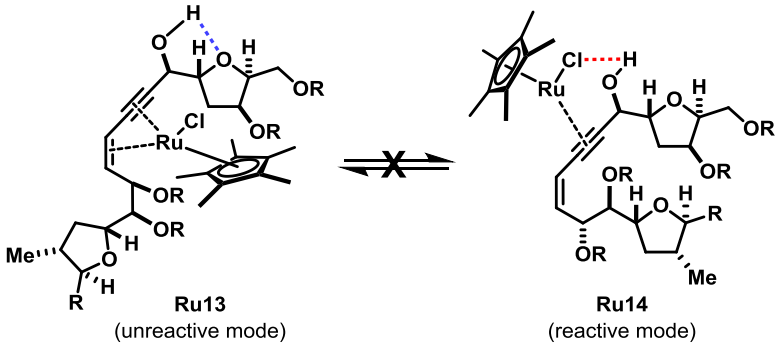


159 162

Scheme 2.34. *trans*-Hydrostannylation under radical conditions. Reactions and conditions: a) Ph_3SnH, BEt_3, toluene, air, 58%.[174]

2.5.1.2 Mechanistic Investigations on *trans*-Hydrometalation on THF-containing Alkynes

A plausible explanation for the failed Ru-catalyzed hydrostannylation might be seen in the unavailability of the hydroxy group for engaging with the polarized [Ru–Cl] bond of **Ru3**. While the proton is presumably trapped between the propargyl alcohol and the adjacent THF-ring, the coordinatively unsaturated catalyst is likely poisoned by the enyne subunit and therefore locked in an unreactive mode **Ru13** (Scheme 2.35).

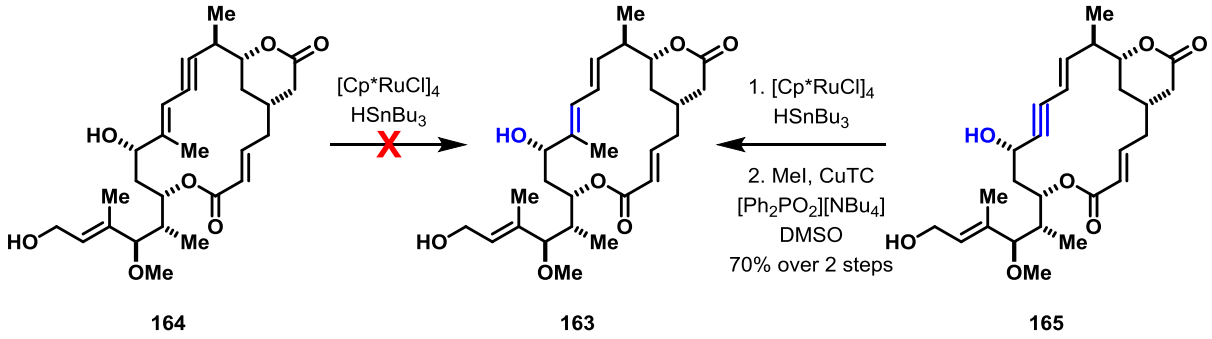


Ru13 (unreactive mode) Ru14 (reactive mode)

Scheme 2.35. Postulated non-equilibrium between reactive mode **Ru14** and unreactive mode **Ru13**.[174]

Without the presence of an interligand hydrogen bonding in proximity to the enyne, the required π–complex **Ru14** is not formed and the conjugated π-system does not engage in the

trans-hydrostannylation, which is in line with the unreactivity of unfunctionalized enynes.[153] This profound sensitivity towards hydrogen bond donors within the chemical surrounding of the enyne is highlighted by the synthesis of WF-1360F[254] by K.-H. Altmann *et. al.* and synthetic studies towards rhizoxin D by the A. Fürstner group.[157,159] Whereas the acetylenic subunit in **164** failed to react, the reversed structural array in **165** facilitated the *trans*-hydrostannylation for the subsequent Stille reaction to **163** likely due to the directing effect of the propargylic –OH group (Scheme 2.36).



Scheme 2.36. Successful *trans*-hydrostannylation depending on interligand hydrogen bonding.[157]

As THF-containing alkynes have not been subjected to the *trans*-addition protocol yet, mechanistic studies by D.-A. Rosca showed the H-donor ability of the simplified propargyl alcohol **166** by observing a significantly shifted –OH proton resonance upon complexation with **Ru3** (δ_H = 2.90 ppm in **166** versus δ_H = 4.51 ppm in **Ru15**) in the ^{1}H-NMR spectra (Figure 2.4). Furthermore, the massive deshielding of the alkynylic C-atoms ($\Delta\delta_C$ = 65–52 ppm) in **Ru15** indicates the four-electron donation of both orthogonal acetylenic π-systems.[153b,255] This stoichiometric experiment also disclosed an instability of **Ru15**, which is not correlated with a redox isomerization,[256] but is degraded to unknown side products above –30 °C. Whether these decomposition pathways emanate from **Ru15** or are deriving from downstream products from the well-known [2+2]-cycloadduct remains unclear.[153a,257]

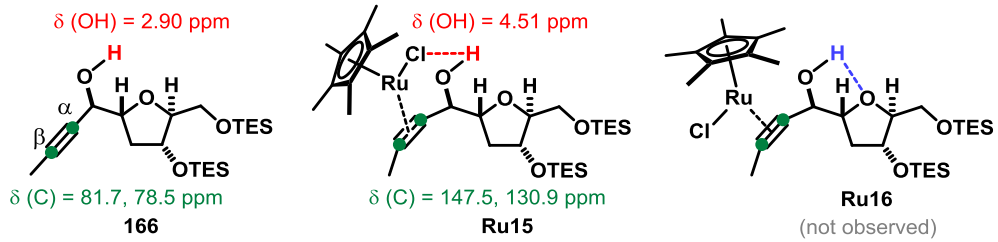
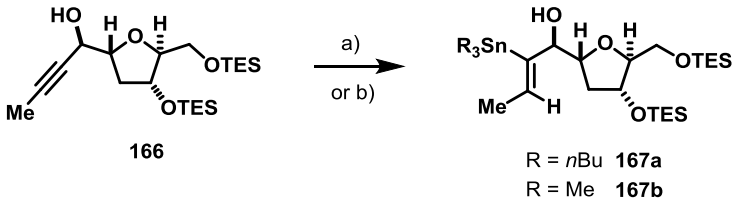


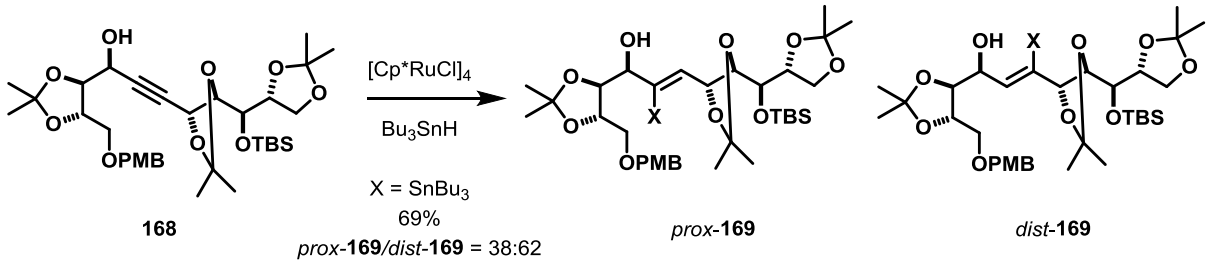
Figure 2.4. NMR analysis of **Ru15** showing four-electron donation and interligand hydrogen bonding.[174,258]

The preliminary results on the catalytic *trans*-hydrostannylation on **166** by M. K. Ilg gave alkenylstannane **167a** in 49% yield with a 97:3 α/β-ratio (Scheme 2.37). Applying the optimized reaction conditions at –50 °C, **167b** was obtained under full conversion as a single isomer according to the ^{1}H-NMR spectra of the crude mixture, but was unstable upon chromatographic purification.



Scheme 2.37. *trans*-Hydrostannylation on model substrate **166**. Reactions and conditions: a) $[Cp^*RuCl]_4$ (4.6 mol%, [Ru] = 18.4 mol%), $HSnBu_3$ (added over 2 h), CH_2Cl_2, α/β = 97:3, 43% (*Z*/*E* = >20:1). b) $[Cp^*RuCl]_4$ (2.5 mol%, [Ru] = 10 mol%), CH_2Cl_2, RT, then −50 °C, $HSnMe_3$ (added over 10 min), α/β = >99:1, *Z*/*E* = >20:1, 56%.

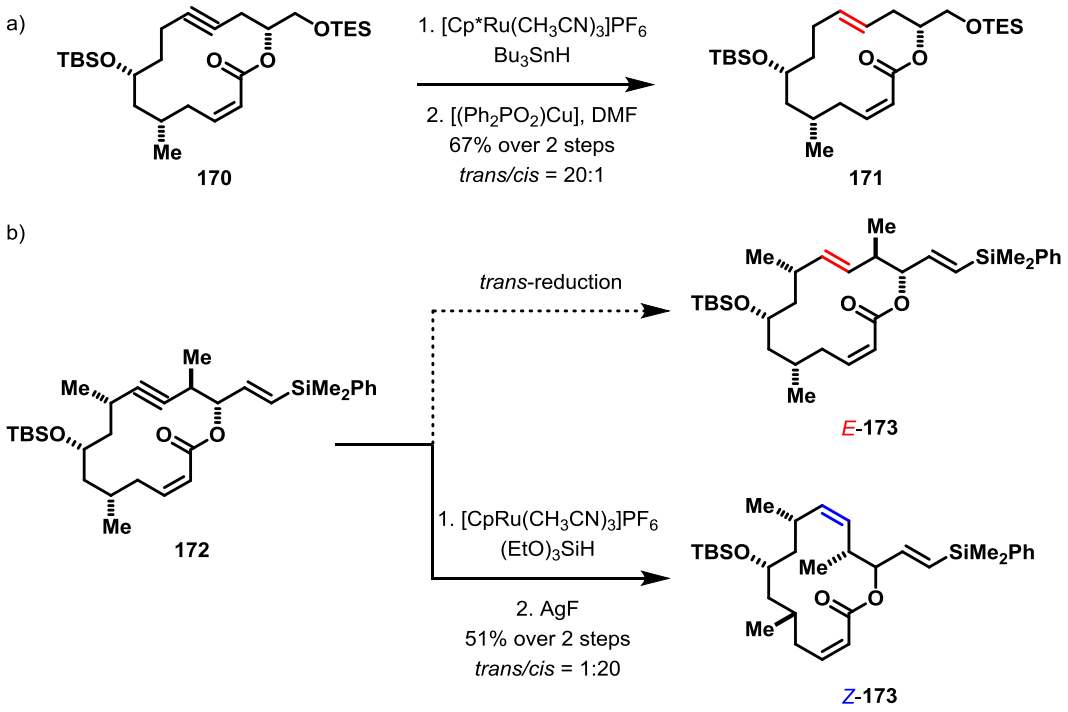
Apparently, comparison of model substrate **166** with enyne **159** allows no conclusion, as to why the *trans*-hydrostannylation had failed. Based on a similar chemical environment of the propargyl –OH substituents (**166** versus **159**), their acidity and thereby their strength in an interligand hydrogen bond should be roughly the same.[259] According to DFT calculations on simple propargyl alcohols, the stabilization energy can range from ca. 2.8–4.8 kcal/mol in favor of the reactive mode **Ru14** in Scheme 2.35.[153b] This beneficial steering effect of the hydroxy group must be compensated by coordination of the enyne and additional stabilization effects in **Ru13**. As a competing coordination of the THF-ring could not be observed with model substrate **166** in **Ru16**, the remarkably dense array of coordination sites should not be responsible for trapping the ruthenium catalyst in this unreactive mode.



Scheme 2.38. Unselective hydrogen bond directed trans-hydrostannylation of **168**.[153a]

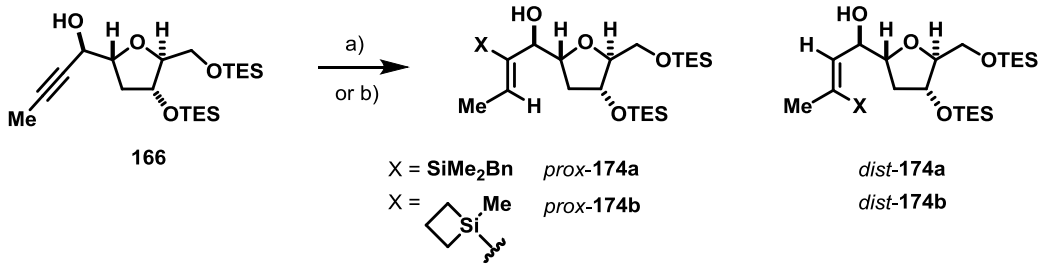
According to the unselectivity of the *trans*-hydrostannylation to propargyl alcohol **168**, which is decorated with –OR groups on either side (Scheme 2.38), the enyne **159** could be an extreme case of "confusing" the catalyst, resulting in no reactivity at all.[153a] Besides these antagonistic coordinative and electronic properties flanking the alkynylic reactive site, the sheer steric bias could prevent the catalyst from binding to the unsaturated moiety. Regarding the failed *trans*-reduction *en route* to callyspongiolide, the sterically unbiased alkyne **170** underwent *trans*-hydrometalation to **171** with high levels of selectivity (Scheme 2.39a), while its analogue **172** with two neighboring methyl substituents refused to participate in the ruthenium-catalyzed *trans*-hydrometalation (Scheme 2.39b).[156] Efforts in reducing the steric clash between the sterically encumbered substrate and the bulky [Cp*Ru]-based catalyst by employing its slimmer [CpRu]-based version resulted in reduction of the alkyne, but afforded *Z*-**173** in moderate yield as a single isomer (Scheme 2.39b).[260] Any attempts in developing a slimmer version of **Ru3** for this unorthodox *trans*-addition of sterically

demanding substrates have been unfruitful, designating such motifs as an important limitation for this method.[258,261]



Scheme 2.39. Studies on the *trans*-reduction towards the total synthesis of callyspongiolide.[156,260]

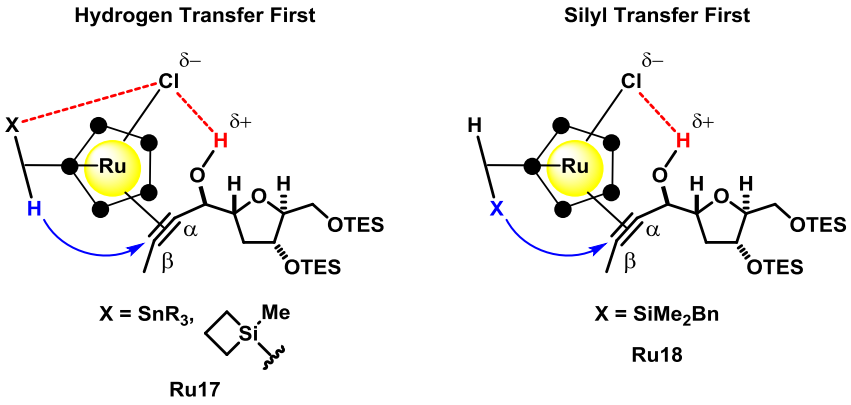
While this steric repulsion resulted in no conversion in both complementary addition protocols with **Ru3**, the successful *trans*-hydrosilylation of **159** gave dienylsilane **161** as the *β*-isomer (see Scheme 2.33). Comparison with the model substrate **166** also showed a high selectivity towards the distal isomer *dist*-**174a** (*prox*-**174a**/*dist*-**174a** = 1:9) (Scheme 2.40), which in turn stands in stark contrast to the observed selectivity of **Ru3** (see Section 1.5.2.2).[153a]



Scheme 2.40. *trans*-Hydrosilylation on model substrate **166**. Reactions and conditions: a) $[Cp^*RuCl]_4$ (2.5 mol%, [Ru] = 10 mol%), $HSiMe_2Bn$, CH_2Cl_2, *prox*-**174a**/*dist*-**174a** = 1:9, 81% (*Z*/*E* = >20:1). b) 1-methylsiletane, $[Cp^*RuCl]_4$ (2.5 mol%, [Ru] = 10 mol%), *prox*-**174a**/*dist*-**174a** = 9:1, 81% (*Z*/*E* = >20:1).[258]

Whereas the hydrostannylation proceeding via an initial hydrogen transfer,[153b] the transfers of the silyl group happens prior to the hydrogen transfer during the hydrosilylation.[143a,b,262] These computational results are in line with the intuitive hydricity of the applied reagents, considering that *σ*-stannane complexes are more hydridic than their *σ*-silane counterparts. This distinguishable feature might explain the observed opposite regioselectivity. Whereas H transfer occurs to the distal

position prior to the stannane delivery at the proximal position, the silyl transfer takes precedence over H-transfer, delivering the $–SiR_3$ on the less bulky β-site. Mechanistic studies in inverting the regioselectivity indicated a correlation between regioselectivity and hydricity of the employed silane.[258] Applying the more hydridic 1-methylsiletane in the *trans*-hydrosilylation of **166,** the opposite regioselectivity was observed, providing the α-isomer *prox*-**174b** in a 9:1-ratio. This preferences in avoiding the steric clash during hydrosilylation has also been observed in functionalizing alkynes lacking of –OH directing groups.[258] Therefore, the steering effect of the interligand hydrogen bond can be overruled by steric effects in exceptional cases. Although the regioselectivity of the hydrosilylation could be inverted on the model substrate, the 1-methylsiletane was not tried on **159**, as meanwhile an alternative route gave promising results in accessing this unsaturated moiety.



Scheme 2.41. Effect of hydricity of the applied reagent on regioselectivity[174].

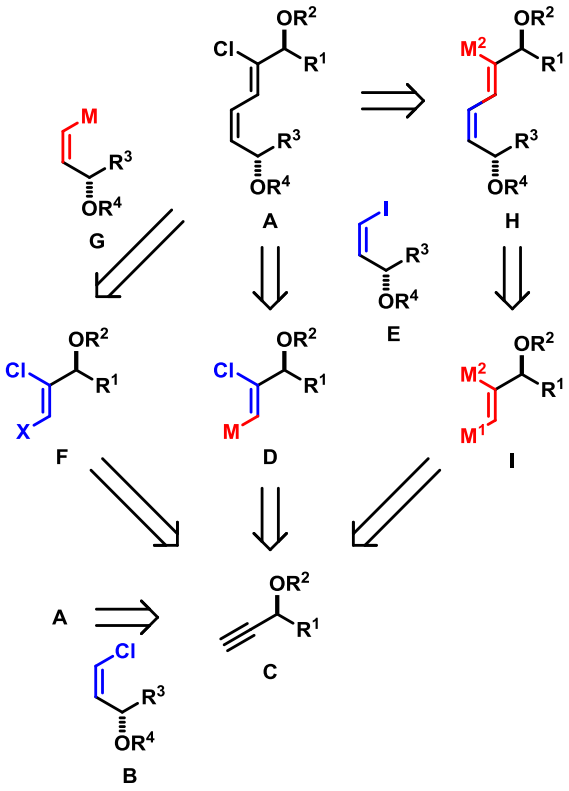
In summary, during the ruthenium-catalyzed *trans*-hydrosilylation of **159**, the preferential formation of the unexpected regioisomer **161** might indicate an underestimated role concerning the hydricity of the applied reagent upon regioselectivity (Scheme 2.41). However, neither the *trans*-hydrosilylation nor the *trans*-hydrostannylation under ruthenium catalysis or radical conditions was able to install the characteristic feature of chagosensine. Therefore, we set off to develop a conceptually new approach towards chlorodienes based on site-selective palladium-catalyzed cross coupling.

2.5.2 Site-Selective Cross Coupling and Subsequent Chloro-Demetalation (4th Generation Synthesis)

Remark: The studies on the model substrate and the preliminary investigations into the Suzuki and Stille reaction were conducted by Dr. A. Letort and Dr. M. K. Ilg, respectively.

2.5.2.1 Retrosynthetic Plan towards 2-Chloro-1,3-dienes

In order to maintain the established synthetic routes for the northern propargyl alcohol and the southern alkenyl halide, various scenarios for a convergent and stereoselective formation of the unique *Z,Z*-chlorodiene entity were considered at the outset of this final attempt (Scheme 2.42).



Scheme 2.42. Strategic considerations; M = metal or metalloid; X = halogen.

The most tantalizing option would comprise of a carbochlorination of alkyne **C** by adding alkenyl chloride **B** directly to the northern alkyne and forging the desired chlorodiene **A** after subsequent reductive elimination in a single step.[263] Despite the recent efforts in establishing the intra-[264] (see Scheme 1.6) and intermolecular[265] carboiodination of alkynes, the analogous carbochlorination using simple alkenyl chloride has not been reported yet. The addition of allylic chlorides[266] and chloroalkynes[267] to alkynes were realized, albeit in low selectivity. A tandem reaction using chloropalladation on ynones and ynoates followed by a Heck reaction with acrylates is the only regio- and stereoselective method for providing chlorodienes in a single step.[268]

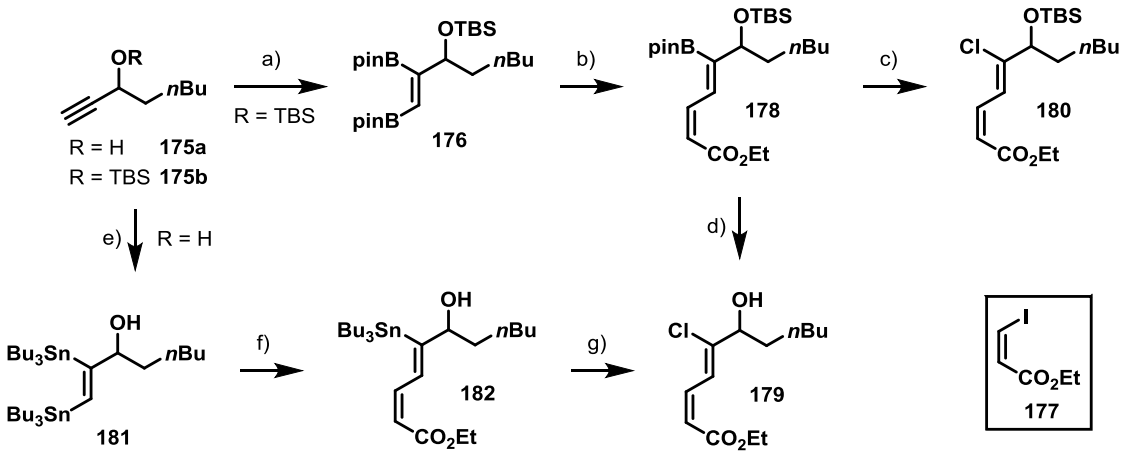
Focusing on the preparation and serial manipulation of bis-functionalized alkenes, the usage of a dihalogenated olefin **F**, a bismetalated building block **I** or a hybridic coupling partner **D** were considered in a site-selective C_{sp^2}-C_{sp^2} cross coupling attempt.[177,269] Inspired by the first total synthesis of *N*-acyl spermidine,[270] the ultimate disconnection approach features the literature-known chloroboration of alkynes **C**. [271] The chloroborane **D** (M = BCl_2) would undergo a Suzuki cross coupling with alkenyl halide **E** in a regio- and stereoselective manner.[272] Addition of trichloroborane to terminal alkynes **C** delivers the metalloid **D** regioselectively at the terminal position. Suffering from isomerization via haloboration of akenylboronate **D** followed by β-dehaloboration,[273] the *in situ* conversion to the corresponding borates or Molander salts[274] is mandatory for suppressing degradation pathways. Concerning the substrate tolerance of chloroboration, propargyl alcohols have been reported to degrade by elimination under these strongly Lewis acidic conditions.[275] Preliminary studies concerning the tolerance of silyl-protected propargyl alcohols **C** (R^2 = TBS) by A. Letort showed complete decomposition of a simplified model substrate, which presumably derives from elimination of the –OR substituent.[276]

In contrast to the low functional group tolerance of chloroboration, the preparation and synthetic utility of bimetallic species **I** or vicinal dihalogenated olefins **F** in the synthesis of challenging polyenes and trisubstituted alkenes has been highlighted in numerous total syntheses.[104b,277] Encouraged by the recent advances in chemoselective cross coupling of geminal dichloroalkenes by the E. Roulland group (see Section 1.4.2.3, Scheme 1.4),[103,278] a vicinal dichloroalkene **F** was envisioned to set the stage for a regioselective oxidative addition, which upon transmetalation with alkenylmetal species **G** would give access to the desired halodiene **A**. However, the preparation of **F** by a formal addition of chlorine to alkynes **B** suffers from functional group intolerance and diminished stereoselectivity.[279]

Alternatively, a dienylmetal species **H** could be converted to the desired chlorodiene by chloro-demetalation. The adduct **H** would originate from a site-selective cross coupling of alkenyl iodide **E** and bismetalla-alkene **I**, which is rapidly accessed by *syn*-addition of the corresponding bimetallic reagent to alkyne **B**.[280] In order to discriminate the two reactive sites, the usage of a mixed dimetalic alkenylspecies **I** ($M^1 \neq M^2$) would guarantee an orthogonal reactivity, which is commonly used in cross coupling.[280] Such a linchpin can exclusively engage with the palladium catalyst by a single reactive site upon transmetalation.[281] However, these bimetallic reagents were found to suffer from hydrolytic degradation, [282] which prompted us to investigate in a catalyst-controlled site-selectivity with a homobimetallic species **I** ($M^1 = M^2$).

Based on the steric bias of the different reactive sites for transmetalation, we anticipated that a sterically encumbered palladium catalyst could discriminate between the terminal and the branched

position in **I**. Commencing with the bisborylation[276] and bisstannylation[174] of alkyne, the envisaged sequence was initially tested on model substrate **175** by A. Letort and M. K. Ilg (Scheme 2.43).



Scheme 2.43. Model studies. $B_2(pin)_2$, $Pt(PPh_3)_4$ (3 mol%), DMF, 80 °C, 75% ; b) **177**, $[(dppf)PdCl_2]$ (3 mol %), K_3PO_4, aq. THF, reflux, 69%; c) i) Ph_3PAuCl, Cs_2CO_3, *i*PrOH, 3 Å MS, 50 °C; ii) NCS, RT, 75%; d) $CuCl_2$, $NaHCO_3$, EtOH/H_2O , 60 °C, 75%; e) $(Bu_3Sn)_2$, $[(t\text{BuNC})_2PdCl_2]$ (10 mol%), THF, 85%; f) **177**, $Pd(PPh_3)_4$ (20 mol%), CuTC, $[Ph_2PO_2][NBu_4]$, DMF, 59%; g) $CuCl_2$, 2,6-lutidine, THF, 74%.[174,276]

By applying the literature-known conditions for the Pt-catalyzed addition of bispinacolboronate to terminal alkyne **175b**,[283] **176** was obtained in good yield. According to the previously reported site-selective cross couplings of bis(alkenyl)boronates,[284] the regioselective Suzuki cross coupling of **176** with alkenyl iodide **177** gave **178** in high yield. Following the standard conditions for copper-mediated chloro-deborylation of arenes[285] resulted in the simultaneous chlorination and deprotection of the silyl ether to give chlorodiene **179**. Switching to homogenous gold complexes as known stoichiometric transmetalating agents for boron compounds,[286] the subsequent chloro-deauration[287] with NCS provided the *Z,Z*-chlorodiene **180**, while maintaining the protection group as well as the stereochemistry.

The complementary distannylation reported by the M. Lautens group was investigated by M. K. Ilg on model substrate **175a** and proved to be applicable, even in the presence of the unprotected alcohol.[288] In contrast to numerous examples of regioselective oxidative addition of alkenyl halides in Stille reactions,[289] the discrimination of bis(alkenyl)stannanes is limited to the site-selective cross coupling of bisstannyl butenoates.[290] A differentiation of the two reactive sites in **181** with respect to transmetalation seemed feasible due the different steric bias of the two tin substituents.

Subjecting **181** to modified Stille reaction conditions including CuTC[291] as a transmetalating agent and Liebeskind salt diphenylphosphinate as a tin scavenger,[292] the dienylstannane **182** was obtained as a single isomer without erosion of the *E/Z*-ratios in both coupling partners.[293]

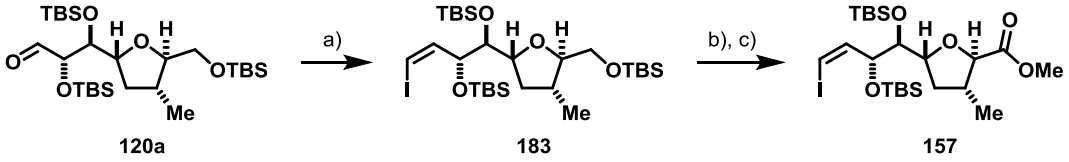
The following chloro-destannylation was tested on dienylstannane **182** by treatment with copper (II) chloride, which was originally reported by T. Takeda *et. al.*.[164] In analogy to the late-stage

derivatization of 5,6-dihydrocineromycin B and nannocystin A by the A. Fürstner group,[160a] the chlorodiene **179** was obtained in high yield with complete retention of the preinstalled stereochemistry. After approval of the two complementary sequences for accessing chloro-1,3-diene selectively, their synthetic utilities towards the macrocyclic core **78** were investigated.

2.5.2.2 Synthesis of the Coupling Partners

2.5.2.2.1 Synthesis of the Southern Fragments

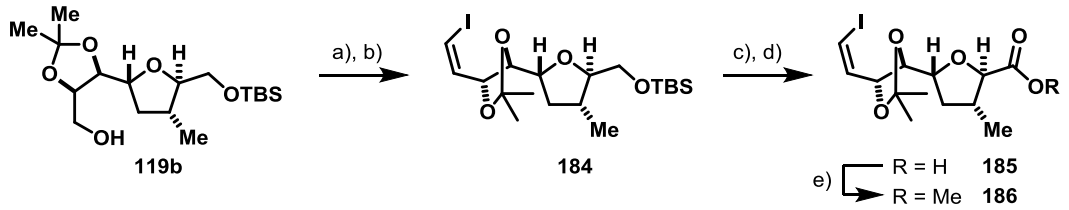
The synthesis of the southern fragments began with the Stork-Zhao olefination of aldehyde **120a**, affording alkenyl iodide **183** in high yield as a single isomer (Scheme 2.44).[294] After discriminating between the silyl ethers in **183**, the liberated primary alcohol was successively oxidized to the corresponding carboxylic acid, which was treated with TMS-diazomethane to give southern fragment **157**.[295]



120a **183** **157**

Scheme 2.44. Synthesis of southern fragment **157**. Reactions and Conditions: a) $[Ph_3PCH_2I]I$, NaHMDS, HMPA, THF, −78 °C, *Z*/*E* = >20:1, 97% (pure *Z*-isomer); b) HF·pyridine, pyridine, THF, 91%; c) (I) TEMPO (20 mol%), BAIB, aq. MeCN; (II) $TMSCHN_2$, THF, 66% over 2 steps.

In order to address the steric bias during oxidative addition of the alkenyl iodide, the acetonide-containing fragment **186** was synthesized analogously (Scheme 2.45). After Parik-Doehring oxidation of **119b**, the crude aldehyde was subjected to Stork-Zhao olefination conditions, providing stereoselectively the *Z*-alkenyl iodide **184**. After protection group and redox manipulation, the carboxylic acid **185** was treated with TMS-diazomethane in methanolic toluene, affording the methyl ester **186** in high yield.[296]



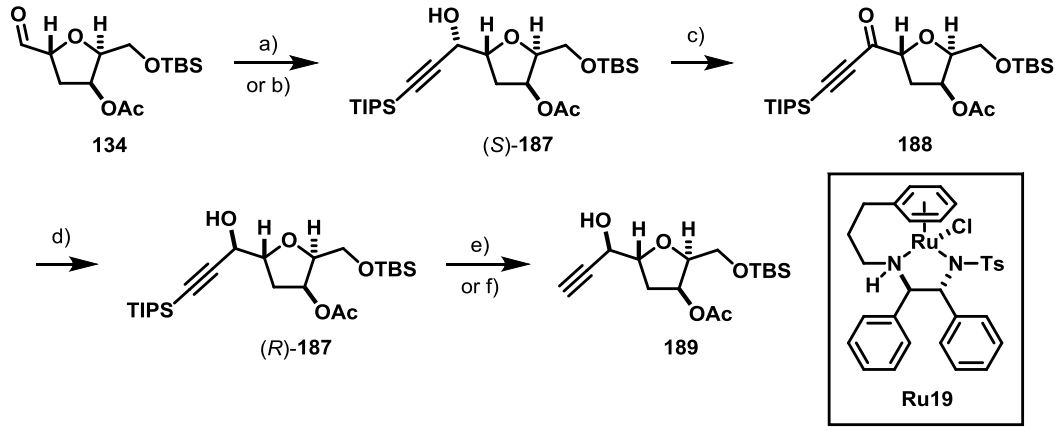
119b **184**

Scheme 2.45. Synthesis of southern fragment **186**. Reactions and Conditions: a) $[SO_3{\cdot}pyridine]$, $(iPr)_2NEt$, DMSO, CH_2Cl_2, –25 °C; b) $[Ph_3PCH_2I]I$, NaHMDS, HMPA, THF, −78 °C, *Z*/*E* = >20:1, 67% over 2 steps (pure *Z*-isomer); c) HF·pyridine, pyridine, THF, quant.; d) TEMPO (30 mol%), BAIB, aq. MeCN, 98%; e) $TMSCHN_2$, toluene/MeOH = 4:1, 75%.

2.5.2.2.2 Synthesis of the Northern Fragment 189

The synthesis of the northern fragment **189** commenced with aldehyde **134** (Scheme 2.46).[217] By switching from the established asymmetric alkynylation with propyne to a silyl-capped acetylene,[217]

the Carreira alkynylation of **134** suffered from self-aldolization, giving the propargyl alcohol **187** in low yield. Alternative reagent-controlled alkynylations as reported by B. M. Trost *et. al.*,[297] L. Pu *et. al.*[298] or the M. Shibasaki[299] group displayed even faster degradation of the starting material **134**.[276] Substrate-controlled alkynylation gave the undesired epimer (*S*)-**187** via a Felkin-Anh transition state in moderate selectivity and yield.[276] After extensive optimization of the reaction conditions, the addition of lithium iodide was found to enhance the selectivity towards the desired epimer (*R*)-**187**, albeit in moderate yield and diastereoselectivity.[300]



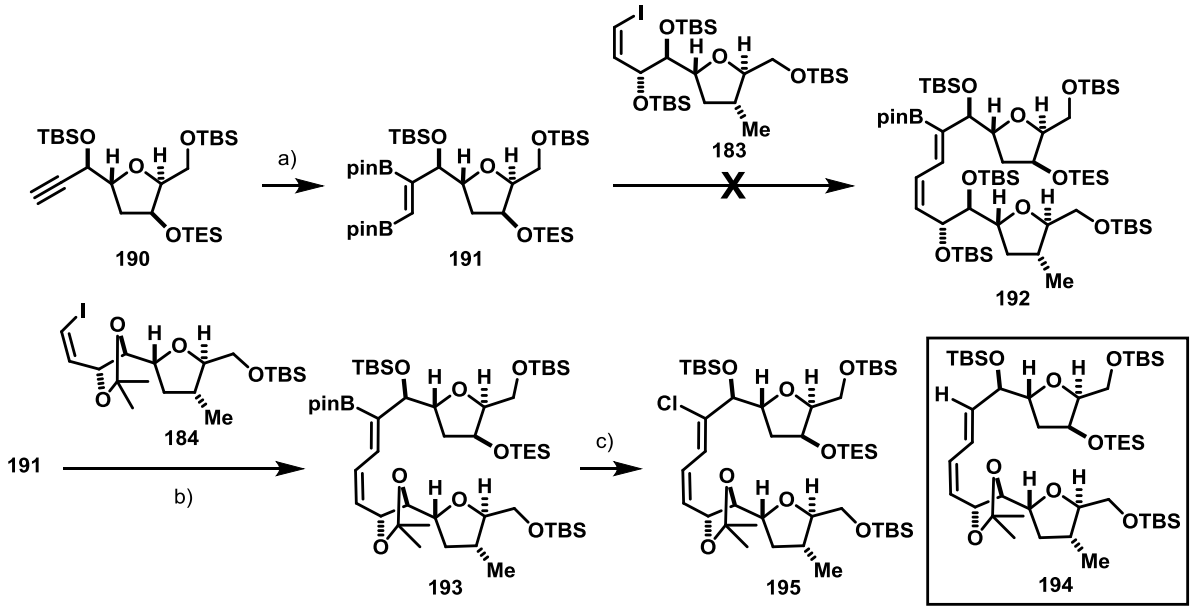
Scheme 2.46. Synthesis of propargyl alcohol **177** via ATH. Reagents and conditions: a) triisopropylsilylacetylene, *n*BuLi, then $LnCl_3{\cdot}(LiCl)_2$, THF, −78 °C, dr = 4:1, 82% (mixture of diastereomers); b) triisopropylsilylacetylene, *n*BuLi, Et_2O, LiI, −40 °C, dr = 1:5, 67% (mixture of diastereomers); c) DMP, $NaHCO_3$, *t*BuOH, CH_2Cl_2, 85%; d) (*S*,*S*)-Teth-TsDpen-RuCl (**Ru19**) (10 mol%), $HCO_2H{\cdot}Et_3N$, CH_2Cl_2, dr = >20:1, 97%, (pure diastereomer); e) TBAF (portionwise), THF, –40 °C, 69%; f) AgF, MeCN, 45%.

Therefore, a three step sequence comprising unselective alkynylation, oxidation of (*S*)-**187** to ynone **188** and subsequent asymmetric transfer hydrogenation (ATH) affording (*R*)-**187** was evaluated.[301] Taking advantage of the Knochel conditions for the alkynylation of hindered ketones,[302] the rapid nucleophilic attack of preformed lithium acetylide to aldehyde **134** was successful without epimerization in the *α*-position. In the presence of *t*-butanol and sodium bicarbonate, the oxidation of (*S*)-**187** with DMP gave ynone **188** without erosion of the *α*-stereocenter. Subjecting **188** to the asymmetric reduction under transfer hydrogenation conditions with Wills' catalyst (**Ru19)** provided (*R*)-**187** in high levels of diastereoselectivity.[303] Selective deprotection of the TIPS group in presence of a TBS-protected primary alcohol in (*R*)-**187** proved to be highly challenging. Neither TBAF nor AgF[304] were capable of differentiating between the two fluoride-labile protection groups. Despite these erratic results, a portion-wise addition of TBAF were found to afford the terminal alkyne **189** in 69% yield.[276]

2.5.2.3 **Suzuki Cross Coupling and Gold-Mediated Chloro-Deboration**[276]

Remark: The herein reported results on bisboronates were conducted by Dr. A. Letort.

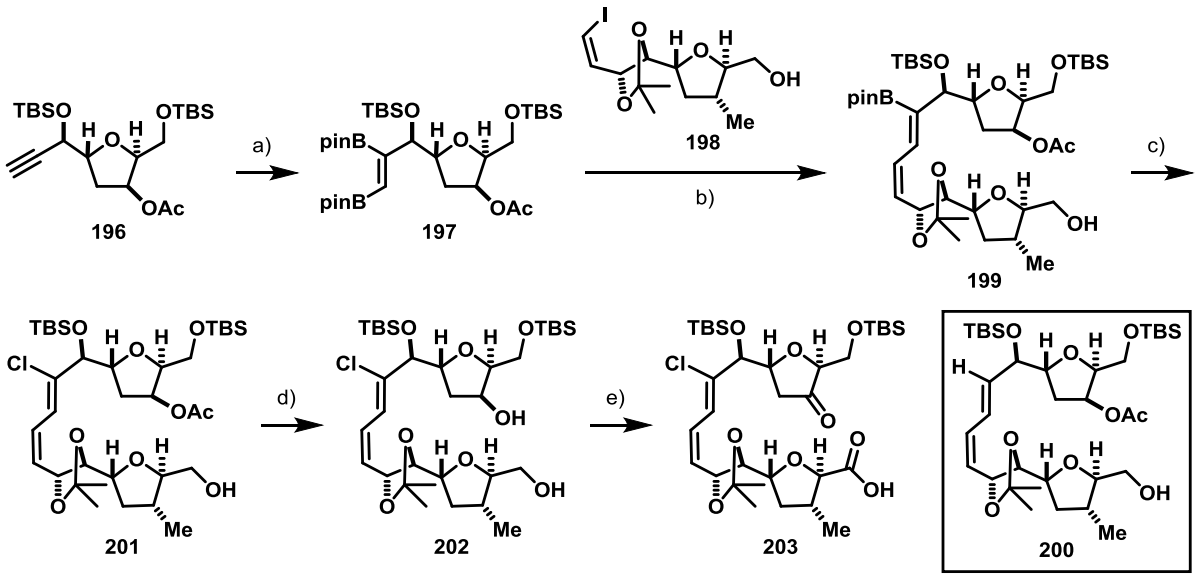
Platinum-catalyzed diboration of alkyne **190** afforded bis(alkenyl)boronate **191** as an unstable intermediate, which degraded upon purification (Scheme 2.47). Thus, the crude product was directly subjected to Suzuki cross coupling with southern fragments **183** and **184**.



Scheme 2.47. Investigations into the site-selective Suzuki reaction of **191** followed by chloro-deborylation of **193** as a proof-of-concept. Reactions and conditions: a) B_2pin_2, $Pt(PPh_3)_4$ (2.5 mol%), DMF, 80 °C; b) Pd_2dba_3 (15 mol%), Ph_3As (60 mol%), Ag_2O, aq. THF, 77% (pure **181** over 2 steps at RT), 56% (**181**/**182** = 2:1, over 2 steps at 60 °C); c) Ph_3PAuCl (2.9 equiv.), Cs_2CO_3, 3 Å molecular sieves, *i*PrOH, then NCS, 66%.

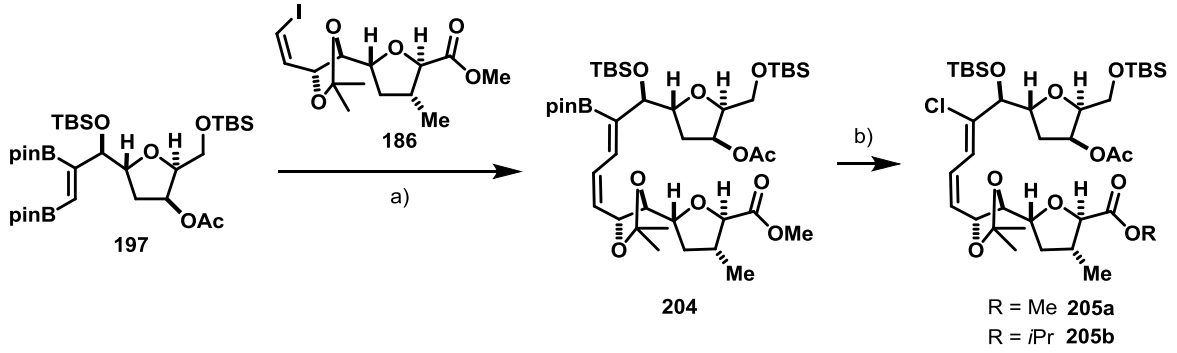
Whereas **183** did not participate, **184** engaged in the palladium-catalyzed fragment assembly giving dienylboronate **193** in 77% yield as a single isomer. At elevated temperature, the cross coupling suffered from enhanced protodeborylation of **193**, providing diene **194** in a 2:1-ratio. Subsequent chloro-deborylation mediated by an excess of a gold(I) salt gave chlorodiene **195** in 66% yield on a very small scale. The impossible differentiation of the two primary TBS silyl ethers in **195** led to a revised protection group strategy in both coupling partners.

Bisborylation of alkyne **196** set the stage for the Suzuki coupling of the corresponding bis(alkenyl)boronate **197** with alkenyl iodide **198** (Scheme 2.48). Dienylboronate **199** was isolated in 66% yield on a small scale, although a doubled reaction time was found to cause massive protodeborylation of **199**, affording diene **200** in 48% yield. Testing the compatibility of the gold-mediated chloro-deborylation with the free hydroxy group in **199** proved to be highly problematic. Neither at ambient temperature nor at elevated temperature was dienyl chloride **201** formed in more than 35% yield. Any attempts towards the synthesis of a *seco*-acid failed due to an unselective oxidation of the primary alcohol in presence of the secondary alcohol in **202**.



Scheme 2.48. Studies towards the synthesis of a suitable precursor for accessing macrocyclic core **78**. Reactions and conditions: a) B_2pin_2, $Pt(PPh_3)_4$ (2.5 mol%), DMF, 80 °C; b) Pd_2dba_3 (10 mol% or 7.5 + 2.5 mol%), Ph_3As (40 mol%), Ag_2O, aq. THF, 66% (pure **199** over 2 steps for 7.5+2.5 mol% [Pd]), 12% (**199**) and 48% (**200**) (**199**/**200** = 1:4, over 2 steps for 10 mol% [Pd]); c) Ph_3PAuCl, Cs_2CO_3, 3 Å molecular sieves, *i*PrOH, then NCS, RT or 50 °C, 30-35%. d) K_2CO_3, MeOH, 90%; e) TEMPO (30 mol%), BAIB, aq. MeCN, 43%.[276]

Using alkenyl iodide **186** and bisboronate **197** in the Suzuki reaction, the cross coupling adduct **204** was isolated in 75% yield (Scheme 2.49). Subsequent transmetalation of dienylboronate **204** with stoichiometry amounts of gold(I) salt gave **205a** in 58% yield on small scale but suffered from transesterification to **205b** under the basic reaction condition.



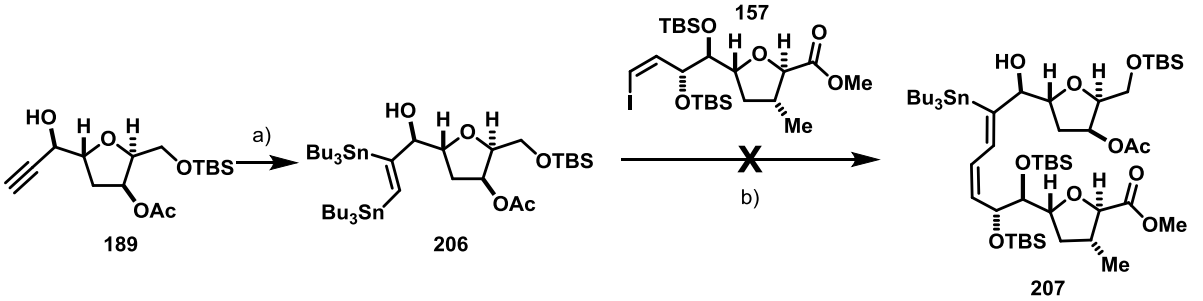
Scheme 2.49. Suzuki cross coupling of **197** and **186** and failed chloro-deborylation of **204**. Reactions and conditions: a) Pd_2dba_3 (10 mol%), Ph_3As (40 mol%), Ag_2O, aq. THF, 75% (over two steps); b) Ph_3PAuCl, Cs_2CO_3, 3 Å MS, *i*PrOH, then NCS, 58% (**205a**), 30% (**205b**).[276]

In summary, the initial results on minor quantities of **190** have showcased the synthetic utility of the envisaged transformation. However, as chlorodiene **195** was a dead-end towards the synthesis of chagosensine, this proof-of-concept was applied on suitable surrogates, which unfortunately displayed major disadvantageous with regard of functional group tolerance during the gold-mediated transmetalation. That is the reason why we had to focus on the complementary tin-based approach.

2.5.2.4 **Synthesis of the Chlorodiene Moiety by Site-Selective Stille Reaction[174]**

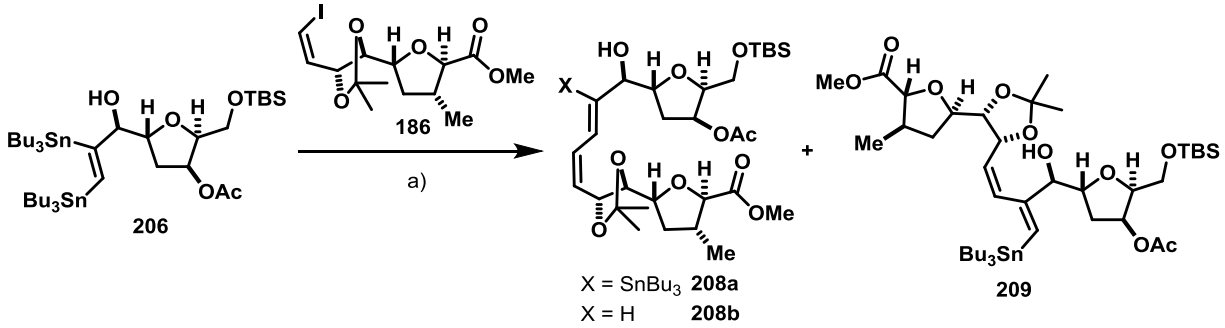
Remark: The preliminary results on the unselective synthesis of the chlorodiene and the macrolactonization were obtained by Dr. M. K. Ilg.

After a successful palladium-catalyzed addition of hexabutylditin to alkyne **189**,[288] preliminary investigations on the Stille reactions were conducted by M. K. Ilg (Scheme 2.50).[174] Once again, the southern fragment **157** containing two bulky protection groups in proximity to the reactive alkenyl iodide did not engage in the Stille reaction due to steric effects.



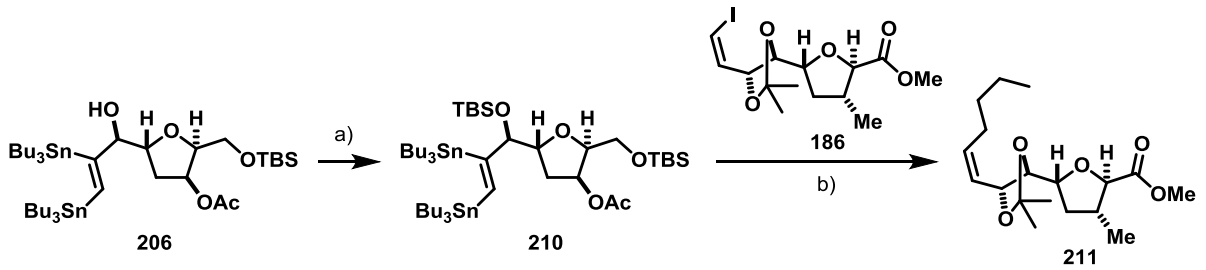
Scheme 2.50. Unfruitful attempt for Stille reaction with alkenyl iodide **157**. Reactions and conditions: a) $(Bu_3Sn)_2$, $Pd(t\text{BuNC})_2Cl_2$ (10 mol%), THF, 76%; b) $Pd(PPh_3)_4$ (20 mol%), CuTC, $[Ph_2PO_2][NBu_4]$, DMF.[174]

In contrast, acetonide derivative **186** gave the dienylstannane **208a** and the regioisomeric dienylstannane **209** in moderate yields but variable ratios (Scheme 2.51). In addition to the unselective course, the formation of protodestannylated diene **208b** was observed, deriving from subsequent protodemetalation of dienylstannane **208a**.



Scheme 2.51. Preliminary results for copper-mediated Stille cross coupling with **186** by M. K. Ilg. Reactions and conditions: a) $Pd(PPh_3)_4$ (40 mol%), CuTC, $[Ph_2PO_2][NBu_4]$, DMF, r.r. = 1.7:1, 40% (**208a**), 24% (**209**, characterized after chloro-destannylation), ca. 5% (**208b**).[174]

According to the studies on the copper-mediated methyl Stille coupling of alkenylstannanes, the presence of unprotected, free hydroxy group entails rapid transmetalation of the alkenylstannane.[161a,305] It is therefore assumed that **206** also engages with CuTC[306] at the internal position, resulting in a mixture of cross coupled products **208a** and **209**. In order to prevent the hydroxy-directing effect, the allylic alcohol in **206** was protected as the TBS-silyl ether **210** (Scheme 2.52). After subjecting **210** to modified Stille conditions, *Z*-butyl substituted alkene **211** was isolated as a single product in ca. 50%.



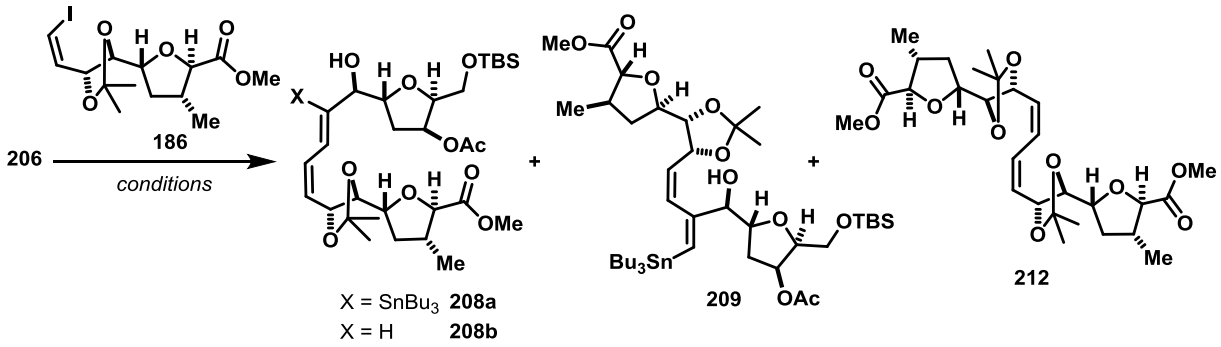
Scheme 2.52. Reactions and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 68%, b) $Pd(PPh_3)_4$ (40 mol%), CuTC, $[Ph_2PO_2][NBu_4]$, DMF, approximately 50%.

The increased steric bulk around the bisstannane **210** apparently prevents the transmetalation of the alkenyl substituent and enables the transfer of the less reactive alkyl substituent on tin to the Pd(II) species. Regarding the rate constants in transmetalation of unbiased cross coupling partners, the conversion of alkenylic carbons is more than 700 times faster than an sp^3-hybridized center.[307] For promoting C_{sp^2}-C_{sp^3} cross coupling of alkyl stannanes, the tin moiety is usually substituted with coordinating ligands facilitating the selective transmetalation of the alkyl substituent.[308] Returning to the parent allylic alcohol **206**, the conditions for a site-selective transformation were re-examined, thereby deliberately excluding copper salts as a transmetalating agents (Table 2.1).

Adapting the conditions used in the ring closure towards the total synthesis of rapamycin (entry 1),[309] **206** was consumed to unknown side products leaving the alkenyl iodide **186** untouched (recovered in 85% yield). The addition of Hünig's base had no effect on the reaction outcome (entry 2).[310] Applying the reaction conditions introduced by Farina,[311] the alkenyl iodide **186** still did not engage in the cross coupling, instead, causing decomposition of **206** (entry 3). Facing a low reactivity, the oxidative addition of **186** must be inhibited due to the steric bias of the substrate and the electronic properties of the Pd(0) species.

Besides their transmetalating abilities, Cu(I) salts are also phosphine scavengers and can thereby shift the equilibrium towards a coordinatively unsaturated palladium species (see Section 2.5.2.5).[293] Thus, a bulky XPhos ligand was applied, but unfortunately displayed no reactivity (entry 4). Maintaining a bulky catalyst system, the biaryl ligand was replaced by electron-rich P*t*Bu_3.[312] At ambient temperature, the Fu catalyst afforded dienylstannane **208a** as a single regioisomer, albeit in low yield (entry 5).

Table 2.1. Screening of reaction conditions for site-selective Stille reaction of bisstannane **206** and alkenyl iodide **186**.

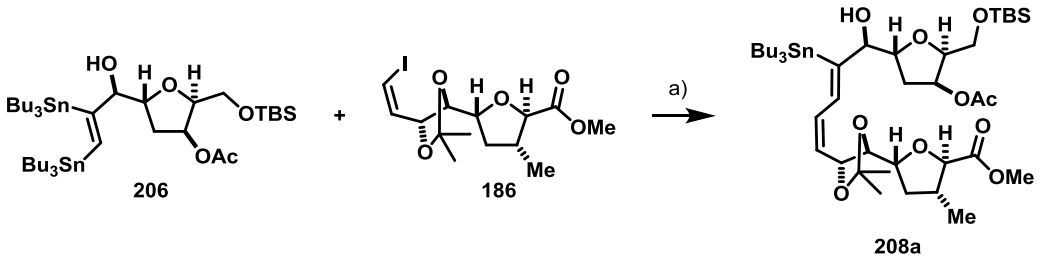


#	Catalyst (mol%)	186/ eq	206/ eq	Additives (eq)	Solvent	T / °C	208a	209	212	208b
1	$Pd(MeCN)_2Cl_2$ (20)	1	1	–	DMF	RT	–	–	–	–
2	$Pd(MeCN)_2Cl_2$ (20)	1	1	Hünig‘s base (1.3)	DMF	RT	–	–	–	–
3	$Pd_2(dba)_3$ (20) $AsPh_3$ (40)	1	1	–	DMF	RT	–	–	–	–
4	Pd_2dba_3 (10), SPhos (20)	1	1.1	–	NMP	RT to 45	–	–	–	–
5	$Pd(PtBu_3)_2$ (20)	1	1	–	DMF	RT	14	–	–	–
6	$Pd(PtBu_3)_2$ (20)	1	1.1	LiCl (3)	NMP	RT	43	15	–	–
7	$Pd(PtBu_3)_2$ (20)	1	1.1	LiCl (3)	NMP	45	21	–	7	12
8	$Pd(PtBu_3)_2$ (20)	1	1.5	$[Bu_4N][Ph_2PO_2]$ (1.1)	NMP	45	50	–	29	–
9	$Pd(PtBu_3)_2$ (20)	1.3	1	$[Bu_4N][Ph_2PO_2]$ (1.1)	NMP	45	33	–	–	–
10	$Pd(PtBu_3)_2$ (20)	1	1.3	$[Bu_4N][Ph_2PO_2]$ (1.1)	NMP	45	31	–	9	–
11	$Pd(PtBu_3)_2$ (20)	1	1.7	$[Bu_4N][Ph_2PO_2]$ (1.1), LiCl (4.8)	NMP	45	62	–	n.d.	–
12	$Pd(PtBu_3)_2$ (20)	1	1.5	$[Bu_4N][Ph_2PO_2]$ (1.1), LiCl (3.4)	NMP	45	51	–	n.d.	–
13	$Pd(PtBu_3)_2$ (10)	1	1.5	$[Bu_4N][Ph_2PO_2]$ (1.1), LiCl (3.4)	NMP	45	65	–	–	–

n.d. = not determined

Regardless of the DFT-calculated neglectable polarity effect in Stille reactions with Fu catalyst,[313] the elementary steps of the cross coupling reaction were believed to be accelerated by adding lithium chloride as well as switching to NMP as the solvent of choice,[314] which has been found to be beneficial in Negishi reactions of aryl chlorides with hindered arylzinc reagents.[315] At ambient temperature the yield of desired product **208a** could be improved to 27% accompanied with the

other regioisomer **209** (15%) along with enhanced degradation of the starting materials after prolonged reaction time (entry 6). Upon elevating the temperature to 45 °C, the amount of **208a** was diminished at the expense of protodestannylated diene **208b** and diene **212** formed by homo-coupling of alkenyl iodide **186** (entry 7). Exchanging lithium chloride with the Liebeskind salt, increased the yield of cross coupled diene **208a** and **212** (entry 8), whereas the formation of the regioisomer **209** and protodestannylated diene **208b** were completely suppressed and unconsumed bisstannane **206** could be recovered for the first time. Despite the beneficial effect of the phosphinate salt, the regressive transmetalation rate facilitates homocoupling of the alkenyl iodide **186**. Using the bimetallic species **206** as the limiting reagent disfavored the dimerization but resulted in a diminished isolated yield of **208a** (entry 9). Returning to alkenyl iodide **186** as the limiting reagent, but decreasing the excess of **206**, the yield of stannyl diene **208a** dropped to 31% along with traces of dimer **212** (entry 10). Besides the identified compounds **208a-b**, **209** and **212**, the Stille reactions in the absence of lithium chloride were rather sluggish. Upon combining the accelerating effect of lithium chloride with the tin-sequestering abilities of the phosphinate salts, a well-reproducible yield of 62% for **208a** was obtained without detecting significant quantities of the other side products (entry 11). Further decrease of **206** to 1.5 equivalents resulted in a diminished yield of **208a** (entry 12). Upon reducing the amount of catalyst, the dienylstannane **208a** was isolated in a remarkable yield of 65% as a single isomer (entry 13). In summary, the successive improvement of a challenging Stille reaction has led to the discovery of the first reliable method for forging the challenging dienylstannane in a regio- and stereoselective manner (Scheme 2.53).

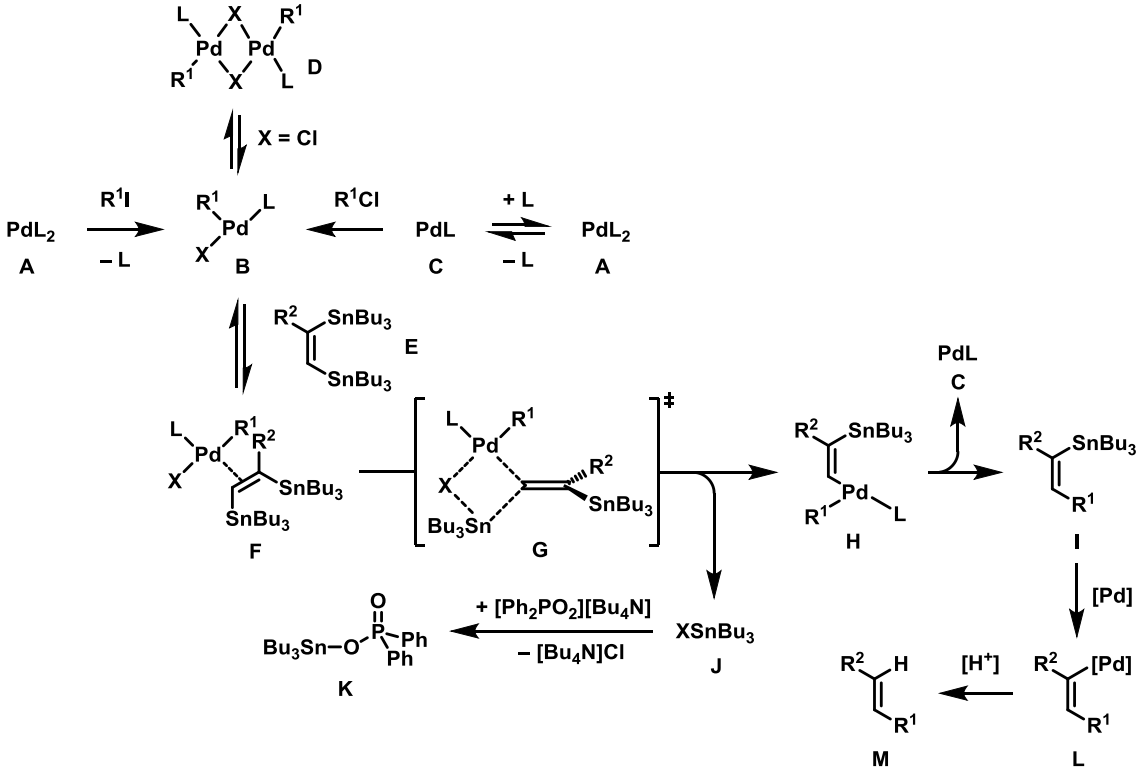


Scheme 2.53. Optimized reaction conditions for Stille reaction. Reactions and conditions: a) (tBu$_3$P)$_2$Pd (10 mol%), [Ph$_2$PO$_2$][NBu$_4$], LiCl, NMP, 45 °C, >20:1 r.r., 65% (pure regioisomer, >20:1 stereoretention), 40% (recovered **206**).

2.5.2.5 Mechanism of Stille Cross Couplings and Homocoupling of Alkenyl Iodides

As the mechanism of the Stille reaction has been thoroughly studied, the following reviews give a good insight in the tenability of each elementary step (Scheme 2.54).[316] Concerning the usage of bulky ligands, the generation of an unsaturated palladium species is enabled on steric ground.[312a] By establishing a free coordination site in the active palladium species, the reaction rate of each elementary step of the catalytic cycle is accelerated.[313,317]

In a general term, monoligated complexes [Pd(PR_3)] such as **C** have been shown to have a lower activation barrier for oxidative addition to aryl halides than the bisligated complexes [Pd(PR_3)$_2$] (**A**).[318] The organic halide in turn shows the following general order of reactivity towards oxidative addition: I > Br > Cl > F.[319] However, the exact mechanism of oxidative addition to the bisligated palladium complexes possessing bulky trialkylphosphine is highly dependent on the applied alkenyl halide. Under the premise of microscopic reversibility, mechanistic studies showed that aryl iodides react by an irreversible associative displacement of a ligand from PdL_2, whereas chloroarenes add irreversibly to a monophosphoric 14-electron species **C**.[320] In terms of reactivity, the introduction of sterically demanding alkyl groups such as *tert*-butyl or biphenyl groups on the phosphine-based ligand enabled the cross coupling of highly challenging electrophiles such as aryl chlorides,[312b] mesylates and tosylates.[321] After oxidative addition, the sheer bulkiness of the ligand prevents the coordination of another ligand to the tricoordinate complex **B**, but instead is found to be in an equilibrium with the dimeric species (**D**).[320] In regard of the site-selective Stille reaction, the Fu catalyst initially undergoes an oxidative addition with alkenyl iodide **186** by an irreversible associative displacement of one P*t*Bu_3. Subsequent halide exchange of complex **B** with added LiCl enables the dimerization to complex **D** (X = Cl).



Scheme 2.54. Mechanism of Stille coupling with bis(alkenyl)stannane **195** with alkenyl halides (X = I, Cl).

Although bimetallic complexes containing triphenylarsene were detected by NMR analysis,[322] the equilibrating monomeric species **B** (L = $AsPh_3$) is not participating in the following transmetalation but proceeds via a dissociative mechanism with [PdR_1XL_2].[323] After displacement of one ligand by

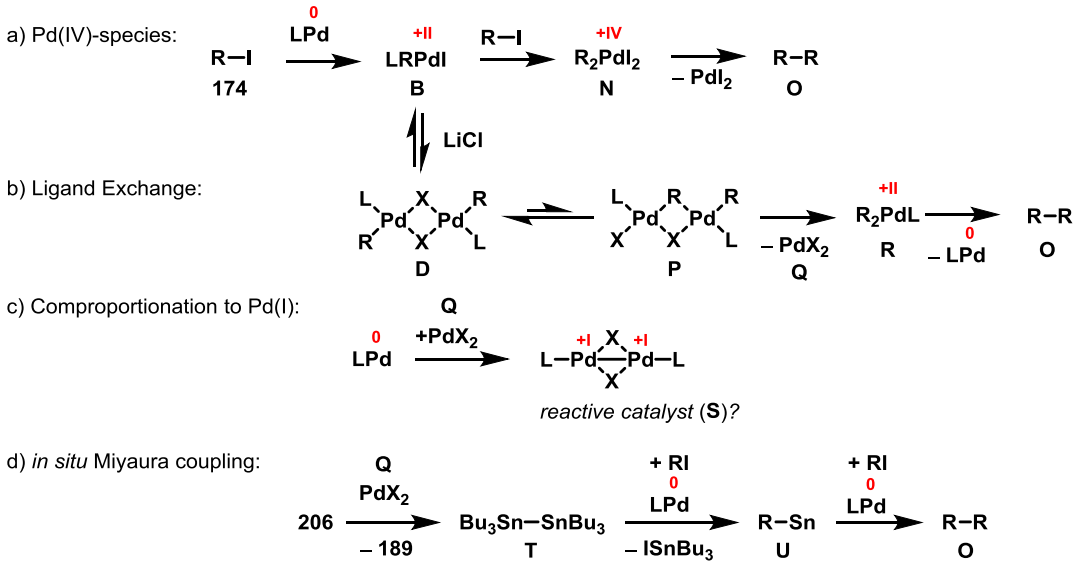
π-coordination of the C=C-double bond, the subsequent transmetalation of the alkenylstannane is occurring via a cyclic transition state for X = halide.[324] In contrast to the dissociative mechanism (L = $AsPh_3$, PPh_3), the bulky trialkyl phosphine ligands are able to stabilize the monomeric complex **B** by agostic interactions.[322] Although the coordination of the alkene moiety is proceeding without expelling a coordinating ligand, the steric bias of T-shaped complex **B** retards the formation of π-complex **F**.[325] In case of X = halide, the following transmetalation is also proceeding via the four-membered transition state **G**. Based on DFT-calculations,[313] the transmetalation of bis(alkenyl)stannane **E** must be the rate-determining step for the site-selective Stille reaction. Hence, the addition of lithium chloride proved to be beneficial, as the rate for transmetalation can be accelerated by lowering the energy of the engaged LUMO of **G**.[326] After liberating Pd species **H** and tin halide **J**, the applied phosphinate salts sequesters the tin waste, which was found to interfere in the transmetalation of complex **B** in Stille reactions.[327] Finally, reductive elimination from T-shaped Pd-species **H** releases cross coupled adduct **I** via a very low activation barrier.[328]

As transmetalation is most likely the rate determining step, the designed reaction conditions aimed for facilitating a single transmetalation of the terminal stannane **F**, while leaving the generated dienylstannane **I** untouched.[313] However, the observed diene **M** is likely formed by a successive transmetalation followed by protodemetalation of **L** upon aqueous work-up or quench by the neighboring hydroxy group.[329] This *in situ* protodemetalation of **L** is supported by the observed abstraction of even less acidic hydrogens under similar reaction conditions.[330]

The other major side product occurs by dimerization of the alkenyl halide **186**, which is a common, but barely understood phenomenon in transition metal-catalyzed cross coupling. Due to the retarded transmetalation step, the accumulation of the Pd(II) species sets the stage for the homocoupling of the alkenyl halide (Scheme 2.45). One possibility is the successive oxidative oxidation, leading to a Pd(IV)-intermediate **N**, which undergoes rapid reductive elimination to form the homocoupled adduct **O** (Scheme 2.55a).[331]

However, a more complex mechanism comprising of bimetallic species is likely to occur. Based on the equilibrium between monomeric complex **B** and dimeric species **C**, the accumulation of bimetallic species **C** could set the stage for a ligand isomerization to give bimetallic complex **P**, which in turn leads to dihalide complex **Q** and a Pd(II)-species **R** (Scheme 2.55b). Subsequent reductive elimination of **R** liberates the observed homocoupled product **O**, whereas the remaining Pd(II) species **Q** cannot reenter the catalytic cycle without further reduction to the catalytically active Pd(0) species. Based on the reductive homocoupling of aryl halides, the addition of sacrificial reagents like a secondary alcohol enabled the reduction of the generated palladium(II)-species **Q**.[332] Concerning the presence of an unprotected secondary alcohol in starting material **206** and coupling product **208a**, the

dimerization could be promoted by an oxidation to the corresponding enone, which would be prone towards further degradation.



Scheme 2.55. Mechanisms for the homocoupling of alkenyl iodide (R–I) and the occurring oxidation states.

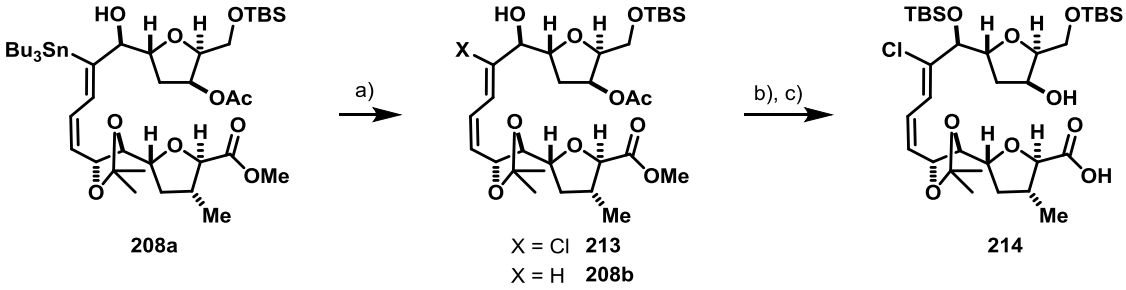
In the presence of a Pd(II) species **Q** originating from side reactions, a comproportionation to a dimeric palladium(I) species could lead to an active catalyst (Scheme 2.55c). The recent success story of Pd(I) dimers in catalyzing a variety of different cross-coupling reactions indicates that the operating catalysts and their oxidation states in the present Stille reaction might be more complicated than expected.[333] Based on Kochi's mechanistic studies concerning homocoupling of aryl halides catalyzed by stoichiometric amounts of $Ni(cod)_2$, an even more complex mechanism involving several oxidation steps could be envisioned by considering single electron transfer mechanisms.[334]

Another explanation for the observed dimerization could derive from coupling partner bisstannane **206**. Based on the microreversibility of catalytic transformation, the addition of distannane **T** to alkynes **189** in Scheme 2.52 could be reversed under the applied reaction conditions, liberating distannane **T** from bis(alkenyl)stannane **206** (Scheme 2.55d). Under palladium catalysis, the alkenyl iodide **186** would react with the released distannane **T** generating the corresponding alkenylstannane **U**.[335] The final Pd-catalyzed cross coupling between **U** and cross coupling partner **186** would give the isolated diene **O** as a formal homocoupled product.[336]

2.5.2.6 Synthesis of *Seco*-Acid and Macrolactonization

During the preliminary investigations into the chloro-destannylation of **208a** conducted by M. K. Ilg,[174] the literature-reported reaction conditions gave considerable amounts of protodestannylated diene **208b** (Scheme 2.55).[146] Increasing the amount of anhydrous copper (II) chloride showed to be beneficial, but could not prevent the formation of diene **208b** entirely. According to the original

procedure, the used twofold excess of $CuCl_2$ is necessarily implying a single electron transfer mechanism.

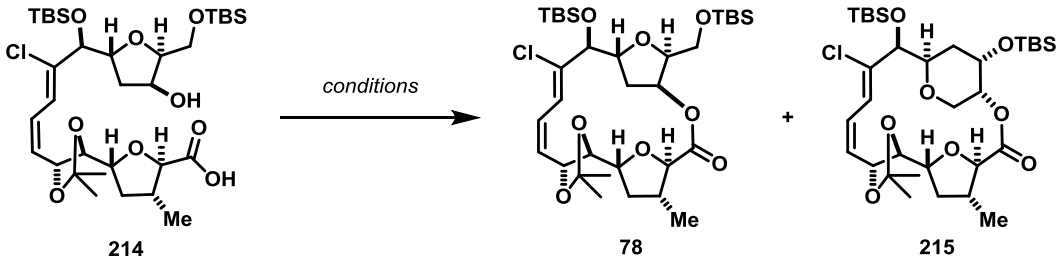


Scheme 2.56. Synthesis of *seco*-acid **214**. Reactions and conditions: a) $CuCl_2$, 2,6-lutidine, THF, 86%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 80%; c) K_2CO_3, H_2O/MeOH/CH_2Cl_2 = 6:9:10, 97%.

The copper-mediated transmetalation of dienylstannane is likely proceeding under stereoretention by a cyclic transition state in analogy to the four-membered transition state in the Stille reaction. The alkenylic copper(II) species then undergoes the disproportionation with the second equivalent of copper(II) chloride to form alkenylcopper(III), which is prone to fast reductive elimination. In case of a slow disproportionation the parent alkenylcopper can be protonated by the free alcohol at the *α*-position. Besides using an excess of reagent, employing 2,6-lutidine as an acid scavenger suppressed protodestannylation of **208a** significantly, which in turn gave chlorodiene **214** in high yield. The role of the added 2,6-lutidine for acting as a ligand for the insoluble copper(II) chloride cannot be ruled out.[337] After establishing the *Z,Z*-chlorodiene subunit of chagosensine for the first time, *seco*-acid **214** was obtained by TBS-protection of the allylic alcohol and subsequent saponification of the acetate and the methyl ester in aqueous methanol (Scheme 2.56).

With **214** in hand, the challenging macrocyclization was investigated under various reaction conditions in order to furnish the strained carbon framework of **78** (Table 2.2).[176,338] The activation of the carboxylic acid **214** as the mixed Yamaguchi anhydride caused major degradation and only traces of a macrocycle with correct molecular weight could be detected by HPLC-MS analysis (entry 1).[339] Switching to the Shiina conditions, a macrolactonization attempt at 40 °C displayed no reactivity (entry 2).[340] Elevating the temperature, the Shiina macrocyclization in refluxing 1,2-dichloroethane showed traces of a new compound with the correct molecular weight (entry 3), but differing in retention time from the macrocycle formed in entry 1. However, the majority of the mixed anhydride degraded to unknown decomposition products exhibiting a dramatic decrease in molecular weight. Under the applied basic reaction conditions, the *in situ* generated mixed anhydride could be prone towards decomposition.

Table 2.2. Screening of macrolactonization conditions towards the macrocyclic core **78**.

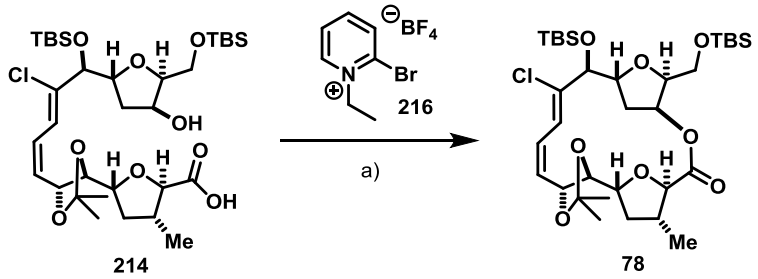


#	conditions	T / °C	**214**	**78**	**215**
1	*Yamaguchi*	RT, 75	–	–	traces
2	*Shiina*	40	–	–	–
3	*Shiina*	60-90	–	traces	–
4	*Corey-Nicolaou; Gerlach*	RT; 120	–	traces	–
5	BEP, $NaHCO_3$, $(CH_2Cl)_2$	70	–	31	9
6	BEP, $NaHCO_3$, $(CH_2Cl)_2$	95	32	23	27
7	BEP, $NaHCO_3$, $(CH_2Cl)_2$	105	50	20	4
8	BEP, $KHCO_3$, $(CH_2Cl)_2$	115	60	–	11
9	BEP, Cs_2CO_3, $(CH_2Cl)_2$	45	–	–	–
10	BEP, $NaHCO_3$, MeCN	80	100	–	–
11	BEP, DMAP, MeCN	80	–	–	–

Inspired by the biosynthetic pathway for the ring closure of macrolides (see Section 1.3.2), the double activation of acid and alcohol by the formal addition of a thiopyridone was investigated.[341] Initially described by E. J. Corey and K. C. Nicolaou,[342] the generation of the 2-pyridyl thioester is conducted by a Mukaiyama condensation[343] with PySSPy and triphenylphosphine (entry 4). In the presence of the pyridine base, the alcohol is deprotonated under refluxing conditions. The opposite charged subunits are engaging in an electrostatic interaction bringing the reactive ends in close proximity for macrolactonization. As HPLC analysis displayed a neglectable conversion of thioester to macrolactone, silver triflate was added to the crude mixture at ambient temperature. The activation by silver salts has been reported by the H. Gerlach group in order to promote challenging cyclizations,[344] but neither at ambient temperature nor under refluxing condition the formation of macrolactone **78** was observed in meaningful quantities (entry 4).

Finally, the modified Mukaiyama[345] macrolactonization using 2-bromo-1-ethyl pyridinium tetrafluoroborate (BEP reagent, **216**)[346] was tested on *seco*-acid **214**. Taking advantage of the mild inorganic base, the conditions are suppressing the formation of ketenes and are suitable for epimerizable substrates.[347] The heterogeneous reaction is usually carried out in dichloromethane at ambient temperature under high dilution conditions ($c = 10^{-3}$ M). Subjecting **214** to the reaction conditions led to no conversion at room temperature. The replacement of dichloromethane with higher boiling 1,2-dichloroethane enabled the heating of the mixture to 80 °C in a pressure Schlenk tube (Young tube). After 24 h, the desired macrolactone **78** was isolated on a 2.3 mg scale in 40% yield for the first time, but was contaminated with 22% of isomer **215** (entry 5), possessing the same molecular weight, albeit a different MS-pattern (see Experimental Section). Extensive NMR analysis of the 4:1 mixture displayed an opening of the northern THF-ring, while C16 participates in macrolactonization forging the 17-membered macrocycle **215**. Concerning the required forcing reaction conditions, silyl-migration under basic[348] or thermal[349] conditions and subsequent opening of the THF-moiety might liberate the corresponding *seco*-acid of **215**. Further increase in temperature from 70 °C to 95 °C facilitated the formation of **215** (entry 6), while the desired 16-membered macrolactone **78** was isolated in a diminished yield. Elevating the temperature to 105 °C showed an ambivalent behavior by enhancing the selectivity towards **78**, albeit in a low overall yield (entry 7).

Exchanging sodium- with the slightly more soluble potassium bicarbonate,[350] the formation of the desired macrocycle **78** was entirely suppressed and **215** was generated exclusively. Applying cesium carbonate caused complete decomposition of *seco*-acid **214** (entry 9), whereas switching to acetonitrile as the solvent resulted in no reactivity (entry 10). Complete degradation of **214** was observed by using DMAP as an organic base (entry 11). Despite the successful ring closure of the macrocyclic core of chagosensine, the optimized Mukaiyama conditions afforded the 16-membered ring **78** in low yield (Scheme 2.57), which made the envisaged late-stage introduction of the missing side chain an impossible task.



Scheme 2.57. Optimized reaction conditions for forcing Mukaiyama macrolactonization of *seco*-acid **214**. Reactions and conditions: a) **216**, $NaHCO_3$, 1,2-dichloroethane, 80 °C, 40% (4:1 mixture of **78** and **215**).

In summary, the stereoselective introduction of the intriguing *Z,Z*-chlorodiene was established for the first time by a newly developed sequence comprised of distannylation, regioselective Stille

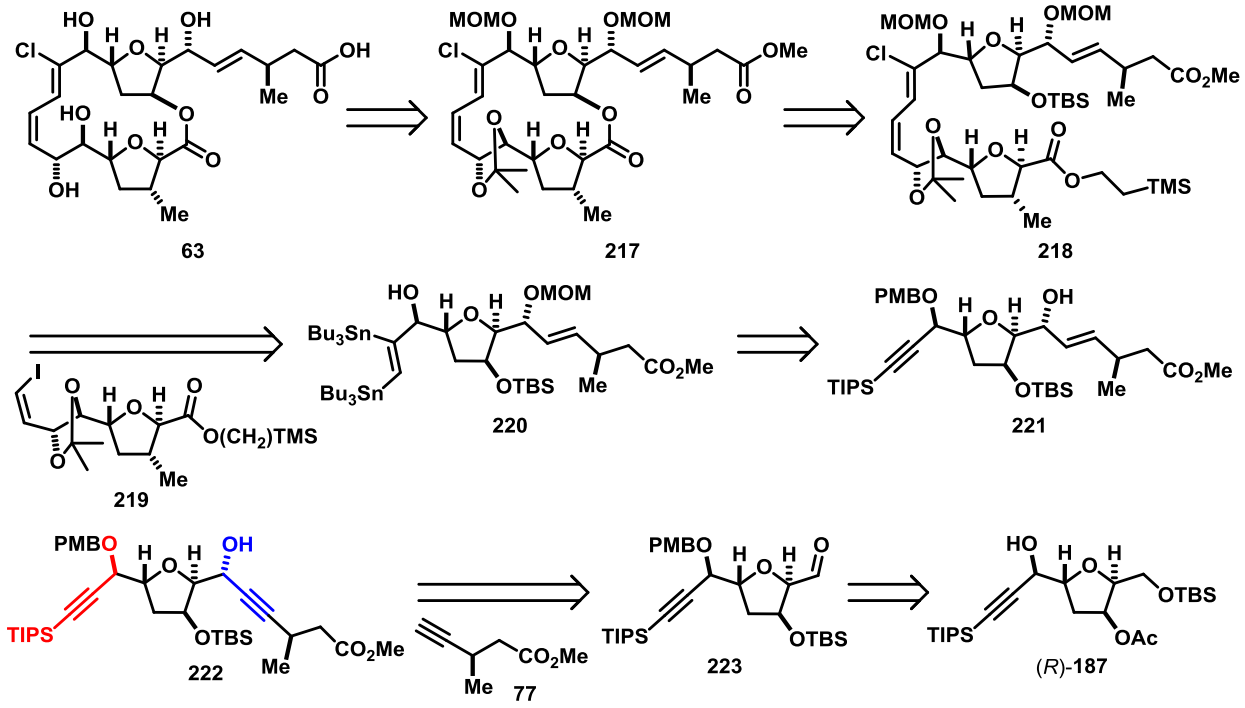
reaction and chloro-destannylation. The final ring closure showcases the superiority of macrolactonization towards the previous approaches by RCM and RCAM, but the low overall yield of the Mukaiyama macrolactonization made it unreasonable to pursue the route. While maintaining the established late-stage transformations, we envisioned to install the entire northern part of chagosensine, before assembling the two fragments in a more convergent manner.

2.6 Initial Efforts towards the Complete Northern Fragment

2.6.1 Revised Retrosynthetic Analysis

Remark: The retrosynthesis of the complete northern fragment was preliminarily investigated by Dr. J. Flasz.

After implementing the propargyl alcohol on the "western" side of the THF-ring by the former route (see Scheme 2.36), the "eastern" side chain in **221** was envisaged to be set by asymmetric alkynylation of **223** with **77** followed by chemoselective *trans*-reduction of diyne **222** (Scheme 2.58).



Scheme 2.58. Retrosynthetic plan towards **63** with northern fragment **220**.

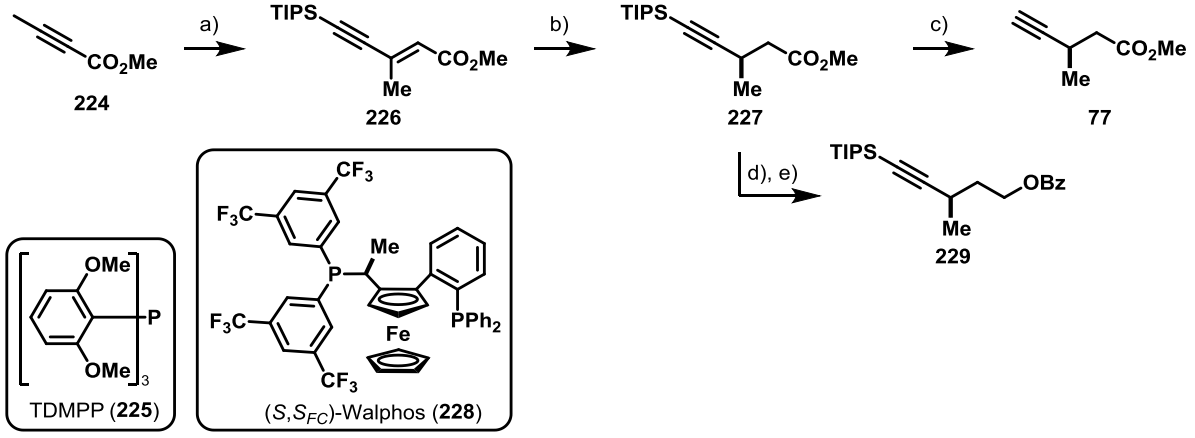
The recent achievements in differentiation two existing alkyne moieties prompted us to test a site-selective *trans*-hydrometalation on **222**, relying on the pronounced hydroxy-directing effect of the unprotected propargyl alcohol (see Section 1.5.2). In addition to this interligand hydrogen bond, capping of the alkyne by bulky silyl substituents was found to protect the acetylenic moiety from *trans*-addition.[153] With regard of the previous unsuccessful attempt of ruthenium-catalyzed hydrostannylation of enyne **159** (see Section 2.5.1), the regioselectivity would give valuable insight in the availability of the adjacent hydroxy group for directing the catalyst towards the proximal position of the unprotected propargyl alcohol. In addition, the behavior of the complementary ruthenium-catalyzed *trans*-hydrosilylation would be an adequate alternative and would provide further insight in the profound selectivity.

After successive protection group manipulations, the Lautens' bisstannylation would provide the northern fragment **220**. Retaining the elaborated late-stage sequence comprising site-selective Stille

reaction and chloro-destannylation, the fragment assembly would give access to the *Z,Z*-configured 2-chloro-1,3-diene entity in **218** in a convergent manner. Subsequent formation of the 16-membered macrolactone **217** would establish the carbon framework ultimately leading to the first total synthesis of chagosensine (**63**).

2.6.2 Synthesis of the Side Chain 77

The tertiary stereocenter of the side chain was introduced by a two-step procedure developed by the B. M. Trost group (Scheme 2.59).[351] First, palladium-catalyzed alkyne-alkyne coupling of TIPS-acetylene with alkyne **224** gave enyne **226** as a single regioisomer by applying ligand **225**.[352] Subsequent chemoselective asymmetric reduction of the α,β-unsaturated alkene in the presence of the conjugated alkyne in **226** was accomplished under copper hydride catalysis.[347c,353] In the presence of the Walphos ligand (**228**), the tertiary stereogenic center was implemented in 95% yield with 90% *ee*, which was determined by derivatization to the corresponding benzoyl ester **229** and HPLC analysis on a chiral stationary phase. Subjecting TIPS-alkyne **227** to a suspension of TBAF in diethyl ether provided the volatile terminal alkyne **77**. After extraction with pentane and careful distillation, the terminal alkyne **77** was stored as a solution in pentane.

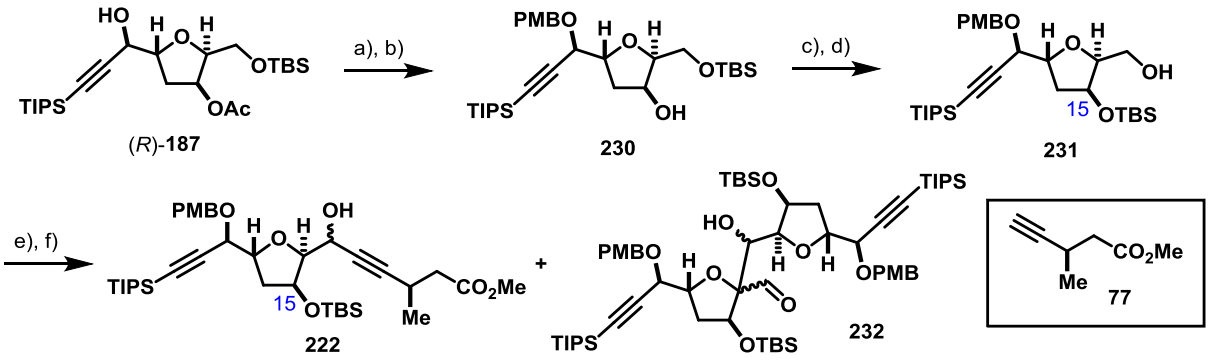


Scheme 2.59. Synthesis of the side chain **77**. Reagents and conditions: a) $Pd(OAc)_2$ (3 mol%), TDMPP (3 mol%), toluene, 91%; b) $Cu(OAc)_2$ (5 mol%), (S,S_{FC})-WalPhos (5 mol%), $Me(EtO)_2SiH$, toluene/*t*BuOH, 4 °C, 79%, 98% *ee*; c) TBAF, Et_2O, 81%; d) $LiAlH_4$, THF, 0 °C, 82%; e) pyridine, BzCl, CH_2Cl_2, 0 °C, 80%.

2.6.3 Unsuccessful Asymmetric Alkynylation – A Striking Mismatched Case

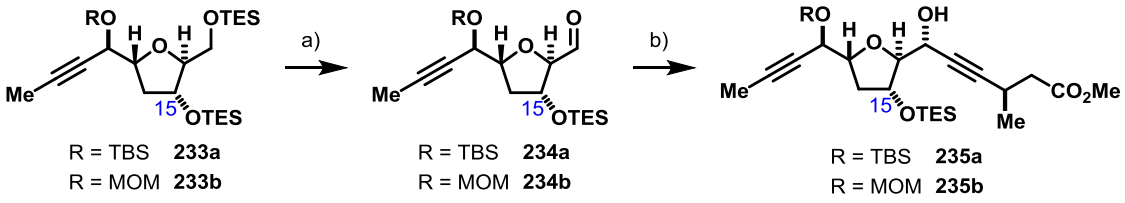
Remarks: The preliminary results on methyl caped alkynes were conducted by Dr. J. Flasz.

The synthesis of the complete northern fragment **220** commenced with PMB-protection of the propargyl alcohol (*R*)-**187** under Lewis acidic conditions (Scheme 2.60). Subsequent saponification of the acetate liberated alcohol **230**. After protection group manipulations, the primary alcohol **231** was isolated in 82% yield over 2 steps. The following oxidation under modified Parikh-Doering conditions set the stage for the asymmetric addition of the side chain **77**.



Scheme 2.60. Synthetic effort towards propargyl alcohol **222**. Reactions and conditions: a) PMB-trichloroacetimidate, $Sc(OTf)_3$ (5 mol%), toluene, 0 °C, 86%; b) K_2CO_3, THF/MeOH (1:1), 0 °C → RT, 90%; c) TBSCl, imidazole, CH_2Cl_2, 93%; d) CSA (30 mol%), THF/MeOH (1:1), 0 °C, 77% (13% of diol); e) [SO_3·pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, −20 °C, 91%; f) **77**, $Zn(OTf)_2$, (−)-*N*-methylephedrine, (iPr)$_2$NEt, toluene, dr = 2:1, 29% (**222**, mixture of diastereomers), 42% (**232**, mixture of diastereomers).

Applying the Carreira conditions for asymmetric alkynylation, the propargyl alcohol **222** was isolated in 29% yield, albeit as a 2:1 mixture of epimers. Besides the low diastereoselectivity, a diastereomeric mixture of aldol **232** was formed upon self-aldolization as the major product in 42% yield. This striking mismatch was rather surprising, as preliminary investigations in the asymmetric addition by J. Flasz had been successful (Scheme 2.61).[217]



Scheme 2.61. Previous results on Carreira alkynylation with side chain **77** by J. Flasz. Reagents and conditions: a) oxalyl chloride, DMSO, −50 °C, then Et_3N, 44% (**234a**), 58% (**234b**) b) **77**, $Zn(OTf)_2$, (−)-*N*-methylephedrine, (iPr)$_2$NEt, toluene, dr = >20:1, 55% (**235a**), 33%(**235b**).[217]

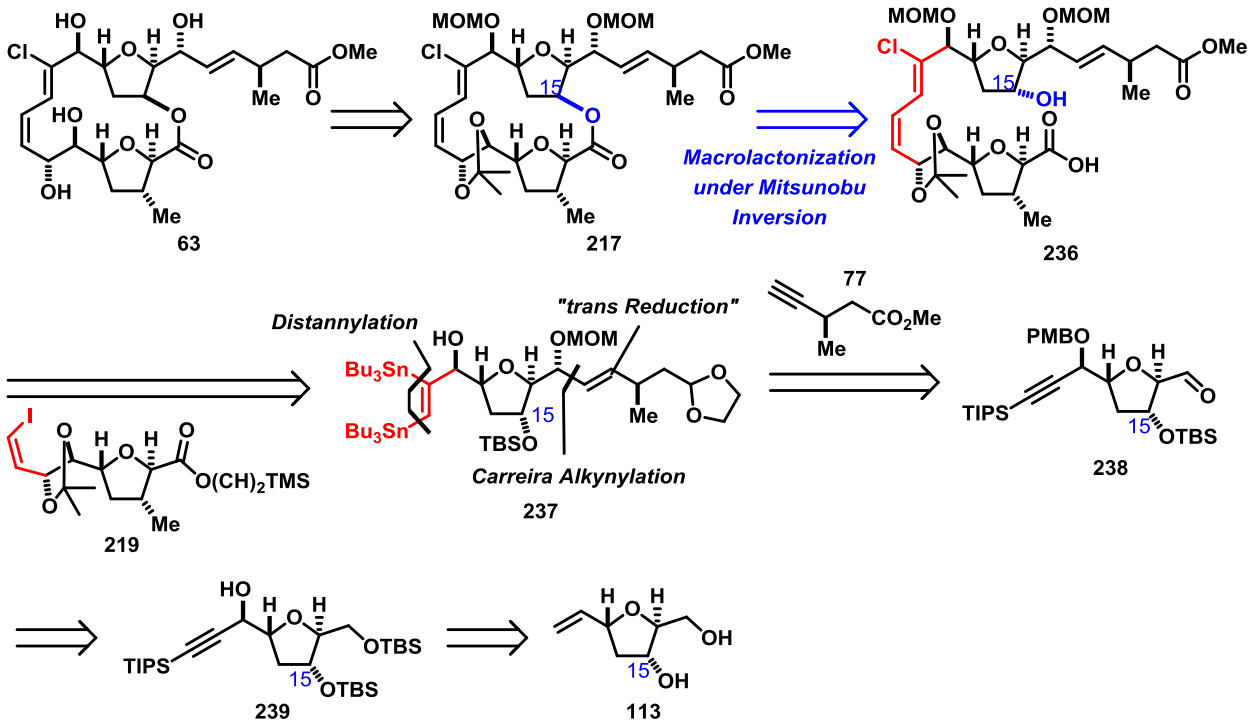
Mainly differing in the stereocenter at C15, the asymmetric alkynylation of aldehydes **234a** and **234b** gave the propargyl alcohols **235a** and **235b** in moderate yields but as a single diastereomer. Based on this intriguing impact of the stereocenter at C15, the corresponding epimer of **231** was prepared, resulting in considerable changes in the retrosynthetic route towards chagosensine.

2.6.4 Synthesis of C15 *epi* Northern Fragment 237

2.6.4.1 Revised Retrosynthetic Plan

Regarding the stereochemical manipulations at C15 in the previous fragment synthesis, the diol **113** originally possessed the opposite configuration of C15. In order to establish the correct configuration of the northern THF-ring, the earlier fragment synthesis towards the macrocyclic core **78** inverted the stereocenter of the secondary alcohol at C15 under Mitsunobu conditions (see Section 2.4.4). While the stereochemistry at C15 seemed to cause complications in the asymmetric alkynylation, we

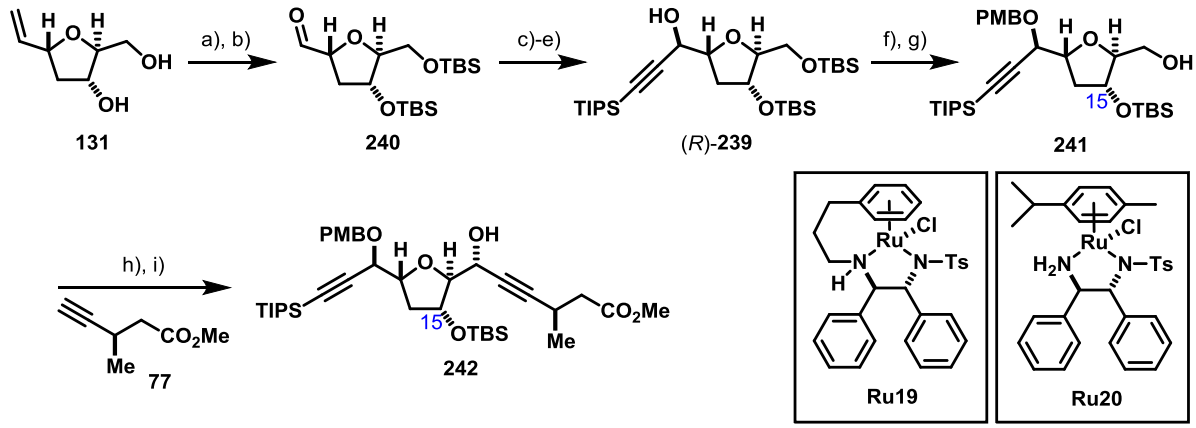
decided to postpone this stereochemical inversion at C15. Hence, the ideal scenarios would implement the correct configuration of the northern THF-ring upon macrolactonization of *seco*-acid **236** under Mitsunobu condition (Scheme 2.62).[354] Furthermore, the activation of the alcohol by DEAD or DIAD and triphenylphosphine might improve the yield of ring closure, as ketene formation from mixed anhydrides is avoided.[233,355] According to the previous retrosynthetic analysis (see Scheme 2.57), the synthesis of the new C15 *epi* northern fragment **237** originates from the same diol **113**. After introduction of the propargyl alcohol in **239**, subsequent protection group management and oxidation to the aldehyde **238** should facilitate the diastereoselective addition of side chain **77** under Carreira conditions.



Scheme 2.62. Revised retrosynthetic plan for new C15-*epi* northern fragment **237**.

2.6.4.2 Carreira Alkynylation on C15-*epi* Precursor

Diol **131** was treated with TBSCl and subsequently ozonized to the aldehyde **240** in high yield (Scheme 2.63). Alkynylation of **240** with TIPS-acetylene under Knochel conditions gave the propargyl alcohol **239** in 96% yield as a mixture of epimers (*R/S* = 1:1.8).[302] After oxidation of the diastereomeric mixture with DMP, a catalytic asymmetric transfer hydrogenation (ATH) of the corresponding enone gave the propargyl alcohol (*R*)-**239** as a single diastereomer. The configuration was confirmed by Mosher ester analysis.

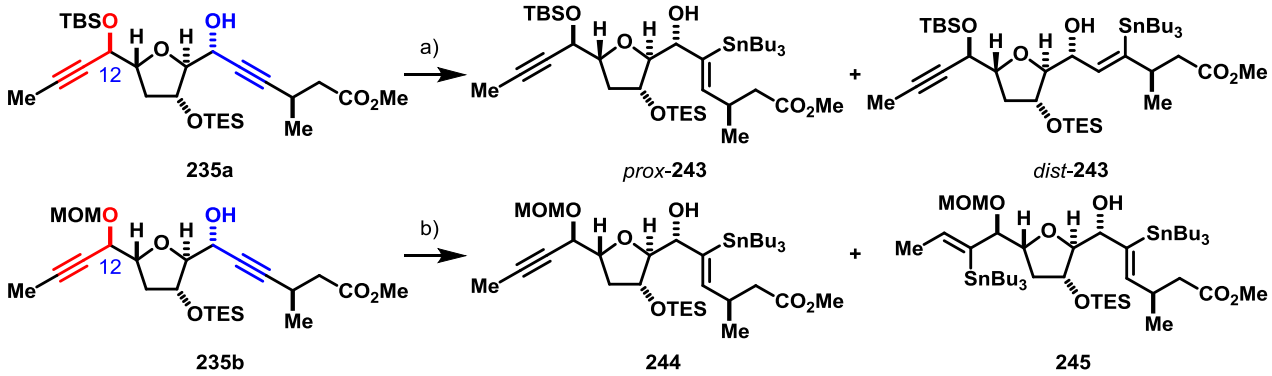


Scheme 2.63. Diastereoselective synthesis of **242**. Reactions and conditions: a) TBSCl, imidazole, CH_2Cl_2, 93%; b) O_3, CH_2Cl_2, −78 °C; PPh_3, 86%; c) triisopropylsilylacetylene, *n*BuLi, then $LnCl_3{\cdot}(LiCl)_2$, THF, −78 °C, dr = 1:1.8, 96% (mixture of diastereomers); d) DMP, $NaHCO_3$, *t*BuOH, CH_2Cl_2, 81%; e) $HCO_2H{\cdot}Et_3N$, (*S*,*S*)-Teth-TsDpen-RuCl (**Ru19**) or (*S*,*S*)-(*p*-cymene)-Ts-Dpen-RuCl (**Ru20**) (10 mol%), CH_2Cl_2, dr = >20:1 for **Ru19** or dr = 3.7:1 for **Ru20**, 94% (pure diastereomer for (*R*)-**239**); f) PMB-trichloroacetimidate, $Sc(OTf)_3$ (5 mol%), toluene, 0 °C, 86%; g) CSA (30 mol%), THF/MeOH = 12/13, 0 °C, 75%, (89% brsm); h) [SO_3·pyridine], (*i*Pr)$_2$NEt, DMSO, CH_2Cl_2, –35 °C, 95%; i) **77**, $Zn(OTf)_2$, (−)-*N*-methylephedrine, (*i*Pr)$_2$NEt, toluene, dr = 5.5:1, 67% (pure diastereomer).

Applying different catalysts in the ATH, the superiority of the tethered ligand in **Ru19** was highlighted by the high >20:1 dr in comparison to the low diastereoselectivity of **Ru20** (dr = 3.7:1) (Scheme 2.62e).[356] This outstanding facial selectivity can be traced back to a profound π,π-interaction of aryl ligand with the alkyne entity, which in turn make ynones ideal substrates for ATH with **Ru19**.[357] After protection group management, the alcohol **241** was subjected to a modified Parikh-Doering oxidation. The crude mixture was reacted with side chain **77** under Carreira conditions, affording propargyl alcohol **242** in high levels of diastereoselectivity. In agreement with the former attempts by J. Flasz (see Scheme 2.60),[217] the reagent-controlled alkynylation proceeded selectively with C15 *epi* precursor **241**.

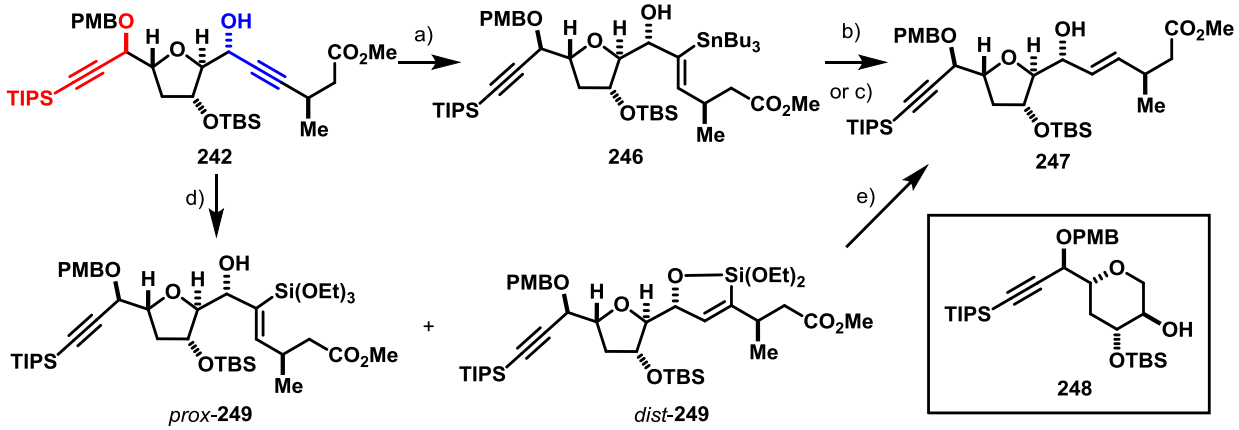
2.6.4.3 Establishment of the *E*-Alkene by *trans*-Reduction

The chemoselective *trans*-reduction of diynes had already been investigated by J. Flasz on propargyl alcohols **235a** and **235b**.[217] Differing in the substituents of the propargyl alcohol at C12, the importance of less coordinative protection groups (TBS < MOM) was investigated in order to guarantee a single site-selective *trans*-addition on the unsaturated side of the unprotected propargyl alcohol (Scheme 2.64). The hydrostannylation of **235a** catalyzed by $[Cp^*RuCl]_4$ (**Ru3**) was highly site-selective but suffered from low regioselectivity in favor of *prox*-**243**. In contrast, the MOM-protected analogue **235b** was neither site- nor regioselective, causing undesired hydrostannylation of the MOM-protected propargyl alcohol as well.



Scheme 2.64. Evaluation of *trans*-hydrostannylation by J. Flasz. Reactions and conditions: a) $[Cp^*RuCl]_4$ (5 mol%, [Ru] = 20 mol%), Bu_3SnH, CH_2Cl_2, *prox*-**243**/*dist*-**243** = 5.9:1, 47% (mixture of regioisomers). b) $[Cp^*RuCl]_4$ (1 mol%, [Ru] = 4 mol%), Bu_3SnH, CH_2Cl_2, **244**/**245** = 2.2:1, 17% of **244** (mixture of regioisomers, *prox*-**244**/*dist*-**244** = 7.3:1), 5% of **245**.[217]

Despite these preliminary results on the dependency of the ruthenium-catalyzed *trans*-hydrostannylation from coordinative sides, our protection group strategy required coordinating PMB-ether at C12 in order to guarantee orthogonal deprotection. However, based on the studies on site-selective *trans*-hydrostannylation of diynes, the introduction of silyl substituents on the alkyne was found to entirely suppress the further addition, assuring complete site-selectivity.[154] Treatment of propargyl alcohol **242** with **Ru3** at ambient temperature in dichloromethane induced an immediate color change from brown to purple, indicating the four-electron donation of the alkyne to the ruthenium complex (see Section 2.5.1).[153b] This step was found to be crucial in order to de-aggregate the tetrameric precatalyst **Ru3**.[258] Cooling to −30 °C followed by slow addition of the tributyltin hydride gave alkenylstannane **235** as a single regioisomer (Scheme 2.65). Focusing on the presumably simple protodestannylation, the CuDPP-mediated defunctionalization of **246** generated allylic alcohol **247** in moderate yield.[154,358] Exchanging the copper salt for a mixture of CuTC and the Liebeskind salt, [155,160b] the THP-ring **248** was isolated as a single product in 83% yield (see Experimental Section). Hence, transmetalation of alkenylstannane to the corresponding alkenylcopper species must induce the observed ring expansion of the adjacent THF-ring to the THP-ring **248**; the mechanism for cleavage of the side chain is unclear and was not further investigated. After gaining the allylic alcohol **247** in moderate 32% yield over 2 steps, the complementary *trans*-hydrosilylation on alkyne **242** was studied.

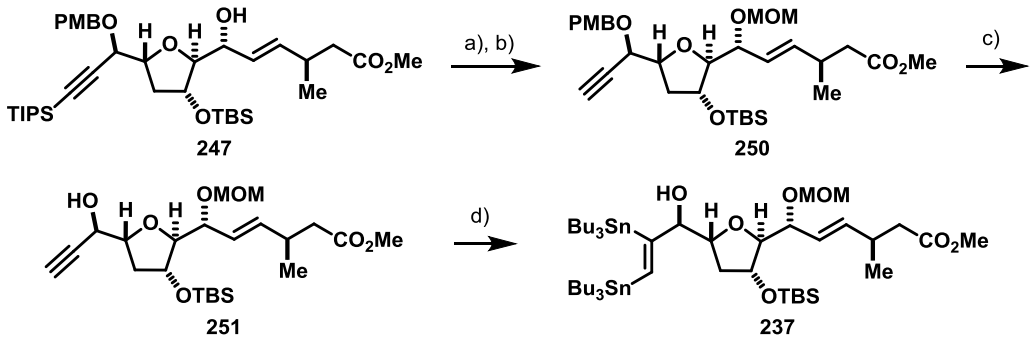


Scheme 2.65. Results on *trans*-reduction by *trans*-hydrostannylation or *trans*-hydrosilylation and subsequent protodemetalation. Reactions and conditions: a) $[Cp^*RuCl]_4$ (2.9 mol%, [Ru] = 12 mol%), RT, then −30 °C, Bu_3SnH (slow addition over 1 h), CH_2Cl_2, −30 °C → −20 °C, *Z*/*E* = >20:1, α/β = >20:1 77% (pure isomer); b) copper diphenylphosphinate (CuDPP), DMF, 42% of **247** (formation of **248** as the major side product); c) CuTC, $[Ph_2PO_2][NBu_4]$, DMF, 83% of **248**; d) $[Cp^*RuCl]_4$ (1.25 mol%, [Ru] = 5 mol%), $(EtO)_3SiH$, CH_2Cl_2, *Z*/*E* = >20:1, *prox*-**249**/*dist*-**249** = 2.2:1; e) TBAF, THF, −40 °C → −30 °C, 50% (pure isomer over 2 steps, formation of **248** as the major side product).

Subjecting alkyne **242** to the *trans*-hydrosilylation under **Ru3** catalysis afforded the *trans* adduct **249** with exclusive site- and stereoselectivity, albeit as a 2.2:1 mixture of α- and β-regioisomers. Facing a reported intrinsic instability of the alkenylsilane *dist*-**249**,[142b] the crude mixture was treated with stoichiometric amounts of TBAF under cryogenic conditions. The immediate protodesilylation liberated allylic alcohol **247** in 50% yield over 2 steps. In analogy to the protodestannylation of **246**, the THP-ring **248** was detected as the major side product, presumably deriving from the *prox*-**249**. Alternative silanes were not tested due to the incompatibility of protodesilylation with the present silyl protection groups. Attempted use of silver fluoride for selective protodesilylation of **249** resulted in an unselective deprotection of the fluoride-labile protection groups.[150b,359]

In summary, the *trans*-hydrostannylation of propargyl alkyne **242** is chemo-, regio- and stereoselective in favor of proximal alkenylstannane **246**, whereas the *trans*-hydrosilylation is providing mixtures of regioisomers *prox*-**249** and *dist*-**249**, but preserves the site-selectivity in favor of the unprotected propargyl alcohol. Subsequent treatment with TBAF afforded allylic alcohol **247** in decent yield. However, the protodemetalation of **246** and **249** was accompanied with a so far unexplainable generation of THP-ring **248** presumably emanating from the α-regioisomer.

With allylic alcohol **247** in hand, the following protection group adjustments set the stage for the oxidative cleavage of the PMB group in **250** with DDQ (Scheme 2.66). The palladium-catalyzed distannylation was applied on alkyne **251**,[288] completing the synthesis of C15 *epi* northern fragment **237** in 22 steps (19 steps LLS).[288]



Scheme 2.66. Synthesis of the C15-*epi* northern fragment **237**. Reactions and conditions: a) MOMCl, TBAI (60 mol%), (*i*Pr)$_2$NEt, CH_2Cl_2, 0 °C → 30 °C, 75%; b) TBAF, THF, −20 °C, 78%; c) DDQ, CH_2Cl_2/pH 7.4 phosphate buffer (4:1), 77%; d) $(Bu_3Sn)_2$, [(*t*BuNC)$_2$PdCl$_2$] (20 mol%), THF, 76%.

The first synthesis of **237** highlights the synthetic utility of the three step sequence of Carreira alkynylation, *trans*-hydrometalation and protodemetalation in order to access *E*-allylic alcohols stereoselectively. Specifically, the ruthenium-catalyzed *trans*-hydrosilylation of triethoxysilane enabled the chemoselective functionalization of the unprotected propargyl alcohol **242** in the presence of a protected propargyl alcohol on a challenging motif. Regarding the extensive synthetic transformations for elaborating the THF-ring, the propargyl alcohol in the "western" part and the significant protection group manipulations (6 out of 19 steps in LLS), the synthesis suffers from a low overall yield of only 0.18% yield, which prompted us to develop a new synthetic route based on enantiopure substrates from the "chiral pool".

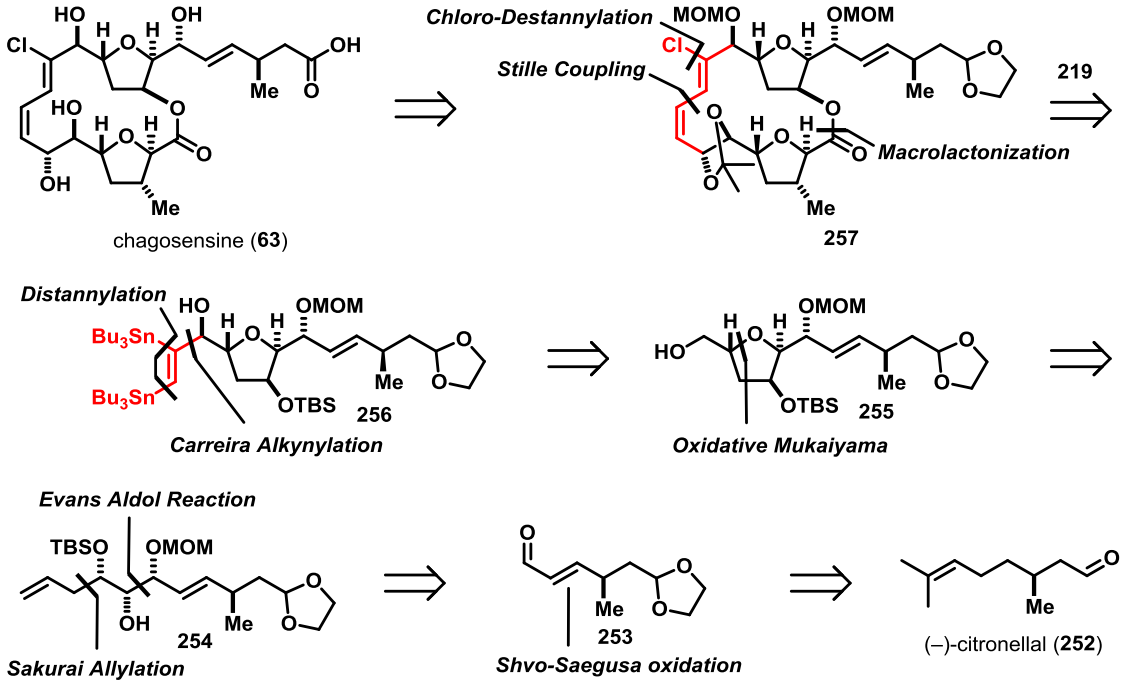
2.7 Completion of the Synthesis of the Putative Structure of Chagosensine by a New Northern Fragment

Remark: The following synthesis was designed and investigated in close collaboration with Dr. J. J. Murphy.

2.7.1 Revised Retrosynthetic Plan with a New Northern Fragment

At the outset of the revised synthesis, (−)-citronellal (**252**) was identified as the ultimate precursor for the framework of the northern fragment **256** (Scheme 2.67). After successive oxidation of the carbon skeleton by ozonolysis and Shvo-Saegusa oxidation, the α,β-unsaturated aldehyde **253** should undergo an asymmetric aldol reaction. Establishing the required *syn*-diol by an auxiliary-based glycolate aldol reaction, the following diastereoselective Sakurai allylation should guarantee the selective synthesis of the all-*syn* triol subunit in **254**. After additional protection group management, the oxidative cyclization under Mukaiyama conditions was expected to differentiate between the two alkene moieties in **254**, giving THF-ring **255** selectively. Subsequent asymmetric alkynylation would install the alkyne functionality as required for distannylation, completing the synthesis of northern fragment **256**. After fragment assembly by site-selective Stille reaction, the following

chloro-destannylation was envisaged to give the chlorodiene entity, which would pave the way for the challenging ring closure to **217** by macrolactonization.



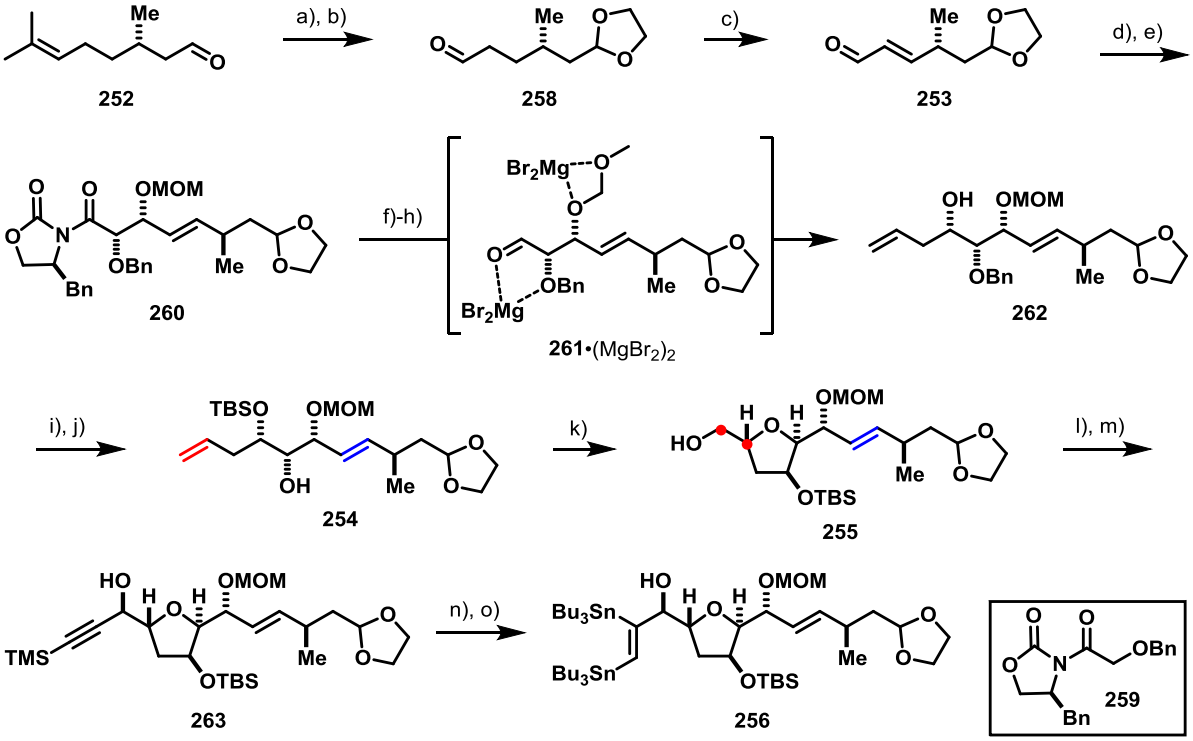
Scheme 2.67. Retrosynthetic approach towards northern fragment **256** commencing with **252**.

2.7.2 Synthesis of Northern Fragment 256

*Remark: The synthetic efforts towards THF-ring **255** were conducted and optimized by J. J. Murphy.*

Commencing with (*S*)-citronellal (**252**), the corresponding dioxolane was generated under acidic conditions (Scheme 2.68). The following ozonolysis was conducted in the presence of Sudan red III as an oxidizable dye; a colour change indicated full conversion of the present alkene, leaving the dioxolane untouched.[360] The oxidation of **258** to the α,β-unsaturated aldehyde **253** was accomplished in a single step using Shvo's conditions in which sodium bicarbonate is employed as a mild base and diethyl allyl phosphate as the terminal oxidant for regenerating the active Pd(0) species.[361] An extensive accumulation of palladium black was found to retard the conversion, bringing the oxidation to a halt. Due to the impossible separation of **258** from **253,** the crude mixture had to be resubjected to the reaction conditions after short filtration through Celite©. In comparison to the literature-known synthesis of the corresponding dimethyl acetal derivative in nine steps,[362] the present sequence shortens the route by no less than six steps. With aldehyde **253** in hand, an auxiliary-controlled glycolate aldol reaction with oxazolidinone **259** afforded the corresponding *syn*-diol with high stereoselectivity.[363] The stereochemistry of this newly generated stereocenter was determined by Mosher ester analysis. The relative *syn*-configuration of the diol was proven by comparison of the present *J*-values with the reported literature.[363] After formation of acetal **260**, the reductive removal of the auxiliary was performed by generating lithium hydroxyborohydride *in*

situ.[364] Subsequent oxidation of the resulting alcohol under modified Parikh-Doering conditions gave the aldehyde **261**, which was treated with two equivalents of magnesium bromide in order to induce an asymmetric addition of TMS-allyl. It is believed, that the first equivalent of $MgBr_2$ coordinates to the MOM-protection group and then the second equivalent coordinates to the aldehyde and the benzyl ether subunit (Scheme 2.68h). In line with this hypothesis is the fact that the addition of an equimolar amount of Lewis acid displayed no reactivity, suggesting bis-complexated species **261** as the reactive intermediate. The stereoselectivity derives from a 1,2-Cram chelate transition state of the benzyl ether, which outweighs a more complex facial selectivity resulting from 1,3-induction by the distal MOM group.[365]



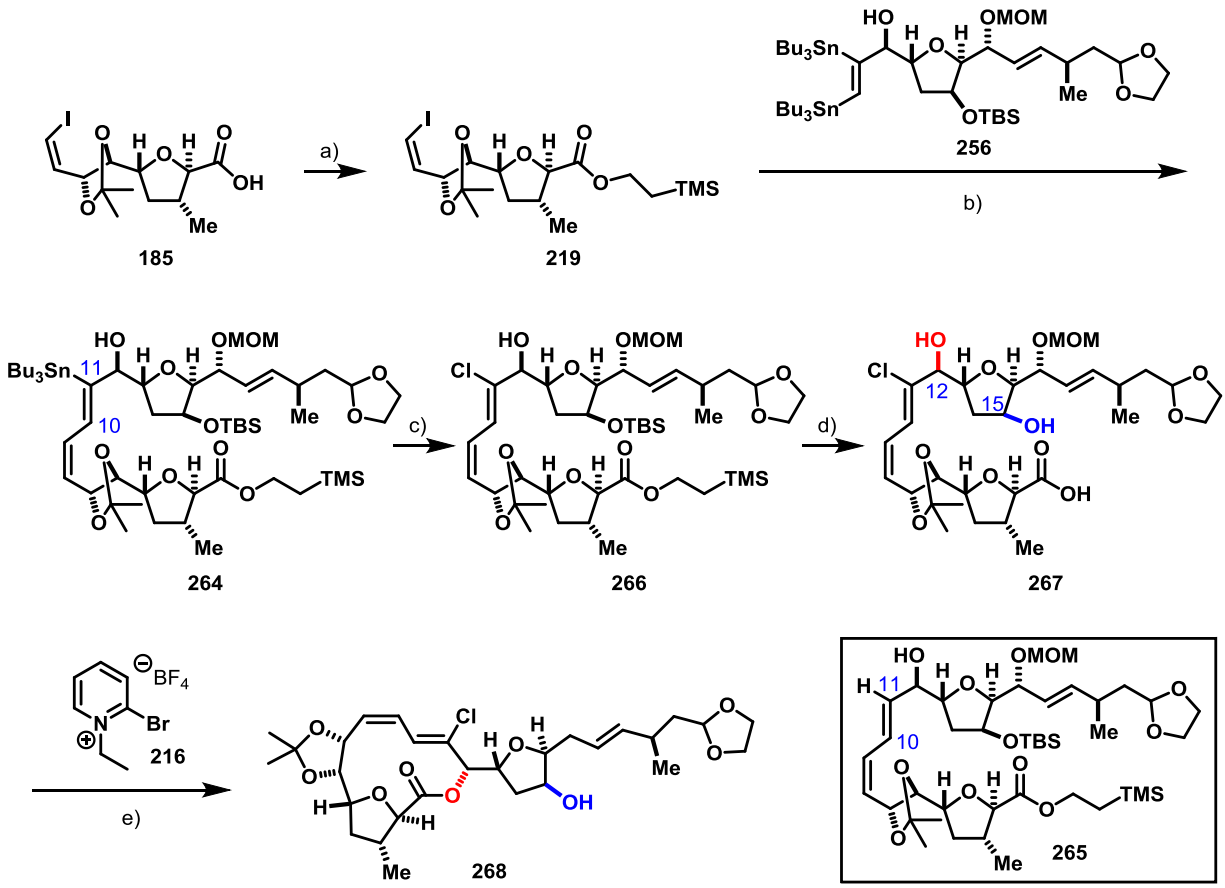
Scheme 2.68. a) Ethylene glycol, $(EtO)_3CH$, CSA (5 mol%), CH_2Cl_2, 98%; b) O_3, Sudan Red III, CH_2Cl_2, then Me_2S, −78 °C → RT, 97%; c) $Pd(OAc)_2$ (4 mol%), diethyl allyl phosphate, $NaHCO_3$, THF, 86 °C, 58%; d) **245**, nBu$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C → −10 °C, dr = 12:1, 80% (pure isomer); e) MOMCl, TBAI (1 mol%), (iPr)$_2$NEt, CH_2Cl_2, 0 °C, quant.; f) $LiBH_3(OH)$, Et2O, 0 °C → RT, 88%; g) [SO_3·pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, −30 °C → −10 °C, quant.; h) $MgBr_2$·(OEt_2), allyltrimethylsilane, CH_2Cl_2, 0 °C → RT, dr = 14:1, 92% (pure isomer); i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 88%; j) DDQ, CH_2Cl_2/pH 7.4 buffer (1:1), 50 °C, 70%; k) $Co(nmp)_2$ (10 mol%), tBuOOH (10 mol%), O_2 (1 atm), iPrOH, 55 °C, dr = >20:1, 69% (pure isomer); l) [SO_3·pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, −30 °C → −20 °C; m) trimethylsilylacetylene, $Zn(OTf)_2$, (−)-*N*-methylephedrine, (iPr)$_2$NEt, toluene, dr = 11:1, 65% (over two steps); n) K_2CO_3, MeOH, 85%; o) $(Bu_3Sn)_2$, [(tBuNC)$_2$PdCl$_2$] (10 mol%), THF, 93%.

After TBS-protection of alcohol **262**, the benzyl ether was cleaved with DDQ at elevated temperature. In order to preserve the acid-labile dioxolane ring, the reaction had to be buffered with pH 7.4 phosphate buffer in a 1:1 ratio with dichloromethane. Treatment of alcohol **254** under oxidative Mukaiyama conditions gave the THF-ring **262** in good yield as a single stereoisomer. Along with the desired cyclization to the primary alcohol **262**, another oxidative cyclization with the competing

internal olefin could be observed, forging the THF-ring in a 5-endo-trig cyclization in 6% yield. This significant regioselectivity on an advanced substrate (r.r. = 12:1) highlights the ability of the cobalt catalyst to differentiate between two differently substituted olefins, which confirms the preliminary results on model substrates.[222] After oxidation of **262** under the modified Parikh-Doering conditions, the asymmetric alkynylation of the corresponding aldehyde needed considerable optimization. Rigorous drying of zinc triflate, *N*-methylephedrine and toluene ensured that traces of water were excluded from the reaction mixture, thus decreasing the amount of self-aldolization.[134a,366] Whereas the previous attempts for a reagent-controlled alkynylation of aldehyde **134** failed (see Section 2.5.2.2.2), the propargyl alcohol **263** was provided in 11:1 dr and high yield under the optimized Carreira conditions. The configuration of the stereogenic center of propargyl alcohol **263** was confirmed by Mosher ester analysis. Liberating the terminal alkyne in presence of a silyl ether was accomplished under basic conditions in methanol. The high yielding Pd-catalyzed distannylation of the corresponding terminal alkyne completed the synthesis of the northern fragment **256** in 15 steps (LLS) and 7.6% overall yield. The revised synthetic route multiplied the overall yield by more than 40 times and produced sufficient amounts for investigating the proposed endgame steps towards chagosensine.

2.7.3 Fragment Assembly Leading to a 13-membered Macrolactone

Introduction of a fluoride-labile ester moiety on the southern carboxylic acid **185** should enable the liberation of the precursors for macrolactonization in a single step (Scheme 2.69). With fragments **256** and **219** in hand, the Stille reaction was performed under the optimized conditions, which gave dienylstannane **264** as a single regio- and stereoisomer in well-reproducible 50% yield on a 0.2 mmol scale (single largest batch). In addition to the extensive analysis of the NOESY spectrum, the preservation of the stereochemistry of **264** during the Stille reaction was unambiguously confirmed by the large *J*-coupling constant between olefinic proton C10 and stannane C11 ($J_{Sn–H}$ = 109 Hz). Furthermore, the *E,Z*-configured diene **265** was additionally formed as a single isomer upon stereoretentive protodestannylation of **264**, which provided further evidence for the correct stereochemistry of the parent dienylstannane. In addition to unconsumed bisstannane **256,** compounds deriving from the southern fragment, such as chloro-iodine exchange and homocoupled alkenyl iodide could be identified as side products in the cross coupling (see Experimental Section).



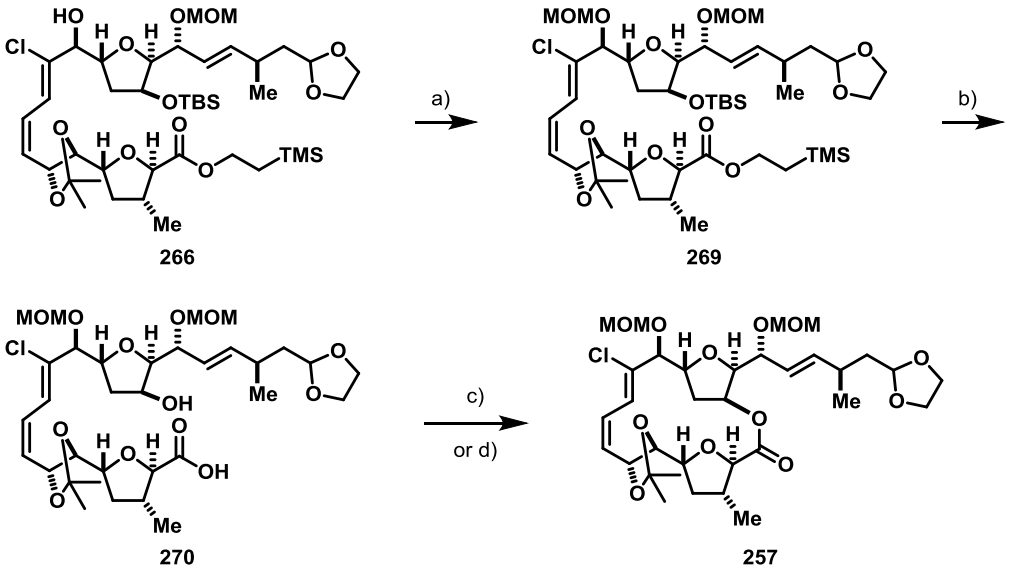
Scheme 2.69. Synthesis of 13-membered macrolactone **268**. Reactions and conditions: a) 2-(trimethylsilyl)ethanol, EDCI, DMAP (20 mol%), CH_2Cl_2, 71% (+7% of epimer) b) **243** (slow addition), $(t\mathrm{Bu}_3\mathrm{P})_2\mathrm{Pd}$ (15 mol%), $[Ph_2PO_2][NBu_4]$, LiCl, NMP, 60 °C, 50% (+ 11% of **265**); c) $CuCl_2$, 2,6-lutidine, THF, 78%; d) TBAF·$(H_2O)_3$, THF, 80%; e) **216**, $NaHCO_3$, 1,2-dichloroethane, 80 °C, 30% (80% brsm).

Subsequent chloro-destannylation of **264** introduced the unique *Z,Z*-chlorodiene **266** in 78% yield with retention of stereochemistry. Following treatment of **266** with TBAF liberated diol-containing *seco*-acid **267**, which was subjected to a Mukaiyama macrolactonization under forcing conditions (see Section 2.5.2.6). Extensive NMR studies of the resulting cyclized macrolactone **268** confirmed a ring closure of the hydroxy group at C12 rather than C15. The formation of the 16-membered macrolactone in this system is evidently less facile than that of the corresponding 13-membered ring **268**. This unexpected outcome can be rationalized either by a close proximity of the two reactive entities giving **268** as the kinetic product or by additional strain imposed by the second "northern" *trans*-configured THF-ring encircled by the 16-membered macrocycle of chagosensine.

2.7.4 Macrolactonization to the 16-membered Macrocycle

Facing an undesired discrimination of the two alcohols via macrolactonization, the allylic alcohol **266** was treated with MOMCl under Finkelstein conditions to provide **269** in good yield at elevated temperature (Scheme 2.70). After releasing the fluoride-labile protection groups, the *seco*-acid **270** was tested in the challenging ring closure. The modified Mukaiyama macrolactonization protocol

enabled the ring closure of **270**, albeit affording the macrocycle **257** in low yield of 27%. Switching to Yamaguchi lactonization conditions, the yield of **257** could be improved to 40%. Despite the high dilution of 0.5 μM, dimerization to the corresponding lactide was observed in 13% yield, which was confirmed by MS-MS fragmentation experiments (see Experimental Section).

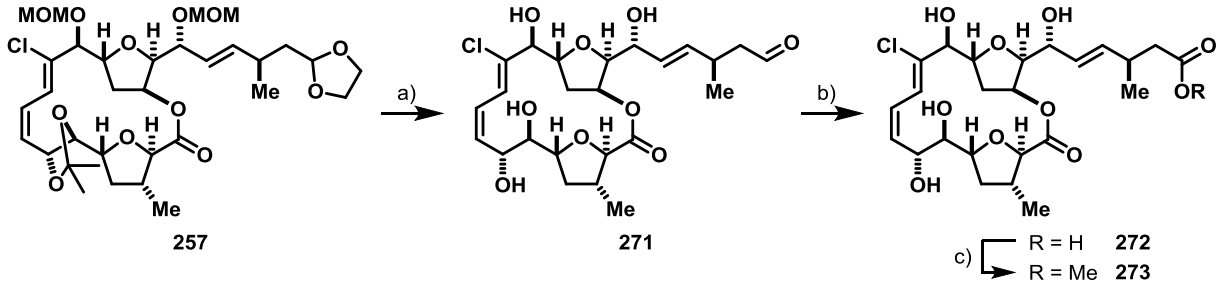


Scheme 2.70. Accessing macrolactone **257**. Reactions and conditions: a) MOMCl, TBAI (25 mol%), $(i\text{Pr})_2$NEt, 1,2-dichloroethane, 50 °C, 92%; b) TBAF·$(H_2O)_3$, THF, 99%; c) 2,4,6-trichlorobenzoyl chloride, $(i\text{Pr})_2$NEt, THF, then DMAP, toluene, reflux, 40% (**217**), about 6% (epimer), 13% (lactide); d) **216**, $NaHCO_3$, 1,2-dichloroethane, 80 °C, 27% (no epimerization).

In contrast to the less basic Mukaiyama conditions (Scheme 2.70d), the presence of Hünig's base under Yamaguchi lactonization conditions caused epimerization of the *α*-position of the *in situ* generated anhydride prior to ring closure, which resulted in the formation of an *α*-epimerized macrolactone in minor quantities (see Experimental Section 5.6). An alternative explanation for the observed epimerization and the low yield is the formation of a highly reactive ketene.[367] Based on an E_2-mechanism, the mixed Yamaguchi anhydride is prone to based-induced elimination, causing numerous side reactions and macrolactonization under loss of the stereochemical information in the *α*-position.[368]

2.7.5 Disclosure of the Mis-Assignment of Chagosensine

With the desired 16-membered macrolactone in hand, the ideal conditions for a single global deprotection were explored using either Brønstedt or Lewis acids. Usage of trifluoroacetic acid, TMSOTf[369] or *B*-bromocatecholborane[370] caused complete degradation of **257**. In contrast to the catechol derivative, dimethylboron bromide gave **271** as a single compound detected by HPLC-MS analysis (Scheme 2.71).[371] Notably, the cleavage of the dioxolane was successful in liberating the aldehyde **271**, which represents only the second example of such a transformation in the literature.[372]

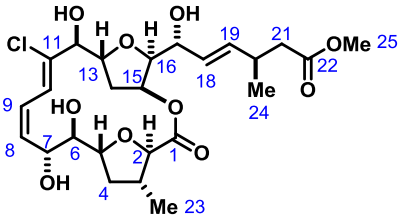


Scheme 2.71. Completion of the total synthesis of the putative structure of chagosensine. Reactions and conditions: a) Me_2BBr, CH_2Cl_2, −78 °C; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; c) CH_2N_2, CH_2Cl_2, 20% over three steps.

The cold reaction mixture was added to a solution of pH 7.4 phosphate buffer, which guaranteed the full hydrolysis of the transient bromoacetal. In presence of the four alcohols and the unsaturated moieties, the subsequent oxidation of the aldehyde **271** was carried out under Pinnick conditions affording the corresponding carboxylic acid **272**.[373] The purification of **272** turned out to be challenging due to its solubility in water. Using an unusual work-up procedure comprising the addition of sodium thiosulfate to quench the oxidant and filtration through a plug of sodium sulfate, the reaction mixture was purified by preparative HPLC. After separation of **272**, the aqueous methanol containing fraction was concentrated by lyophilization, which led to decomposition of the putative natural product. Due to the unexpected instability of **272**, esterification with diazomethane was envisioned to increase the stability of the compound. Since the methyl ester of chagosensine (**64**) had been characterized by the isolation team, ultimate comparison with a derivate of the natural product is possible. After global deprotection and Pinnick oxidation, the crude mixture was treated with diazomethane affording methyl ester **273** in approximately 20% yield over 3 steps.

Comparison of **273** with **64** displayed massive discrepancies in ^{1}H- and ^{13}C-NMR spectra among the entire framework (see Table 3.1 and Appendix 8.2.3). As a detailed discussion will follow in Section 3.5, only the deviation in the ^{13}C-NMR is shown in Table 2.3. The most salient divergences with $\Delta\delta$ = 18.2 ppm and $\Delta\delta$ = 14.8 ppm at C12 and C13, respectively, showcase a humongous difference with the reported data. Regarding the remaining signals of the northern THF-ring (C14-16), this trend towards higher chemical shifts is maintained, although the aberrance is smaller by ranging from $3.7 \leq \Delta\delta \leq 6.1$ ppm. Across the 16-membered macrolactone, the third largest deviation is located at C5 in the southern THF-ring. With a chemical shift of δ_{C5} = 72.4 ppm, the resonance energy of C5 in **64** is rather low in comparison to its counter partner in **273** (δ_{C5} = 81.7 ppm). This overall downfield shift can be observed across the entire carbon skeleton of **273**, which in turn indicates a significant, yet unknown shielding effect in the naturally occurring polyketide **64**.

Table 2.3. Comparison of the ^{13}C NMR data of synthetic **273** with those of chagosensine methyl ester (**64**) reported in the literature; color code: $\Delta\delta \leq 0.5$ ppm; **$0.5 < \Delta\delta < 1.0$ ppm**; **$\Delta\delta \geq 1.0$ ppm**



position	64	273	Δδ
1	170.5	171.3	**0.8**
2	80.8	87.1	**6.8**
3	36.6	36.4	**–0.2**
4	38.0	38.9	**0.9**
5	72.4	81.7	**9.3**
6	75.5	81.8	**6.3**
7	72.0	71.5	**–0.5**
8	133.6	137.2	**3.6**
9	128.2	123.6	**5.4**
10	126.9	123.2	**–3.7**
11	136.2	137.1	**0.9**
12	61.3	79.5	**18.2**
13	70.7	85.5	**14.8**
14	32.9	39.0	**6.1**
15	72.7	76.4	**3.7**
16	81.8	86.9	**5.1**
17	67.2	72.1	**4.9**
18	128.5	128.9	**0.4**
19	133.4	138.0	**4.6**
20	30.4	34.0	**3.6**
21	40.2	41.8	**1.6**
22	172.0	173.2	**1.2**
23	14.8	19.5	**4.7**
24	19.5	20.4	**0.9**
25	51.2	51.8	**0.6**

As all the stereocenters in **273** were confirmed by Mosher analysis, NOESY and comparison with literature-known compounds, its spectroscopic and analytical data clearly prove the stereochemical mis-assignment of chagosensine (**63**) by the isolation team. Based on the inaccessibility of the original raw data and the unknown reference peak in the reported spectrum, the massive deviation could be caused by a cooperative effect of a systematical error and a mis-assigned stereochemistry, which prompted us to reconsider the data that led to the structural assignment of the natural product.

3 Synthetic Studies towards the Stereochemical Revision of Chagosensine

3.1 Stereocenters with Questionable Structural Determination

Since the raw data are unavailable and the spectroscopic correlations are solely depicted in the reported chemical structure, the structural revision of chagosensine focused exclusively on the stereochemistry. Upon re-evaluation of the methods used to determine the absolute and relative stereochemistry of the natural product, we identified two possible fallacies in the stereochemical assignment of chagosensine by the isolation team.

In analogy to the structural assignment of the northern THF-ring of haterumalide NA (**10a**) by the D. Uemura group (see Section 1.4.1),[87] the absolute stereochemistry of the same entity in the northern part of **63** had been assigned on the basis of *J*-coupling values with the adjacent side chain. Although the isolation of chagosensine was reported after the stereochemical revision of haterumalide (**10b**) (see Section 1.4.2),[95] which unambiguously disclosed the *syn*-relationship of this exact motif, the T. Řezanka group still correlated the high *J*-value of 7.7 Hz between the allylic alcohol at H17 and H16 embedded in the THF-ring with a *trans*-relationship.[170] Furthermore, comparison of the *J*-coupling constants within the THF-ring indicates no further similarities (Figure 3.1). Whereas **10b** has small *J*-values ranging from 0 to 3.7 Hz, **63** shows a very different coupling pattern by reaching *J*-values of up to 8.1 Hz.

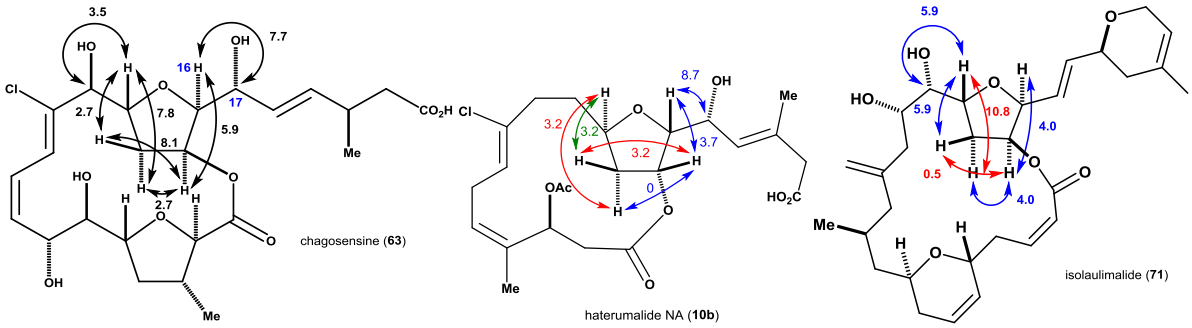


Figure 3.1. Comparison of *J*-coupling constants of chagosensine (**63**), revised haterumalide NA (**10b**) and isolaulimalide (**71**).

Another related macrolide having the same relative and absolute stereochemistry in the THF-ring, isolaulimalide (**71**), also exhibits a distinguishable multiplicity within the 5-membered ring.[374] Comparison of **63** with **71** displays one major discrepancy in the bridging lactone. While **63** shows a very broad coupling pattern (J_{H15} = 8.1, 5.9, 2.9 Hz), the multiplicity in **71** is rather narrow (J_{H19} = 4.0, 4.0, 0.5 Hz). Regarding the stereochemical relationship of the THF-ring with the flanking secondary alcohol embedded in the macrocycle, the *anti*-configuration between H12 and H13 in **63** correlates with *J* = 3.5 Hz, while **71** has *J* = 5.9 Hz for the opposite *syn*-configuration. This small *J*-value not only

contradicts the Karplus equation,[96a] but also stands in striking contrast to the previous assumption concerning the stereochemistry of the adjacent side chain. This apparent oxymoron emphasizes on an existing misconception in structural determination of neighboring stereocenters, which are embedded in ring systems and conformationally flexible alkyl chains.[375] Without considerable levels of rigidity, the relative arrangement of these stereogenic centers are not visualized accurately by a Newman projecting (see Section 1.4.2.1).

In agreement with this underestimated conformational flexibility of the northern part, the stereochemical assignment of the southern 6,7-diols by ECCD also disregarded the required known molecular conformation in order to determine the absolute configuration of the two secondary alcohols (see Section 2.1).[171-172,376] The exciton chirality method (ECD) correlates the signed order of the bisignate CD with the absolute orientation of the interacting chromophores, which have to occupy a fixed conformation.[172c] Therefore, the stereochemical assignment of diols has been a valuable and reliable tool in determining the absolute configuration as long as the conformation is known.[377] In contrast, macrocycles possessing a highly flexible framework cannot be described by a single conformation. The detectable physical properties rather emanate from the population of various conformers, which are affected by solvent effects, hydrogen bonding, dipol-dipol interactions and sterics. By assuming a pseudo-equatorial position of the two alcohols as the fixed conformation depicted in Figure 2.1b, the postulated orientation of the interacting chromophores bears no evidence, resulting in a doubtful determination of the relative and absolute stereochemistry at C6 and C7. To the best of our knowledge, the usage of ECCD for the stereochemical assignment of secondary diols embedded in a macrocyclic system has been exclusively applied by the T. Řezanka group, resulting in the mis-assignment of lytophilippines[375a] and chagosensine.[170] Hypothetically speaking, even in the case of a single conformation of the two chromophores in **70** (see Figure 2.1b), the presence of the adjacent chlorodienyl violates another precondition for ECD, as additional strong CD bands potentially lead to misinterpretations of the CD splitting.[378] This objectionable exciton coupling with a nonequivalent chromophore was actually described by the isolation team, “this additional contribution includes a *p*-MeOCinn/8,10-diene interaction”; but was neglected for the stereochemical analysis.[170] Dienes are intrinsically chiral chromophores,[379] which can alter their first chiral sphere by adopting predominantly either a s-*cis*[380] or an s-*trans*[381] conformation in a ring system. Based on the low lying π-π* transition at ca. 240 nm,[382] the dipole transition moments of the conjugated systems at C8-C11 are coupling with the two equal chromophores at C6 and C7. In addition to these interchromophoric interactions, the presence of dissymmetric substituents in the second and third chiral sphere can easily tune the Cotton effect in the CD spectra.[383] In order to consider all these different excitonically-coupled chromophores with several transitions it is

important to calculate a CD spectrum for comparison with the experimental data,[384] which has been successfully applied for the structural revision of other natural products.[385]

In view of the structural similarities with amphidinolide C (**72**), the *J*-values of **63**, **72** and **273** were compared in order to narrow down the possible permutations in the southern part (Figure 3.2). While the coupling pattern of the tertiary stereogenic center in **63** and **72** matches, the synthesized methyl ester **273** shows a rather small J_{2-3} = 4.2 Hz for a *trans*-relationship between H2 and H3. On the opposite side of the 5-membered ring, the *J*-value of **63** (J_{4-5} = 6.5 Hz) is smaller than the corresponding couplings in **72** (J_{5-6} = 11.7 Hz) and **273** (J_{4-5} = 8.4 Hz). Whereas the coupling constant between H6 and H7 in **63** was big (J_{6-7} = 10.0 Hz), **273** shows no coupling between *anti*-configured 6,7-diol, highlighting the unpredictability of the relative stereochemical relationships within the macrocyclic scaffold.

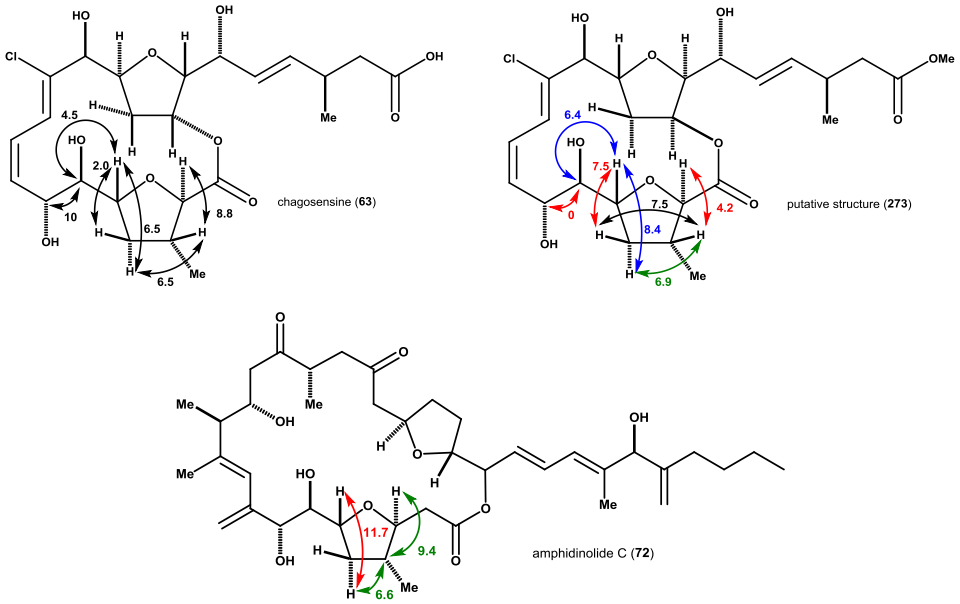


Figure 3.2. Comparison of *J*-coupling constants of chagosensine (**63**), the synthesized putative structure of chagosensine (**273**) and amphidinolide C (**72**)

In summary, five stereocenters have a questionable stereochemical assignment. The assembly of two possible permutations in the northern THF-ring with four permutations in the southern 6,7-diol adds up to a total of eight diastereoisomers for the stereochemical revision of chagosensine. Since the spectral comparison with related natural products was to no avail, we initially considered to narrow the compound library to the most promising candidate by predicting the NMR spectra of each putative structure, which has been successfully applied in the stereochemical determination of leiodermatolide.[386] In the past decade, the quantum-chemistry-based computation of chemical shifts and multiplicity have improved in accuracy and diminished calculation time.[387] However, the biggest source of errors derives from the contribution of the free solvation energies on the population of the several conformations, which are each contributing to an average calculated NMR spectrum.[388]

In case of mandelalide A, the synthesis of its putative structure **274a** was accomplished by J. Willwacher,[389] proving the stereochemical mis-assignment by the isolation team (Figure 3.3). After conducting in depth calculation on narrowing down the possible permutations for structural revision, the computational results turned out to be inconsistent.[390] Finally, the introduction of an "inverted" northern part by a divergent total synthesis enabled the structural revision of mandelalide A (**274b**).[391]

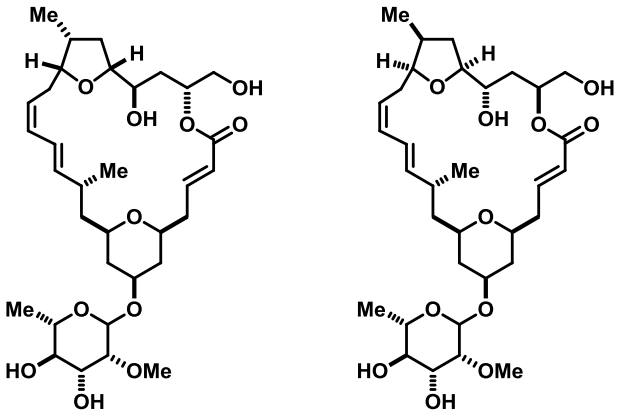
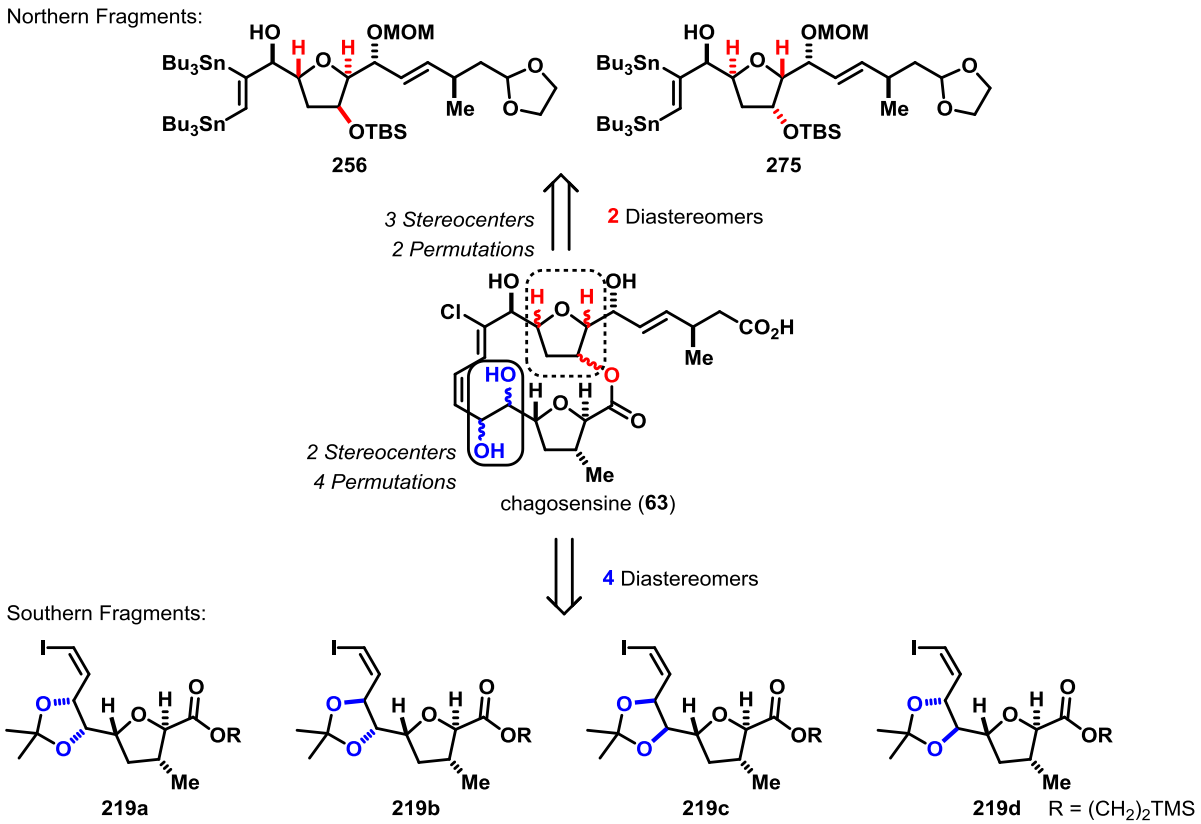


Figure 3.3. Putative (**274a**) and revised structure (**274b**) of mandelalide A.

Despite the fundamental difficulties in predicting macrocyclic systems, a further complication in calculating the chemical shifts of chagosensine derives from the used NMR solvent system containing a mixture of deuterated methanol and deuterated pyridine. Hence, the cooperative effects of the protic solvents are nearly impossible to predict. Thus, the quantum-chemistry-based computation of NMR spectra was not employed for the structural reassignment of chagosensine.

As no conclusive remarks could be obtained by comparison of the spectroscopic data and the prediction of NMR and CD would take considerable amount of calculation time for an accurate description of the conformational populations, we decided to pursue an exclusive synthetic approach for the stereochemical revision of chagosensine, leaving no reasonable permutation aside (Scheme 3.1).



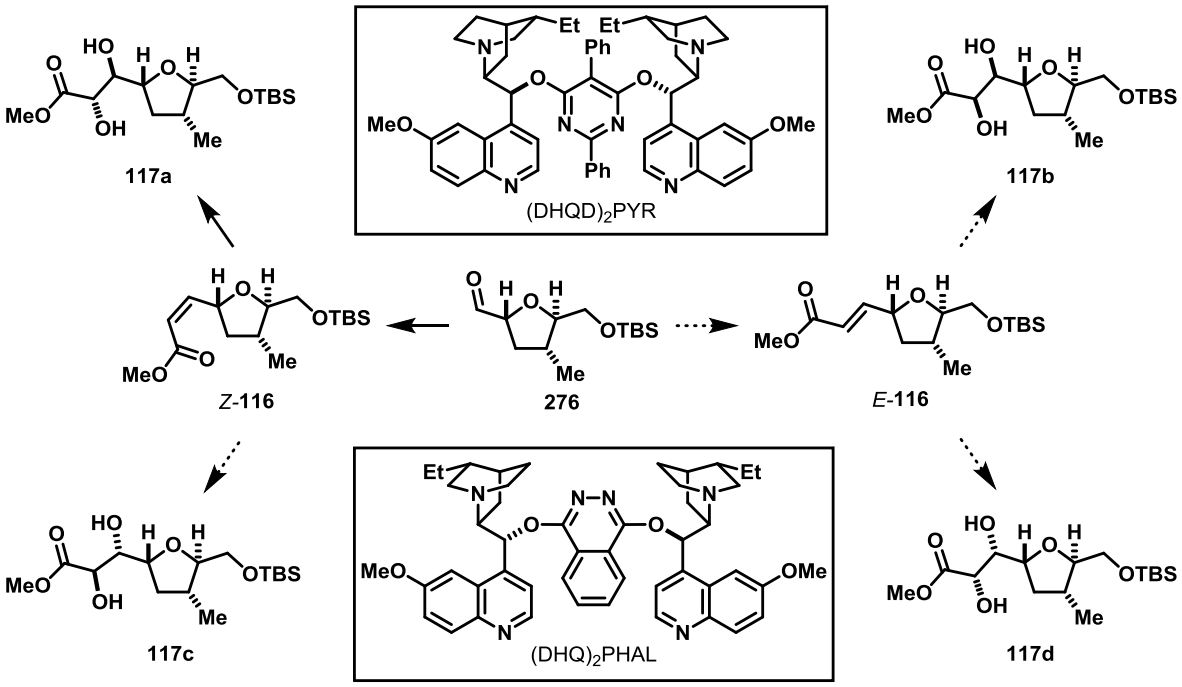
Scheme 3.1. Strategy towards determination of revised structure of chagosensine.

Encouraged by our previous results using site-selective Stille cross coupling for the synthesis of macrocyclic core **78** (see Section 2.5.2) and **273** (see Section 2.7.3), we were confident that a "combinatorial" coupling of the two northern permutations with the four southern fragments should allow us to access the compound library. Considering the synthesis of the required coupling partners, we planned to apply most of the synthetic protocols from the earlier fragment routes to expedite the venture.

3.2 Synthesis of the Four Southern Fragments

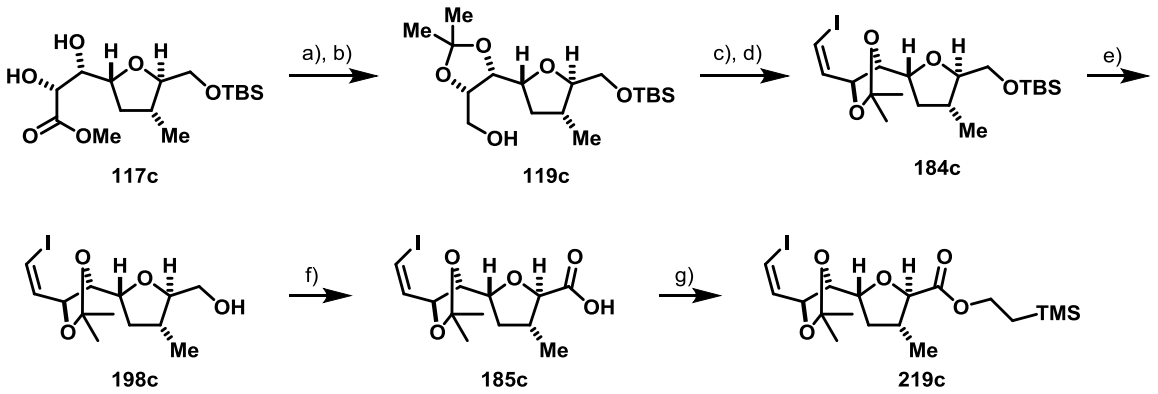
3.2.1 Completion of the Synthesis of the Southern Fragment 219c

The previously outlined synthetic route towards the southern fragment bares the possibility of accessing all four diastereomers (see Section 2.4.3 and 2.5.2.2.1). Switching the olefination of aldehyde **276** from *Z*- to *E*-selectivity, the corresponding α,β-unsaturated esters *Z*-**116** and *E*-**116** can be subjected to the diastereoselective Sharpless dihydroxylation using either $(DHQD)_2PYR$ or $(DHQ)_2PHAL$ (Scheme 3.2). The remaining transformations towards the southern fragments **219b-d** would parallel the previous route leading to **219a**.



Scheme 3.2. Retrosynthesis for diverted synthesis of diols **117a-d** by the previous route.

Owing to the accumulation of the diastereomer **117c** during the moderately diastereoselective Sharpless dihydroxylation of *Z*-**116** (see Section 2.4.3), the route towards **117c** was investigated (Scheme 3.3). After acetonide protection of diol **117c**, the ester moiety was overreduced to the alcohol **119c** followed by an oxidation to the corresponding aldehyde. Subsequent olefination under Stork-Zhao conditions afforded *Z*-alkenyl iodide **184c** in moderate yield, albeit with good stereoselectivity.[294] Liberation of the primary alcohol by treatment with TBAF resulted in **198c**, which was then oxidized to corresponding carboxylic acid **185c**. Subsequent esterification completed the synthesis of southern fragment **219c**.

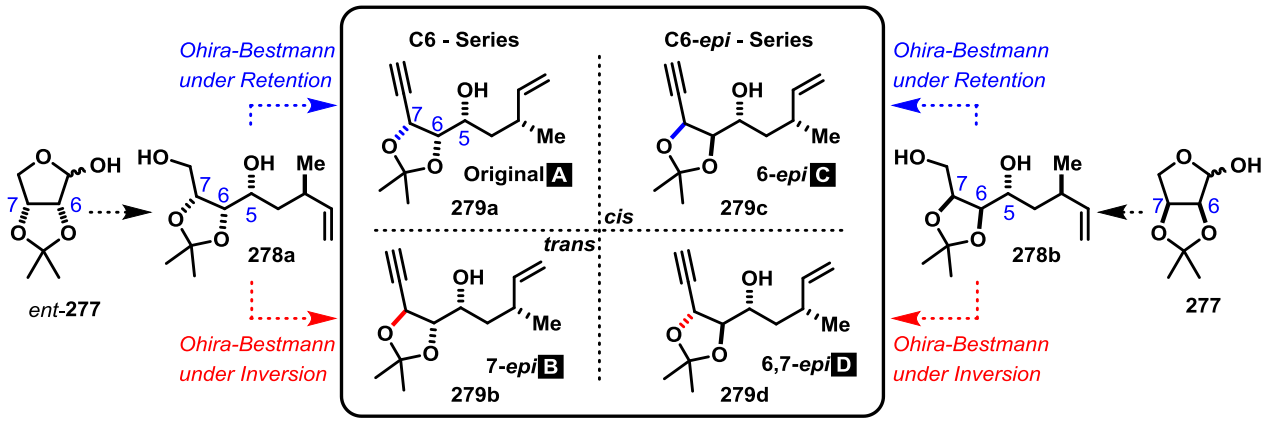


Scheme 3.3. Synthesis of diastereomeric southern fragment **219c** applying the previous route. Reactions and conditions: a) CSA (10 mol%), 2,2-dimethoxypropane, 48%; b) $LiAlH_4$, THF, 0 °C, 63%; c) [SO_3·pyridine], ($iPr)_2NEt$, DMSO, CH_2Cl_2, –25 °C; d) [Ph_3PCH_2I]I, NaHMDS, HMPA, THF, –78 °C, *Z*/*E* = >20:1, 45% over 2 steps (pure *Z*-isomer); e) HF·pyridine, pyridine, THF, quant.; f) TEMPO (30 mol%), BAIB, aq. MeCN, 89%; g) 2-(trimethylsilyl)ethanol, EDCI, DMAP (20 mol%), CH_2Cl_2, 77%.

In principle, the advanced intermediate *E*-**116** could afford the other two out of four diastereomers maintaining the same sequence. However, the synthetic utility of such a diverted synthesis to access the other diastereoisomers **117b** and **117d** was not investigated; rather we envisaged the divergent synthesis employing a "chiral pool" strategy outlined in the next section.

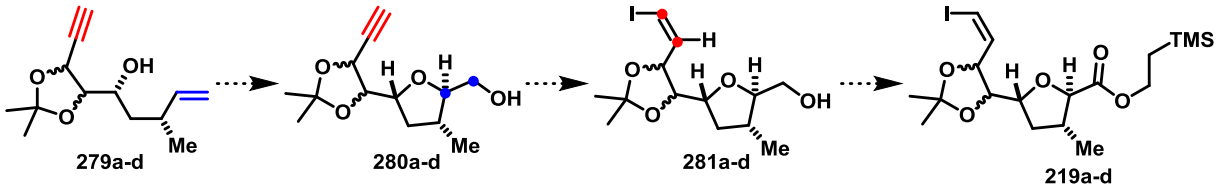
3.2.2 A New Divergent Synthesis of the Southern Fragments 219a-d

A novel route was developed commencing with two different enantiomeric starting materials from the "chiral pool" (Scheme 3.4). Notably, the new synthetic pathway potentially represents a new entry to the total synthesis of amphidinolide C.



Scheme 3.4. Outlined retrosynthetic strategy for the divergent synthesis of alkynes **279a-d**.

Starting with literature-known enantiomeric acetals **277** and *ent*-**277** deriving from isoascorbic acid and D-ribose, respectively, a reagent-controlled homocrotylation was planned to install the methyl-branched stereocenter and the terminal alkene for oxidative cyclization. The diastereomeric diol **278a** and **278b** would then set the stage for a homologation of aldehydes and acetals, which, under Ohira-Bestmann conditions, would provide the corresponding alkynes with either retention (**279a** and **279c**) or inversion (**279b** and **279d**) of the α-stereocenter, respectively.



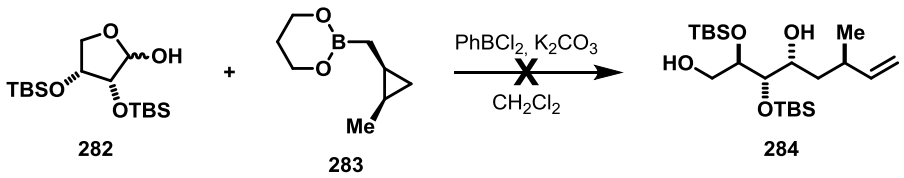
Scheme 3.5. Final parallel retrosynthetic plan for the synthesis of the southern fragments **219a-d**.

The alkynes **279a-d** were envisioned to undergo oxidative cyclization under Mukaiyama conditions with cobalt catalyst $Co(nmp)_2$ (Scheme 3.5). Considering the Baldwin's rules, such a cyclization to the *trans* THF-rings **280a-d** was anticipated to discriminate between the alkene moiety (blue), leading to the desired 5-exo-trig ring closure, and the alkyne subunit (red), which would forge different rings by either a 5-exo-dig or by a more favorable 6-endo-dig cyclization.[392] Highlighting the synthetic utility of radical chain chemistry on advanced intermediates in natural product synthesis, a *trans*-selective hydroindation of the alkyne would provide the alkenyl iodide **281a-d** in a stereoselective fashion. Reproduction of the previous procedures for successive oxidation and subsequent esterification would then complete the divergent synthesis of the four southern fragments **219a-d**.

3.2.3 Asymmetric Homocrotylation of Aldehydes

3.2.3.1 Stoichiometric Addition of Chiral Boronates

Regarding the enantioselective homocrotylation of aldehydes, recent achievements can be seen in the addition of stoichiometric homocrotylboration reagents **283**[393] or the addition of isoprene under reductive Ni-catalysis discovered by Y. Tamaru *et. al*.[394]



Scheme 3.6. Attempted homocrotylation with boronate **283**.

Following the literature procedure, a five step sequence provided boronate **283** in 11% overall yield (literature reported overall yield: 51%).[393a] Borate **283** was first added to simplified lactol **282** (Scheme 3.6). The transformation is complicated by the existing equilibrium between the reactive aldehyde and the predominant lactol **282**. Under the strongly Lewis acidic conditions, the hemiacetal might form an oxonium ion, which could undergo a subsequent homocrotylation similar to the BF_3-mediated allylation[395] and alkynylation[396] of acetals. Concerning the acetonide as the preferred protection group, the stoichiometric amounts of dichlorophenylborane would facilitate the liberation of the corresponding diol in **277**. Treatment of the literature-known TBS analogue **282** showed no product formation under the reported reaction conditions.[393b] This lack of reactivity and the time-

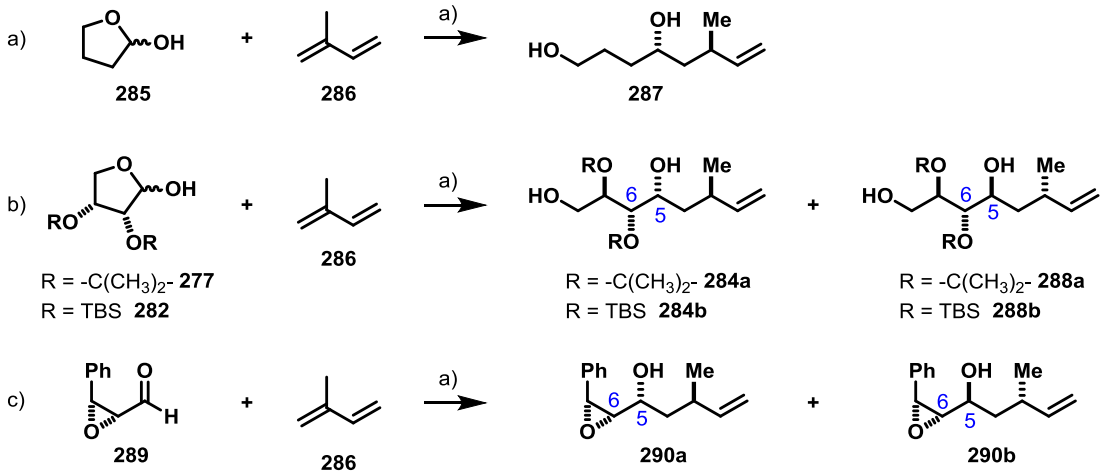
consuming synthesis of **283**, in combination with adjustments in the protection group strategy, encouraged us to investigate the alternative homocrotylation by Ni-catalyzed reductive coupling.

3.2.3.2 Studies towards the Catalyst-controlled Reductive Coupling of Isoprene

Remark: The retrosynthetic approach was designed in collaboration with Dr. J. J. Murphy. The following synthesis and the optimization of the reaction conditions were carried out by Dr. J. J. Murphy.

3.2.3.2.1 Previous Reports on the Diastereoselective Addition of Isoprene to Lactols under Nickel Catalysis

The practicality of lactols in the Ni-catalyzed reductive coupling was initially shown by Y. Tamaru *et. al.*, who achieved an exclusive 1,3-*anti* selectivity in the formation of **287** by adding isoprene (**286**) to **285** (Scheme 3.7a).[397] Aiming at a fragment synthesis of amphidinolide C, which requires *syn*-relationship between H5 and H6 in **284**, the C. D. Spilling group studied the substrate-controlled diastereoselectivity of lactols **277** and **282** under the same reaction conditions (Scheme 3.7b).[398] Subjecting **277** and **282** to the Ni-catalyzed homoallylation reaction, the undesired 5,6-*anti*-diols **288a** (65%, **284a**/**288a** = 1:3) and **288b** (63%, **284b**/**288b** = 1:6) were obtained in moderate selectivity. Based on a profound substrate-control by a Felkin-Anh transition state,[399] the usage of the epoxide **289** allowed to invert the stereoselectivity of the Tamaru reaction, providing **290a** diastereoselectively in a 5,6-*syn* fashion *en route* to amphidinolide C (Scheme 3.7c).[398]



Scheme 3.7. Reported opening of acetal **285**[397] and southern fragment synthesis of amphidinolide C[398] by Ni-catalyzed reductive coupling. Reactions and conditions: a) **286**, $Ni(acac)_2$ (10 mol%), then lactol **277**, **282**, **285** or aldehyde **289**, Et_3B, THF, 83% (**287**, dr = >20:1), 63% (mixture of diastereomers, **284a**/**288a** = 1:3), 65% (mixture of diastereomers, **284b**/**288b** = 1:6), 63% (mixture of diastereomers, **290a**/**290b** = 2.5:1).

Our initial efforts to reproduce the reported results for **277** failed completely and no monomeric addition products were detected. Instead, the addition of a dimer of isoprene to the aldehyde was observed. Measurement of the equilibrium between acetal and reactive form in the ^{1}H-NMR spectra

showed, that the aldehyde existed in only minor quantities and as such decreased the reaction rate, even though the diene was used in large excess.[400] Usage of **289** did not seem to be an adequate alternative, as the formation of the literature-known product **290a** would impose an elongated synthesis towards **219a-d**.[399]

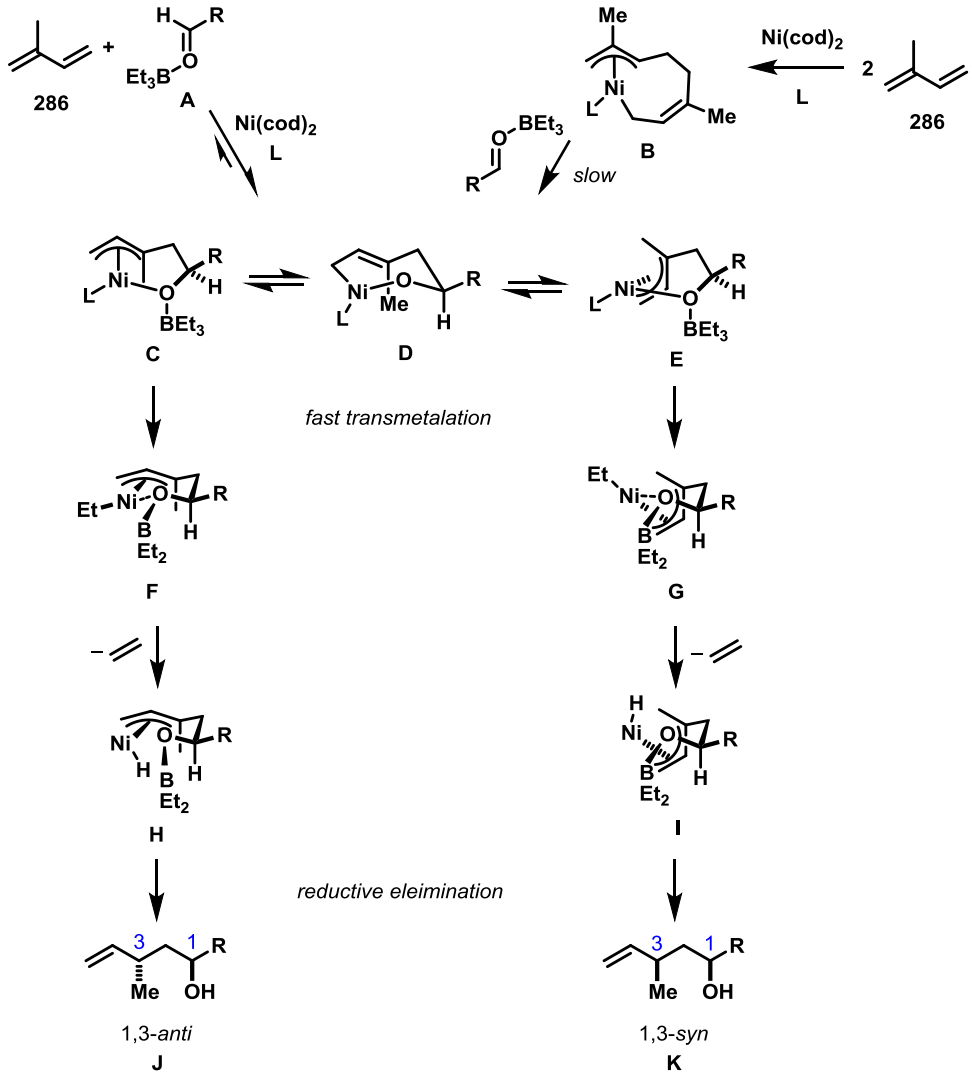
3.2.3.2.2 Mechanism of the Diastereoselective Homocrotylation by Reductive Coupling

Switching from triethylborane to dimethylzinc as the reductive alkylating agent, the addition of a dimer **B** of isoprene (**286**) to the aldehyde **A** has been reported as the major product.[401] The Ni-catalyzed dimerization and oligomerization of dienes has been investigated in detail by G. Wilke[402] *et. al.* and by P. van Leeuwen *et. al.*,[403] who showed the influence of the applied ligand on the outcome of the dimerization. The formation of cyclodimers is facilitated by cooperative electronic and steric effects in monodentate ligands. Applying hexafluoroisopropyl phosphite resulted in high selectivity towards dimerization due to the strong electron-accepting properties and a cone angle 125°< Θ <155°.[403]

Concerning the mechanism of the reductive addition of dienes to aldehydes, the oxidative cyclization of monomeric diene, nickel(0)-species and aldehyde activated by triethylborane initially provides the metallacyclic allyl alkoxynickel complex **D** (Scheme 3.8).[399] The pre-equilibrium of isoprene with its dimerized species **B** can lead to a disrupted formation of **D**, as a stoichiometric amount of **B** has been found to exhibit a very slow reactivity towards aldehydes.[404] The minor quantities of equilibrating aldehydes in lactol **277** in Scheme 3.7 mean that the formation of the metallacycle **C** would be even slower.

Further mechanistic studies with stoichiometric amounts of nickel by the S. Ogoshi group revealed the reversibility of the carbon-carbon bond formation.[404] Therefore, the scission of the nickel-oxygen bond in **C** by trialkylborane or dialkylzinc must occur rapidly, as the regioisomeric products like 1,2 or 1,4-methyl substituted adducts are usually not generated under the applied reaction conditions and the kinetic intermediate is isolated exclusively.[399]

In the case of triethylborane as a reductant, the breaking of the Ni–O bond goes along with the transfer of the ethyl substituent (**F**). The subsequent β-H-elimination liberates ethylene and generates the allyl-nickel hydride species **H** in close proximity to the internal position. The following rapid reductive elimination liberates **J** in a 1,3-*anti* disposition.

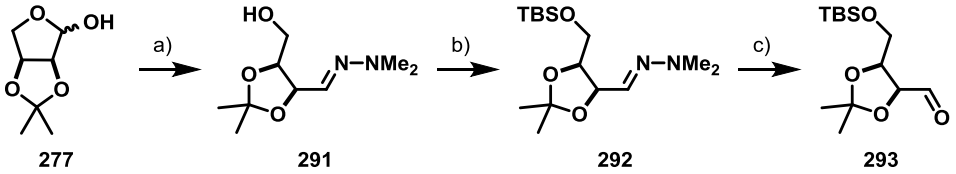


Scheme 3.8. Mechanism of Ni-catalyzed reductive coupling of isoprene (**286**) in regard of the 1,3-selectivity.

If the scission of the strong Ni–O-bond is slow, **C** is able to interconvert via η^1-complex **D** to η^3-complex **E** by twisting the coordinating allyl substituent. After ethyl transfer to **G**, liberation of ethylene and subsequent reductive elimination of **I**, the 1,3 *syn*-configured product **K** is obtained. Depending on the applied monodentate ligand, the 1,3-stereoselectivity (**J** vs. **K**) might be altered by favoring either **F** or **G** in the transmetalation step.

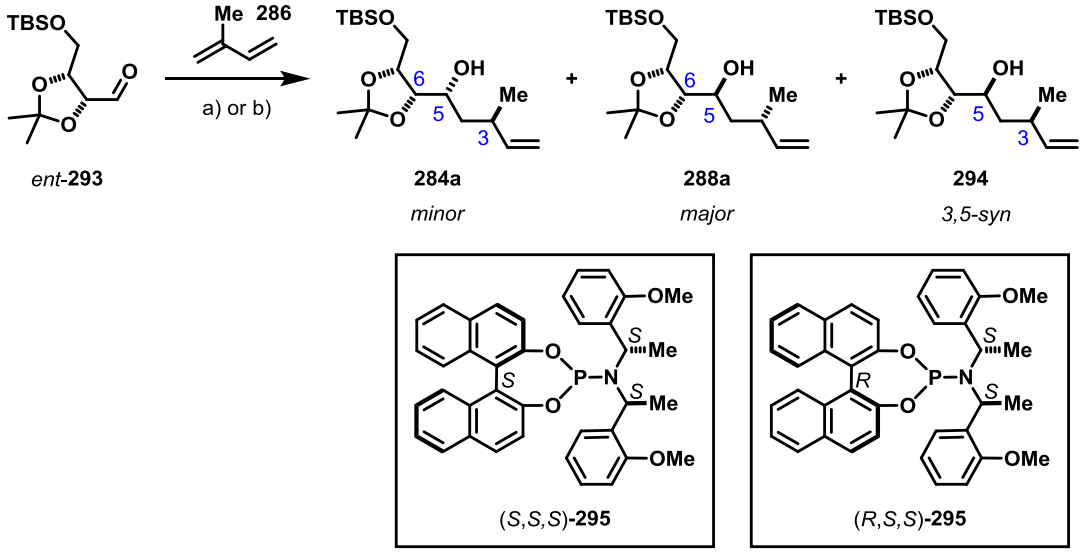
3.2.3.2.3 Diastereoselective Reductive Coupling of Aldehyde 293 and *ent*-293

In order to increase the reactivity, the lactols **277** and *ent*-**277** were converted by a literature procedure into **293** and *ent*-**293**, respectively.[405] The synthesis of **293** is depicted in Scheme 3.9. After addition of hydrazine, the alcohol **291** was protected with TBSCl. Liberation of the aldehyde **293** was conducted by ozonolysis of hydrazone **292**.



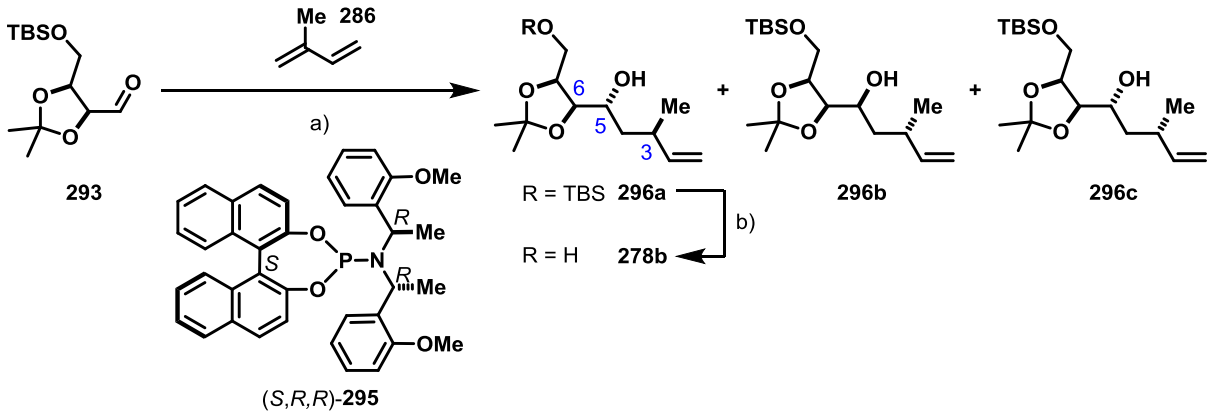
Scheme 3.9. Synthesis of aldehyde **293** for Ni-catalyzed reductive coupling. Reactions and conditions: a) *N,N*-dimethylhydrazine, EtOH, reflux; b) TBSCl, imidazole, CH_2Cl_2, 0 °C → RT, 90% over 2 steps; c) O_3, −78 °C, then DMS, −78 °C → RT, 69%.

With both aldehydes **293** and *ent*-**293** in hand, the diastereoselectivity of the Tamaru reaction was investigated by J. J. Murphy, aiming for a predominant catalyst-control and a minor match/mismatch effect.[400] Unfortunately, after screening various ligands, this pronounced substrate-control could not be overruled (Scheme 3.10). In the mismatched case, the best result was obtained with the (*S,S,S*)-Feringa ligand **282** providing C5-epimers in an unfavorable **284a**/**288a** = 1:2 ratio as well as the unexpected 3,5-*syn* diastereomer **294**.



Scheme 3.10. Studies using phosphoramidite ligands **295** in the Ni-catalyzed reductive coupling of **286** to aldehyde *ent*-**293**. Reactions and conditions: a) $Ni(cod)_2$ (10 mol%), (*S,S,S*)-**295** (10 mol%), **286**, Et_3B, toluene, dr (**284a**/**288a**) = 1:2, 30% (pure **288a**), 15% (pure **284a**), 30% (pure **294**); b) $Ni(cod)_2$ (10 mol%), (*R,S,S*)-**295** (10 mol%), **286**, Et_3B, toluene, dr (**284a**/**288a**) = 1:5.2, **294** (ca. 5%).

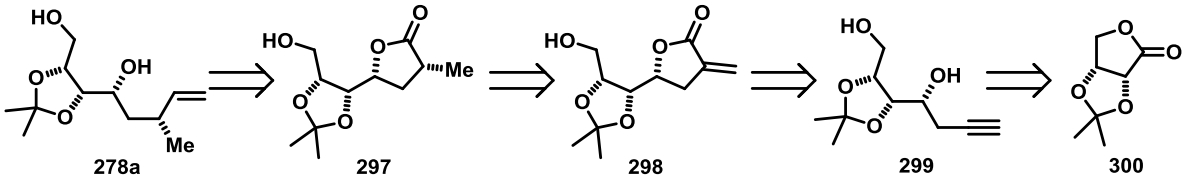
Switching to the ligand (*R,S,S*)-**295**, the undesired diastereoselectivity was enhanced to 1:5 dr, along with minor amounts of the 3,5-*syn* isomer **294**. Despite the unsuccessful attempts to overwrite the facial selectivity dictated by the substrate, the selectivity of the reductive coupling with enantiomeric aldehyde **293** can be enhanced by applying enantiomeric ligand (*S,R,R*)-**295**. In addition to the profound Felkin-Anh selectivity, the present matched case affords the desired epimer **296a** in 5:1 ratio and 59% yield (Scheme 3.11).



Scheme 3.11. Optimized conditions for the reductive coupling of **286** to aldehyde **293** in the matched case using (*S,R,R*)-**295**. Reactions and conditions: a) $Ni(cod)_2$ (5 mol%), (*S,R,R*)-**295** (5 mol%), **286**, Et_3B, toluene, **296a**/**296b**/**296c** = 5.2:1:0.58, 60% (mixture of diastereoisomers, **296a**/**296c** = 9:1); b) TBAF, THF, 0 °C, 96%

3.2.3.3 Accessing the Homocrotyl Adduct 278a by Pd-catalyzed Carbonylation

In order to outmaneuver the unsuccessful Tamaru reaction with aldehyde *ent*-**293**, we envisioned to access the homocrotylated adduct **278a** by introducing a γ-lactone **297** (Scheme 3.12). Applying a two-step sequence comprising the reduction of the lactone **297** to the acetal and subsequent Wittig olefination should afford the desired diol **278a** required for the synthesis of southern fragment **219a-b**.

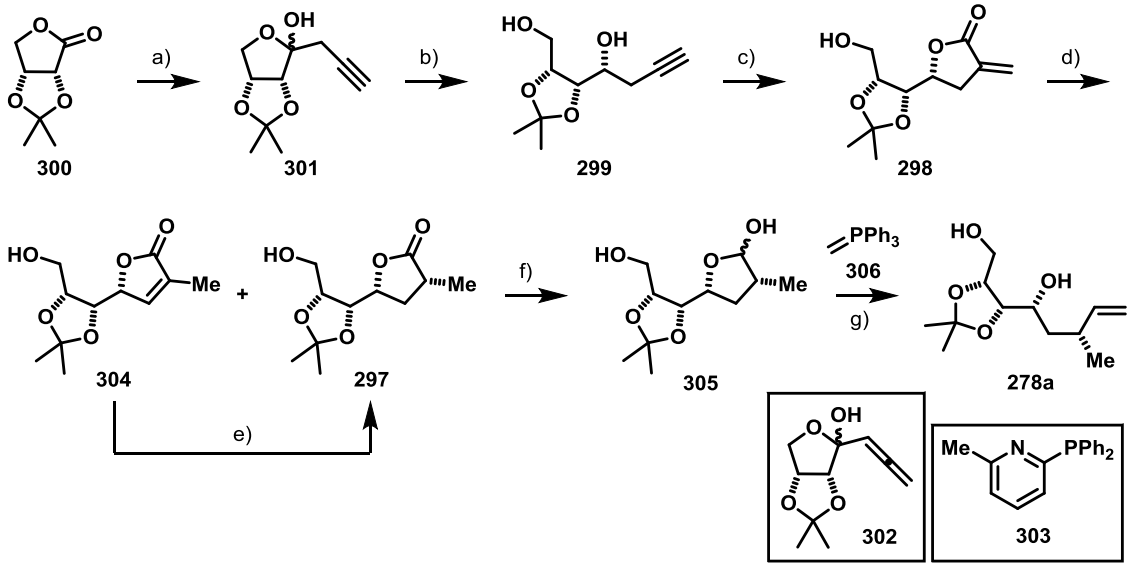


Scheme 3.12. Retrosynthetic approach towards diol **278a** by a six step sequence.

The tertiary stereogenic center would be introduced by a literature-known hydrogenation of the exocyclic α,β-unsaturated ester **298** or by upstream isomerization of the double bond to the thermodynamically favored butenolide, which upon subsequent hydrogenation reduces to the same γ-lactone. The lactone derives from a palladium-catalyzed carbonylation of homopropargyl alcohol **299** created by addition of allenyl magnesium bromide to the commercially available lactone **300** followed by a diastereoselective reduction of the generated hemi-ketal. The outlined route might open a novel synthetic pathway to butenolides by Pd-catalyzed carbonylation and olefin isomerization.

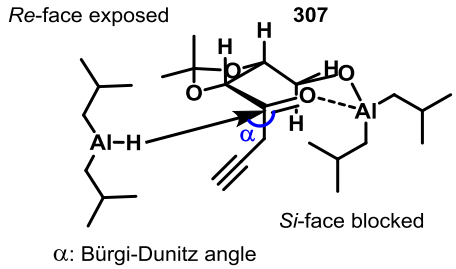
The chemoselective addition of the allenylic Grignard reagent to lactone **300** gave ketal **301** in favor of the terminal alkyne (**301**/**302** = 19:1) (Scheme 3.13).[406] Keeping the reaction temperature below −65 °C prevents the dimerization of propargyl bromide to a variety of volatile side products.[407] Using catalytic amounts of $HgCl_2$ enables generation of the propargyl Grignard reagent at low temperatures

by amalgamation of the magnesium.[408] However, neither the precise nature of the reactive Grignard reagent - allenylic versus propargyl species - nor the role of the mercury salt are understood.[409] The substitution of toxic mercury salts by zinc chloride was not investigated, as the procedure was highly reliable and the generated Grignard reagent could be stored over weeks without erosion of selectivity and reactivity.[410]



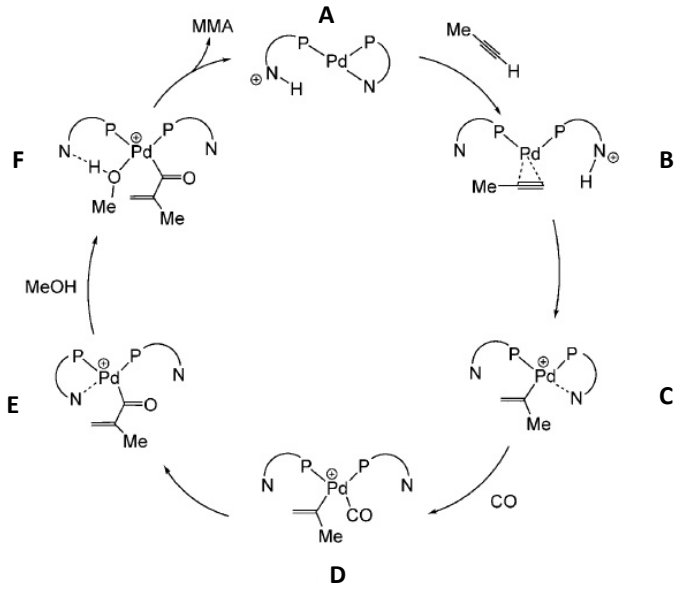
Scheme 3.13. Synthesis of diol **278a**. Reactions and conditions: a) propargyl bromide, Mg, $HgCl_2$, −20 °C → 0 °C; then **300**, THF; −78 °C, **301**/**302** = 19:1; b) Dibal-H, THF, −78 °C, dr = 19:1, 80% over 2 steps (pure diastereomer); c) CO_2 (60 bar), $Pd(OAc)_2$ (0.1 mol%), PPTS·H_2O (2 mol%), **303** (3 mol%), BHT (10 mol%), NMP, 45 °C; d) H_2 (1 atm), Pd/C (5 mol%), EtOAc, **297**/**304** = 0.8:1; e) H_2 (1 atm), Pd/C (5 mol%), EtOAc, dr = 19:1, 92% over 2 steps (pure isomer **297**), f) Dibal-H, CH_2Cl_2, −78 °C; g) **306**, toluene, −78 °C → RT, 91% over 2 steps.

However, a prolonged storage of the ketal induces isomerization of the alkyne **301** to the allene **302**. Subsequent reduction of hemiketal **301** by adding a fourfold excess of Dibal-H in THF afforded the diol **299** in 80% yield and 95:5 dr. The absolute stereochemistry of **299** was confirmed by X-ray crystal structure analysis (see Appendix 8.1). Switching from THF to a non-coordinative solvent such as toluene resulted in an erosion of diastereoselectivity (3:1 dr). In term of reaction setup, the internal reaction temperature had to be kept under −70 °C and the lactol **301** needed to be added to the solution of Dibal-H in THF. In regard of the observed diastereoselectivity, the preformed aluminium alkoxide is presumably chelating the distal ketone in a seven-membered ring (**307**),[411] which blocks the *Re*-face for the attack of an additional aluminium hydride by adapting the Bürgi-Dunitz angle α (Scheme 3.14).[412] The observed solvent effect might be correlated to the nucleophilicity and basicity of the aluminium hydride and the equilibrium between cyclic ketal **301** and ketone **307** for the 1,4-Cram chelation transition state.



Scheme 3.14. Proposed transition state of a 1,4-Cram chelation to explain the observed diastereoselectivity.

The previous research on the regioselective palladium-catalyzed carbonylation of alkynes[413] applied the Drent[414] ligand diphenylpyridylphosphine in presence of catalytic amounts of acid (Scheme 3.15). In the catalytic cycle, the initial protonation of the pyridine **A** facilitates a regioselective hydropalladation (**B**) in favor of the branched product (**C**).[415] The following migratory insertion of carbon monoxide (**D** to **E**) sets the stage for the final reductive elimination (**F**) by an alcohol moiety, which liberates the catalytically active species **A**.



Scheme 3.15. Mechanistic cycle for Pd-catalyzed carbonylation of terminal alkynes in methanol affording MMA.[415]

By careful optimization of the relative stoichiometry between palladium acetate, PTSA and ligand **303** the carbonylation could be conducted with 0.1 mol% of catalyst. Extensive screening of the reaction conditions showed that traces of allene deriving from **302** inhibit the carbonylation and must be removed beforehand by successive recrystallizations of alkyne **299**.[416] Due to the high electrophilicity of the formed acrylate, the presence of BHT as a radical scavenger prevented the polymerization of **298** initiated under air.[417] In contrast to the observed cleavage of the acetonide group in toluene and methanol under the applied acidic conditions, the usage of NMP as the solvent of choice indicated no diol formation. Because of the inherent instability of **298**, the reaction mixture was filtered through a pad of Florisil© and directly subjected to the literature-known hydrogenation of butenolides applied in a fragment synthesis of amphidinolide C (**72**).[418] Soluble palladium species

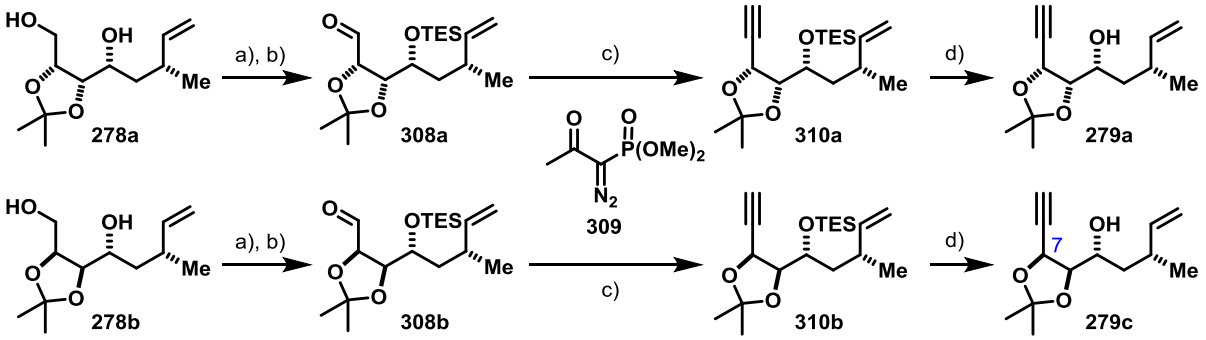
and remaining NMP caused a prolonged reaction time, which induced polymerization of the acrylate through an enolate mechanism.[419] Thus, the mixture had to be purified by flash chromatography after 1 h of reaction time, which afforded γ-lactone **297** and butenolide **304** in a 0.8:1-ratio. The inseparable mixture was resubjected to the Pd-catalyzed hydrogenation conditions, which gave the desired γ-lactone **297** in 92% yield with 19:1 dr. Reduction of **297** afforded the lactol **305**, which was subject to Wittig olefination. By preparing and isolating ylide **306** beforehand,[420] these salt free conditions provided alkene **278a** in high yield without epimerization of the basic-labile α-stereogenic center.[421]

In conclusion, the mismatched case in the Tamaru reaction prompted us to develop a new approach towards the homocrotylated adduct **278a** by a five step sequence comprised of propargylation, diastereoselective reduction, Pd-catalyzed carbonylation, hydrogenation of the α,β-unsaturated ester **298**, reduction and subsequent olefination of lactol **305**. The step discrepancy between the two routes commencing from different enantiomers highlights the advantage and disadvantage of Ni-catalyzed reductive diene addition to aldehydes (see Scheme 3.10 and 3.11). On the one hand, the diastereoselective addition gives direct access to the challenging homocrotylated adduct **278b**. On the other hand, the profound substrate-control can currently not be overruled by reagent-control, hence limiting its synthetic utility for synthesizing all possible diastereomers by a similar route.

3.2.4 Divergent Synthesis of Alkynes 279a-d

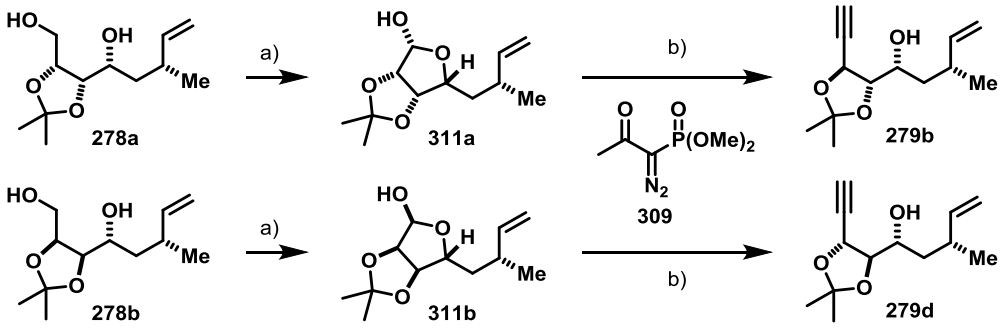
The elaborated production of the diols **278a-b** by two different synthetic routes paved the way for the divergent synthesis of a library of the southern fragments. At the stereochemical crossroad of Ohira-Bestmann homologation under either retention or inversion of the α-stereogenic center, an underestimated and often unrecognized pitfall in numerous total syntheses,[422] the diols **278a-b** were split in two parts (Scheme 3.16 and 3.17). Under the premise of preserving the stereochemistry of the α-position of the acetonide, the diols **278a** and **278b** were bis-protected by treatment with TESCl (Scheme 3.16). Subsequent Swern oxidation at slightly elevated temperature (−40 °C) cleaved the primary silyl ethers and liberated the corresponding alcohols *in situ*, which were immediately oxidized to the corresponding aldehydes **308a** and **308b**, respectively.[423] While **308a** was obtained as a single diastereomer, the isolation of aldehyde **308b** suffered from inevitable epimerization at the α-position. After subjecting **308a** and **308b** to Seyferth-Gilbert[424] homologation with the Ohira-Bestmann reagent[425] (**309**), treatment of **310a** and **310b** with TBAF for easier separation of the diastereomers provided the desired alkynes **279a** and **279c** under retention of stereochemistry. Notably, the deprotonation of methanol with KHMDS was superior to the commonly used suspension of sodium hydride.[158,389] While the homologation with formation of **279c** suffered from moderate

yield as well as epimerization at C7, the diastereomeric alkyne **279a** was isolated as a single diastereomer in satisfying 81% yield over 2 steps.



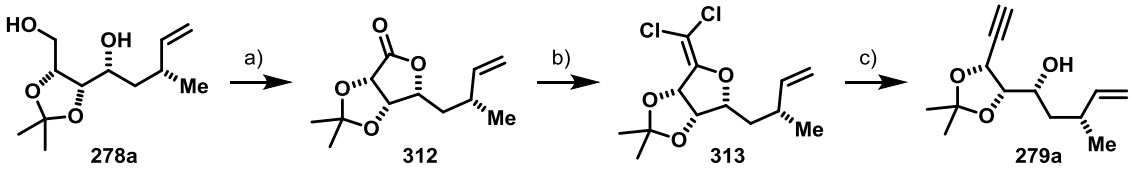
Scheme 3.16. Homologation with retention of stereochemistry on aldehydes **308a** and **308b**. a) TESCl, DMAP (20 mol%), pyridine, quant. b) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C → −35 °C; then $(i\text{Pr})_2\text{NEt}$, −78 °C → RT, 81% (**308a**, dr = 12.5:1), 77% (**308b**, dr = 3.8:1); c) MeOH, KHMDS, THF 0 °C → −78 °C, **309**, then aldehyde **308**, −78 °C → −50 °C; d) TBAF·$(H_2O)_3$, THF, 0 °C → RT, 81% over 2 steps (**279a**, pure diastereomer), 38% over 2 steps (**279c**, contains approximately 10% of **279d** (C7-*epi*)).

Commencing with the selective oxidation of diols **278a** and **278b,** acetals **311a** and **311b** were obtained in quantitative yields by using IBX. (Scheme 3.17).[426] Drawing our attention to the homologation under inversion of the stereochemistry in the *α*-position, the addition of Ohira-Bestmann reagent (**309**) to a basic solution of lactols **311** must be performed under refluxing conditions due to the equilibrium between lactol and reactive aldehyde.[427] The rather high reaction temperature induces epimerization of the *α*-position to the aldehyde, as the *anti*-configuration of the 5-membered ketal is the thermodynamic product.[428] Subjecting the crude lactols **311a** and **311b** to these reaction conditions, the *anti*-acetonides **279b** and **279d** were isolated with high levels of diastereoselectivity, albeit in marginal yields. In line with the literature precedents, the low yields of alkynes **279b** and **279d** is caused by a cooperative effect rooting in the thermal decomposition of **309**, the *in situ* formed diazoalkene as well as the resulting alkylidenecarbene at elevated temperature.[422a,b,428]



Scheme 3.17. Homologation under inversion of *α*-stereocenter. Reactions and conditions: a) IBX, DMSO, quant. (**311a** and **311b**); b) K_2CO_3, **309** (slow addition), MeOH, reflux, 25% over 2 steps (**279b**, pure diastereomer), 28% over 2 steps (**279d**, pure diastereomer).

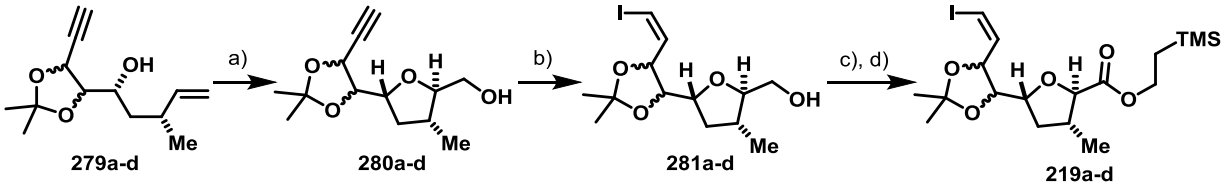
Different homologation methods such as Seyfert-Gilbert[424a] and Colvin[429] rearrangement were also screened but afforded alkyne **279a** in very low yields because of TMS-capping[430] and dipolar cyclization.[431] Applying a Corey-Fuchs[432] approach on Ramirez olefin **313**,[433] which was generated by Piancatelli oxidation[434] to lactone **312** and subsequent phosphine-mediated olefination with CCl_4,[435] suffered from extensive polymerization, affording alkyne **279a** in low yield (Scheme 3.18).



Scheme 3.18. Synthetic studies towards the alkynylation via Ramirez olefin **313**. Reactions and conditions: a) TEMPO (20 mol%), BAIB, CH_2Cl_2, 95%; b) PPh_3, CCl_4, THF, reflux, 84%; c) lithium sand, THF, reflux, 35%.

3.2.5 Synthesis of the Four Southern Fragments by Parallel Synthesis

The oxidative cyclization under Mukaiyama conditions with $Co(nmp)_2$ needed to discriminate between the two unsaturated moieties, which has not been investigated for terminal alkynes. The total synthesis of amphidinolide C (**72**) and F showed the chemoselective formation of a simple *trans* THF-ring by engaging with the terminal alkene in the presence of an internal alkyne.[218b,d] Subjecting the alkynes **279a-d** to the standard conditions forged exclusively the *trans* THF-rings **280a-d** in good yields and exquisite diastereoselectivity, setting the stage for the radical hydroindation of the alkynes (Scheme 3.19).[436] In general, radical addition of dichloroindium hydrides generated *in situ* by reduction of indium trichloride and Dibal-H displays high selectivity in favor of the *Z*-isomer.[437] Quenching of the *Z*-alkenylindium dichloride with iodine gives the desired *Z*-alkenyl iodide with stereoretention. In the presence of alcohols, carbonyls, acetals and carboxylates the radical hydroindation has been applied to simple[427b,438] and advanced intermediates[439] in total synthesis. The challenging substrates **280a-d** would highlight its synthetic utility as substitute for the Stork-Zhao olefination (see Section 2.5.2.2.1).



Scheme 3.19. Accessing all promising diastereomers **219a-d** of the southern fragment. Reactions and conditions: a) O_2 (1 atm), $Co(nmp)_2$ (10 mol%), *t*BuOOH (10 mol%), *i*PrOH, 55 °C, dr = >20:1, 64% (pure isomer of **280a**), 66% (pure isomer of **280b**), 63% (pure isomer of **280c**), 58% (pure isomer of **280d**); b) $InCl_3$, Dibal-H, Et_3B (20 mol%), then I_2, THF, −40 °C, *Z*/*E* = >20:1, 67% (**281a**), 92% (**281b**), 79% (**281c**), 88% (**281d**); c) TEMPO (30 mol%), BAIB, aq. MeCN, 80% (**185a**), 88% (**185b**), 89% (**185c**), 93% (**185d**); d) 2-(trimethylsilyl)ethanol, EDCI, DMAP (20 mol%), 2-(trimethylsilyl)ethanol, CH_2Cl_2, 0 °C → RT, 78% (**219a**), 84% (**219b**), 77% (**219c**), 60% (**219d**).

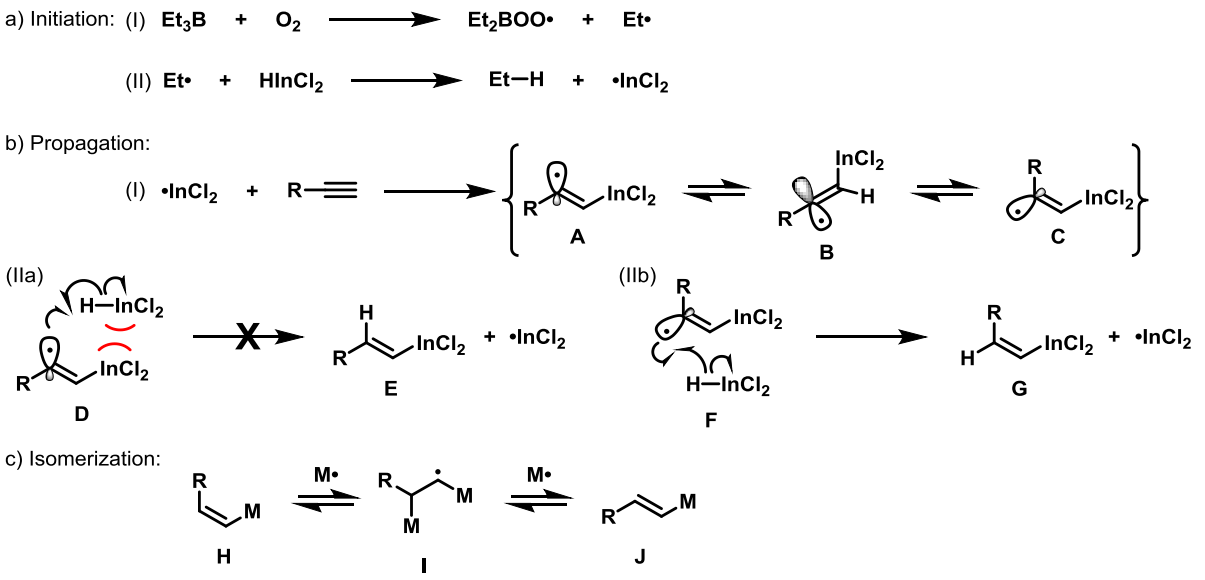
Treatment of **280a-d** under the reported conditions afforded the *Z*-alkenyl iodides **281a-d** in good to excellent yields with high *Z/E*-ratios.[437] Comparison of the data collected from **281a** (see Section 2.5.2.2.1) and **281c** (see Section 3.2) accessed by the former route provided ultimate proof of the correct stereochemical assembly of all the stereocenters. Consecutive oxidation by TEMPO and NMO in aqueous acetonitrile afforded the carboxylic acids **185a-d**. Subsequent esterification facilitated by EDCI gave the southern fragments **219a-d** in good overall yields.

In summary, the new synthetic route commences with two enantiomeric starting materials deriving from the "chiral pool" feedstock. Since the substrate-control in the nickel-catalyzed reductive coupling could not be overwritten by applying chiral phosphoramidite ligands, we outmaneuvered the mismatched case with an innovative sequence comprised of palladium-catalyzed carbonylation of homopropargyl alcohols and subsequent hydrogenation to install the challenging homocrotyl moiety. After executing the divergent routes to access the tetraols **278a** and **278b** diastereoselectively, the synthetic pathway again branched out in order to generate alkynes **279a-d** by an Ohira-Bestmann alkynylation either with retention or inversion of the α-stereogenic center. Selective oxidative cyclization to **280a-d** has showcased the fidelity of the cobalt catalyst towards olefinic entities. Finally, the introduction of the *Z*-alkenyl iodides **281a-d** has demonstrated the selectivity and orthogonality of certain radical additions. Taking the different precursors of the commercially available, enantiopure starting materials into account, the total step count ranges from 12 steps for **219b** to 15 steps for **219d**.

3.2.6 Mechanism of *trans*-Hydroindation

The *Z*-selective hydroindation is a radical chain addition to terminal alkynes, also referred as an atom transfer radical addition (ATRA) (Scheme 3.20). Dichloroindium hydride, preformed from indium trichloride and Dibal-H, is treated with triethylborane as a radical initiator. Upon exposure to oxygen, ethyl radicals are released (Scheme 3.20a) (I)), which abstract the hydride of the preformed dichloroindium hydride and release ethane (Scheme 3.20a) (II)). The dichloroindenyl radical adds regioselectively to the terminal position of the alkyne generating a radical in the adjacent position. Concerning the hybridization of the alkenyl radical, the isomeric sp^2-hypridized radicals **A** and **C** can interconvert via the p-orbital visualized in **B**. The observed stereoselectivity is not determined by fixation of the radical in structure **A** or **C**, as they resemble two extreme mesomeric structures equilibrating via mesomeric structure **B**. Therefore, the hydrogen abstraction from dichloroindium hydride must set the stereochemistry of the corresponding *Z*-alkenylindium. The abstraction of hydrogen via **D** is causing a steric clash between the sterically encumbered dichloroindium moieties preventing the formation of *E*-alkenylindium **E**. The terminal dichloroindium substituent thus facilitates the approach from the opposite side giving *Z*-alkenylindium **F** with excellent selectivity. The

final quench of **G** with iodine releases the *Z*-alkenyl iodide under stereochemical retention. Besides the anticipated iodo-demetalation, the alkenylmetal species **G** have been used for cross coupling reactions, alkylations and alkynylations.[440]



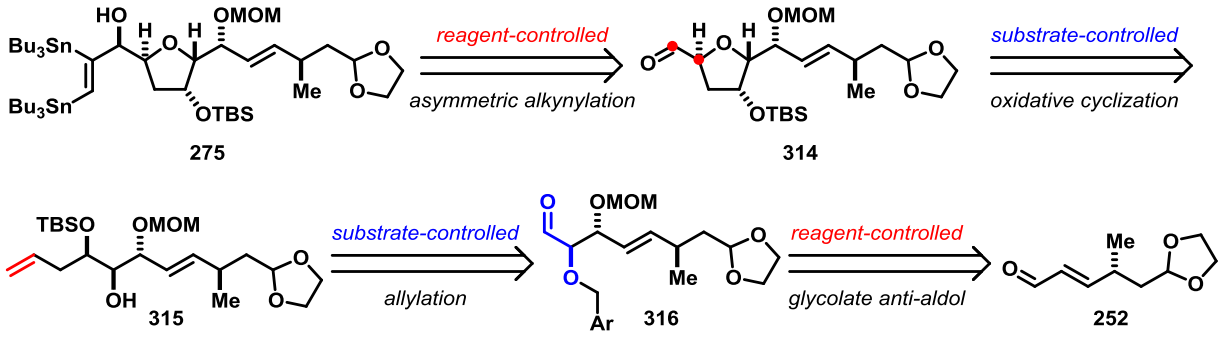
Scheme 3.20. Mechanism of the radical chain hydroindation and the stereoselectivity.

An isomerization of **H** to the thermodynamically favorable *E*-alkenylmetal species **J** is unlikely to occur due to the low reactivity of indenyl radicals. In contrast, addition of more reactive radicals such as stannanes, silanes and germanes are able to add subsequently to *Z*-alkenylmetal species **H**, resulting in the formation of radical **I**, which eliminates under overall isomerization of the double bond (Scheme 3.20c).

3.3 Synthesis of the "Inverted" Northern Fragment

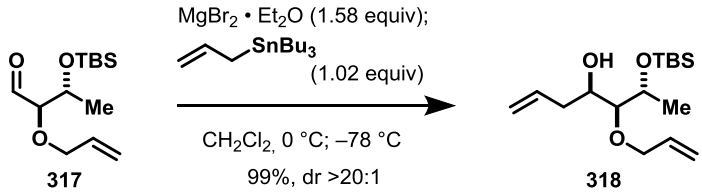
3.3.1 Retrosynthetic Analysis for "Inverting" the Northern THF-Ring

The retrosynthetic analysis of the diastereomeric northern fragment **275** was conducted with the aim of maintaining the synthetic transformations such as Lautens' bisstannylation, oxidative Mukaiyama cyclization and diastereoselective allylation, while accessing all the required stereogenic centers by switching from a *syn*-selective to an *anti*-selective aldol reaction with aldehyde **253** (Scheme 3.21). Retaining the reagent-controlled Carreira alkynylation of aldehyde **314**, the *trans*-configured THF-ring would derive from the diastereoselective oxidative cyclization of **315** catalyzed by the established cobalt catalyst $Co(nmp)_2$.



Scheme 3.21. Retrosynthetic plan for inverted THF-ring containing northern fragment **275**.

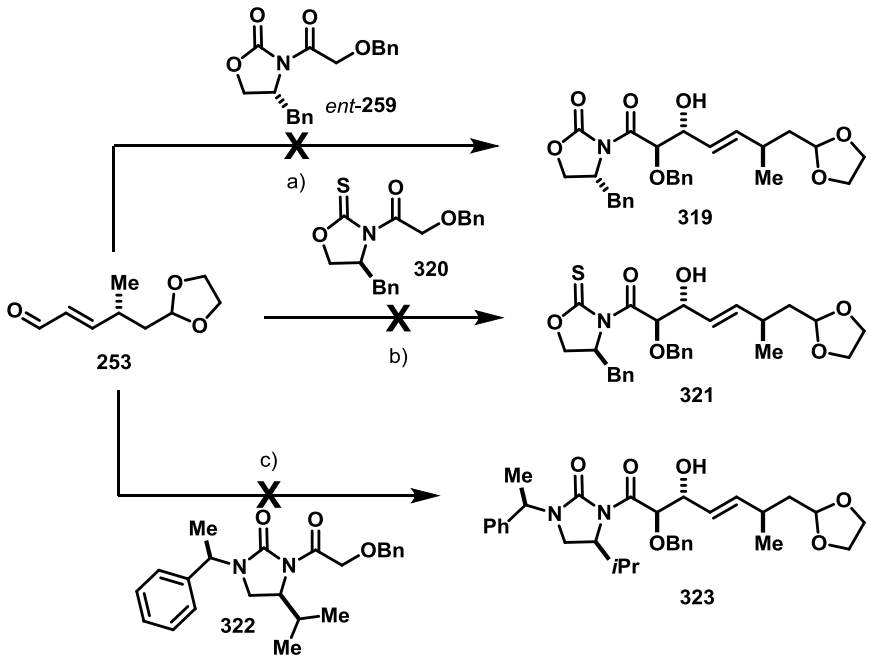
With a *syn*,*anti*-relationship in the triol moiety, the diastereoselective synthesis of **315** was inspired by a substrate-controlled Keck allylation in the enantioselective synthesis of apoptolidin sugars (Scheme 3.22). Hence, a magnesium-mediated 1,2-Cram chelation between the carbonyl and the allyl ether in **317** provided triol **318** in quantitative yield as a single isomer.[441] While **317** has a non-coordinating silyl ether group in the β-position, the MOM group in **316** might also engage in a 1,3-Cram chelation, presumably interfering in the selectivity of the allylation.[365] However, this outlined retrosynthetic analysis of **275** matches with the previous route to diastereomeric northern fragment **256** up to the aldol reaction.



Scheme 3.22. Diastereoselective Keck allylation towards the apoptolidin sugars.[441]

3.3.2 Auxiliary-based *anti* Glycolate Aldol Reaction

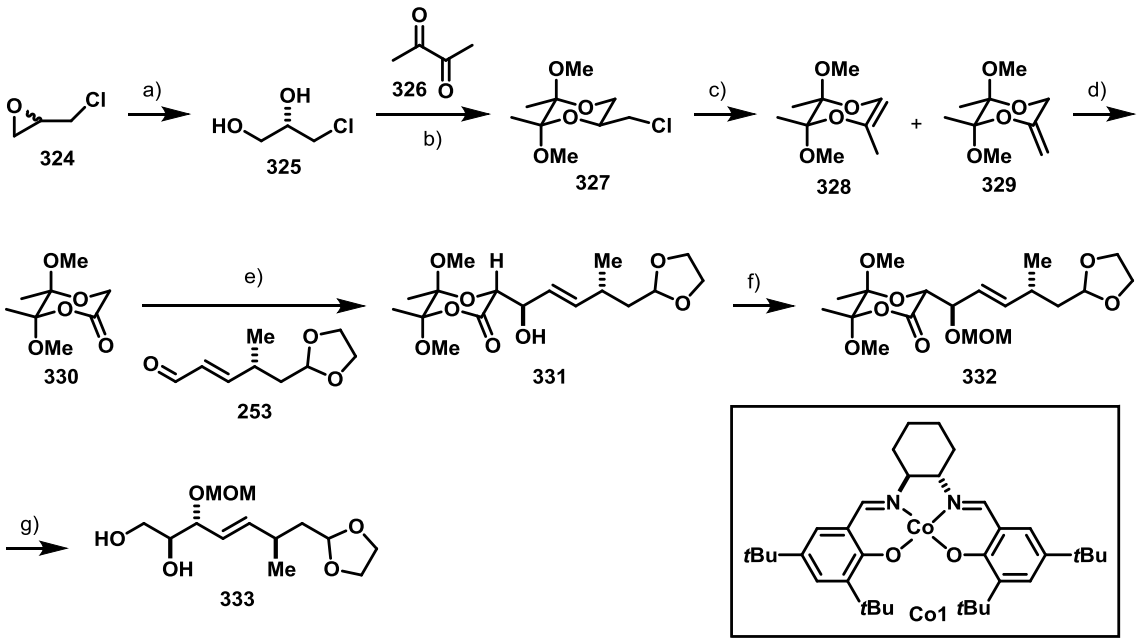
As the diastereoselective formation of *anti*-diols is more challenging than the synthesis of the corresponding *syn*-adducts by glycolate aldol reactions,[442] we initially tried to maintain an auxiliary-based approach. Usage of oxazolidinones and oxazolidinethiones as auxiliaries were successfully applied for the *anti*-selective aldol reactions by the Evans[443] group and the Crimmins group,[444] respectively. Subjecting aldehyde **253** to the reported Lewis acidic conditions with *ent*-**259**,[443] no reactivity was observed and the starting materials could be reisolated (Scheme 3.23). In order to evaluate the compatibility of the dioxolane under the Crimmins conditions, **253** was first applied to the *syn*-selective aldol reaction using 1.5 equivalents of $TiCl_4$, which gave a mixture of isomers. Switching to the *anti*-selective conditions, the exposure of **253** to a fourfold excess of $TiCl_4$ resulted in complete decomposition.



Scheme 3.23. Failed attempts in the auxiliary-based, *anti*-selective aldol reactions. Reactions and conditions: a) $Sn(OTf)_2$, *i*Pr_2NEt, TMEDA, −78 °C, 0% (no reactivity). b) $TiCl_4$ (1.5 equiv.), (−)-sparteine, CH_2Cl_2, −78 °C, dr = 2.7:1, 49% (pure *syn* diastereomers), 10% (pure *anti* diastereomers). c) LiHMDS, THF, −78 °C, 0% (no selectivity).

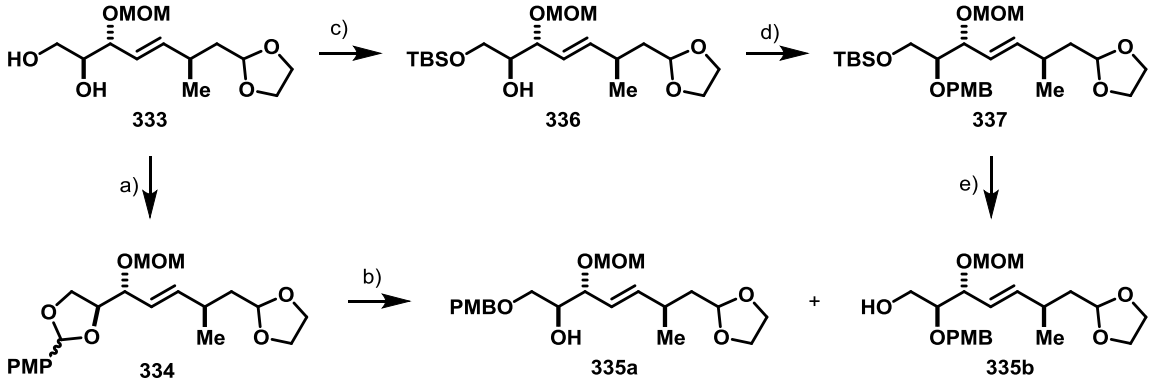
Next, we turned our attention to the *anti*-selective aldol reactions operating under basic conditions. A report on aldol reactions with an auxiliary deriving from Boc-L-valine accomplished the enantio- and diastereoselective addition to *α,β*-unsaturated aldehydes.[445] Applying the reported reaction conditions to the addition of the lithium enolate of urea **322** to aldehyde **253** displayed in our hands no selectivity. Furthermore, an attempted reproduction of the literature-known example showed no selectivity either.

Inspired by the concept of self-regeneration of stereocenters (SRS) developed by D. Seebach,[446] the S. V. Ley group introduced a novel auxiliary for the *anti*-selective glycolate aldol reaction based on chiral 2,3-diacetal protected glycolic acid **330**[447] (Scheme 3.24). This methodology has been applied in the total synthesis of rapamycin[448] and carolacton[449] by S. V. Ley *et. al.* and A. Kirschning *et. al.*, respectively. Starting from racemic epichlorohydrine (**324**), a kinetic resolution by epoxide hydrolysis provided diol **325** in decent yield and high enantiomeric excess (95% *ee*).[450] The ketal formation with 2,3-butandione (**326**) in the presence of methanol transposed the implemented chirality of the parent diol to the *O,O*-ketal, which placed the methoxy substituents in the axial position in **327**. The formation of lactone **330** was accomplished following the literature procedure by elimination of HCl in **327** and subsequent ozonolysis of the generated mixture of **328** and **329**.[451]



Scheme 3.24. Synthesis of Ley auxiliary **330** and its utility in glycolate *anti*-aldol reaction with **253**. Reactions and conditions: a) **Co1** (0.5 mol%), acetic acid (5 mol%), CH_2Cl_2, then **324**, THF/H_2O (3.5:1), 30% (95% *ee*); b) **326**, CSA (10 mol%), $(MeO)_3CH$, MeOH, reflux, 87%; c) KO*t*Bu, THF, reflux, **328**/**329** = 1:2.5; d) O_3, CH_2Cl_2, −78 °C, then DMS, −78 °C → RT, 42%. e) LiHMDS, THF, −78 °C, then **253**, dr = 9.4:1, 49% (pure diastereomer). f) MOMCl, TBAI (5 mol%), $(iPr)_2NEt$, CH_2Cl_2, 0 °C → RT, 76%; g) $LiAlH_4$, THF, 0 °C → reflux, 83%.

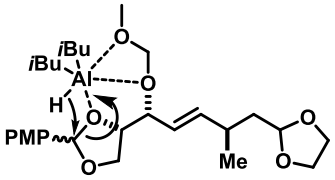
The aldol reaction with the Ley auxiliary **330** and aldehyde **253** afforded allyl alcohol **331** as a 9.4:1 mixture of diastereomers. The absolute configuration of the secondary alcohol was confirmed by Mosher ester analysis. The protection of the allylic alcohol with MOMCl gave **332** in 76% yield. The chiral ketal was removed under reducing conditions by treatment of **332** with excess lithium aluminium hydride in refluxing THF.[448b]



Scheme 3.25. Accessing primary alcohol **335b** by subsequent protection for diol discrimination. Reactions and conditions: a) *p*-anisaldehyde dimethyl acetal, PPTS (5 mol%), CH_2Cl_2, 73; b) Dibal-H, toluene, −78 °C, 46% (mixture of regioisomer, **335a**/**335b** = 6:1); c) TBSCl, imidazole, CH_2Cl_2, 0 °C, 85%; d) NaH, TBAI (5 mol%), PMBBr, DMF, 0 °C → RT, r.r. = 6.8:1, 88% (mixture of regioisomer, r.r. = 8:1); e) HF·pyridine, pyridine, THF, 83% (**335b**, pure regioisomer).

The initial attempt at discriminating the hydroxy groups in **333** envisaged regioselective reductive opening of the corresponding PMP-acetal **334** (Scheme 3.25). Treatment of **334** with Dibal-H should facilitate the formation of the secondary PMB-ether **335b** for steric reasons.[452] However, a

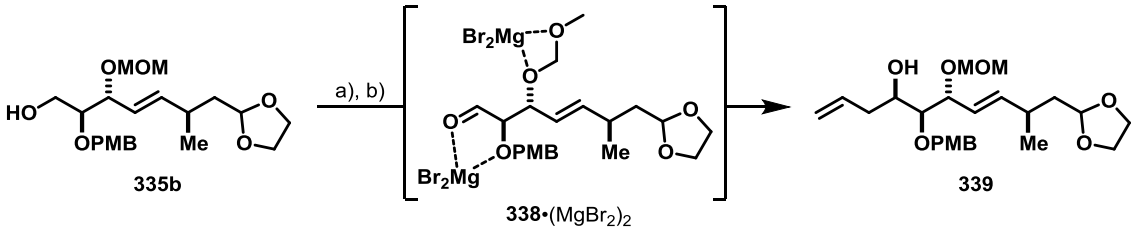
presumed pre-complexation of the metal-directing MOM group and the aluminium hydride prompted the regioselective opening in favor of the primary protected alcohol **335a** (6:1 r.r.) (Scheme 3.26).[347c,453]



Scheme 3.26. Opposite regiochemical outcome facilitated by MOM-precomplexation.

Therefore, an alternative protection group strategy comprising regioselective TBS-protection, subsequent PMB-protection under basic conditions inducing silyl migration and liberation of primary alcohol **335b** with HF·pyridine complex had to be pursued. Additionally, the relative *anti* stereochemistry introduced by the auxiliary-based glycolate aldol addition was confirmed by Mosher ester analysis of **336**.

After oxidation under Parikh-Doering conditions, the corresponding aldehyde **338** was found to be prone towards epimerization on silica gel (Scheme 3.27). Treatment of crude aldehyde **338** with a twofold excess of magnesium dibromide facilitated the diastereoselective Keck allylation in good yield (81% over 2 steps) and high selectivity (>20:1 dr).[454] The observed facial selectivity likely derives from 1,2-Cram chelation of the Lewis acid with the proximal PMB-ether in the depicted adduct. The configuration of the introduced stereogenic center of homoallyl alcohol **339** was fully established by Mosher ester analysis.



Scheme 3.27. 1,2-Stereoinduction in Keck allylation under Lewis acidic conditions. Reactions and conditions: a) [SO_3·pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, –20 °C → −10 °C, 95%; b) $MgBr_2$·(OEt_2), then allyl tributyltin, −78 °C, dr = 15:1, 80% over 2 steps.

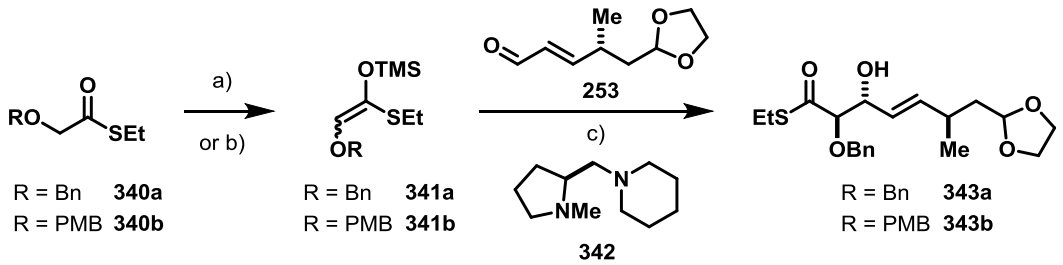
In summary, the anticipated route towards a diastereoselective entry of triol **339** was accomplished by an auxiliary-based glycolate *anti*-aldol reaction and a substrate-controlled allylation under Lewis acidic conditions. Nevertheless, the present synthesis adds three unsatisfactory additional steps to the overall route owing to the protection group manipulations for discrimination of diol **333**.

3.3.3 Asymmetric Mukaiyama Aldol Reaction

The tin-mediated Mukaiyama aldol seemed to be an adequate alternative for the *anti*-selective diol formation.[455] The initial reports on enantioselective aldol reactions with α,β-unsaturated aldehydes

by T. Mukaiyama *et. al.* inspired T. Fukuyama *et. al.* to apply the chiral diamine mediated transformation to the total synthesis of (+)-leinamycin (Scheme 3.28).[456] Hence, reduction of the thioester to the corresponding aldehyde can be conducted in a single step under Fukuyama conditions.[457] Moreover, the commercially available chiral diamine **342** is also accessible in large quantities following the reported synthesis.[458]

The silyl enol ethers **341a** and **341b** were synthesized according to the literature protocols.[8i] Trapping of the kinetic enolate of thioesters **340a** or **340b** was accomplished at −78 °C in 72:22 and 60:40 *Z/E*-ratio, respectively (Scheme 3.29). Conducting the deprotonation of **340b** with LiTMP at −105 °C afforded the kinetic silyl enol ether **341b** in *Z/E* = 9:1 ratio. Notably, the *Z*-silyl enol ether reacts exclusively with the present aldehyde under the Mukaiyama aldol conditions leaving the *E*-silyl enol ether untouched.[455]



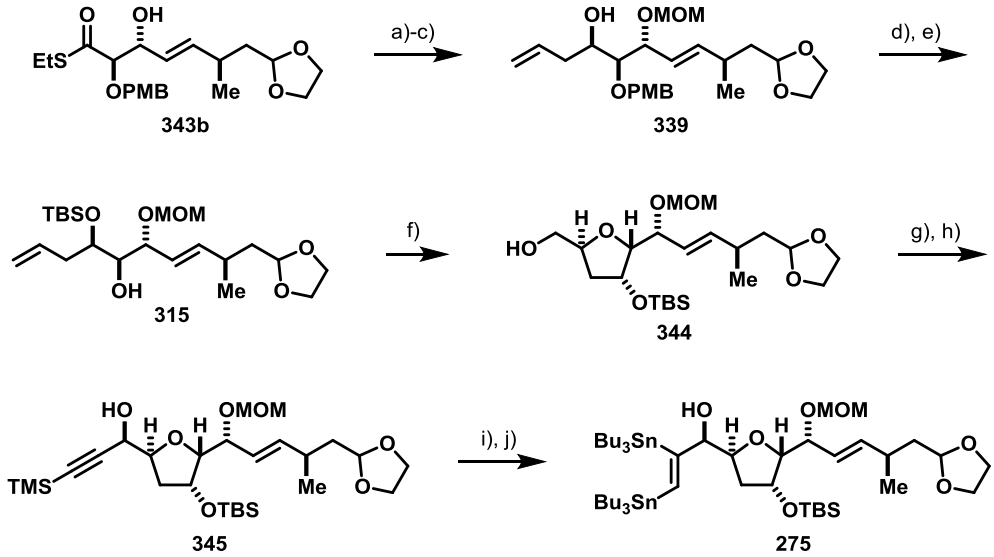
Scheme 3.28. Synthesis of silyl enol ethers and their performance in the asymmetric Mukaiyama aldol reaction. Reactions and conditions: a) LDA, TMSCl, THF, −78 °C, quant. for **341a** (*Z*/*E* = 72:22) and **341b** (*Z*/*E* = 6:4) b) *n*BuLi, tetramethylpiperidine, THF, 0 °C, then **340b**, TMSCl, −105 °C, *Z*/*E* = 9:1, 97%; c) $Sn(OTf)_2$, $nBu_2Sn(OAc)_2$, **341**, then **253**, CH_2Cl_2, −78 °C, 33% (**343a**, dr = >20:1), 55% (**343b**, dr = 19:1, 8.0 mmol scale, no full conversion), 65% (**333b**, dr = >20:1, 3.6 mmol scale).

The asymmetric Mukaiyama aldol reaction of aldehyde **253** with benzyl enol silyl ether **341a** provided the allylic alcohol **343a** with high selectivity (>20:1 dr), albeit in low yield (33%). Mosher ester analysis proved the expected stereochemistry. Changing to the PMB derivative **341b**, which was initially formed as a 6:4 mixture of *Z/E* silyl enol ether, improved the yield of the aldol reaction to 68% of **343b**, while retaining the high levels of diastereoselectivity (>20:1 dr). Addition of the silyl enol ether with a higher ratio of *Z/E* = 9:1 ratio gave good results on scales of 3.6 mmol (65%, >20:1 dr) and 8.0 mmol (55%, 19:1 dr, no full conversion).

3.3.4 Completion of the Synthesis of Diastereomeric Northern Fragment

The allylic alcohol **343b** was protected by treatment with MOMCl under Finkelstein conditions before reducing the thioester under Fukuyama conditions (Scheme 3.29). In the presence of triethylsilane a catalytic amount of palladium on carbon afforded the aldehyde **316**. After approximately 2 h, the conversion stopped and the catalyst decomposition could not be compensated by simply adding more palladium on carbon. Instead, the reaction mixture had to be filtered through Celite© twice

before resubjecting the mixture to Fukuyama conditions, this time using acetone instead of dichloromethane as the solvent. Surprisingly in this empirically optimized protocol, the reduction of thioester **343b** reached full conversion. Presumably, the present metal directing groups in combination with the generated ethanthiol are poisoning the catalyst and therefore make a two batch process in two different solvents mandatory for achieving full conversion.



Scheme 3.29. Completed synthesis of the northern fragment **275**. Reactions and conditions: a) MOMCl, TBAI (1 mol%), (iPr)$_2$NEt, CH_2Cl_2, 0 °C → RT, 81%; b) Et_3SiH, Pd/C (2 × 10 mol%), CH_2Cl_2, then acetone; c) $MgBr_2 \cdot (OEt_2)$, CH_2Cl_2, −30 °C then allyl tributyltin, −78 °C, dr = >20:1, 49% (two steps, ca. 80% conversion); d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 84%; e) DDQ, CH_2Cl_2/7.4 phosphate buffer (4:1), 0 °C 83%; f) O_2 (1 atm), Co(nmp)$_2$ (10 mol%), tBuOOH (10 mol%), iPrOH, 55 °C, r.r. = >20:1, dr = >20:1, 69% (pure isomer); g) [$SO_3 \cdot$pyridine], (iPr)$_2$NEt, DMSO, CH_2Cl_2, –25 °C → −10 °C; h) trimethylsilylacetylene, Zn(OTf)$_2$, (−)-*N*-methylephedrine, (iPr)$_2$NEt, toluene, dr = 19:1, 89% (pure diastereomer, two steps); n) K_2CO_3, MeOH, 84%; o) (Bu_3Sn)$_2$, [(tBuNC)$_2PdCl_2$] (10 mol%), THF, 75%.

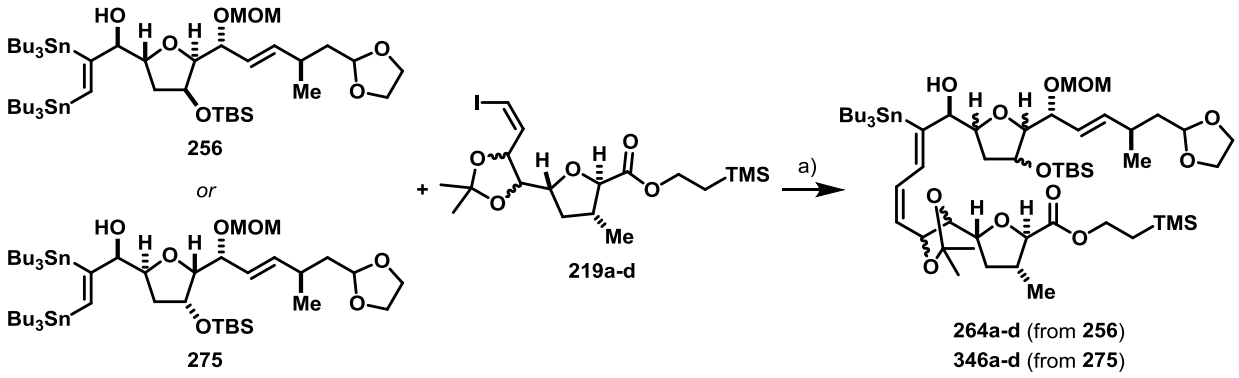
Subjecting the crude mixture of the Fukuyama reduction to the conditions for diastereoselective Keck allylation, the homoallyl alcohol **339** was isolated in 49% yield over 2 steps. Conversion of aldehyde **316** reached approximately 80% due to complexation of the Lewis acid by residual ethanethiol. The identical analytic data of both homoallyl alcohols produced by two different routes (see Scheme 3.27) confirmed the stereostructure. Subsequent treatment of **339** with TBSCl followed by the oxidative cleavage of the PMB-ether afforded **315** in 70% yield over 2 steps. In contrast to the elevated temperature required for benzyl deprotection (see Scheme 2.68j) in Section 2.7.2), the more electron-rich arene could be oxidized at 0 °C in the presence of a buffer system. Under an atmosphere of oxygen, **315** was cyclized by the Pagenkopf catalyst to the *trans* THF-ring **344** in good yield (69%) with high levels of chemo- and diastereoselectivity (>20:1 dr, >20:1 r.r.). The competing ring closure via a 5-endo-trig cyclization was not observed. Once again, the stereochemical array of the triol subunit had no influence on the overall outcome of the intramolecular oxidative Mukaiyama reaction.

Under Parikh-Doering conditions, alcohol **344** was oxidized to aldehyde **314**, which was subjected to Carreira alkynylation without further purification. Adapting the asymmetric alkynylation conditions used for accessing the northern fragment **256** (see Scheme 2.68m) in Section 2.7.2) caused decomposition of the aldehyde through self-aldolization. Hence, the desired propargyl alcohol **345** was obtained in low yield of 7%. The meticulous drying of all reagents enhanced the selectivity towards addition of the TMS-acetylene to 29-36% yield and 13:1 dr. By increasing the amounts of reagents to a 5.5-6.2-fold excess, the Carreira alkynylation resulted in a remarkable increase in yield of 89% over two steps with high diastereoselectivity of 19:1. The stereochemistry of the propargyl alcohol **345** was assigned by Mosher ester analysis. Apparently, the present reagent-controlled alkynylation constitutes a mismatched case, which requires a large excess of chiral reagents to overrule the inherent substrate bias. After liberation of the terminal alkyne under basic conditions, the palladium-catalyzed distannylation completed the synthesis of the new northern fragment **275** containing the opposite stereochemistry of the THF-ring.

In summary, the longest linear sequence of 14 steps afforded the northern fragment **275** in 4.3% overall yield. By switching from an auxiliary-based approach to a tin-mediated Mukaiyama aldol reaction, the *anti*-diol **343b** was obtained in good stereoselectivity, which paved the way for the synthesis of **275** in meaningful quantities. In combination with the scalable route of the four diastereomeric southern fragments the stage was set to establish a library of diastereoisomers for the stereochemical reassignment of chagosensine.

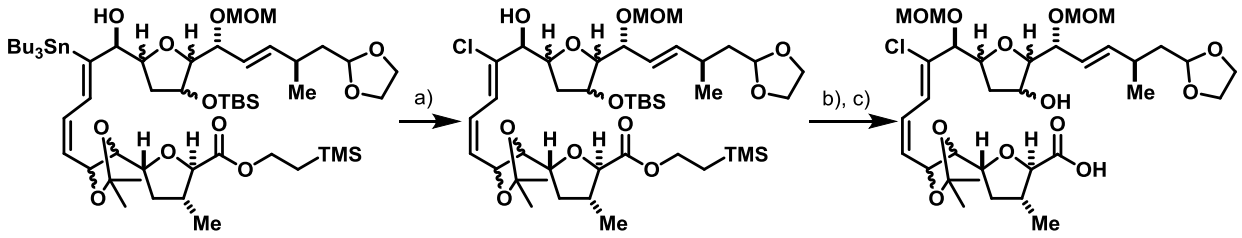
3.4 Establishment of the Macrocyclic Library

Applying the optimized reaction conditions for the site-selective Stille reaction, the two northern fragments **256** and **275** were coupled subsequently with each southern fragment **219a-d** (Scheme 3.30). With yields ranging from 32% for **346c** to 70% for **346d**, the "combinatorial" fragment assembly highlights the synthetic utility of the developed regioselective cross coupling by forging the diene entity of **264a-d** and **346a-d** independent from the present stereogenic centers.



Scheme 3.30. Stille coupling of northern fragments **256** and **275** with **219a-d** .Reactions and conditions: a) (tBu$_3$P)$_2$Pd (20 mol%), [Ph$_2$PO$_2$][NBu$_4$], LiCl, NMP, 60 °C, 50% (**264a**), 41% (**264b**), 46% (**264c**), 50% (**264d**), 53% (**346a**), 46% (**346b**), 32% (**346c**), 70% (**346d**).

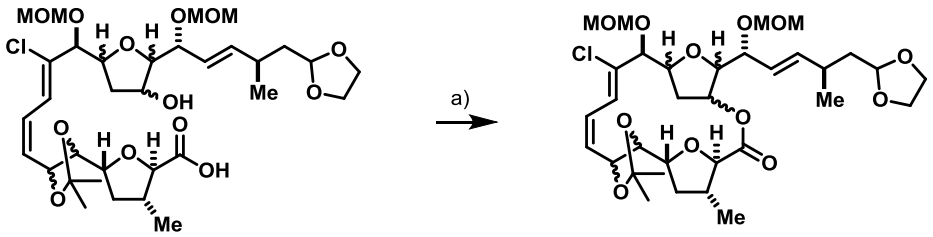
The stereoselective formation of the chlorodienes **266a-d** and **347a-d** was achieved by the copper-mediated chloro-destannylation of **264a-d** and **346a-d**, respectively (Scheme 3.31). After MOM-protection of the remaining alcohol moiety, the *seco*-acids **270a-d** and **348a-d** were obtained by deprotection of the two fluoride-labile groups.



264a-d **266a-d** **270a-d**
346a-d **347a-d** **348a-d**

Scheme 3.31. Synthesis of *seco*-acids **270a-d** and **348a-d**. Reactions and conditions: a) $CuCl_2$, 2,6-lutidine, THF, 78% (**266a**), 89% (**266b**), 89% (**266c**), 63% (**266d**), 98% (**347a**), 98% (**347b**), 96% (**347c**), 89% (**347d**); b) MOMCl, TBAI (20 mol%), $(i\text{Pr})_2\text{NEt}$, 1,2-dichloroethane, 50 °C, 92% (**269a**), 87% (**269b**), 80% (**269c**), 81% (**269d**), 86% (from **347a**), 74% (from **347b**), 81% (from **347c**), 66% (from **347d**); c) TBAF·$(H_2O)_3$, THF, 0 °C, 99% (**270a**), 99% (**270b**), 99% (**270c**), 95% (**270d**), 99% (**348a**), 99% (**348b**), 98% (**348c**), 85% (**348d**).

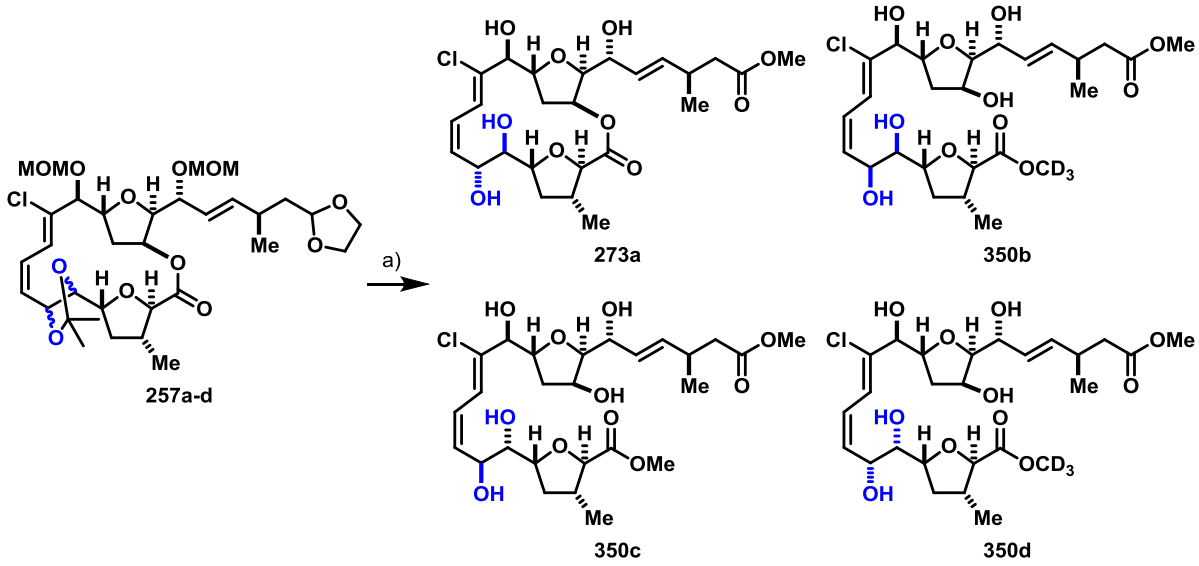
The challenging ring closure under forcing Yamaguchi lactonization conditions proved to be affected tremendously by the present stereochemistry (Scheme 3.33). The best results were obtained in combination with the **b**-series, which furnished the 16-membered macrolactone in 61% yield for **257b** and 72% yield for **349b**. The **d**-series (**257d** and **349d**) showed lower reactivity in the macrolactonization and decomposed under the harsh reaction conditions. The **c**-series was found to be highly dependent on the stereochemistry of the northern THF-ring; whereas a marginal yield of 14% was obtained for **257c**, **348c** with the "inverted" THF-ring afforded the macrolactone **349c** in 51% yield. The same effect could be observed in case of **348a** by forging the macrolactone **349a** in only 19% yield. Besides the observed decomposition of the *in situ* formed mixed Yamaguchi anhydride at elevated temperature, the formation of the corresponding lactides was detected in all cases by HPLC-MS analysis in minor quantities.



270a-d **257a-d**
348a-d **349a-d**

Scheme 3.32. Ring closure under Yamaguchi conditions. Reactions and conditions: a) 2,4,6-trichlorobenzoyl chloride, $(i\text{Pr})_2\text{NEt}$, THF, then DMAP, toluene, reflux, 40% (**257a**), 61% (**257b**), 14% (**257c**), 11% (**257d**), 19% (**349a**), 72% (**349b**), 51% (**349c**), 21% (**349d**).

With a library of diastereomeric macrolactones (**257a-d** and **349a-d**) in hand, the final three-step sequence comprising of Lewis acid promoted global deprotection, Pinnick oxidation and methyl ester formation with diazomethane was tested on the seven diastereoisomers. In agreement with the synthesis of the putative structure **273a** of chagosensine, the isolation by preparative HPLC under similar conditions afforded diastereoisomers **273b-d** possessing the original stereochemistry on the northern THF-ring (Scheme 3.33).



Scheme 3.33. Synthesis of the diastereomeric analogues of chagosensine methyl ester and their methanolysis during NMR measurement. Reactions and conditions: a) (I) Me_2BBr, CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 20% (**273a**), 54% (**350b**), 18% (**350c**), 26% (**350d**).

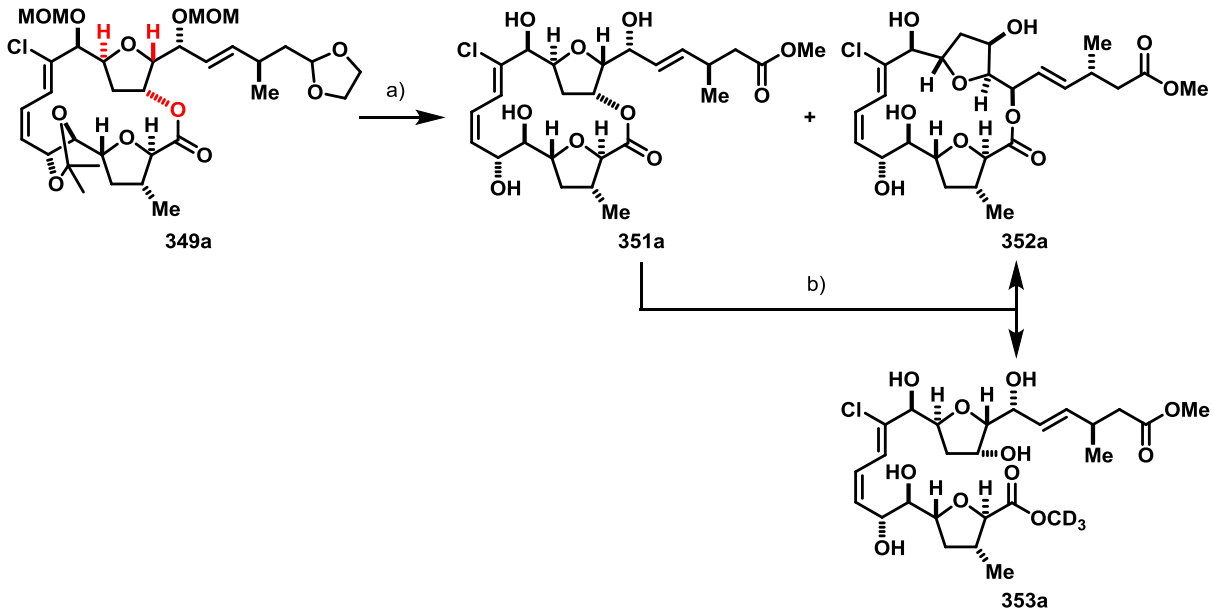
Dissolving purified compound **273b** in the reported NMR solvent of a 1:1-mixture of deuterated pyridine and deuterated methanol, the desired macrolactone opened over a period of approximately 24 h by attack of deuterated methanol. The formation of the deuterated methyl ester **350b** was confirmed by HRMS analysis as well as extensive NMR studies. Treatment of **273c** with regular methanol caused the same opening to the corresponding non-deuterated methyl ester **350c** at ambient temperature. This inherent instability of the 16-membered macrolactone was also observed in the NMR analysis of isolated macrolide **257d**, resulting in solvolysis to the corresponding deuterated methyl ester **350d**.

In conclusion, the macrolactone **273a** is the only stable derivative of the **273**-series. By contemplating the reasons for the observed degradation, the complex influence of the stereocenters of the southern diol pattern must stabilize the tetrahedral intermediate formed by addition of methanol. Presumably, the perfectly aligned hydrogen bonds of the diol subunit stabilize this intermediate. The successive collapse of the tetrahedral intermediate opens the macrolactone resulting in formation of **350b-d**. In regard to the stability of the isolated natural product, the isolation team dissolved the sponge *Lucetta chagosensis* in a 1:1 mixture of chloroform and methanol in order to extract chagosensine. Neither the natural carboxylic acid **63** nor any of the produced derivatives were

reported to decompose in the NMR solvent mixture, suggesting that **273b-d** cannot correspond to the structure of chagosensine.

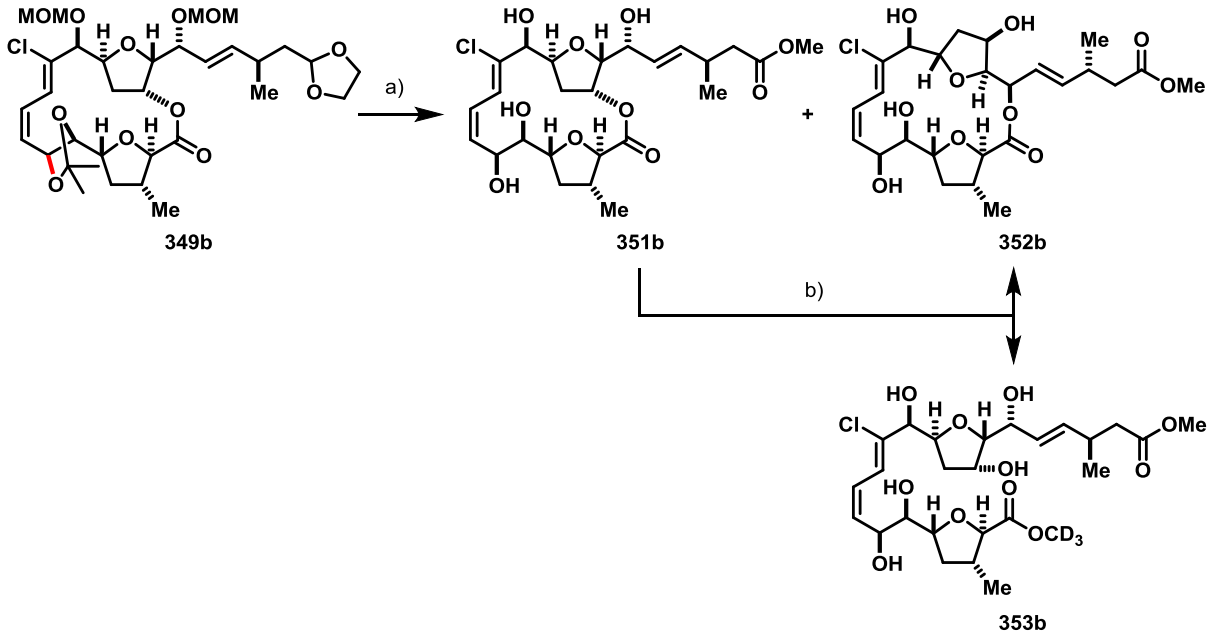
Therefore, the ongoing exploration to identify the correct stereochemical assignment of naturally occurring chagosensine focused on the **349**-series. This permutation contains an "inverted" northern THF-ring, similarly expressed in the northern part of haterumalide NA (see Section 1.4.2). Assuming similar biosynthetic pathways for the different natural products, a likely combination of the northern part of haterumalide NA (**10b**) and the southern sector deriving from amphidinolide C (**72**) would lead to **351a** as the most promising stereochemical arrangement of chagosensine. Subjecting **349a** to the sequence towards the methyl ester provided a mixture of two compounds possessing the correct molecular weight by HPLC-MS analysis (Scheme 3.34).

The presumable product **351a** was isolated by preparative HPLC. When dissolved in the NMR solvent mixture, however, this compound had converted to the 18-membered methyl ester **352a** and the opened deuterated-methyl ester **353a**, which were confirmed by HMBC-NMR analysis. Resubjecting the NMR sample to the HPLC-MS analysis, the complete degradation of the parent ester **351a** as well as the formation of both **352a** and **353a** were confirmed. This demonstrates the considerable ring strain of the 16-membered macrocycle. In contrast to the solvolysis of macrolactones **350b-d** (see Scheme 3.33), the stereochemical predisposition of **351a** must facilitate intramolecular transesterification to the 18-membered macrolactone **352a**, which is stable in the NMR solvent mixture. Upon inverting the stereochemistry of the northern THF-ring, the adjacent allylic alcohol at C17 is able to attack the macrolactone at C1, causing the expansion to the 18-membered cycle.



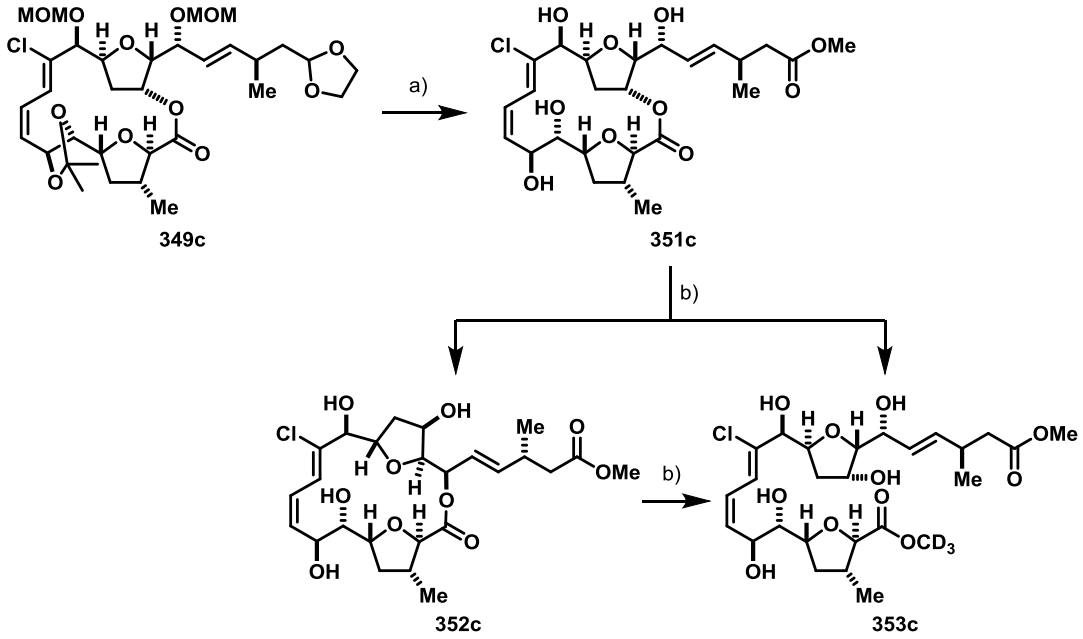
Scheme 3.34. Final sequence for **349a** and attempted isolation of **351a** resulting in D_3-methyl esters **353a** and 18-membered methyl ester **352a**. Reactions and conditions: a) Me_2BBr, CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 28% (**351a**), 16% (**352a**); b) D_3COD/D_5-pyridine (1:1), **352a**/**353a** = 0.9:1.

Treatment of **349b** with the NMR solvent displayed the same reactivity (Scheme 3.35). After separation of two constitutional isomers **351b** and **352b** by preparative HPLC, the clean fraction of the 16-membered macrolactone **351b** converted into a mixture of **352b** and **353b** in the NMR sample.



Scheme 3.35. Final sequence for **349b** and attempted isolation of **351b** resulting in D_3-methyl esters **353b** and 18-membered methyl ester **352b**. Reactions and conditions: a) Me_2BBr, CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 25% (**351b**), 28% (**352b**); b) D_3COD/D_5-pyridine (1:1), **351b**/**352b**/**353b** = 1:1.1:0.7.

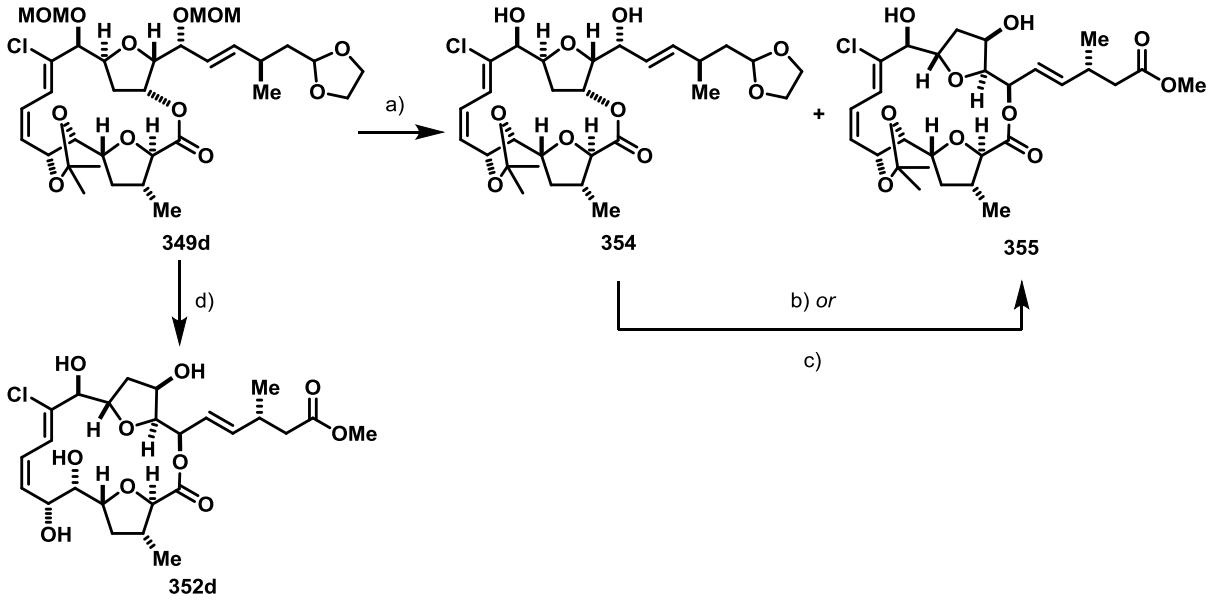
Whether the immediate transesterification of **351b** to **352b** occurred partially upon exposure to the basic solvent mixture or upon prolonged storage of the clean fraction at −30 °C is not clear. Either way, these intriguing observations highlight the inherent instability of the macrocyclic systems. Whereas the 18-membered macrolactones **352a-b** were stable in the reported solvent mixture, the ^{1}H-NMR analysis of the clean fraction of **351c** displayed methanolysis of the 16-membered **351c** as well as the *in situ* formed 18-membered macrocycle **352c** (Scheme 3.36).



Scheme 3.36. Degradation of **351c** and **352c** to open deuterated methyl ester **353c**. Reactions and conditions: a) Me_2BBr, CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 19%; b) D_3COD/D_5-pyridine (1:1), **351c**/**352c**/**353c** = 1:0.26:0.12; ratio after 24 h **351c**/**352c**/**353c** = 1:0.56:1.28.

Notably, the rate of solvolysis was much higher for the smaller, 16-membered ring providing further evidence for the considerable ring strain in all the diastereomeric isomers. Facing a similar destructive opening of the macrocycles **351a-c** as in the **273b-d** series, the single remaining candidate **351d** for the revision of the correct structure of chagosensine initially defied global deprotection under the applied Lewis acidic conditions leaving the acetonide group of the southern diol untouched in **354** (Scheme 3.37).

As the derivatization of the natural product included acetonide **65** (see Section 2.1), the comparison of **354** with the reported data would be possible. However, the NMR analysis of the isolated compound indicated the same behavior; ultimate ring expansion of the macrocycle to the 18-membered cycle **355**. After separation of the *a priori* 16-membered macrocycle **354** by preparative HPLC, treatment with protic NMR solvent mixture caused intramolecular transesterification to the 18-membered macrocycle **355**. Additionally, expansion of the 16-membered ring in aprotic, non-nucleophilic acetonitrile at ambient temperature supports the highly favorable nucleophilic attack by the adjacent allylic alcohol, releasing considerable amount of ring strain. An additional attempt of global deprotection of macrolactone **349d** using a 40-fold excess of dimethylboron bromide finally enabled the cleavage of all the Lewis-labile protection groups giving access to the 18-membered methyl ester **352d**. Hence, the existence of a parent 16-membered macrocycle (**351d**) could not be confirmed, as **352d** was exclusively observed by HPLC-MS analysis.



Scheme 3.37. Uncompleted deprotection of **349d** to acetonide-containing macrolactone **354**, which rapidly transesterifies to 18-membered derivative **355**. Reactions and conditions: a) (I) Me_2BBr (25 equiv.), CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 37% (**354**), 18% (**355**); b) D_3COD/D_5-pyridine (1:1), quant. (**355**); c) toluene, reflux, quant. (**355**); d) (I) Me_2BBr (40 equiv.), CH_2Cl_2, −78 °C; (II) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O (4:4:1), 0 °C; (III) CH_2N_2, CH_2Cl_2, 23% (**352d**), 15% (**354**).

According to the conformational arrangement in the putative (**10a**) and the revised structure (**10b**) of haterumalide NA (see Section 1.4.2.1), an explanation for this pronounced ring expansion can be seen in the conformation of the "inverted" northern THF-rings **351a-d** (Figure 3.4). Whereas in the *threo* stereochemistry of **273a-d** the allyl alcohol at C17 is pointing away from the bridging ester moiety, the *erythro* alignment of the triol subunit (C15-C17) in **351a-d** brings the reactive centers in close proximity leading to the observed intramolecular transesterification.

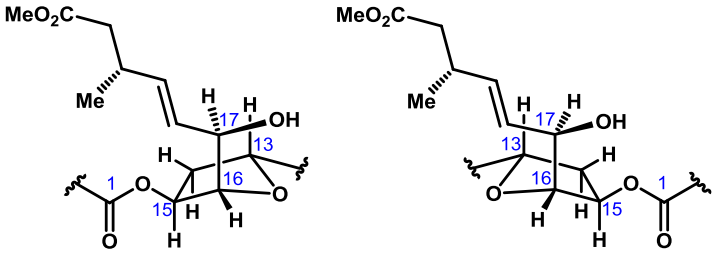
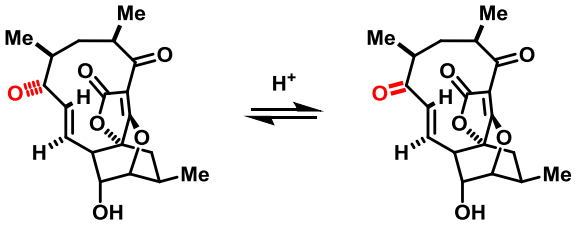


Figure 3.4. Conformational changes in the THF-rings induced by *threo* (**273a-d**) or *erythro* (**351a-d**) configuration.

After discovering a profound tendency of the **351**-series to form the 18-membered rings **352a-d**, we drew our attention to the only stable diastereomer **273a**, the putative structure of the natural product. A thermal interconversion under aprotic conditions might give access to either an 18-membered derivative or an atropisomer (Scheme 3.38).

In natural products,[459] atropisomerism is usually correlated with biaryl [460] or heterobiaryl[461] systems that have an axial chirality. Based on the rigidity of strained macrocycles, the rotational barriers of C_{sp^2}–C_{sp^3}- and C_{sp^3}–C_{sp^3}-bonds can be unsurmountable, which might also result in atropisomerism. The most prominent example is abyssomicin C,[462] which showed different dihedral angle along the enone subunit of the two atropisomers in the X-ray crystal structure analysis (Scheme 3.38).[463]



atrop-abyssomicin C (**356a**) abyssomicin C (**356b**)

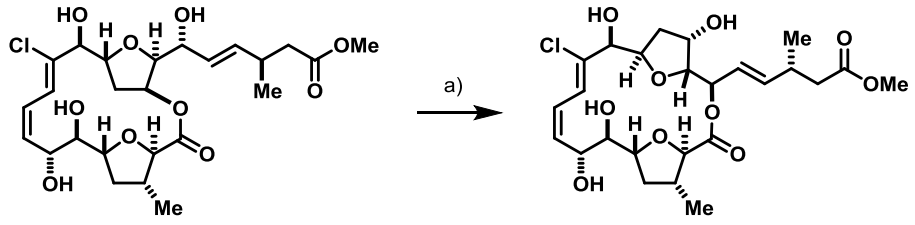
Scheme 3.38. Synthesis of *atrop*-abyssocicin C (**356a**) by RCM or NHK and its interconversion to **356b** under acidic conditions.

Concerning the stereocomplexity of chagosensine (**63**), the above described phenomenon of atropisomerism might possibly be attributed to the eight synthesized diastereoisomers **273a-d** and **351a-d** which may possess a hidden conformational isomer of the rigid 16-membered ring. Hence, the unsuccessful attempt at structural revision of chagosensine as well as the immanent instability of the prepared macrocycles could emanate from an *a priori* kinetic product forged during the macrolactonization under the forcing Yamaguchi conditions. Perhaps the thermodynamic product would have an even higher transition state, which makes its formation less favorable than the cyclization to the kinetic product. The unique chlorodiene entity may constitute an insurmountable rotational barrier. As chlorine substituents induce conformational rigidity in natural products (see Section 1.3.3.2), the heteroatom increases the rotational barrier across neighboring carbon-carbon bonds by its sheer steric bias.[83a] Furthermore, the hydrogen-bond accepting abilities of the chlorine might contribute to a hydrogen bond network that further reduce the degree of rotational freedom of the highly oxidized carbon skeleton.[464] The two *trans*-configured THF-rings enclosed in the 16-membered macrolactone also increase the stiffness of the macrocyclic system. Recollection of the exclusive cyclization of *seco*-acid **267** to the 13-membered macrolactone **268** (see Section 2.7.4) emphasizes the additional ring strain present in the 16-membered macrolactone. The limited flexibility of these macrolactones can be seen clearly in the presence of two observable rapidly interconverting conformers in **257a** and **257c** (see Experimental Section).

Regarding the biosynthetic pathway of polyketides (see Section 1.4.2), such macrocyclic systems are furnished primarily by polyketide synthases. In the second stage, the carbon scaffold is further functionalized by enzymes decorating the natural product with the characteristic functional groups such as oxygens and chlorines. Hence, the introduction of the chlorine by the flavin-depending

halogenases (see Section 1.3.3.2) occurring on the intricate macrocyclic system could presumably result in a different conformational stereoisomer, an atropisomer.

Nevertheless, despite the slow conversion rate, a solution of **273a** in toluene under reflux gave the 18-membered macrocycle **357** as single constitutional isomer (Scheme 3.39). Therefore, the existence of a clandestine atropisomer is merely speculative and will not be discussed any further. However, this thermally induced interconversion indicates that **357** is the thermodynamic product, which in turn suggests that the isolated 16-membered natural product exists dubiously as a kinetic product.



273a (putative structure of chagosensine) **357** (thermodynamic product)

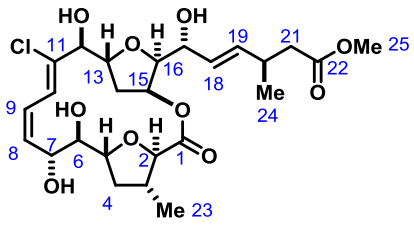
Scheme 3.39. Thermal conversion of **273a** into 18-mebered macrolactone **357**. Reactions and conditions: a) toluene, reflux, 268 h, 75%.

3.5 NMR Comparison

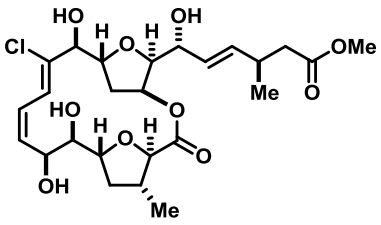
Besides the rapid opening of the strained 16-membered ring to the corresponding deuterated methyl ester **350**, the ^{1}H-NMR data of the mixtures containing decomposing macrolactones **273b** and **273d** allow comparison with the stable isomer **273a** as well as the methyl ester of the isolated natural product (**64**) (Table 3.1).

The stereochemical permutations of the southern 6,7-diol have a tremendous effect on the entire carbon framework, even on the distal side chain (C17-22). However, the biggest deviation in chemical shifts are observed in the southern part differing by $\Delta\delta_{H5} = 0.61$ ppm between **273b** and **273d**. Comparison with naturally occurring methyl ester **64** shows major discrepancies over the entire skeleton. The relatively high chemical shift at H2 ($\delta_{H2} = 4.38$ ppm) in **64** is beyond that of any of the synthesized derivatives **273**.

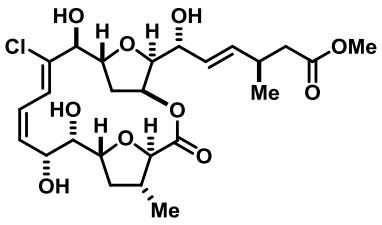
Table 3.1. Comparison of ^{1}H-NMR shifts of **273**-series with **64**.



273a



273b



273d

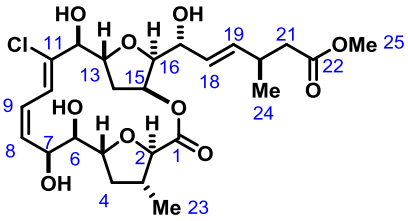
atom number	**64**	**273a**	**273b**	**273d**
2	4.38	4.09	3.99	3.77
3	2.38	2.54	2.42	2.19
4a	2.14	2.22	1.99	2.00
4b	1.96	1.35	1.89	1.40
5	4.19	3.77	4.07	3.46
6	4.03	4.02	3.45	3.71
7	4.31	4.66	4.78	4.19
8	5.93	6.07	5.71	5.60
9	6.17	6.35	6.42	6.30
10	6.42	6.93	7.19	6.76
12	4.42	4.32	4.33	4.29
13	4.15	4.28	4.46	4.19
14a	2.14	1.73	2.00	2.19
14b	1.58	1.67	1.79	1.85
15	5.08	5.40	5.39	5.42
16	4.20	4.20	4.10	4.19
17	4.52	4.54	4.42	4.47
18	5.52	5.55	5.53	5.53
19	5.71	5.60	5.73	5.83
20	2.75	2.54	2.58	2.56
21a	2.45	2.18	2.24	2.19
21b	2.33	2.15	2.18	2.19
23	0.98	0.83	0.96	0.92
24	1.08	0.85	0.90	0.90
25	3.67	3.58	3.51	3.52

Concerning the discrepancies in the chlorodiene motif (H8-H10), the reported chemical shifts of the isolated natural product (**64**) are overall upfield shifted, ranging from $\Delta\delta_{H10}$ = 0.34-0.77 ppm. The surprisingly low value of δ_{H10} = 6.42 ppm must derive from a shielding effect exclusively present in **64**. Concerning the crucial bridging of the macrolactone in H15, the synthesized lactones exhibit a significant downfield shift differing by $\Delta\delta_{H15}$ = 0.31-0.34 ppm from **64**, whereas the diastereomers **273a-b,d** themselves only deviate by $\Delta\delta_{H15}$ = 0.04 ppm. In contrast, the ^{1}H-signals of the side chain in **64** experienced a more pronounced deshielding effect, which is manifested in the relatively upfield shifted resonance frequencies of H20-H21 and H24-H25. Within the diastereomeric series the values fluctuate by $\Delta\delta_{H25}$ = 0.07 ppm in the most extreme case for the ester functionality. Especially, the high shift of δ_{H20} = 2.75 ppm of **64** in the allylic proton is unmatched by the synthesized methyl esters **273** and the parent, protected macrocycles **257**. Overall, the differences in the chemical shifts between the natural product and synthesized methyl ester are scattered over the entire carbon scaffold providing no indications for further stereochemical adjustments.

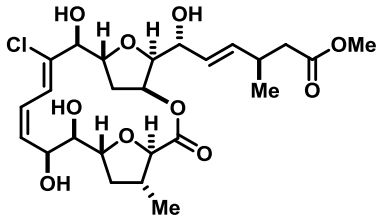
With two short-lived 16-membered rings **351b-c** containing the inverted northern THF-ring in hand, the ^{1}H-NMR comparison gives further insight into the similarities and discrepancies of the synthesized methyl ester with the reported natural product regarding the chemical shifts (Table 3.2) and the their multiplicities (see Appendix 8.2.6).

In analogy to the **273**-series (Table 3.1), the most significant downfield shifts refer to the chlorodiene motif (H9-H10) and the H15-hydroxy group engaged in the 16-membered macrolactone (Table 3.2). Whereas **273b** exhibited a massive downfield shift of δ_{H10} = 7.19 ppm for H10, the same proton in the diastereomeric macrocycle **351b** is upfield shifted by $\Delta\delta_{H10}$ = 0.58 ppm, indicating the influence of the stereochemical inversion of the northern THF-ring. Correlating with a smaller differences in the entire *Z,Z*-chlorodiene motif, the synthesized methyl esters **351b-c** still deviate by $\Delta\delta_{H9}$ = 0.24-0.28 ppm and $\Delta\delta_{H10}$ = 0.19-0.23 ppm. This trend towards smaller discrepancies between **64** and **351b-c** can also be observed in the side chain at H20-21 by leveling the discrepancies of $\Delta\delta_{H20}$ = 0.09-0.10 ppm and $\Delta\delta_{H21}$ = 015-0.18 ppm. The newly configured northern fragment clearly brings, to a certain extent, the ^{1}H-NMR spectra more in line with the reported spectra of **64**. However, the ^{1}H-signals of the northern THF-ring deviate tremendously from the natural product. With $\Delta\delta_{H12}$ = 0.44 ppm, $\Delta\delta_{H13}$ = 0.35-0.41 ppm and $\Delta\delta_{H15}$ = 0.45-0.47 ppm the resonance frequencies of the **351**-series are much higher than in **64**. In both diastereomeric series, the H15-signals are more downfield (δ_{H15} = 5.39-5.55 ppm), whereas **64** has surprisingly low chemical shift for a macrolactone (δ_{H15} = 5.08 ppm).

Table 3.2. Comparison of ^{1}H-NMR shifts of **64** with methyl esters **351b-c**.



351b

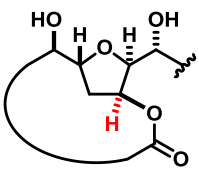


351c

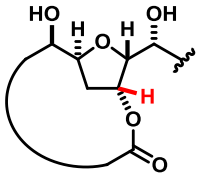
atom number	**64**	**351b**	**351c**
2	4.38	4.00	4.01
3	2.38	2.66	2.60
4a	2.14	1.99	2.47
4b	1.96	1.98	1.63
5	4.19	3.86	3.66
6	4.03	4.39	3.86
7	4.31	4.74	4.91
8	5.93	5.56	5.99
9	6.17	6.41	6.45
10	6.42	6.61	6.65
12	4.42	4.86	4.86
13	4.15	4.50	4.56
14a	2.14	2.24	2.60
14b	1.58	1.86	1.82
15	5.08	5.55	5.53
16	4.20	4.07	4.07
17	4.52	4.50	4.52
18	5.52	5.84	5.82
19	5.71	5.84	5.85
20	2.75	2.66	2.65
21a	2.45	2.28	2.27
21b	2.33	2.18	2.17
23	0.98	0.90	0.87
24	1.08	0.93	0.93
25	3.67	3.51	3.51

Taking the signals from similar macrocyclic esters such as haterumalide NA (**10**) and isolaulimalide (**71**) into account, the striking mismatch of **64** in chemical shift and multiplicity at the bridging lactone is highlighted in Table 3.3. Disregarding the impact of the different NMR solvents, the chemical shift of all representatives is at least $\Delta\delta_H$ = 0.21 ppm (**10**) higher than the reported value. Moreover, the depicted examples have the same relative stereochemistry in the THF moiety, which ideally should correlate with a similar coupling pattern. This assumption seems to be valid concerning the synthesized methyl esters **273** and **351**, as they exhibit the same small coupling constants present in **10** and **71**. In striking contrast, the isolated natural product **64** is reported to have a broad multiplicity with *J*-values of $J_{(15\text{-}14b)}$ = 8.1, $J_{(15\text{-}16)}$ = 5.9, $J_{(15\text{-}14a)}$ = 2.9 Hz.

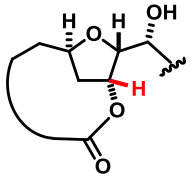
Table 3.3. Comparison of macrocyclic ester moiety in C15 of **64** with synthesized methyl esters and similar natural products.



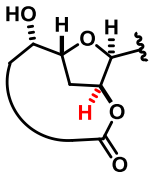
273



351



haterumalide NA (**10b**)



isolaulimalide (**71**)

macrocycle	*δ* [ppm]	multiplicity, *J*-value [Hz]
64	5.08[a]	ddd, 8.1, 5.9, 2.9
273a	5.41-5.39[a]	m
273b	5.39[a]	td, 3.1, 1.2
273d	5.42[a]	t, 3.1
351b	5.57-5.54[a]	m
351c	5.53[a]	t, 3.2 Hz
10	5.29[b]	dd, 3.7, 3.2
71	5.44[c]	td, 4.0, 0.5

a) CD_3OD/[D_5]-pyridine 1:1 (v/v). b) CD_3OD. c) C_6D_6.

This intriguing discrepancy indicates a highly questionable assignment of the relative stereochemistry of the northern THF-ring by the isolation team based on cross peaks in the NOESY spectrum. Lacking of any spectral data in the publication, the isolation team outlined the observed correlations in the two-dimensional NMR experiments by drawing arrows within the chemical structure (Figure 3.5).[170] The entire carbon scaffold is basically divided into two isolated sets of signals, which are separated by the chlorine-substituted quaternary carbon at C11 and the ester subunit at C1. Limited to minor correlations in close proximity, the NOESY of **63** shows no interaction between the northern and southern subunit, which is highly unusual for strained and intricate macrocycles.

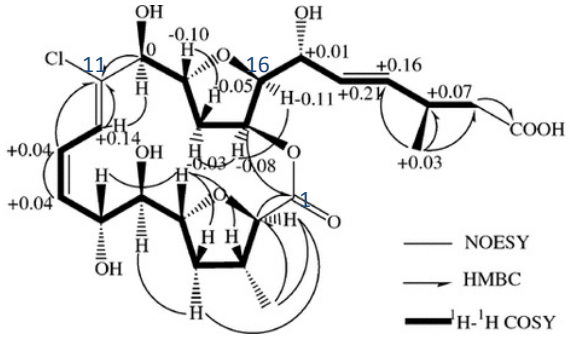


Figure 3.5. Schematic representation of the observed correlation for **63** by 2D-NMR measurement by the isolation team.[170]

Whereas the NOESY correlations of **63** is limited to neighboring protons along the carbon skeleton, the synthesized methyl esters **273a** and **351b** exhibit a rather distinctive NOESY interaction, exemplarily visualized for H10, which is exchanging with H5 and H7 in the southern part as well as H13 in the northern fragment (Figure 3.6). A more detailed analysis of the significant cross peaks in the NEOSY spectra of all macrolactones can be found in the Appendix 8.2.2, which clearly indicate an even more profound correlation between the two opposite THF-rings encased in the 16-membered macrocycle. In addition to the inherent instability of the synthesized macrocycles **273b-d** and **351a-d**, the absence of cross peaks for transannular interactions in the NOESY prompted us to doubt the existence of the strained carbon framework in **63**.

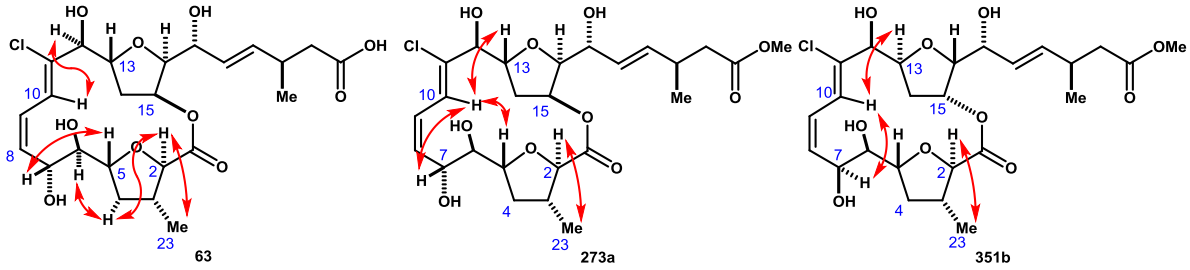
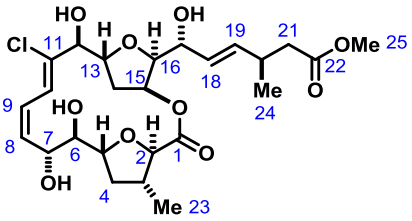


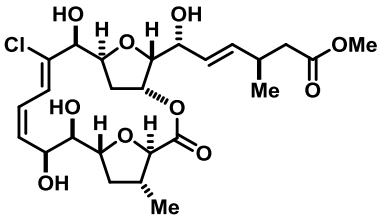
Figure 3.6. Characteristic NOESY of chagosensine (**63**) and synthesized methyl esters **273a** and **351b**.

Next, we drew our attention to the obtained ^{13}C-NMR spectra of the putative structure **273a** of chagosensine and short-lived isomer **351b**. The most significant deviations ($\Delta\delta_C > 5.0$ ppm) are highlighted in Table 3.4. Despite the different stereochemical settings of the southern diol, the signals of C2 and C5 in the proximate *trans* THF-ring are downfield shifted by $\Delta\delta_{C2}$ = 4.6-6.3 ppm and $\Delta\delta_{C5}$ = 8.1-9.3 ppm respectively. Exhibiting a low chemical shift for carbons embedded in THF-rings, the C5 signal in **64** (δ_{C5} = 72.4 ppm) is either influenced by a strong shielding effect of a neighboring group or is not part of a cyclic ether. Comparison of the diastereomeric 6,7-diol shows a significant downfield shift of C6 in **351b**, matching with the reported chemical shift of **64**, although the influence of the stereochemical inversion of the neighboring alcohol at C7 might contribute to this shielding effect.

Table 3.4. Comparison of ^{13}C-NMR shifts of putative structure (**273a**) and methyl ester **351b** with methyl ester of isolated chagosensine **64**.[170] Color code: $\Delta\delta \leq 0.5$ ppm; $0.5 < \Delta\delta < 1.0$ ppm; $\Delta\delta \geq 1.0$ ppm



273a
(putative structure of chagosensine)



351b

atom number	**64**	**273a (putative)**	**Δδ (64–273a)**	**351b**	**Δδ (64–351b)**
1	170.5	171.3	–0.8	172.7	–2.2
2	**80.8**	**87.1**	**–6.3**	**85.4**	**–4.6**
3	36.6	36.4	0.2	35.1	1.5
4	38.0	38.9	–0.9	37.3	0.7
5	**72.4**	**81.7**	**–9.3**	**80.5**	**–8.1**
6	75.5	81.8	–6.3	75.2	0.3
7	72.0	71.5	0.5	70.1	1.9
8	133.6	137.2	–3.6	134.3	–0.7
9	128.2	123.6	4.6	126.1	2.1
10	126.9	123.2	3.7	121.5	5.4
11	136.2	137.1	–0.9	138.3	–2.1
12	**61.3**	**79.5**	**–18.2**	**70.0**	**–8.7**
13	**70.7**	**85.5**	**–14.8**	**69.5**	1.2
14	32.9	39.0	–6.1	32.4	0.5
15	72.7	76.4	–3.7	76.9	–4.2
16	81.8	86.9	–5.1	85.5	–3.7
17	**67.2**	**72.1**	**–4.9**	**76.6**	**–9.4**
18	128.5	128.9	–0.4	131.5	–3.0
19	133.4	138	–4.6	135.7	–2.3
20	31.2	34.0	–2.8	33.9	–2.7
21	40.2	41.8	–1.6	41.8	–1.6
22	172	173.2	–1.2	173.4	–1.4
23	14.8	19.5	–4.7	17.3	–2.5
24	19.5	20.4	–0.9	20.2	–0.7
25	51.2	51.8	–0.6	51.4	–0.2

Regarding the unique *Z,Z*-chlorodiene motif (C8-C11) of chagosensine, the stepwise decrease in chemical shift from C10 to C8 indicates the conjugation of the unsaturated system in of **64**, **273a** and **351b**, resulting in the most deshielded carbon in the γ-position (C8). Concerning the two allyl alcohols flanking the northern THF-ring at C12 and C17, the upfield shifts of δ_{C12} = 61.3 and δ_{C17} = 67.2 ppm are at the lower end of the chemical shift area for simple secondary allyl alcohols (^{13}C-NMR ($[D]_5$-pyridine): δ = 65.0-74.0 ppm).[465] While the exocyclic carbon at C17 is still within the outlined range, the allylic carbon neighboring the chlorine substituent at C12 must experience a counter-intuitive shielding effect in proximity to an electron-withdrawing group, the chlorodiene.

Comparison of the putative structure **273a** with the isolated methyl ester **64** indeed displays the most striking deviation of $\Delta\delta_{C12}$ = −18.2 ppm in the allyl alcohol. The adjacent C13, engaged in the THF-ring, also massively differs by $\Delta\delta_{C13}$ = −14.8 ppm. These extraordinary downfield shifts are partially compensated by switching to the diastereomer **351b**. Thus, the inversion of the northern THF-ring has a tremendous shielding effect, moving the resonance signals to δ_{C12} = 70.0 ppm and δ_{C13} = 69.5 ppm, which is even dropping below the reported value of the natural product ($\Delta\delta$ = 1.1 ppm). Although this overall decrease in resonance frequencies can be observed in the entire scaffold, the significant discrepancy of $\Delta\delta_{C12}$ = −8.7 ppm essentially excludes the allylic alcohol as the structural motif neighboring the distinguishable chlorodiene. Whether the inversions of the three stereocenters of the northern THF-ring or the permutations of the diol subunit at C7 are responsible for the massive decrease in chemical shift, especially at C12 and C13, remains unknown. In summary, the very low value of δ_{C12} = 61.3 ppm for an allylic alcohol in proximity to an alkenyl chloride in **64** cannot be consolidated with the obtained data of **273a** and **351b**. Regarding similar motifs found in natural products (**32**) and natural-product-based analogues (**358** and **359**), the significantly higher carbon shifts support the notion of a mistaken structural assignment of **63** by misguided structural analysis of both connectivity and stereochemistry (Figure 3.7).

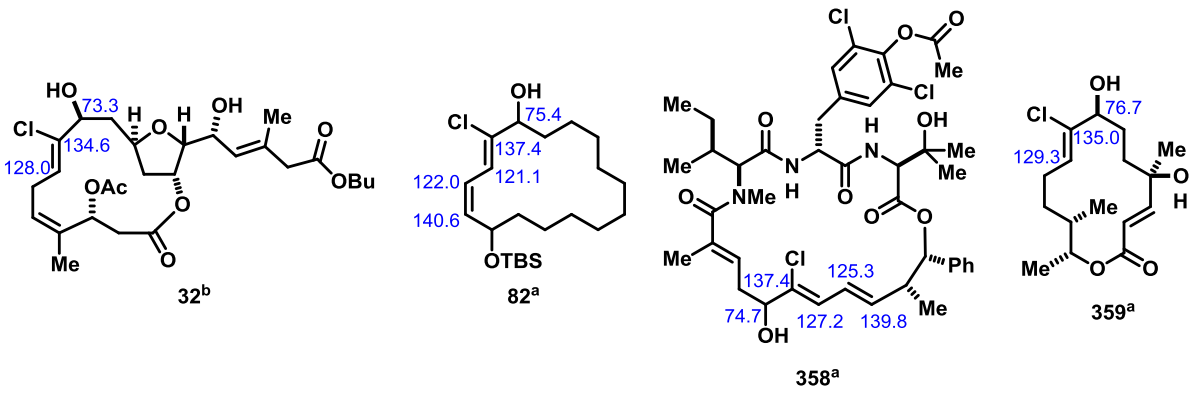
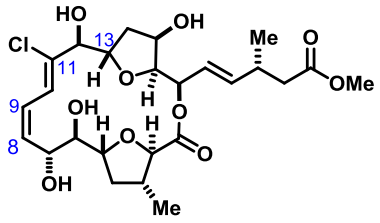


Figure 3.7. ^{13}C-NMR signals of chlorine containing allyl alcohols. NMR solvent: a) $CDCl_3$, b) CD_3OD.

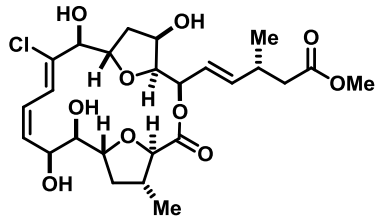
Regardless of the different NMR solvents, the reported ^{13}C-values of the allyl alcohol in **32**, **82**, **358**, and **359** match with the synthesized macrocycles **273a** and **351b** by ranging from δ = 73.3-

76.7 ppm.[109] Notably, the stereochemistry of *Z,E*-configured chlorodiene in **358** has the lowest shift within the diene motif at the *β*-position of the chlorine substituent, whereas *Z,Z*-chlorodiene **82** aligns perfectly with a stepwise drop in resonance energy from the *γ*- to *α*-position, which in turn provides further evidence for the correct *E/Z*-geometry in the unique feature of chagosensine and the synthesized putative derivatives. As a significant solvent effect cannot be ruled out, the 18-membered derivatives **352** and **357** can give further information about the ^{13}C-signals of identical subunits encircled in differing ring sizes (Table 3.5).

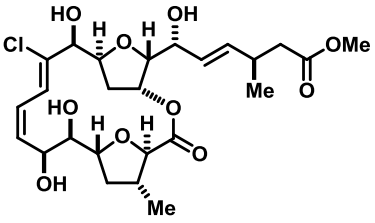
Table 3.5. Comparison of ^{13}C-NMR shifts of 18-membered analogues with the parent 16-membered ring and **64**.



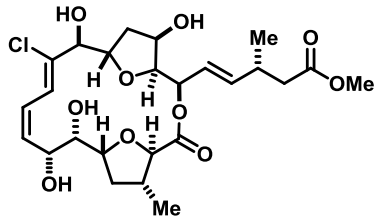
352a



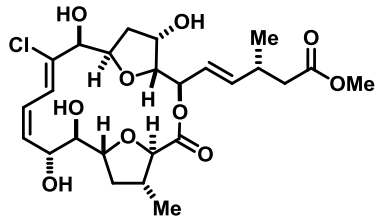
352b



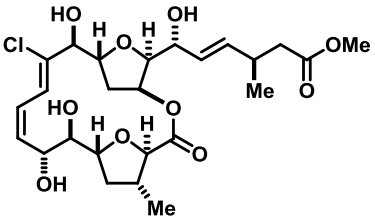
351b



352d



357



273a

#	64	352a	Δδ	352b	Δδ	351b	352d	Δδ	357	Δδ	273a
8	133.6	133.7	−0.1	135.2	−1.6	134.3	134.8	−1.2	133.8	−0.2	137.2
9	128.2	125.0	3.2	126.8	2.1	126.1	125.1	3.1	124.1	2.1	123.6
10	126.9	124.5	2.4	123.4	3.5	121.5	124.1	2.8	120.8	6.1	123.2
11	136.2	137.3	−1.1	140.0	−3.8	138.3	137.2	−1.0	137.1	−0.9	137.1
12	**61.3**	**78.0**	**−16.7**	**77.4**	**−16.1**	**70.0**	**78.5**	**−17.2**	**86.2**	**−24.9**	**79.5**
13	70.7	78.3	−7.8	76.9	−6.2	69.5	79.5	−9.5	77.0	−6.3	85.5

Measurements of the **352**-derivatives mismatch in the same manner as the putative structure (**273a**), deviating enormously at C12 by $\Delta\delta_{C12}$ = −16.1-−17.2 ppm. In contrast, 18-membered ring **357** deriving from thermally induced transesterification of **273a** experiences a tremendous deshielding effect, resulting in the most extreme discrepancy of $\Delta\delta_{C12}$ = −24.9 ppm. This downfield shift for C12 is also present in **352b** ($\Delta\delta_{C12}$ = −16.1 ppm) after ring expansion from the parent 16-membered macrolactone **351b**. Therefore, the conformational predisposition of the carbon skeleton including variations in ring size and stereochemistry influence the chemical shift of certain motifs such as C12 and C13 significantly, while other subunits such as C8-C11 retain their signals within a narrow range.

3.6 Outlook

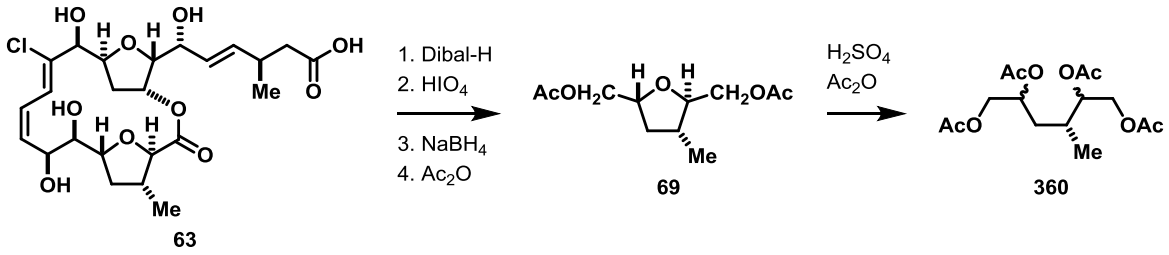
Except for the unproven existence of a buried atropisomer, the unsuccessful reassignment of chagosensine is most likely rooted in a fundamental misinterpretation of the obtained data by the isolation team. Besides the various discrepancies found in the NMR spectra, further support for the structural mis-assignment of chagosensine can be found in the HRMS, λ_{max} and the derivatization by oxidative degradation of the isolation paper.

At first sight, the reported HRMS data seemed reliable, as each compound was analyzed by HRFABMS. However, the reported calculated values for chagosensine (**63**) and its methyl ester (**64**) with *m/z* = 517.2151 and *m/z* = 531.2308 respectively, are not accurate and the correct calculated HRMS-values are *m/z* = 517.18350 and *m/z* = 531.19915. HRMS analysis of the synthesized methyl esters **273** and **351** also match with these correct molecular weights. Based on the HRFABMS-value reported by the isolation team, the total formula of chagosensine ($C_{24}H_{33}O_{10}Cl$) is incorrect and a more accurate calculation of the theoretical chemical compositions including one chlorine atom would lead to a total formula like $C_{25}H_{38}O_9Cl$, correlating with a degree of unsaturation (DU) of six rather than eight in the putative structure **273a**.[466]

Besides this fundamental mistake in the analysis of the HRMS data, the arguably most salient feature of chagosensine, the *Z,Z*-configured 2-chloro-1,3-diene motif, was found to have an absorption maximum at λ_{max} = 230 nm.[170] In contrast, all synthesized compounds as well as 7-chloroocta-4,6-dienoic acids, which was used as a reference in the isolation paper, have a λ_{max} > 244 nm, differing by more than 0.25 eV.[467] In order to visualize this enormous difference in excitation, the attachment of a nitro group at benzene causes the same bathochromic shift from λ_{max} = 254 nm (benzene) to λ_{max} = 269 nm (nitrobenzene).[468] On the other extreme, the unsubstituted butadiene exhibits a λ_{max} of 217 nm in ethanol.[469] Switching to chloroprene (2-chloro-1,3-butadiene), the effect of the attached halogen in the absorption spectra can be seen by moving the maximum towards higher wavelengths (λ_{max} = 223 nm).[469] The conjugation of two separated alkenes to an unsaturated system results in gain of resonance energy, which can be depicted easily by a Frost-Musulim diagram.[470] Based on steric reasons, the conjugated system may be slightly out of plane, which increases the gap between HOMO and LUMO, correlating with a decrease in absorption wavelength. Despite the well-known effects of distortion altering the effective conjugation length of π-electron systems[471] in polyenes such as β-carotenoids,[472] the absorption maximum of **63** is too low for a conjugated chlorodiene entity. Therefore, the chromophoric issue is also raising the question, if this unique feature of chagosensine is truly present in the natural product.

Finally, the extensive derivatization of chagosensine comprised of Mosher ester analysis and oxidative degradation suggest a highly sophisticated determination of the absolute stereochemistry.

Nevertheless, the oxidative degradation pathway of the southern part of **63** ends in a highly questionable intermediate **360** (Scheme 3.40). During the structural elucidation of amphidinolide L by J. Kobayashi *et. al.*, the derivatization of the natural product by glycol cleavage and treatment with acetic anhydride ended in an expected formation of a diastereomeric mixture of acetate **360**.[473] In contrast to this logical unselective derivatization, the isolation team of chagosensine treated THF-ring **69** under the same harsh reaction conditions, describing **360** as a single diastereomer (Scheme 3.40).[170] The reported data match suspiciously well with one of the two diastereoisomers of the J. Kobayashi group.[473]



Scheme 3.40. Oxidative degradation pathway of the southern part of **63** leading to **360** reported as a single isomer.[170]

Whether these mistakes represent a singular lapse or a continuity of incorrect structural determinations, we analyzed further assignments of natural products isolated by the T. Řezanka group, which were proven to be mis-assigned by total synthesis of the putative structure. The isolation team has published incorrect structural assignments for the trocheliophorolide[474] family including trocheliophorolide B[475] (**361**) and D (**362**),[476] fulicerine (**363**),[477] methyl nonactate[478] (**364**) and the trilactone[479] (**365**) of nonactin,[480] gobienine A[481] (**366**) as well as lytophilippines[375a] (**367a**) (Figure 3.8).

In the case of the macrolide lytophilippine, the first total synthesis of the putative structure **367a** by the E. Lee group proved its mis-assignment displaying remarkable deviations across the entire carbon skeleton in the ^{13}C- and ^{1}H-NMR spectra.[482] After achieving the synthesis of the macrocyclic core structure,[483] the M. Hiersemann group aimed for its structural revision by inverting the stereochemistry of the northern THF-ring and the adjacent secondary alcohol.[484] Without reporting the NMR solvent in the isolation paper, the extensive comparison of the obtained diastereomer **367b** in a variety of NMR solvents revealed deep-seated configurational issues in the structural determination of lytophilippine A. These ambitious synthetic efforts have also suffered from a questionable structural assignment including major scientific mistakes within the publication of the T. Řezanka group.[375a] Similar to chagosensine, no raw data is provided and visualization of the two-dimensional NMR data by superficial drawings of different subgroups is prevalent.

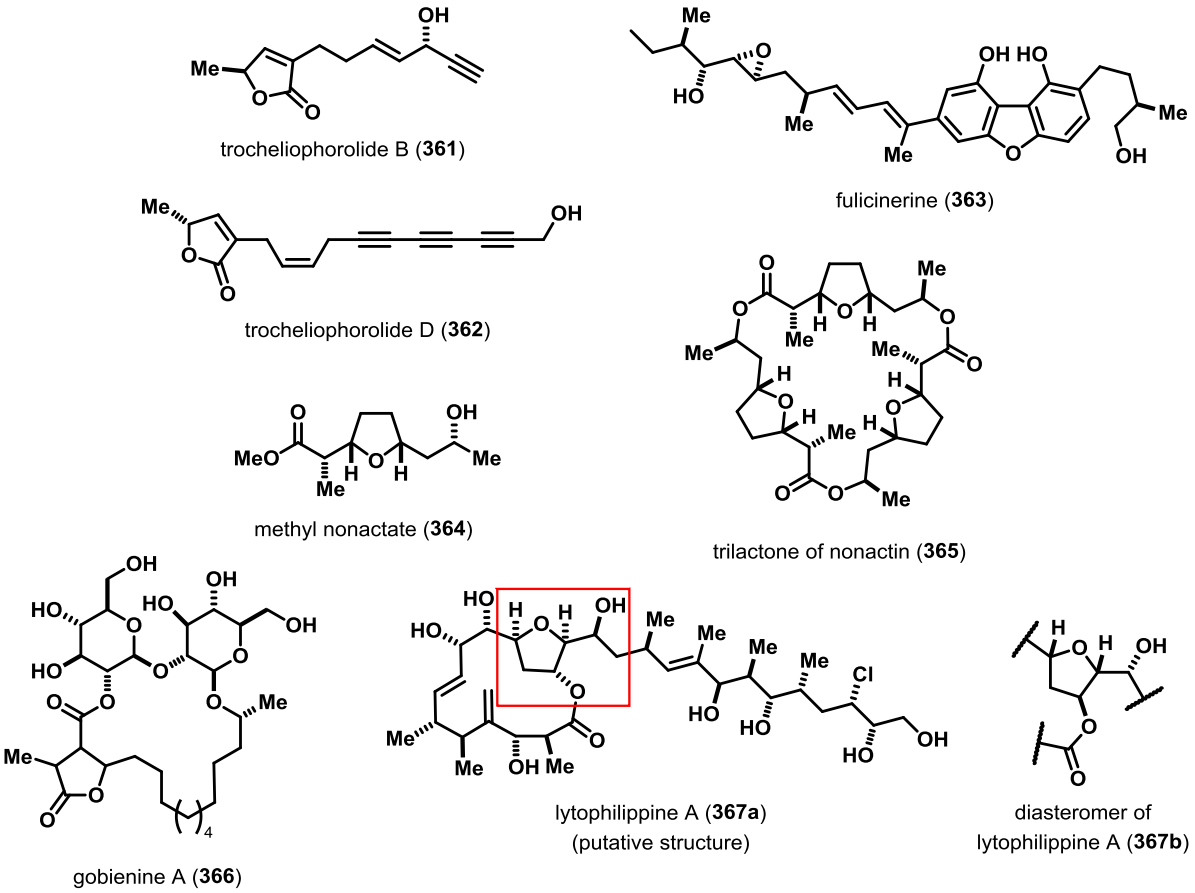


Figure 3.8. Incorrect structures of natural products assigned by the Řezanka group.

Therein, the nOe correlation of the northern 5-membered ring is presented as a *syn*-THF entity in which all protons are exchanging during the NOESY experiment (Figure 3.9). While in this figure all substituents are pointing to the same side, the final stereochemistry of lytophilippine A in Figure 3.8 depicts the bridging ester on the other side, thereby breaking the all-*syn*-configuration from the NOESY spectrum. Further contradictions within the isolation paper can be found concerning stereochemical assignments, connectivity and derivatization.[485]

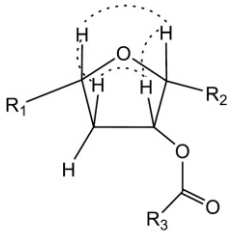


Figure 3.9. NOE correlations for protons on the THF-ring of lytophilippine A (**367a**) by the isolation team.[375a]

In conclusion, the dramatic spectroscopic discrepancies scattered over the entire structure along with the instability of the macrocyclic core provide no obvious clue for the structural revision of chagosensine. The unavailability of the original, even after consultation with the isolation team,[486] make it impossible to elucidate the correct structure of chagosensine.

4 Summary and Conclusion

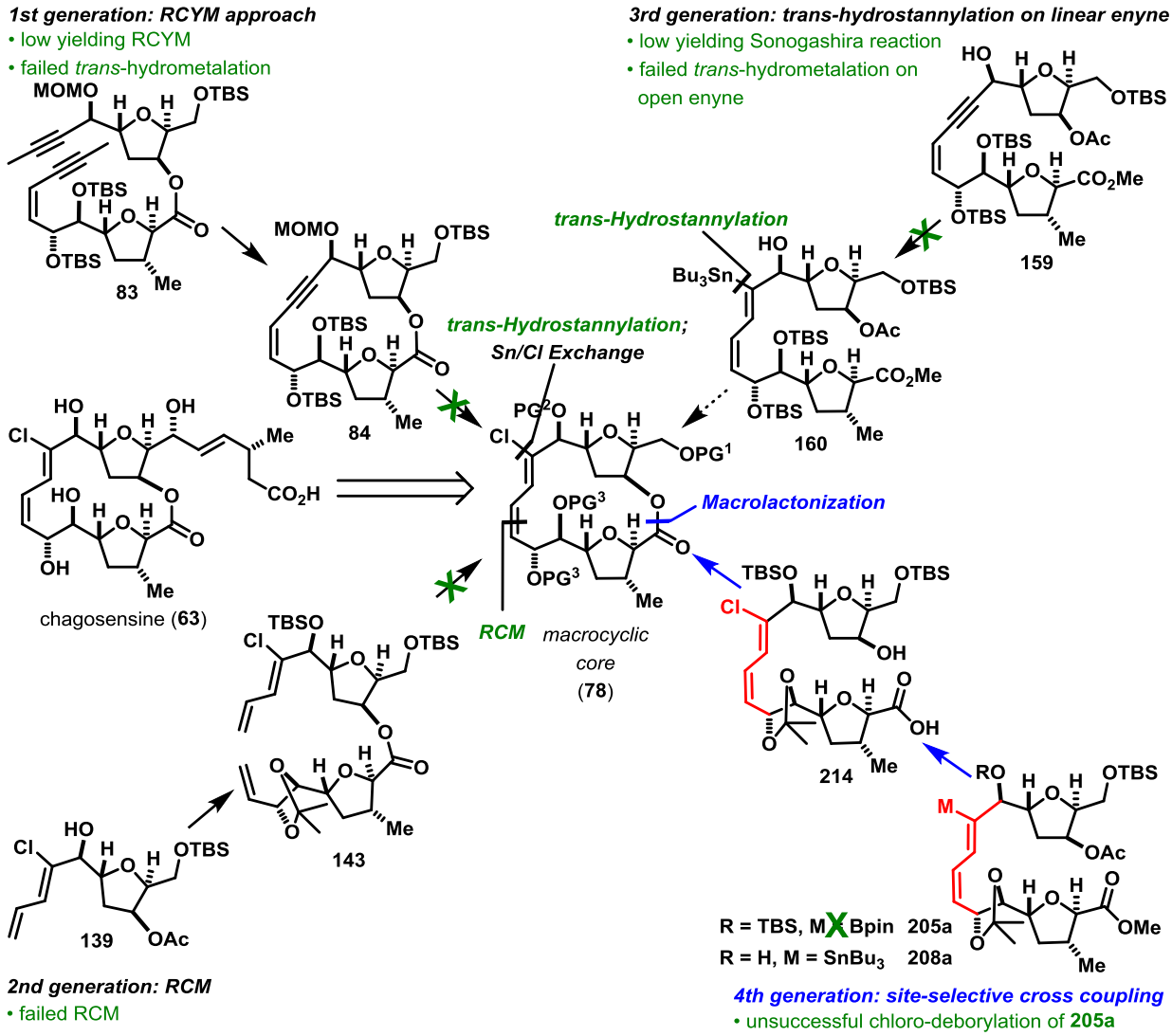
Isolated in 2003 as a secondary metabolite of the sponge *Leucetta chagosensis*, the polyketide chagosensine (**63**) exhibits an intriguing molecular architecture containing a total of 11 stereogenic centers. This remarkably dense array emanates from a highly oxygenated carbon framework decorating the scaffold with four secondary alcohols, two unsaturated moieties and two 2,5-*trans*-disubstitueted tetrahydrofuran rings, which impose considerable strain onto the encircling 16-membered macrocyclic core. Furthermore, the unique *Z,Z*-configured 2-chloro-1,3-diene is arguably the most salient feature, which, to the best of our knowledge, is unprecedented in nature. Despite the favorable biological properties of chlorine-containing small molecules, chagosensine has remained surprisingly unappreciated. Although neither a total synthesis nor a fragment synthesis had been reported yet, the synthetic community is well aware of this marine macrolide, as six methodology reports and four reviews are referring to the isolation paper until 2018. Either the synthetic challenge posed by the target or the untested biological activity might be responsible for this ambivalent recognition. Therefore, still lacking of synthetic validation of the putative structure, we embarked on the synthetic endeavor towards the first total synthesis of chagosensine.

In the initial period, we focused on furnishing the highly adorned 16-membered macrolactone as the core structure (Scheme 4.1). The introduction of the missing side chain was envisaged after establishment of **78**. The ultimate challenge was the stereoselective implementation of the unique chlorodiene embedded in the macrocyclic framework, which was initially envisioned to be furnished subsequently or simultaneously either by ring-closing alkyne (RCAM) or alkene metathesis (RCM). However, neither RCAM of **83** (Scheme 4.1, 1st generation), nor RCM of **143** (Scheme 4.1, 2nd generation) could forge the corresponding 16-membered ring towards the macrocyclic core **78** in sufficient quantities. By strategically separating the disconnection point of ring closure from the synthesis of the challenging *Z,Z*-chlorodiene, a macrolactonization was envisioned to give the strained macrocycle. After pursuing an unsuccessful *trans*-hydrostannylation on enyne **159** (Scheme 4.1, 3rd generation), a conceptually novel sequence comprising of bismetalation, regioselective cross coupling and chloro-demetalation was initially investigated on a model substrate providing promising results with either the boron- or tin-based transformations (Scheme 4.1, 4th generation).

Inspired by a former fragment synthesis of amphidinolide C, the synthesis of the southern fragment was established by M. K. Ilg, whereas the initially troublesome construction of the northern fragment was accomplished as a group effort. Testing of the complementary Suzuki and Stille cross coupling on advanced substrates **205a** and **208a**, respectively, displayed the superiority of the tin-based

transformation. While the gold-mediated chloro-deborylation of dienylboronate **205a** suffered from functional group intolerance, the tin-based sequence afforded the *Z,Z*-configured chloro-1,3-diene motif in high yield with excellent selectivity. Treatment of **214** under forcing Mukaiyama conditions eventually forged the strained macrolactone **78** accessing the core structure of chagosensine for the first time.

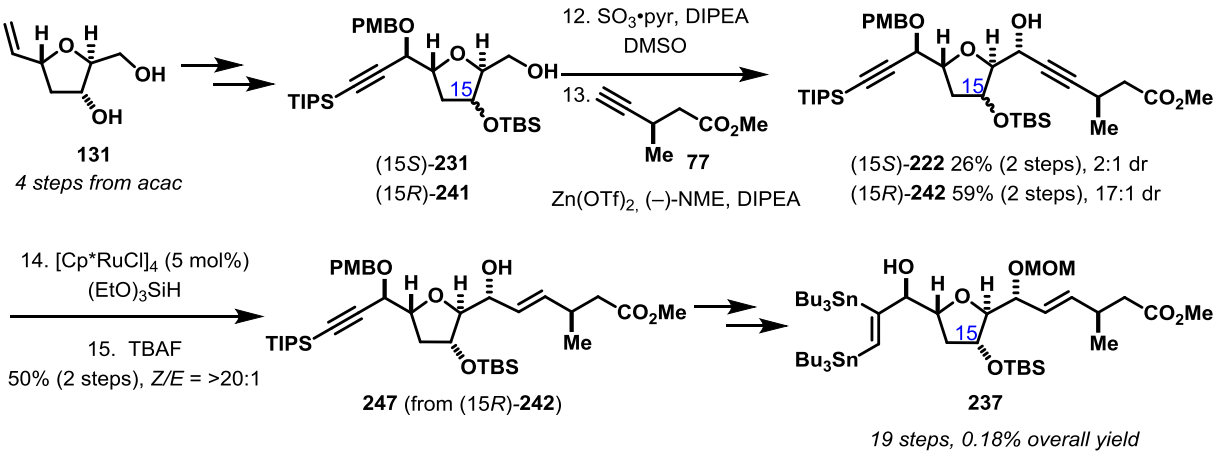
In summary, by exploring the frontiers of the well-established methods of RCAM, RCM and *trans*-hydrometalation, the encountered limitations and the considerable ring strain have led to a conceptually new approach to chlorodienes. Commencing with a site-selective Stille cross coupling at the terminus of a bisstannyl alkene with an elaborated alkenyl iodide, the following chloro-destannylation of the remaining site paved the way for the first synthesis of **78** embodying all structural features of the macrocyclic core of chagosensine (**63**).



Scheme 4.1. Synthetic plan of action towards macrocyclic core structure **78**.

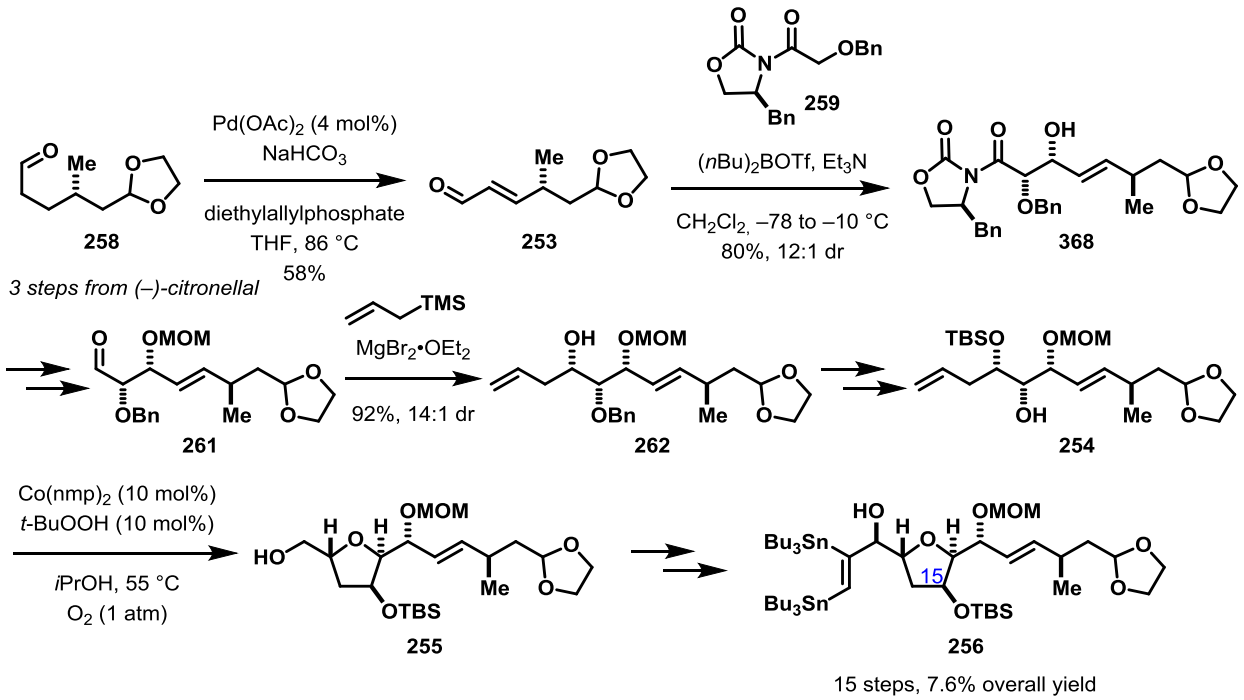
However, facing a low yielding synthesis of this fragmentary macrolactone in combination with an uncertain stereoselective introduction of the side chain, a revised retrosynthetic plan towards **63** was

envisaged. Maintaining the established late-stage transformations, the implementation of the complete northern fragment was anticipated to commence with the previously established diol **131** (Scheme 4.2). After modified Parikh-Doering oxidation of the alcohols (15*S*)-**231** and (15*R*)-**241**, the subsequent Carreira alkynylation was highly dependent on the stereochemical setting of the applied THF moiety. The asymmetric addition of the side chain **77** to (15*R*)-**241** gave the propargyl alcohol **222** in good yield with high diastereoselectivity, whereas alkynylation of aldehyde (15*S*)-**231** suffered from self-aldolization and low facial selectivity (dr = 2:1). Applying the ruthenium-catalyzed *trans*-hydrosilylation on diyne (15*R*)-**242**, the corresponding alkenylsiloxane was obtained in excellent chemo- and stereoselectivity. Following protodesilylation of the crude mixture merged the two regioisomeric addition products to the same alkene **247**, but suffered from a side reaction, which was even more profound in the complementary sequence based on hydrostannylation/protodestannylation. Subsequent protection group management of **247** and introduction of the bis-stannyl alkene entity completed the low yielding synthesis of the northern fragment **237** possessing the epimeric stereochemistry at C15 (15*R*) in regard of chagosensine (15*S* in **63**).



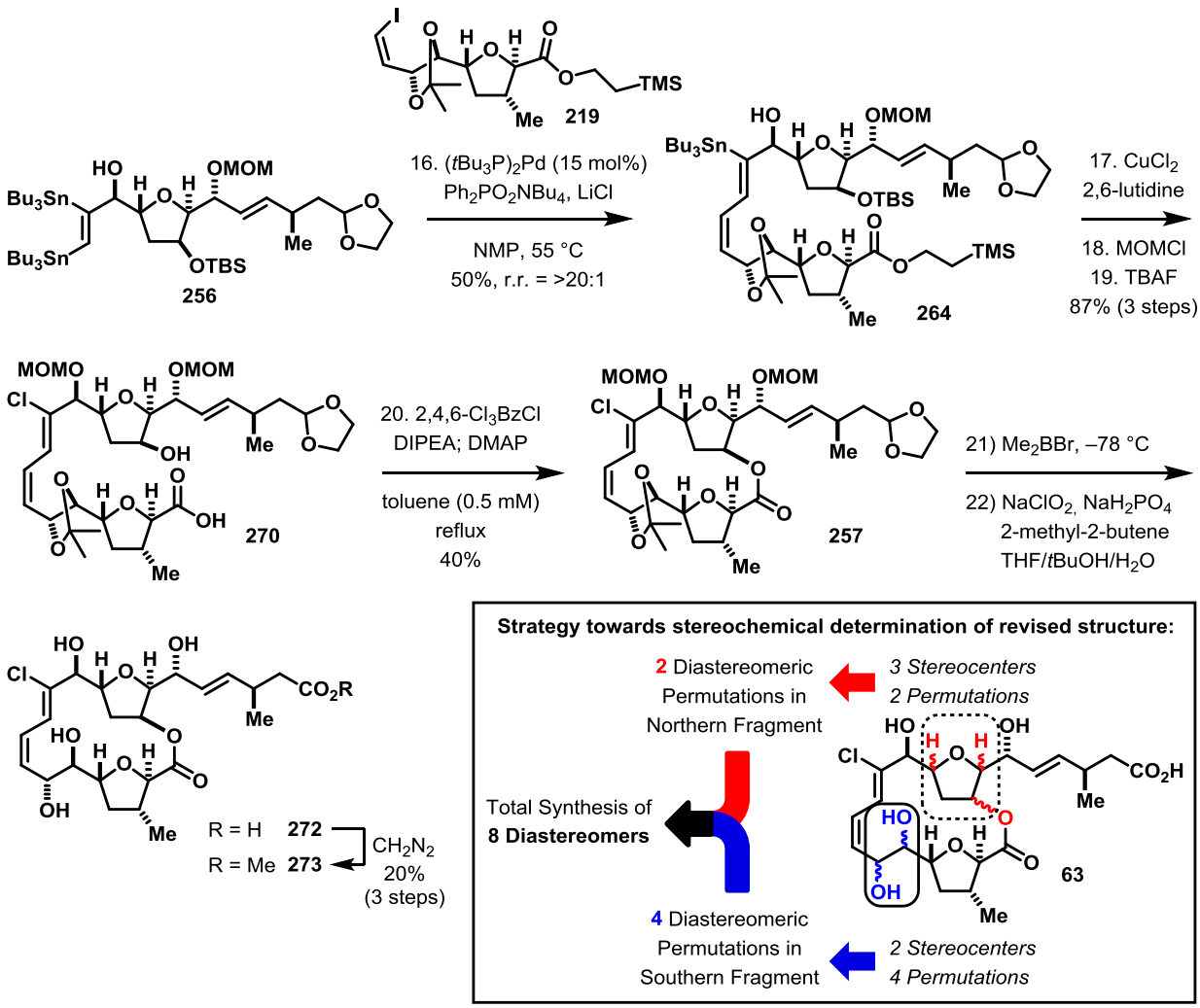
Scheme 4.2. Initial synthesis of the complete northern fragment **237** by *trans*-reduction of propargyl alcohol **247**.

After revision of the retrosynthetic plan for the northern part, an improved route started with (−)-citronellal as the ultimate precursor (Scheme 4.3). Installing the all-*syn* triol entity in **261** by an auxiliary-based *syn* glycolate aldol reaction and subsequent diastereoselective Sakurai allylation set the stage for the oxidative Mukaiyama cyclization of **254**. The following introduction of the bis(alkenyl)stannane moiety accomplished the synthesis of northern fragment **256** in a remarkable overall yield of 7.6% over 15 steps.



Scheme 4.3. Revised total synthesis of the northern fragment **256**.

Subjecting the complete northern fragment **256** and alkenyl iodide **219** to the optimized conditions for site-selective Stille reaction gave the challenging dienylstannane **251** as a single regioisomer in 50% yield (Scheme 4.4). Chloro-destannylation installed the most salient feature of chagosensine, the unique chlorodiene, in high yield, setting the stage for a challenging macrolactonization. An unexpected macrolactonization of a diol-containing *seco*-acid to the corresponding strained 13-membered macrocycle was observed. Therefore, additional protection of the allyl alcohol moiety led to the ring closure of *seco*-acid **270** under forcing Yamaguchi macrolactonization conditions. After global deprotection and Pinnick oxidation, the putative natural product **272** degraded inevitable upon lyophilization. This unexpected instability prompted us to generate the more stable methyl ester **273**. Comparison with the methyl ester **64** of the isolated the natural product displayed major discrepancies along the entire carbon framework in the ^{1}H- and ^{13}C-NMR. After clearly proving the mis-assignment of the stereochemistry by the isolation team, the final part of this thesis aimed for the elucidation of the correct stereochemistry of chagosensine.



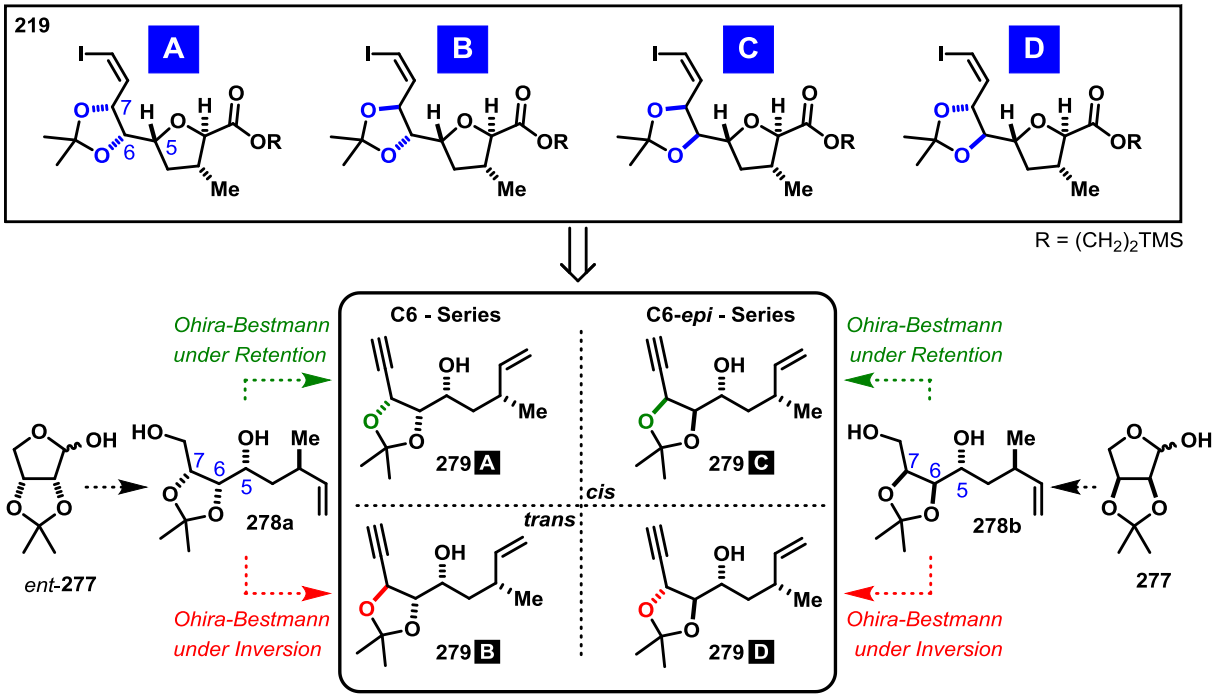
Scheme 4.4. Completed total synthesis of the putative structure (**272**) and strategy towards the stereochemical revision of chagosensine (**63**).

By re-evaluating the subunits with questionable stereochemistry, we identified two major issues in the stereochemical determination of **63** by the isolation team (Scheme 4.4). The most striking peril point was the absolute stereochemistry of the northern THF-ring. In reminiscence of the structural mis-assignment of haterumalide NA (**10**), the misleading *J*-coupling analysis of the THF-ring with the adjacent side chain is inconclusive due to the high conformational flexibility of 5-membered rings and their substituents. Inversion of the stereochemical disposition correlates with three new stereocenters in the second possible permutation of the northern fragment **275**.

Additionally, considerable doubts in the stereochemical assignment of the 6,7-diol in the southern part have resulted from the violated prerequisites for the exciton chirality method (ECD) used to assign this substructure. Without knowledge of the molecular conformation, the application of this method on macrocycles is potentially misleading and has been, to the best of our knowledge, exclusively applied by the T. Řezanka group in the structural assignment of **63** and lytophilippine (**367a**), which are both incorrect. Furthermore, the evidently observed interactions of the attached

chromophores with the adjacent chlorodiene subunit leading to an inconclusive CD splitting renders the necessity of providing four diastereomers. With two permutations in the north and four permutations in the south, additional seven diastereomers (**273b-d** and **351a-d**) had to be synthesized.

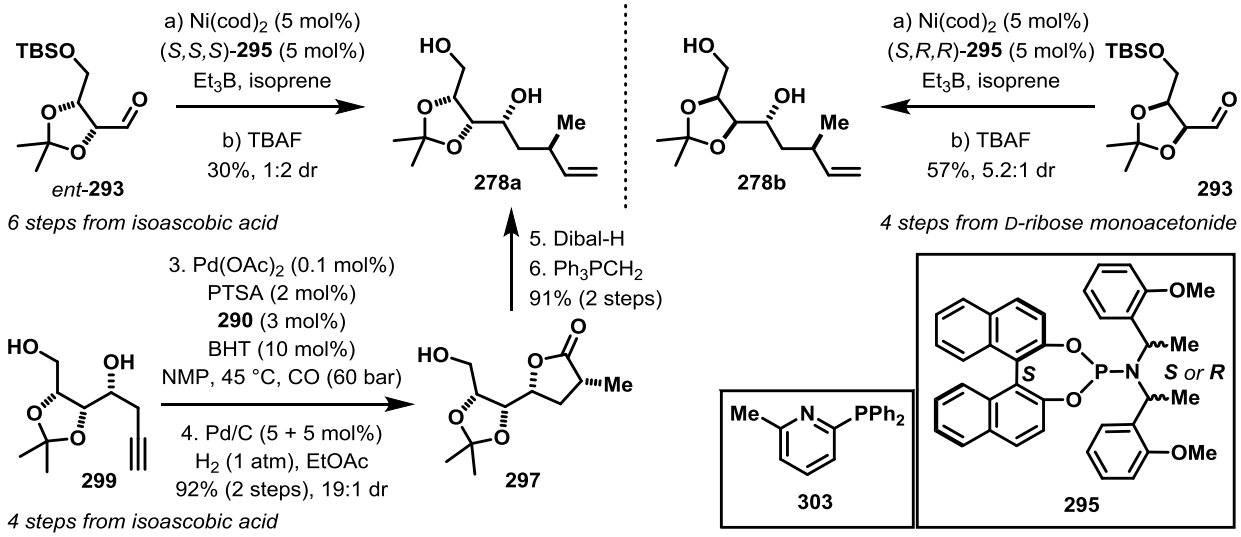
In the new retrosynthetic plan for the four diastereomeric southern fragments **219a-d**, a highly convergent approach was envisioned to provide quick access to the southern coupling partners for the Stille reaction (Scheme 4.5). Intending to forge the *Z*-alkenyl iodide by a radical hydroindation, the *trans* THF-moiety should derive from a chemoselective oxidative cyclization of diastereomeric alcohols **279a-d**. Commencing with two readily available enantiomeric lactols **277** and *ent*-**277** from the "chiral pool", a stereospecific reductive coupling with isoprene was planned to install the homocrotylated adducts **278a** and **278b**. Aiming for the final diversification for accessing all possible permutations, homologation of the corresponding aldehyde moiety was envisioned to either occur under retention or inversion of the α-stereocenter.



Scheme 4.5. Diverted retrosynthetic approach towards four diastereomeric fragments **219a-d**.

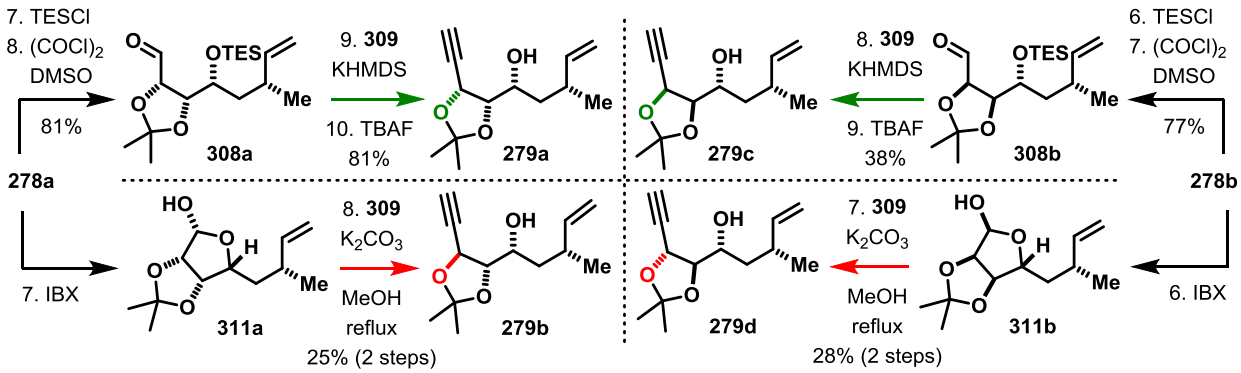
Using phosphoramidite ligand (*S,R,R*)-**295** in the Ni-catalyzed reductive coupling of aldehyde **293** with isoprene, **278b** was obtained in high yield with good selectivity. In contrast to this matched case, a profound substrate-control for *ent*-**293** could not be overruled, giving diastereomer **278a** in low yield and selectivity. In order to outmaneuver the encountered limitations of the diastereoselective nickel-catalyzed reductive coupling, a novel route via lactone **297** was envisaged, featuring diastereoselective reduction of a propargyl ketone, a regioselective palladium-catalyzed carbonylation of **299** and diastereoselective hydrogenation of the corresponding α,β-unsaturated

ester. The following Dibal-H reduction of **297** and a Wittig olefination provided **278a** in five additional steps. Notably, this sequence also marks a new entry point for the synthesis of butenolides and the polyketide amphidinolide C (**72**) and F.



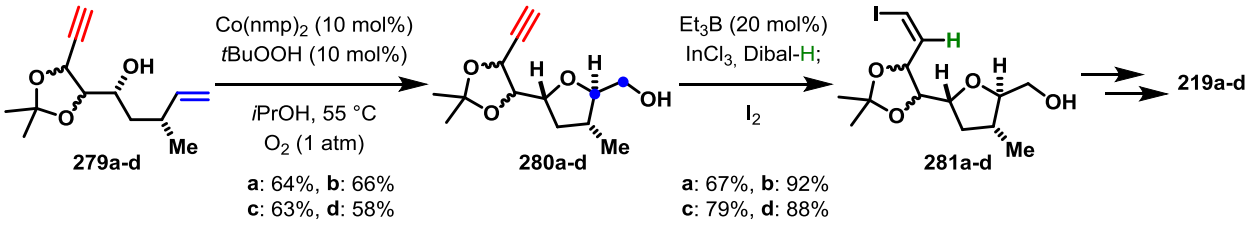
Scheme 4.6. Envisaged catalyst-controlled reductive coupling of **293** and *ent*-**293** with isoprene and synthetic detour for accessing mismatched adduct **278a**.

After accomplishing the stereoselective synthesis of the two diastereomeric diols **278a** and **278b**, the stage was set for a stereodivergent approach towards the four diastereomeric alkynes **279a-d**. By switching the conditions and precursors for the Ohira-Bestmann homologation from an aldehyde to a lactol, the reaction occurred either under retention or inversion of the α-stereogenic center (Scheme 4.7).



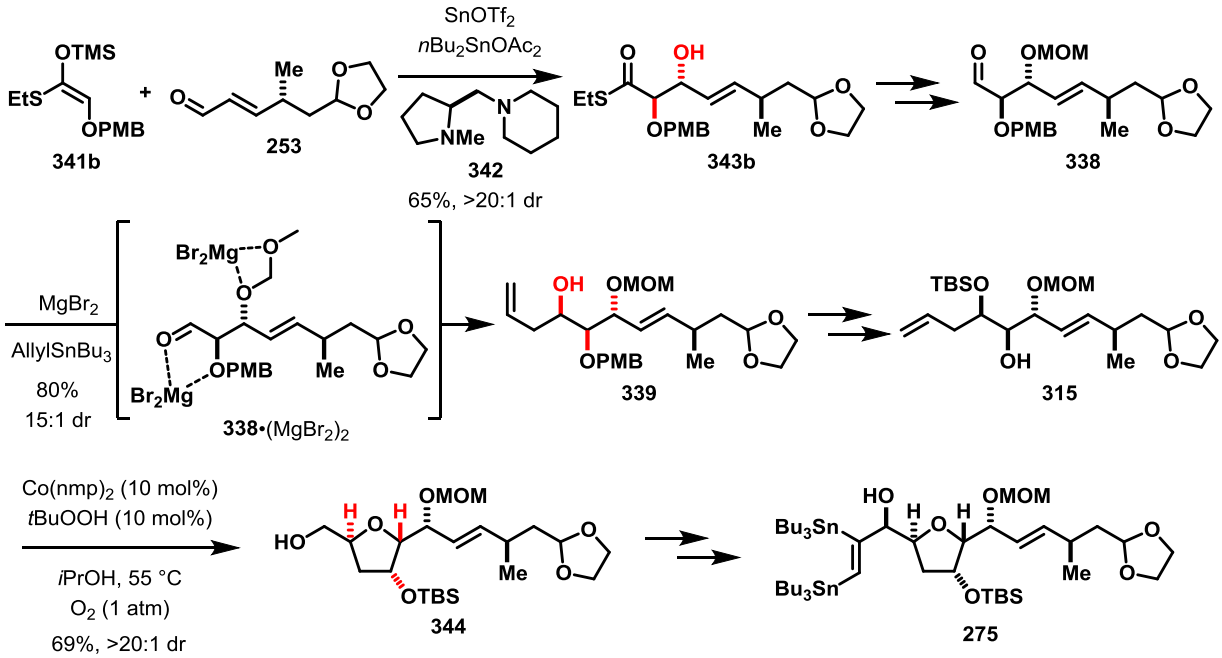
Scheme 4.7. Divergent synthesis of all four diastereomeric precursors **279a-d** for the southern fragment.

With a stereoselective route to all four promising permutations of the southern domain in hand, the parallel synthesis began with the Co-catalyzed oxidative Mukaiyama cyclization of **279a-d**, successfully differentiating between the terminal alkyne and the alkene moiety, (Scheme 4.8). The *Z*-alkenyl iodides **281a-d** were installed by a *trans*-selective radical hydroindation of alkynes **280a-d**, which led to the synthesis of the southern fragments **219a-d** after oxidation and esterification.



Scheme 4.8. Parallel synthesis of four diastereomeric southern fragments **219a-d**.

Differing in the absolute stereochemistry of the THF-ring, the retrosynthetic analysis of diastereomeric northern fragment **275** envisaged to introduce the diol entity in **343b** by an asymmetric *anti* glycolate aldol reaction with aldehyde **253** (Scheme 4.9). While maintaining the remaining diastereoselective transformations, the stereochemical "inversions" of the THF-ring in **344** should be set by pure substrate-control. Subsequent Carreira alkynylation occurring under reagent-control would highlight the stereoselective flexibility of the designed route.

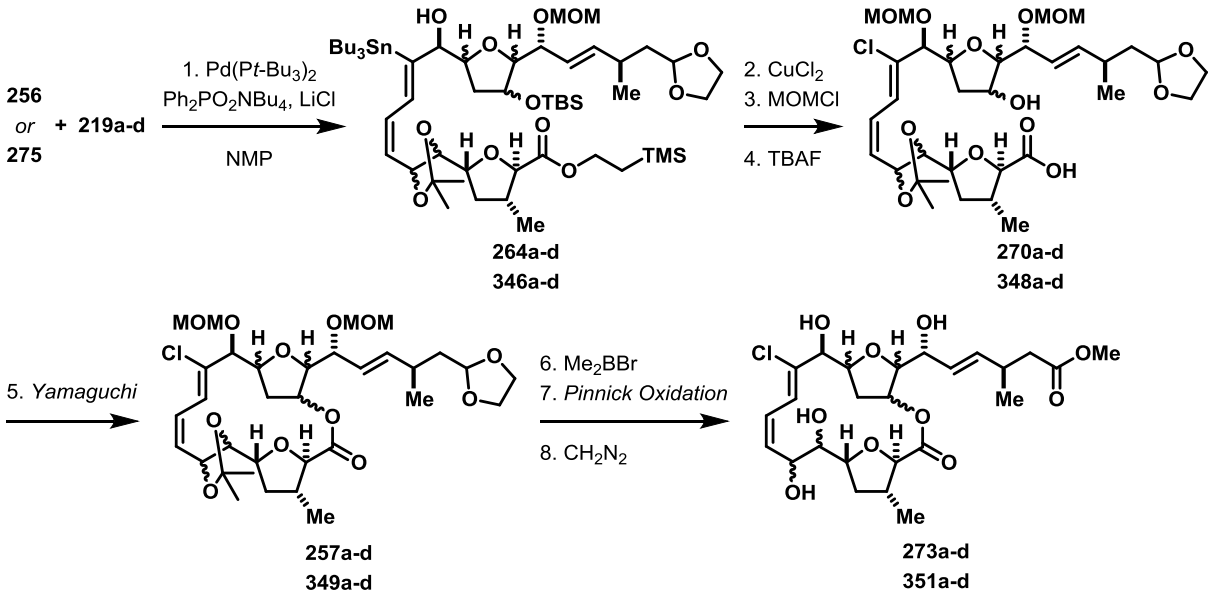


Scheme 4.9. Synthesis of the diastereomeric northern fragment **275** with an inverted stereochemistry of the THF-ring.

An *anti*-selective asymmetric Mukaiyama aldol reaction with aldehyde **253** laid the fundament for the selective synthesis of **275** based on the existing route (Scheme 4.9). Maintaining the sequence of the previous diastereoselective reactions in Scheme 4.3, the modularity of the designed route gave diastereomeric distannane **275** in 14 steps and 4.3% overall yield. In summary, by orchestrating an ensemble of substrate- and reagent-controlled transformations in combination with enantiomeric pure starting materials deriving from the "chiral pool", a concise and highly convergent synthesis of four southern and two northern fragments *en route* to the structural elucidation of chagosensine was achieved.

The divergent synthesis commenced with the "combinatorial" coupling of the two northern fragments **256** and **275** with each of the four southern fragments **219a-d** under the optimized reaction conditions for the site-selective Stille cross coupling, creating a library of eight diastereomers **264a-d** and **346a-d** (Table 4.1).

Table 4.1. Completion of the compound library with promising diastereomers **273a-d** and **351a-d**.



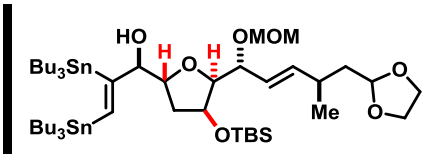
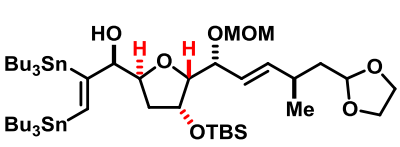
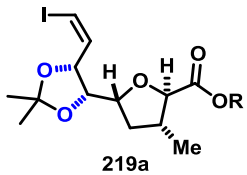
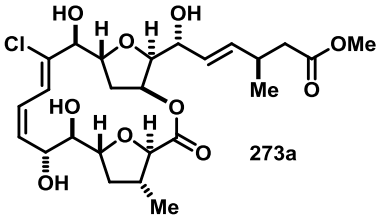
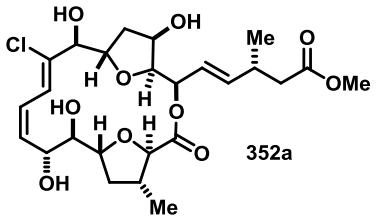
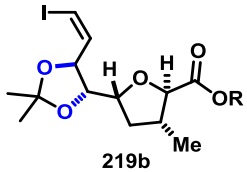
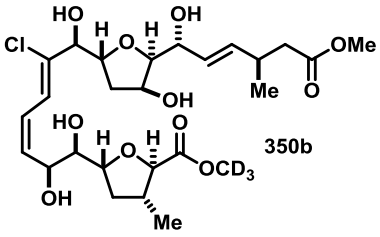
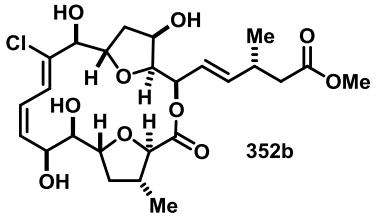
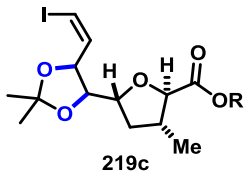
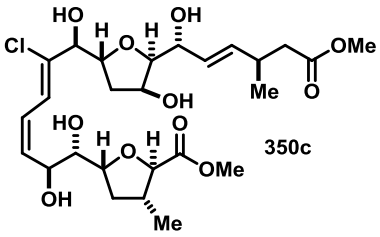
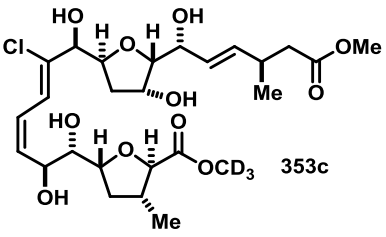
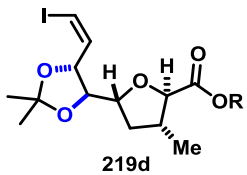
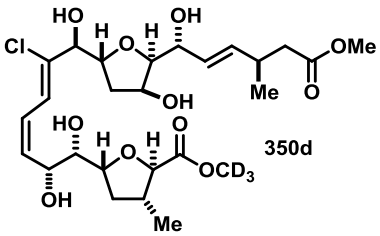
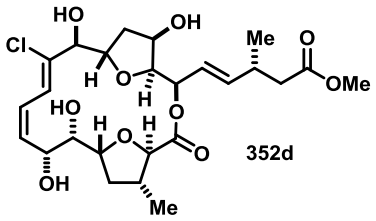
step#	**273a**	**273b**	**273c**	**273d**	**351a**	**351b**	**351c**	**351d**
1	50%	41%	46%	49%	42%	46%	32%	70%
2-4	87%	69%	70%	48%	45%	72%	76%	50%
5	40%	61%	14%	11%	19%	72%	51%	21%
6-8	20%	54%	18%	26%	28%	25%	19%	23%

Following the established sequence comprised of chloro-destannylation, MOM-protection and treatment with TBAF, the parallel synthesis afforded the *seco*-acids **270a-d** and **348a-d** in high yields, setting the stage for the challenging macrolactonization under forcing Yamaguchi conditions. The impact of stereochemistry on pre-organization for ring closure is evident in the varying yields of the different diastereomeric macrolactones **257a-d** and **349a-d** ranging from 11-72%. With all eight macrocycles in hand, the final sequence comprising global deprotection, oxidation and treatment with diazomethane completed the synthesis of **273a-d** and **351a-d.**

After preparative HPLC separation of the *a priori* final compounds, most macrolactones were found to be surprisingly unstable, suffering either from solvolysis to the corresponding open systems **350b-d** and **353c** and/or ring expansion forging the 18-membered macrocycles **352a-d**. Interestingly, within the **273**-series, the putative structure **273a** is the only stable representative with the proposed stereochemistry of the northern THF-ring. Although the solvolysis occurs rather rapidly, the initial

^{1}H-NMR spectra of the short-living, parent 16-membered rings **273b** and **273d** could be recorded for comparison with the natural product, indicating major discrepancies along the entire scaffold. While deuterated methanol opened these 16-membered macrolactones during NMR measurement, the compound **273c** was transferred with methanol into the open bis-methyl ester **350c** before NMR analysis.

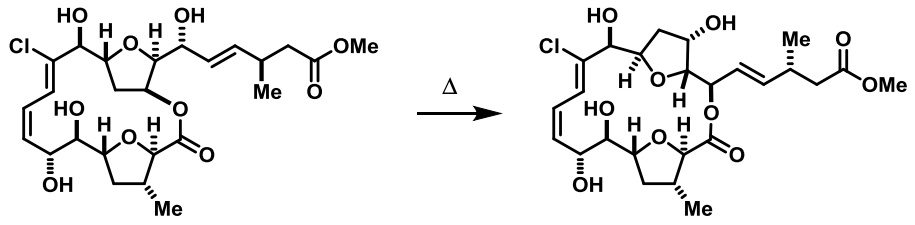
Table 4.2. Final compound table including solvolysis and ring expansion by transesterification.

	 256	 275
 219a	 273a	 352a
 219b	 350b	 352b
 219c	 350c	 353c
 219d	 350d	 352d

Besides suffering from methanolysis of the strained macrolactone at ambient temperature, the **351**-series displayed a more profound degradation pattern including ring expansion by intramolecular attack of the adjacent allyl alcohol at C17. The conformational predisposition of the

stereochemically inverted northern THF-rings must facilitate an intramolecular transesterification releasing considerable ring strain, as the 18-membered analogues **352a-d** seem to be the thermodynamic products. Disregarding macrolactone **352c**, which also underwent methanolysis during NMR analysis, the expanded macrolactones **352a-b** and **352d** were stable upon prolonged exposure to methanol. Regarding the NMR analysis of the parent 16-membered macrolactone, the initially isolated methyl ester **351b** could be confirmed by ^{1}H- and ^{13}C-NMR, while **351c** degraded so rapidly that only a ^{1}H-NMR spectrum could be obtained. Containing the original southern motif, the isolated fraction of the presumable 16-membered macrocycle directly decomposed to a mixture of the ring extended derivative **352a** and the deuterated methyl ester **353a** upon treatment with the NMR solvent. This instability was also observed in case of **351d**, which, based on HPLC analysis, converted immediately under the reaction conditions to the stable 18-membered macrolactone. Interestingly, during Lewis acidic global deprotection of **349d**, a mixture of acetonide containing compounds could be isolated, resembling the putative 16-membered macrocycle **354** and its ring enlarged analogue **355**. Treatment of **354** with the reported NMR solvent mixture induced an immediate transesterification of the highly strained macrolactone to the corresponding 18-membered ring **355**, which was confirmed by HPLC-MS and NMR analysis. As the original natural product was isolated by extraction with methanolic chloroform and was further purified by LC with aqueous methanol, the degradation of the putative natural products **273b-d** and **351a-d** confirms that they do not represent chagosensine.

The formation of the ring extended macrocycles **352a-d** as the exclusive thermodynamic product in the **351**-series prompted us to explore the thermally induced interconversion of the only stable diastereomer **273a**. Slow conversion over 11 days in refluxing toluene afforded the expected 18-membered macrocycle **357** as the thermodynamic product in the **273**-series as well.



273a
(putative structure)

357
(thermodynamic product)

Scheme 4.10. Thermal conversion of the putative structure (**273a**) of chagosensine into 18-mebered macrolactone **357**.

The recorded NMR-studies for the unstable diastereoisomers **273b**, **273d** and **351b-d** and the stable putative isomer **273a** showcased major discrepancies with the natural product in ^{1}H- and ^{13}C-NMR along the entire framework of this intriguing macrolide. Comparison with other natural products bearing similar entities, the existence of an allylic alcohol in proximity to the chlorodiene entity in

chagosensine is highly unlikely. Alongside the scattered deviation in the NMR spectra, the observed absorption maxima of the synthesized compounds mismatch significantly with the reported λ_{max}-value by $\Delta\lambda_{max} > 14$ nm. Furthermore, a false HRMS analysis and a highly questionable structural analysis of a diastereomeric mixture as a single isomer render a structural revision of this marine macrolide based on the reported data impossible.

In summary, despite the unsuccessful attempt to find the correct stereochemistry of chagosensine (**63**), the described efforts mark the first reported synthetic studies towards this natural product. During our four-generation enduring synthetic approach towards the macrocyclic core, we investigated the chemical frontiers of a variety of different transformations such as metathesis, Pd-catalyzed cross coupling, *trans*-hydrometalation and macrolactonization. By establishing a sequence comprising of a novel site-selective Stille reaction with two advanced fragments and a subsequent chloro-destannylation, the synthesis of the unique *Z,Z*-chlorodiene of chagosensine was realized for the first time. The macrolactonization under forcing Yamaguchi conditions gave initial access to the strained 16-membered macrolactone, resulting in the total synthesis of the putative structure of chagosensine.

After identifying two subunits with questionable stereochemical determination by the isolation team, we set off to synthesize the remaining seven diastereoisomers. Facing two likely permutations in the northern part, the previous retrosynthetic analysis provided a valuable entry point to the other diastereomers by switching from a *syn*- to an *anti*-selective asymmetric aldol reaction. The route towards the four diastereomeric southern fragments, differing in the 1,2-diol moiety, marked a proving ground for contemporary transition metal-catalyzed reactions and turned into a new fragment synthesis also applicable to amphidinolide C.

The site-selective Stille reaction turned out to be a reliable and selective methodology, regardless of the different stereochemical arrangements of the cross coupling partners. The following parallel synthesis afforded all diastereomeric isomers of the 16-membered macrolactone. After conducting the final three-step sequence, the strained diastereomers of chagosensine were found to suffer either from methanolysis or ring expansion to the corresponding 18-membered macrolactone. Neither the ^{1}H-NMR spectra of the mixture containing the unstable isomers, nor the data of the stable macrocycles were anywhere close to the reported chemical shifts of the natural product. Despite the unfruitful attempt for stereochemical revision of chagosensine, the herein reported diverted total synthesis of eight diastereoisomers represents a highly convergent and selective route by orchestrating an ensemble of transition metal-catalyzed reactions, stereoselective metal-mediated additions, auxiliary-based transformations and the use of substrates from the “chiral pool” (Figure 4.1). By pushing the frontiers of novel reactions as well as the well-established

transformations, the limitations of the applied methods have been disclosed, which launched the development of conceptually new approaches in the field of stereoselective synthesis. This unforeseen avalanche nicely illustrates the importance of total synthesis in methodology development.

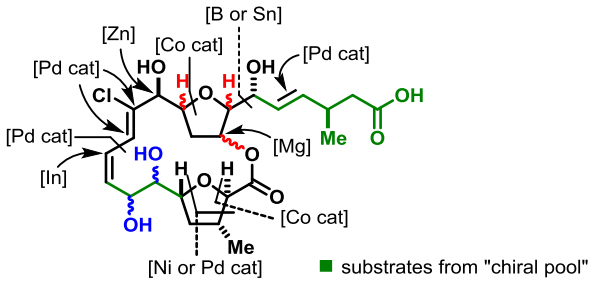


Figure 4.1. Applied metals or metalloids for the diverted synthesis of eight diastereomers of the putative structure of chagosensine – A playground for stereoselective transformation.

In terms of the attempted structural revision of chagosensine, the irreconcilable discrepancies in the spectroscopic data showcase a deep-rooted constitutional mis-assignment by the isolation team. The unavailability of the original raw data, even after consultation with the isolation team, makes it impossible to identify the correct structure of this marine macrolide. Finally, despite a contemporary view of total synthesis as a means for supplying synthetic materials, the current work reinforces a traditional fundamental purpose for the endeavor; structural elucidation of isolated natural products.

5 Experimental Section

5.1 General Experimental Methods

All reactions were carried out under Ar in flame-dried glassware unless water was used as solvent or it is otherwise noted. The following solvents and organic bases were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene); hexane, toluene (Na/K); Et_3N, diisopropylamine, diisopropylethylamine, 2,6-lutidine, HMPA, CH_2Cl_2, DMA, NMP (CaH_2); MeOH, EtOH, *i*-PrOH (Mg, stored over 3 Å MS). DMF, DMSO, 1,4-dioxane, MeCN and pyridine were dried by an adsorption solvent purification system based on molecular sieves. All other commercially available compounds (ABCR, Acros, Alfa Aesar, Aldrich, Fluka, STREM, TCI) were used as received unless otherwise noted. The following compounds were prepared according to the cited protocol: (*Z*)-7-((t-butyldimethylsilyl)oxy)dodeca-8-en-2,10-diyn-4-ol,[178] ((2,4,6-triethylbenzene-1,3,5-triyl)tris(propane-3,1-diyl))tris(diphenylsilanol),[178] Me_2BBr,[487] MOMCl,[488] $PPh_3CH_2I_2$,[489] $Co(nmp)_2$,[222] $Pd(t\text{-BuNC})_2Cl_2$,[490] (*S*)-4-benzyl-3-(2-(benzyloxy)acetyl)oxazolidin-2-one,[491] 4,4,4-trichlorobutene,[235] 4,4,4-trichlormethylstyrene,[131a] diethyl allyl phosphate,[492] tetrabutylammonium diphenylphosphinate,[161a] diazomethane,[493] methylenetriphenylphosphorane.[432]

Thin phase chromatography (TLC) was performed on Macherey-Nagel precoated plates (POLYGRAM® SIL/UV254). Detection was achieved under UV light (254 nm) and by staining with either acidic *p*-anisaldehyde, cerium-ammonium-molybdenate or basic $KMnO_4$ solution.

Flash chromatography was performed with Merck silica gel 60 (40-63 µm pore size) using predistilled or HPLC-grade solvents. In some cases, fine Merck silica gel 60 (15-40 µm pore size) was necessary as indicated within the experimental procedures.

NMR-spectra were recorded on Bruker DPX 300, AMX 300, AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated. Chemical shifts (δ) are reported in ppm relative to TMS; coupling constants (*J*) are given in Hz. Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, hept: heptet, sept: septet, m: multiplet. The abbreviation br indicates a broad signal. ^{13}C spectra were recorded in [^1H]-decoupled manner and the values of the chemical shifts are rounded to one decimal point. Signal assignments were established using NOESY, HSQC and HMBC and other 2D experiments; numbering schemes as shown in the inserts. All spectra from 500 MHz and 600 MHz spectrometers were acquired by the NMR department under the guidance of Dr. Christophe Farès at the Max-Planck-Institut für Kohlenforschung.

IR spectra were recorded on Alpha Platinum ATR (Bruker) at ambient temperature, wavenumbers ($\tilde{\nu}$) are given in cm^{-1}.

Mass spectrometric samples were measured by the department for mass spectrometry at the Max-Planck-Institut für Kohlenforschung under the guidance of Prof. Wolfgang Schrader using the following devices: MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Bruker ESQ3000, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan). The characteristic ion measured by high resolution mass spectrometry is given as the $[M+Na^+]$-adduct, unless otherwise noticed.

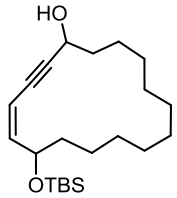
Optical rotations were measured with an A-Krüss Otronic Model P8000-t polarimeter at a wavelength of 589 nm. The values are given as specific optical rotation with exact temperature, concentration (c/(10 mg/mL)) and solvent.

LC-MS analyses were conducted on a Shimadzu LC-MS 2020 instrument (pumps LC-20AD, autosampler SIL-20AC, column oven CTO-20AC, diode array detector SPD-M20A, controller CBM-20A, ESI detector and software Labsolutions) with a ZORBAX Eclipse Plus column (C18 1.8 µm, 4.6 mm ID × 50 mm (Agilent)) or a YMC-ODS-A C18 column (S-5 µm, 120 Å, 4.6 mm ID × 150 mm). A binary gradient of MeCN or MeOH in water was used as eluent at a flow rate of 0.8 mL/min or 1.0 (4.6 mm ID). The oven temperature was kept at 35 °C and the detection wave length at 250 nm. Conditions for each compound are specified below.

5.2 RCAM Approach

5.2.1 Model Studies

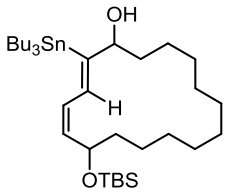
(*Z*)-6-((t-Dimethylsilyl)oxy)cyclohexadec-4-en-2-yn-1-ol (**80**). 5 Å MS (200 mg) was added to a solution of (*Z*)-7-((t-butyldimethylsilyl)oxy)dodeca-8-en-2,10-diyn-4-ol (**79**) (28.5 mg, 68.1 µmol) in toluene (50 mL) at ambient temperature and the mixture was stirred for 30 min. The mixture was heated to 110 °C before a freshly prepared solution of ((2,4,6-triethylbenzene-1,3,5-triyl)tris(propane-3,1-diyl))tris(diphenylsilanol) (13.2 mg, 15.0 µmol, 22 mol%) and complex **Mo2** (9.1 mg, 13.6 µmol, 20 mol%) in toluene (1 mL) was added, which had been stirred for 5 min prior to use. Stirring was continued at 110 °C for 30 min. The mixture was cooled to ambient temperature, the molecular sieves were filtered off through a pad of Celite®, which was carefully rinsed with EtOAc, and the combined filtrates were concentrated. The residue was purified by flash chromatography (hexane/EtOAc 20:1 to 4:1) to afford the title compound as a colorless oil (22.3 mg, 90%); the diastereomers could be separated by flash chromatography (hexane/*t*-butyl methyl ether 20:1).



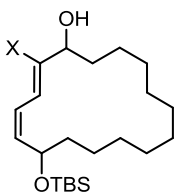
Spectral data for the faster eluting diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84 (dd, *J* = 10.9, 8.8 Hz, 1H), 5.48 (ddd, *J* = 10.8, 2.1, 0.8 Hz, 1H), 4.63 (td, *J* = 8.2, 4.9 Hz, 1H), 4.55 (ddd, *J* = 7.8, 5.1, 2.0 Hz, 1H), 1.79–1.66 (m, 2H), 1.53 (brs, 1H), 1.44–1.28 (m, 18H), 0.89 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 107.7, 95.2, 81.5, 71.2, 63.6, 37.9, 36.9, 27.1 (2C), 26.9, 26.7, 26.1, 25.63, 25.60, 23.74, 23.71, 18.4, –4.1, –4.6 ppm.

Spectral and analytical data for the slower eluting diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (dd, *J* = 10.9, 8.9 Hz, 1H), 5.48 (d, *J* = 10.9 Hz, 1H), 4.66–4.52 (m, 2H), 1.89–1.65 (m, 4H), 1.47–1.28 (m, 17H), 0.89 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 147.1, 107.7, 95.0, 81.8, 71.2, 63.2, 37.7, 36.7, 27.3, 27.1, 26.72, 26.71, 26.1, 26.0, 25.7, 23.8, 23.7, 18.3, –4.1, –4.7 ppm. IR (film): $\tilde{\nu}$ = 3432, 2927, 2856, 1461, 1361, 1071, 1018, 907, 835, 776, 732 cm^{-1}. MS (ESIpos) m/z (%): 387.3 (100 (M+Na)). HRMS (ESIpos): m/z calcd for $C_{22}H_{40}O_2SiNa$: 387.2690, found: 387.2692.

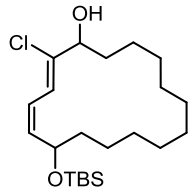
(2*Z*,4*Z*)-6-((*t*-Dimethylsilyl)oxy)-2-(tristannyl)cyclohexadeca-2,4-dien-1-ol (81). A solution of Bu_3SnH (5.5 µL, 20 µmol) in CH_2Cl_2 (0.1 mL) was added dropwise over 90 min *via* syringe pump to a solution of enyne **80** (7.1 mg, 19 µmol) and $[Cp^*RuCl]_4$ (1.0 mg, 3.7 µmol, 19 mol%) in CH_2Cl_2 (0.1 mL). All volatiles were evaporated and the residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 19:1) to afford the title compound as a pale yellow oil (10 mg, 79%, *Z*/*E* > 20:1, α/β > 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 11.4 Hz, J_{SnH} = 115 Hz, 1H), 5.93 (dt, *J* = 11.2, 1,2 Hz, 1H), 5.42 (ddd, *J* = 11.2, 8.6, 1,1 Hz, 1H), 4.62 (q, *J* = 7.0 Hz, 1H), 4.24 (ddd, *J* = 9.6, 4.7, 2.9 Hz, 1H), 1.54–1.38 (m, 12H), 1.36–1.25 (m, 20H), 1.03–0.96 (m, 5H), 0.91–0.86 (m, 10H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4, 137.3, 135.1, 127.2, 81.1, 68.5, 37.23, 37.18, 29.4, 27.6, 27.5, 27.4, 27.2, 27.0, 26.6, 26.3, 26.1, 25.3, 24.3, 18.4, 13.9, 11.7, −4.0, −4.5 ppm. ^{119}Sn NMR (150 MHz, $CDCl_3$): δ = –53.5 ppm. IR (film): $\tilde{\nu}$ = 3481, 2954, 2926, 2855, 1462, 1251, 1071, 1005, 836, 775, 676 cm^{-1}. MS (EI) *m/z* (%): 599 (13), 597 (12), 468 (14), 467 (57), 466 (25), 265 (45), 464 (19), 463 (25), 365 (47), 364 (19), 363 (35), 362 (14), 361 (19), 281 (11), 251 (16), 249 (13), 218 (18), 217 (100), 195 (12), 193 (11), 179 (12), 177 (17), 175 (12), 135 (35), 121 (34), 107 (12), 95 (16), 93 (21), 91 (12), 81 (16), 79 (16), 75 (24), 73 (13), 67 (17). HRMS (ESIneg): *m/z* calcd for $C_{34}H_{67}O_2SiSn$ $[M-H]^-$: 655.3937, found: 655.3946.



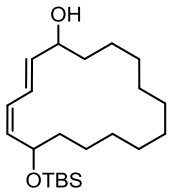
(*Z*,*Z*)-Chlorodiene 82a (X = Cl) and Diene 82b (X = H). A solution of dienylstannane **81** (9.7 mg, 15 µmol) in THF (0.2 mL) was added to a suspension of copper(II) chloride (5.0 mg, 37 µmol) in THF (0.15 mL). The resulting mixture was stirred at ambient temperature for 24 h. The mixture was diluted with *t*-butyl methyl ether (2.5 mL) and the reaction was quenched with sat. $NaHCO_3$ (3 mL). The aq. phase was extracted with *t*-butyl methyl ether (3 × 4 mL). The combined organic phases were washed with brine



(5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 15:1 to 10:1) to afford chlorodiene **82a** (4.0 mg, 67%) along with diene **82b** (0.3 mg, 6%) as a colorless oil each.



Spectral and analytical data of **82a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 11.0, 0.9 Hz, 1H), 6.30 (td, *J* = 11.0, 1.3 Hz, 1H), 5.64 (ddd, *J* = 11.0, 8.4, 0.9 Hz, 1H), 4.49 (dddd, *J* = 8.3, 7.2, 5.6, 1.3 Hz, 1H), 4.33 (dd, *J* = 10.2, 4.6 Hz, 1H), 1.93–1.78 (m, 2H), 1.71–1.65 (m, 1H), 1.53–1.49 (m, 1H), 1.45–1.40 (m, 1H), 1.38–1.30 (m, 11H), 1.23–1.07 (m, 4H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.6, 137.4, 122.0, 121,1, 75.4, 69.2, 37.1, 34.7, 27.6, 27.5, 27.1, 26.9, 26.3, 26.0, 25.9, 25.2, 24.2, 18.3, –4.1, –4.6 ppm. IR (film): $\tilde{\nu}$ = 3368, 2927, 2856, 1727, 1461, 1360, 1251, 1074, 835, 775, 734, 663, 584 cm^{-1}. MS (ESIpos) *m/z* (%): 423.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{41}O_2ClSiNa$: 423.2457, found: 423.2453.



Spectral and analytical data for **82b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (dd, *J* = 15.3, 11.2 Hz, 1H), 5.94 (t, *J* = 11.1 Hz, 1H), 5.54 (dd, *J* = 15.1, 8.9 Hz, 1H), 5.42 (dd, *J* = 11.0, 8.5 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 4.19 (td, *J* = 9.4, 4.2 Hz, 1H), 1.77–1.69 (m, 2H), 1.46–1.40 (m, 2H), 1.36–1.29 (m, 12H), 1.17–1.06 (m, 4H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 ppm (s, 3H). IR (film): $\tilde{\nu}$ = 3433, 2926, 2855, 1729, 1461, 1257, 1074, 948, 835, 775, 670 cm^{-1}. MS (ESIpos) *m/z* (%): 389.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{42}O_2SiNa$: 389.2846, found: 389.2845.

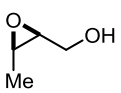
5.3 RCM Approach

5.3.1 Synthesis of Southern Acid Fragements 124a and 124b

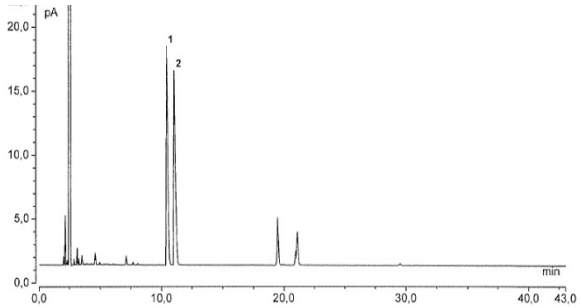
(*Z*)-But-2-en-1-ol (S1). Quinoline (4.21 mL, 35.7 mmol) was added to a suspension of Pd/$BaSO_4$ (10%, 1.90 g, 17.8 mmol) in methanol (125 mL) and the resulting mixture was stirred for 20 min at ambient temperature. 2-Butyn-1-ol (**112**) (25.0 g, 357 mmol) was added and seven balloons of hydrogen were slowly bubbled through the suspension over 12 h. The reaction progress was monitored by GC-MS and the reaction was immediately stopped by replacing the H_2 atmosphere with Ar as soon as the starting material was fully consumed. The mixture was filtered through a pad of Celite® eluting with CH_2Cl_2 (40 mL). The resulting yellow solution was carefully concentrated via distillation (Vigreux column, 400 mbar, 30 °C) and the residue distilled (75 mbar, 75–80 °C) to afford the title compound as a pale yellow liquid (16.8 g, 232 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64–5.59 (m, 2H), 4.21 (d, *J* = 3.1 Hz, 1H), 4.20 (d, *J* = 4.6 Hz, 1H), 1.67 (d, *J* = 5.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 1 29.3, 127.4, 58.4, 13.1 ppm. IR (film): $\tilde{\nu}$ = 3407, 3024, 2932, 1738, 1657, 1446, 1378, 1260, 1040, 813, 696 cm^{-1}. MS (EI) *m/z* (%): 72 (29), 57 (100), 54

(12), 43 (30), 41 (20), 39 (30), 31 (12), 29 (25), 27 (12). HRMS (EI): *m/z* calcd for C_4H_8O: 72.0575, found: 72.0575. The analytical and spectroscopic data are in agreement with those reported in the literature.[494]

((2*S*,3*R*)-3-Methyloxiran-2-yl)methanol (S2). A 500 mL jacketed Schlenk flask was charged with



activated powdered 4 Å MS (14 g) and CH_2Cl_2 (500 mL) and the resulting suspension was cooled to –20 °C. (+)-Diethyl L-tartrate (2.45 g, 11.9 mmol) and Ti(O*i*-Pr)$_4$ (2.94 mL, 9.92 mmol) were added, followed by allylic alcohol **S1** (14.3 g, 198 mmol). The mixture was stirred for 45 min at the same temperature before *t*-BuOOH (5.5 M in decane, 54 mL, 0.30 mol) was added *via* a dropping funnel over 60 min. Stirring was continued for 40 h at –20 °C. For work up, the septum was removed, dimethyl sulfide (21.8 mL, 297 mmol) was added and the resulting mixture stirred open to the atmosphere at ambient temperature for 24 h. The mixture was filtered through a pad of Celite® which was rinsed with CH_2Cl_2 (300 mL). The combined filtrates were evaporated and the residue was purified by flash chromatography (pentane/Et_2O 4:1) followed by distillation (12 mbar, 59–64 °C) to yield the title compound as a colourless oil (12.9 g, 74%, 90% *ee*). $[\alpha]_D^{20}$ = –4.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (dq, *J* = 11.3, 3.6 Hz, 1H), 3.68 (ddd, *J* = 11.6, 6.2, 3.7 Hz, 1H), 3.19–3.11 (m, 2H), 2.09 (brs, 1H), 1.31 (d, *J* = 5.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 60.8, 56.9, 53.0, 13.5 ppm. IR (film): $\tilde{\nu}$ = 3397, 2930, 1451, 1040, 986, 877, 829, 783, 731 cm^{-1}. MS (EI) *m/z* (%): 45 (100), 44 (43), 43 (48), 31 (32), 29 (26), 27 (16). HRMS (ESIpos): *m/z* calcd for $C_4H_8O_2Na$: 111.0416, found: 111.0416. The *ee* was determined by GC (30 m, BGB-176/BGB-15 G/618, 80 1/min 120 8/min 220 3/min iso, flow rate 0.50 bar H_2: minor enantiomer t_R = 10.7 min, major enantiomer t_R = 11.1 min). The analytical and spectroscopic data are in agreement with those reported in the literature.[495]



No.	Ret.Time min	area-% %
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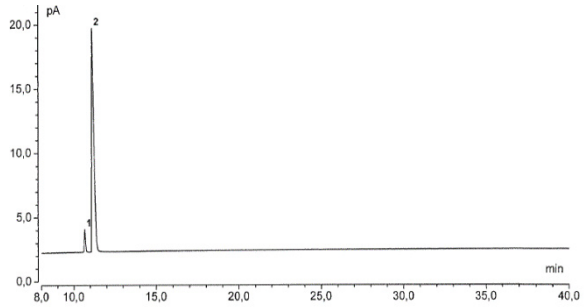
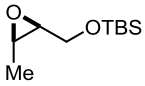
2	11,05	49,90



No.	Ret.Time min	area-% %
1	10,67	4,77
2	11,10	95,23

***t*-Dimethyl(((2*S*,3*R*)-3-methyloxiran-2-yl)methoxy)silane (113).** Imidazole (12.9 g, 190 mmol), DMAP



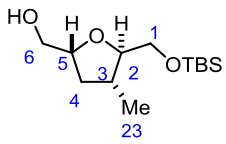
(892 mg, 7.30 mmol) and TBSCl (26.5 g, 176 mmol) were added to a solution of epoxy alcohol **S2** (12.9 g, 146 mmol) in CH_2Cl_2 (280 mL) at 0 °C. The resulting mixture was

stirred at ambient temperature for 3.5 h. The reaction was quenched with sat. NH_4Cl (200 mL) and the aq. phase extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (pentane/Et_2O 99:1) to yield the title compound as a colourless oil (28.4 g, 96%). $[\alpha]_D^{20}$ = +7.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.76 (d, *J* = 11.5, 4.8 Hz, 1H), 3.67 (ddd, *J* = 11.6, 6.0 Hz, 1H), 3.05 (qd, *J* = 5.5, 4.3 Hz, 1H), 2.99 (dt, *J* = 6.0, 4.6 Hz, 1H), 1.25 (d, *J* = 5.5 Hz, 3H), 0.90 (s, 9H), 0.082 (s, 3H), 0.076 (s, 3H) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 61.9, 57.1, 52.4, 25.9, 18.5, 13.5, –5.2, –5.3 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1472, 1391, 1361, 1254, 1091, 1006, 975, 939, 886, 834, 775, 666 cm^{-1}. MS (EI) *m/z* (%): 145 (46), 116 (11), 115 (100), 101 (65), 85 (25), 75 (38), 73 (20), 59 (30). HRMS (ESIpos): *m/z* calcd for $C_{10}H_{22}O_2SiNa$: 225.1281, found: 225.1281.

(2*R*,3*R*)-1-((*t*-Butyldimethylsilyl)oxy)-3-methylhex-5-en-2-ol (114). A solution of allylmagesnium chloride (2 M in THF, 22.2 mL, 44.5 mmol) was added to a suspension of copper(I) iodide (847 mg, 4.45 mmol) in THF (70 mL) at –25 °C. The resulting mixture was stirred for 10 min, before a solution of compound **113** (6.00 g, 29.6 mmol) in THF (20 mL) was added dropwise over 30 min. The resulting mixture was stirred at −25 °C for 6 h. The reaction was quenched with sat. NH_4Cl (50 mL) and the aq. phase extracted with *t*-butyl methyl ether (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 300:1) to afford the title compound as a pale yellow oil (5.57 g, 77%, r.r. 10:1) and its regioisomer **S3** as a colourless oil (310 mg, 4%). $[\alpha]_D^{20}$ = –13.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (dddd, *J* = 16.8, 10.1, 7.9, 6.4 Hz, 1H), 5.09–4.97 (m, 2H), 3.70 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.48 (dd, *J* = 9.6, 7.7 Hz, 1H), 3.41 (td, *J* = 7.4, 3.0 Hz, 1H), 2.54 (brs, 1H), 2.43–2.34 (m, 1H), 1.95 (dddt, *J* = 13.9, 8.9, 7.9, 1.1 Hz, 1H), 1.66 (dddd, *J* = 12.9, 11.0, 5.8, 2.8 Hz, 1H), 0.90 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.3, 116.2, 75.2, 65.2, 37.3, 35.7, 26.0, 18.4, 15.2, –5.2, −5.3 ppm. IR (film): $\tilde{\nu}$ = 3484, 2955, 2929, 2858, 1463, 1362, 1254, 1093, 993, 911, 835, 777, 670 cm^{-1}. MS (EI) *m/z* (%): 187 (15), 145 (13), 105 (57), 95 (100), 89 (13), 75 (82), 73 (25), 67 (11). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{28}O_2SiNa$: 267.1751, found: 267.1751.

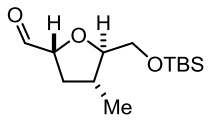
Spectral and analytical data of the regioisomer **S3**: $[\alpha]_D^{20}$ = +2.1 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1H), 5.09–4.97 (m, 2H), 4.02 (qd, *J* = 6.5, 2.7 Hz, 1H), 3.76 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.72 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.15–2.06 (m, 2H), 1.69 (dddd, *J* = 10.2, 8.7, 4.0, 2.7 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.3, 116.4, 70.8, 65.1, 44.9, 30.1, 26.0, 19.5, 18.2, −5.5, −5.5 ppm. IR (film): $\tilde{\nu}$ = 3443, 2956, 2929, 2858, 1472, 1362, 1254, 1094, 992, 911, 836, 776, 670 cm^{-1}. MS (EI) *m/z* (%): 105 (63), 95 (34), 75 (100), 73 (16). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{28}O_2SiNa$: 267.1751, found: 267.1749.

((2*R*,4*R*,5*R*)-5-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyltetrahydrofuran-2-yl)methanol (115). A



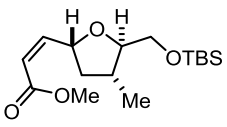
solution of alcohol **114** (4.00 g, 16.4 mmol) in *i*-PrOH (10 mL) was added to a solution of $Co(nmp)_2$ (925 mg, 1.64 mmol) in *i*-PrOH (90 mL). The pale red solution was purged with O_2 for 15 min before *t*-BuOOH (0.29 mL, 1.64 mmol) was added in one portion. The mixture was stirred at 55 °C under oxygen atmosphere (balloon) for 5 h, during which time the solution turned green. After cooling to ambient temperature, the solvent was evaporated. The residue was partitioned between sat. NH_4Cl (50 mL) and *t*-butyl methyl ether (50 mL) and the aq. phase extracted with *t*-butyl methyl ether (2 × 80 mL). The combined organic phases were washed with water (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 25:1 to 20:1) to yield the title compound as a pale yellow oil (3.36 g, 79%). $[\alpha]_D^{20}$ = −16.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (dtd, *J* = 9.8, 5.7, 3.2 Hz, 1H, H-5), 3.69 (ddd, *J* = 11.6, 6.4, 3.2 Hz, 1H, H-6), 3.69 (AB, *J* = 11.0, 4.5 Hz, 1H, H-1), 3.66 (AB, *J* = 11.0, 4.5 Hz, 1H, H-1), 3.53 (dt, *J* = 8.4, 4.5 Hz, 1H, H-2), 3.49 (dt, *J* = 11.9, 5.8 Hz, 1H, H-6), 2.15 (dddq, *J* = 10.8, 8.2, 7.0, 6.6 Hz, 1H, H-3), 2.06 (ddd, *J* = 12.0, 7.1, 5.8 Hz, 1H, H-4), 1.95 (t, *J* = 6.2 Hz, 1H, 6-OH), 1.41 (ddd, *J* = 11.9, 10.5, 9.8 Hz, 1H, H-4), 1.07 (d, *J* = 6.6 Hz, 3H, H-23), 0.90 (s, 9H, TBS), 0.07 (s, 6H, TBS) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 86.2 (C2), 79.3 (C5), 65.1 (C6), 65.0 (C1), 36.8 (C4), 36.5 (C3), 26.1 (3C, TBS), 18.6 (TBS), 17.5 (C23), –5.1 (TBS), –5.2 ppm (TBS). IR (film): $\tilde{\nu}$ = 3432, 2955, 2929, 2857, 1729, 1462, 1388, 1361, 1253, 1128, 1085, 1054, 1005, 906, 834, 775, 729, 649 cm^{-1}. MS (EI) *m/z* (%): 229 (15), 203 (49), 185 (29), 117 (28), 115 (17), 111 (12), 105 (28), 103 (10), 101 (11), 93 (33), 89 (10), 83 (12), 81 (22), 75 (100), 73 (48), 69 (21), 59 (17), 57 (21), 55 (22), 43 (12), 41 (18). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{28}O_3SiNa$: 283.1700, found: 283.1700.

(2*R*,4*R*,5*R*)-5-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyltetrahydrofuran-2-carbaldehyde (276).

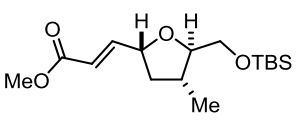


Hünig's base (11.0 mL, 63.4 mmol) was added to a solution of alcohol **115** (3.28 g, 12.7 mmol) in CH_2Cl_2 (110 mL) at –25 °C. In a second flask, a suspension of sulfur trioxide pyridine complex (5.04 g, 31.7 mmol) in DMSO (9.00 mL, 126 mmol) was stirred for 10 min at ambient temperature before it was added to the alcohol solution at –25 °C (rinsing with CH_2Cl_2 (5 mL)). The resulting mixture was stirred for 30 min at –25 °C. The mixture was poured into pH 7 phosphate buffer (50 mL) and *t*-butyl methyl ether (50 mL) and the aq. phase was extracted with *t*-butyl methyl ether (3 × 100 mL). The combined organic phases were washed with pH 7 phosphate buffer (100 mL) and brine (100 mL) before they were dried over Na_2SO_4, filtered and concentrated under high vacuum to yield the crude aldehyde as a yellow oil, which was used in the next step without further purification. For analytical purposes an aliquot was purified by flash chromatography (hexane/*t*-butyl methyl ether 9:1): $[\alpha]_D^{20}$ = +3.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (d, *J* = 2.2 Hz, 1H), 4.28 (ddd, *J* = 8.8, 7.4, 2.2 Hz, 1H), 3.77–3.71 (m, 1H), 3.68 (d, *J* =

4.1 Hz, 1H), 3.64 (dd, *J* = 7.9, 4.0 Hz, 1H), 2.35 (dt, *J* = 12.2, 7.4 Hz, 1H), 2.22 (dtd, *J* = 14.2, 7.4, 2.4 Hz, 1H), 1.58 (dt, *J* = 12.2, 9.0 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.1, 87.8, 82.8, 64.3, 36.5, 35.4, 26.1, 18.5, 17.3, –5.2, –5.3 ppm. IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1734, 1462, 1388, 1361, 1254, 1130, 1087, 1058, 1004, 939, 834, 776, 671 cm^{-1}. MS (EI) *m/z* (%): 229 (25), 201 (34), 185 (13), 145 (12), 143 (11), 129 (13), 117 (11), 115 (18), 105 (11), 103 (19), 101 (20), 89 (13), 75 (100), 73 (72), 59 (23), 57 (12), 55 (12), 41 (14). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{26}O_3SiNa$: 281.1543, found: 281.1545.

Methyl (*Z*)-3-((2*R*,4*R*,5*R*)-5-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyltetrahydrofuran-2-yl)-acrylate (116). 

18-Crown-6 (7.37 g, 27.9 mmol) was added to a solution of KHMDS (3.03 g, 15.2 mmol) in THF (60 mL). After cooling to –78 °C, methyl O,O'-bis(2,2,2-trifluoroethyl)phosphonoacetate (3.22 mL, 15.2 mmol) was added dropwise and the resulting mixture was stirred for 20 min. Next, a solution of aldehyde **276** (3.27 g, 12.7 mmol) in THF (15 mL) was added dropwise over 10 min. The resulting mixture was stirred for 3 h at –78 °C before it was poured into sat. NH_4Cl (70 mL). The aq. phase was extracted with EtOAc (3 × 70 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified twice by flash chromatography (fine SiO_2, hexane/*t*-butyl methyl ether 99:1) to yield the title compound (*Z*)-**116** as a pale yellow oil (2.50 g, 63% over two steps, *Z*/*E* 12:1); additional fractions contained the undesired (*E*)-**116** (190 mg, 5% over two steps) and traces of the β/γ-unsaturated ester **S4** (79 mg, 2% over two steps). Analytical and spectral data of (*Z*)-**116**: $[\alpha]_D^{20}$ = +40.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 11.7, 7.3 Hz, 1H), 5.75 (dd, *J* = 11.7, 1.6 Hz, 1H), 5.37 (dddd, *J* = 9.8, 7.4, 5.9, 1.6 Hz, 1H), 3.69 (s, 3H), 3.68–3.65 (m, 2H), 3.61 (ddd, *J* = 8.2, 5.0, 4.1 Hz, 1H), 2.48 (ddd, *J* = 12.4, 7.0, 5.9 Hz, 1H), 2.24–2.13 (m, 1H), 1.30 (ddd, *J* = 12.1, 10.6, 9.8 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 152.3, 118.5, 86.5, 75.8, 65.0, 51.5, 41.4, 36.7, 26.1, 18.6, 17.5, –5.2, –5.2 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2857, 1724, 1648, 1462, 1438, 1404, 1254, 1198, 1180, 1083, 1038, 1005, 837, 777, 674 cm^{-1}. MS (EI) *m/z* (%): 258 (18), 257 (100), 227 (16), 225 (30), 197 (28), 169 (15), 165 (13), 139 (28), 137 (15), 133 (39), 121 (35), 117 (58), 111 (35), 107 (20), 105 (33), 89 (23), 81 (11), 79 (18), 75 (45), 73 (37), 59 (13). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{30}O_4SiNa$: 337.1806, found: 337.1806.

Analytical and spectral data of (*E*)-**116**: $[\alpha]_D^{20}$ = +17.3 (c = 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 

δ = 6.94 (dd, *J* = 15.6, 5.2 Hz, 1H), 6.04 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.54 (dddd, *J* = 9.9, 6.0, 5.2, 1.6 Hz, 1H), 3.73 (s, 3H), 3.70 (d, *J* = 4.4 Hz, 1H), 3.68 (d, *J* = 4.2 Hz, 1H), 3.60 (dd, *J* = 8.1, 4.1 Hz, 1H), 2.30 (ddd, *J* = 11.5, 7.0, 5.9 Hz, 1H), 2.22 (ddq, *J* = 10.4, 8.1, 6.5 Hz, 1H), 1.39 (dt, *J* = 11.6, 10.0 Hz, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 149.0, 119.5,

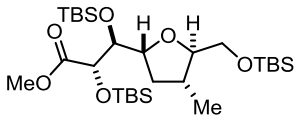
86.5, 77.7, 64.6, 51.7, 41.7, 36.5, 26.1, 18.5, 17.4, –5.15, –5.19 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1728, 1662, 1462, 1436, 1361, 1300, 1258, 1166, 1125, 1089, 1006, 837, 777, 675 cm^{-1}. MS (ESIpos) *m/z* (%): 337.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{30}O_4SiNa$: 337.1806, found: 337.1807.

Diol 117a. Potassium hexacyanoferrate (5.61 g, 17.0 mmol), K_2CO_3 (2.36 g, 17.0 mmol), potassium osmate (VI) dihydrate (126 mg, 0.341 mmol), $(DHQD)_2PYR$ (150 mg, 0.171 mmol) and methanesulfonamide (540 mg, 5.68 mmol) were sequentially added to a mixture of alkene *Z*-**116** (1.79 g, 5.68 mmol) in *t*-BuOH/H_2O (1:1, 100 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 72 h before it was poured into a solution of sat. NH_4Cl, sat. NaS_2O_3 and water (1:1:2, 100 mL). The mixture was vigorously stirred for 10 min at ambient temperature, diluted with EtOAc. The aq. phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified twice by flash chromatography (fine SiO_2, hexane/EtOAc 19:1 to 8:1) to yield the desired diol (1.33 g, 67%, dr = 5:1) and the undesired diastereoisomer **117c** (215 mg, 11%) as colourless oil each. Analytical and spectral data of the major diastereoisomer **117a**: $[\alpha]_D^{20}$ = –8.0 (c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.29 (dd, *J* = 9.2, 4.3 Hz, 1H, H-7), 4.05 (ddd, *J* = 10.0, 5.6, 3.4 Hz, 1H, H-5), 3.78 (s, 3H, H-9), 3.74 (ddd, *J* = 8.4, 4.4, 3.6 Hz, 1H, H-6), 3.67 (dd, *J* = 10.9, 4.0 Hz, 1H, H-1), 3.62 (dd, *J* = 10.9, 4.6 Hz, 1H, H-1), 3.54 (ddd, *J* = 8.6, 4.6, 4.0 Hz, 1H, H-2), 3.39 (d, *J* = 9.6 Hz, 1H, 7-OH), 2.75 (d, *J* = 8.5 Hz, 1H, 6-OH), 2.12 (ddqd, *J* = 10.6, 8.6, 6.8, 6.6 Hz, 1H, H-3), 2.07 (ddd, *J* = 11.8, 6.8, 5.6 Hz, 1H, H-4), 1.64 (dt, *J* = 11.4, 10.6 Hz, 1H, H-4), 1.07 (d, *J* = 6.4 Hz, 3H, H-23), 0.89 (s, 9H, TBS), 0.06 (s, 6H, TBS) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (C8), 87.0 (C2), 78.7 (C5), 73.7 (C7), 73.4 (C6), 64.6 (C1), 52.5 (C9), 37.4 (C4), 36.0 (C3), 26.0 (3C, TBS), 18.5 (TBS), 17.0 (C23), –5.2 (TBS), −5.2 ppm (TBS). IR (film): $\tilde{\nu}$ = 3458, 2954, 2929, 2857, 1740, 1461, 1440, 1388, 1253, 1128, 1080, 1004, 836, 777, 647 cm^{-1}. MS (EI) *m/z* (%): 292 (14), 291 (77), 259 (25), 155 (11), 231 (39), 230 (15), 229 (82), 213 (11), 186 (12), 185 (80), 181 (17), 171 (24), 167 (11), 157 (12), 153 (11), 149 (15), 145 (13), 143 (14), 139 (27), 129 (11), 127 (13), 126 (12), 121 (19), 117 (48), 115 (66), 113 (11), 109 (23), 107 (11), 105 (24), 103 (12), 101 (14), 97 (19), 93 (23), 89 (22), 85 (12), 81 (23), 75 (88), 73 (100), 69 (12), 59 (16), 55 (14), 43 (12), 41 (11). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{32}O_6SiNa$: 371.1860, found: 371.1863.

Analytical and spectral data of the minor diastereoisomer **117c**: $[\alpha]_D^{20}$ = −17.6 (c = 1.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.32 (t, *J* = 4.4 Hz, 1H, H-7), 4.03 (ddd, *J* = 9.2, 7.4, 6.0 Hz, 1H, H-5), 3.80 (s, 3H, H-9), 3.81 (ddd, *J* = 9.2, 7.4, 6.0 Hz, 1H, H-6), 3.64 (dd, *J* = 11.7, 4.3 Hz, 1H, H-1), 3.60 (dd, *J* = 11.0, 4.6 Hz, 1H, H-1), 3.48 (dt, *J* = 8.6, 4.4 Hz, 1H, H-2), 3.31 (d, *J* = 4.8 Hz, 1H, 7-OH), 2.53 (d, *J* = 6.0 Hz, 1H, 6-OH), 2.28 (ddd, *J* = 12.4, 6.8, 6.0 Hz, 1H, H-4), 2.10 (dddq, *J* = 10.8, 8.5, 7.0, 6.6 Hz, 1H, H-3), 1.55 (ddd, *J* = 12.4, 10.6, 9.2 Hz, 1H, H-4), 1.07 (d, *J* = 6.6 Hz, 3H, H-23), 0.89 (s, 9H, TBS), 0.05 (s, 6H, TBS) ppm.

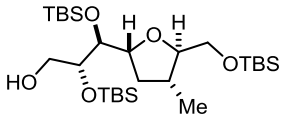
^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2 (C8), 86.6 (C2), 78.4 (C5), 75.2 (C6), 72.7 (C7), 64.8 (C1), 52.7 (C9), 38.4 (C4), 36.2 (C3), 26.1 (3C, TBS), 18.5 (TBS), 17.3 (C23), –5.19 (TBS), –5.21 ppm (TBS). IR (film): $\tilde{\nu}$ = 3439, 2954, 2929, 2857, 1741, 1462, 1388, 1254, 1129, 1087, 1004, 837, 777, 671 cm^{-1}. MS (ESIpos) *m/z* (%): 371.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{32}O_6SiNa$: 371.1860, found: 371.1858.

Compound 118a. 2,6-Lutidine (1.75 mL, 15.0 mmol), DMAP (51.0 mg, 0.42 mmol, 20 mol%) and



TBSOTf (2.88 mL, 12.5 mmol) were sequentially added to a solution of diol **117a** (728 mg, 2.09 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 24 h. The reaction was quenched with aq. half-sat. NH_4Cl (10 mL) and the aq. phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 99:1) to afford the title compound as a colourless oil (1.12 g, 86%). $[\alpha]_D^{20}$ = –4.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (d, *J* = 3.4 Hz, 1H), 4.04 (ddd, *J* = 10.0, 6.6, 5.2 Hz, 1H), 3.84 (dd, *J* = 6.7, 3.4 Hz, 1H), 3.69 (s, 3H), 3.64 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.60 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.43 (dt, *J* = 8.8, 4.6 Hz, 1H), 2.14–2.00 (m, 2H), 1.47–1.36 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 85.1, 79.3, 78.1, 75.2, 65.0, 51.7, 37.5, 37.0, 26.1, 26.1, 25.8, 18.5, 18.4, 18.4, 17.0, –4.1, –4.7, –5.0, –5.2, −5.2 (2C) ppm. IR (film): ṽ = 2954, 2927, 2856, 1736, 1462, 1388, 1361, 1253, 1129, 1091, 1005, 836, 778, 673 cm^{-1}. MS (EI) *m/z* (%): 521 (16), 520 (35), 519 (83), 388 (10), 387 (34), 355 (11), 295 (15), 256 (11), 255 (57), 229 (42), 223 (18), 185 (50), 163 (14), 149 (21), 147 (18), 117 (20), 115 (18), 89 (24), 75 (18), 73 (100). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{60}O_6Si_3Na$: 599.3590, found: 599.3596.

Alcohol 119a. Dibal-H (1.2 M in toluene, 2.86 mL, 3.43 mmol) was added to a solution of ester **118a**



(900 mg, 1.56 mmol) in toluene (18 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h. The mixture was poured *via* cannula into sat. Rochelle salt (15 mL) and the emulsion was vigorously stirred at ambient temperature for 2 h. The phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 19:1) to afford the title compound **119a** as a colourless oil (838 mg, 98%). $[\alpha]_D^{20}$ = −4.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (ddd, *J* = 10.2, 5.7, 3.3 Hz, 1H), 3.78 (ddd, *J* = 10.5, 6.9, 3.6 Hz, 1H), 3.73 (ddd, *J* = 6.8, 3.4, 1.9 Hz, 1H), 3.67–3.59 (m, 3H), 3.57–3.53 (m, 1H), 3.53–3.49 (m, 1H), 3.45 (ddd, *J* = 10.4, 8.9, 3.3 Hz, 1H), 2.09 (ddt, *J* = 11.3, 8.9, 6.6 Hz, 1H), 2.00 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.66–1.56 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.04 ppm (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 86.1, 79.9,

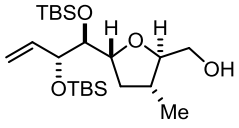
78.3, 75.9, 64.6, 62.8, 37.6, 36.5, 26.3, 26.1, 26.0, 18.6, 18.4, 18.4, 16.5, −3.9, −4.5, −4.5, −4.8, −5.3 (2C) ppm. IR (film): $\tilde{\nu}$ = 3461, 2954, 2929, 2886, 2857, 1472, 1462, 1388, 1361, 1252, 1129, 1075, 1004, 832, 773, 672 cm^{-1}. MS (EI) *m/z* (%): 493 (14), 492 (30), 491 (72), 360 (18), 359 (63), 267 (47), 231 (12), 229 (54), 228 (12), 227 (71), 209 (24), 199 (11), 197 (11), 186 (13), 185 (83), 171 (22), 159 (10), 149 (20), 147 (15), 135 (33), 117 (39), 115 (24), 107 (13), 103 (15), 89 (25), 75 (29), 73 (100). HRMS (ESIpos): *m/z* calcd for $C_{27}H_{60}O_5Si_3Na$: 571.3641, found: 571.3642.

Aldehyde 120a. Hünig's base (1.60 mL, 9.21 mmol) was added to a solution of alcohol **119a** (722 mg, 1.32 mmol) in CH_2Cl_2 (10 mL) at –25 °C. In a second flask, sulfur trioxide pyridine complex (523 mg, 3.29 mmol) was suspended in DMSO (0.93 mL, 13.2 mmol) and the suspension was stirred for 10 min at rt, before it was added to the alcohol solution at –25 °C and the flask was rinsed with CH_2Cl_2 (2 mL). The resulting mixture was stirred for 45 min at –25 °C. The mixture was poured into pH 7 phosphate buffer (15 mL) and *t*-butyl methyl ether (15 mL), the phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with pH 7 phosphate buffer (20 mL), followed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 50:1 to 30:1) to yield aldehyde **120a** as a colourless oil (678 mg, 94%). $[\alpha]_D^{20}$ = +12.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (d, *J* = 1.0 Hz, 1H), 4.08–3.99 (m, 2H), 3.90 (dd, *J* = 6.2, 1.9 Hz, 1H), 3.65–3.61 (m, 2H), 3.47 (dt, *J* = 8.7, 4.4 Hz, 1H), 2.16–1.99 (m, 2H), 1.58–1.48 (m, 1H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 85.8, 81.0, 79.6, 78.7, 64.8, 37.5, 36.6, 26.1, 26.1, 26.0, 18.5, 18.5, 18.4, 16.8, −4.4, −4.5, −4.6, −4.8, –5.2, –5.2 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2886, 2857, 1736, 1472, 1463, 1388, 1361, 1252, 1131, 1084, 1005, 832, 774, 672 cm^{-1}. MS (EI) *m/z* (%): 505 (12), 490 (13), 489 (33), 475 (10), 373 (13), 357 (24), 231 (17), 230 (18), 229 (100), 289 (13), 186 (12), 185 (71), 183 (10), 171 (15), 149 (14), 147 (14), 115 (21), 103 (14), 75 (31), 73 (83), 57 (12). HRMS (ESIpos): *m/z* calcd for $C_{27}H_{58}O_5Si_3Na$: 569.3484, found: 569.3485.

Terminal alkene 122a. A solution of Tebbe reagent (0.5 M in toluene, 0.12 mL, 60 µmol) was added to a solution of aldehyde **120a** (30 mg, 55 µmol) in THF (1.8 mL) at 0 °C. After stirring for 1 h at the same temperature, the reaction was diluted with *t*-butyl methyl ether (2 mL) and quenched by slow addition of a solution of NaOH (1 M, 0.2 mL). After drying over Na_2SO_4 the mixture was filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 300:1) to afford the title compound as a yellow oil (20 mg, 68%). $[\alpha]_D^{20}$ = +2.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (ddd, *J* = 17.3, 10.4, 6.9 Hz, 1H), 5.16–5.04 (m, 2H), 4.08 (ddt, *J* = 6.9, 3.1, 1.2 Hz, 1H), 3.85 (ddd, *J* = 10.0, 6.5, 5.4 Hz, 1H), 3.66 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.61 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.51 (dd, *J*

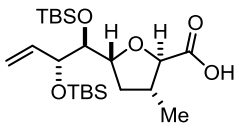
= 6.5, 3.0 Hz, 1H), 3.43 (dt, *J* = 8.6, 4.7 Hz, 1H), 2.11–2.03 (m, 1H), 1.98 (ddd, *J* = 11.6, 7.0, 5.5 Hz, 1H), 1.34 (q, *J* = 10.8, 9.9 Hz, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.90–0.88 (m, 27H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05–0.04 (m, 6H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.9, 115.5, 84.9, 79.8, 79.5, 76.1, 65.0, 37.9, 37.0, 26.1, 26.0, 25.9, 18.5, 18.3, 18.3, 17.1, −4.1, −4.3, −4.4, −4.6, −5.4 (2C) ppm. IR (film): $\tilde{\nu}$ = 2955, 2928, 2886, 2857, 1472, 1361, 1252, 1130, 1076, 1005, 834, 776, 671 cm^{-1}. MS (EI) *m/z* (%): 487 (25), 229 (44), 185 (100), 171 (68), 73 (59). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{60}O_4Si_3Na$: 567.3692, found: 567.3690.

Alcohol 123a. Pyridine (0.61 mL, 7.6 mmol) was slowly added to a Teflon® vial charged with



HF·pyridine (0.11 mL, 1.2 mmol) and the resulting mixture was diluted with THF (0.58 mL). An aliquot of this solution (1.1 mL) was added dropwise to a solution of silyl ether **122a** (25 mg, 46 µmol) in THF (0.3 mL) in a second Teflon® vial. The resulting mixture was stirred at ambient temperature for 18 h. The mixture was diluted with *t*-butyl methyl ether (2 mL) and the reaction was carefully quenched with sat. $NaHCO_3$ (2 mL). The phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 17:1) to afford the title compound **123a** as a pale yellow oil (14.7 mg, 74%). $[\alpha]_D^{20}$ = −6.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.17–5.07 (m, 2H), 4.07 (ddt, *J* = 7.1, 3.4, 1.1 Hz, 1H), 3.90 (ddd, *J* = 10.0, 6.4, 5.4 Hz, 1H), 3.75–3.68 (m, 1H), 3.54–3.45 (m, 3H), 2.15–1.99 (m, 2H), 1.90 (br s, 1H), 1.39 (q, *J* = 10.9 Hz, 1H), 1.03 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.08–0.06 (m, 9H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.8, 115.8, 84.8, 79.7, 79.6, 76.1, 63.1, 37.8, 35.2, 26.1, 25.9, 18.5, 18.3, 16.2, −4.1, −4.1, −4.3, −4.7 ppm. IR (film): $\tilde{\nu}$ = 3454, 2955, 2929, 2885, 2856, 1462, 1361, 1252, 1076, 1035, 922, 833, 776, 672 cm^{-1}. MS (EI) *m/z* (%): 373 (80), 259 (44), 185 (25), 171 (74), 127 (58), 115 (100), 75 (31), 73 (84), 71 (45). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{46}O_4Si_2Na$: 453.2827, found: 453.2826.

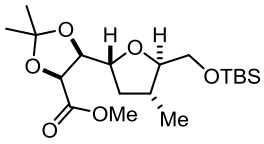
Carboxylic Acid 124a. NMO·H_2O (38 mg, 0.33 mmol) and tetrapropylammonium perruat (1.1 mg,



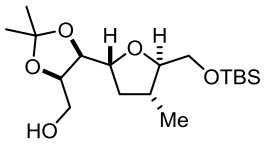
3.2 µmol) were added to a solution of alcohol **123a** (14 mg, 33 µmol) in acetonitrile (0.14 mL). After stirring for 9 h at ambient temperature, the mixture was diluted with EtOAc (5 mL) and the reaction was quenched with pH 5 phosphate buffer (5 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The yellow residual oil (7.4 mg, 51%) was used without further purification. $[\alpha]_D^{20}$ = +19,3 (c = 0.73, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.21–5.11 (m, 2H), 4.16–4.06 (m, 2H), 3.91 (d, *J* = 9.7 Hz, 1H), 3.56 (dd, *J* = 6.2, 3.3 Hz, 1H), 2.33 (dddd, *J* = 11.5, 9.7, 6.5, 3.3 Hz, 1H), 2.12 (ddd, *J* = 11.9, 6.6, 5.2 Hz, 1H), 1.48 (q, *J* = 11.6 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.08

(s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6, 138.4, 116.5, 82.1, 81.7, 79.0, 76.3, 39.9, 37.7, 26.0, 25.9, 18.3, 18.3, 17.0, −3.9, −4.2, −4.2, −4.7 ppm. IR (film) $\tilde{\nu}$ = 2956, 2928, 2856, 1726, 1463, 1253, 1077, 1024, 835, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 467.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{44}O_5Si_2Na$: 467.2620, found: 467.2616.

Acetonide 118b. PTSA·H_2O (50.5 mg, 0.27 mmol) was added to a solution of diol **117** (2.0 g, 5.7 mmol) in 2,2-dimethoxypropane (60 mL). The resulting mixture was stirred at ambient temperature for 4 h. The reaction was quenched with sat. $NaHCO_3$ (50 mL), the phases were separated and the aq. phase extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 20:1) to afford the title compound as a colourless oil (1.98 g, 89%). $[\alpha]_D^{20}$ = +10.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.55 (d, *J* = 6.8 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 1H), 3.97 (ddd, *J* = 9.4, 6.7, 5.7 Hz, 1H), 3.73 (s, 3H), 3.71 (dd, *J* = 10.7, 3.9 Hz, 1H), 3.63 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.56 (ddd, *J* = 7.3, 5.2, 3.6 Hz, 1H), 2.26–2.17 (m, 2H), 1.62 (s, 3H), 1.46–1.36 (m, 1H), 1.40 (s, 3H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 111.5, 85.9, 81.3, 76.8, 75.7, 64.7, 52.3, 38.1, 36.8, 26.9, 26.0, 25.8, 18.4, 17.8, –5.2, –5.3 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2858, 1765, 1734, 1461, 1380, 1253, 1202, 1166, 1091, 1005, 871, 838, 777 cm^{-1}. MS (EI) *m/z* (%): 331 (25), 241 (19), 230 (11), 229 (57), 185 (39), 171 (10), 159 (16), 157 (14), 139 (51), 117 (95), 115 (14), 107 (12), 101 (10), 89 (22), 75 (54), 73 (100), 59 (24), 55 (10), 43 (26), 41 (12), 40 (42). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{36}O_6SiNa$: 411.2173, found: 411.2174.



Alcohol 119b. A solution of $LiAlH_4$ (1 M in THF, 2.83 mL, 2.83 mmol) was added to a solution of ester **118b** (550 mg, 1.42 mmol) in THF (14 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 1 h. The mixture was cooled to 0 °C and the reaction was carefully quenched with MeOH until gas evolution ceased. The resulting mixture was poured via cannula into sat. Rochelle salt (15 mL), the flask rinsed with *t*-butyl methyl ether (5 mL) and the emulsion vigorously stirred at ambient temperature overnight. The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 19:1) to afford the title compound **119b** as a colourless oil (487 mg, 95%). $[\alpha]_D^{20}$ = +2.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72–3.65 (m, 2H), 4.08 (dd, *J* = 6.3, 3.8 Hz, 1H), 3.72–3.65 (m, 3H), 3.65–3.59 (m, 2H), 3.12 (t, *J* = 6.5 Hz, 1H), 2.24–2.12 (m, 2H), 1.63 (ddd, *J* = 14.0, 13.8, 9.7 Hz, 1H) 1.50 (s, 3H), 1.37 (s, 3H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 108.7, 86.5, 78.9, 77.5, 76.0, 64.4, 61.6, 38.3, 36.0, 27.6, 26.0, 25.8, 18.4, 17.1, –5.3, –5.3 ppm. IR (film): $\tilde{\nu}$ = 3475, 2955, 2930, 2857, 1462, 1378, 1251, 1216, 1168, 1124, 1078, 1040, 1005, 836, 777, 668 cm^{-1}. MS (EI)



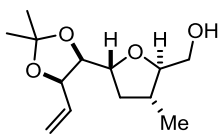
m/z (%): 303 (28), 245 (30), 229 (43), 227 (35), 185 (38), 157 (18), 153 (18), 145 (21), 135 (57), 131 (17), 117 (47), 115 (15), 109 (20), 107 (13), 105 (29), 101 (15), 97 (16), 95 (19), 93 (15), 89 (18), 85 (14), 81 (28), 75 (98), 73 (100), 59 (73), 57 (22), 55 (24), 43 (52), 41 (25). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{36}O_5SiNa$: 383.2224, found: 383.2226.

Aldehyde 120b. Hünig's base (1.40 mL, 8.03 mmol) was added to a solution of alcohol **119b** (579 mg, 1.61 mmol) in CH_2Cl_2 (8 mL) at –25 °C. In a second flask, sulfur trioxide pyridine complex (639 mg, 4.01 mmol) was suspended in DMSO (1.15 mL, 16.1 mmol) and stirred for 10 min at ambient temperature, before it was added to the alcohol solution at –25 °C and the flask was rinsed with CH_2Cl_2 (2 mL). The resulting mixture was stirred at –25 °C for 45 min. The cold mixture was poured into pH 7 phosphate buffer (15 mL) and *t*-butyl methyl ether (15 mL), the phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with pH 7 phosphate buffer (20 mL), followed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under high vacuum to yield crude aldehyde **120b** as a pale yellow oil, which was pure by NMR spectroscopy. $[\alpha]_D^{20}$ = –30.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66–9.59 (m, 1H), 4.34–4.29 (m, 2H), 4.01 (dtd, *J* = 8.0, 3.8, 2.0 Hz, 1H), 3.65–3.59 (m, 2H), 3.55 (dt, *J* = 8.7, 4.4 Hz, 1H), 2.17–2.06 (m, 2H), 1.57 (s, 3H), 2.52 (ddd, *J* = 14.8, 5.2, 1.5 Hz, 1H), 1.40 (s, 3H), 1.05 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.6, 111.3, 86.7, 81.6, 81.3, 75.6, 64.6, 37.0, 36.7, 27.1, 26.0, 25.5, 18.4, 17.1, –5.3 ppm (2C). IR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1732, 1461, 1381, 1361, 1252, 1214, 1164, 1075, 1004, 835, 776, 667 cm^{-1}. MS (EI) *m/z* (%): 301 (59), 243 (24), 230 (18), 229 (100), 213 (15), 201 (38), 185 (57), 183 (27), 171 (38), 157 (29), 145 (15), 143 (16), 129 (22), 117 (40), 115 (15), 113 (18), 105 (17), 103 (20), 101 (22), 75 (59), 73 (63), 59 (18), 43 (15). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{34}O_5SiNa$: 381.2068, found: 381.2068.

Terminal alkene 122b. A solution of Tebbe reagent (0.5 M in toluene, 5.0 mL, 62 mmol) was added to a solution of aldehyde **120b** (97 mg, 0.27 mmol) in THF (0.60 mL) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with *t*-butyl methyl ether (2 mL) and the reaction was quenched by slow addition of a solution of NaOH (1 M, 1.0 mL). After drying over Na_2SO_4, the mixture was filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 30:1 to 15:1) to afford the title compound as a colourless oil (64 mg, 66%). $[\alpha]_D^{20}$ = +5.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (ddd, *J* = 17.2, 10.1, 8.5 Hz, 1H), 5.28 (ddd, *J* = 17.1, 1.6, 0.9 Hz, 1H), 5.22 (ddd, *J* = 10.2, 1.7, 0.7 Hz, 1H), 4.47 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.06 (dd, *J* = 7.4, 6.3 Hz, 1H), 3.94 (ddd, *J* = 9.6, 7.4, 5.6 Hz, 1H), 3.74 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.65 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.57 (ddd, *J* = 7.5, 5.4, 3.8 Hz, 1H), 2.26–2.09 (m, 2H), 1.51 (s, 3H), 1.39 (s, 3H), 1.30–1.20 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.7, 118.9, 109.4,

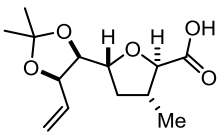
85.7, 81.6, 79.0, 77.5, 64.9, 37.9, 36.6, 27.8, 25.9, 25.6, 18.3, 17.8, –5.4, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1461, 1378, 1369, 1252, 1215, 1125, 1063, 1001, 924, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 379.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{36}O_4SiNa$: 379.2275, found: 379.2273.

Alcohol 123b. Pyridine (2.7 mL, 33 mmol) was slowly added to a Teflon® vial charged with



HF·pyridine (0.47 mL, 5.2 mmol) and the resulting mixture was diluted with THF (2.9 mL). An aliquot of this solution (6.0 mL) was added dropwise to a solution of silyl ether **122b** (64.0 mg, 0.180 mmol) in THF (1.0 mL) in a second Teflon® vial. The resulting mixture was stirred at ambient temperature for 18 h. The mixture was diluted with EtOAc (5 mL) and the reaction was carefully quenched with sat. $NaHCO_3$ (10 mL). The phases were separated and the aq. phase was extracted with EtOAc (4 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 6:1 to 3:2) to afford the title compound **123b** as a pale yellow oil (32.3 mg, 74%). $[\alpha]_D^{20}$ = +1.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddd, *J* = 17.1, 10.2, 8.5 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.6, 0.9 Hz, 1H), 5.25 (ddd, *J* = 10.2, 1.6, 0.7 Hz, 1H), 4.48 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.09 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.99 (ddd, *J* = 9.8, 7.6, 5.5 Hz, 1H), 3.82 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.59 (ddd, *J* = 8.6, 3.9, 2.7 Hz, 1H), 3.52 (dd, *J* = 11.9, 3.9 Hz, 1H), 2.25–2.12 (m, 2H), 1.53 (s, 3H), 1.41 (s, 3H), 1.32–1.27 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.4, 119.1, 109.5, 86.0, 81.7, 78.9, 77.6, 62.2, 37.6, 34.4, 27.9, 25.6, 16.2 ppm. IR (film): $\tilde{\nu}$ = 3466, 2984, 2958, 2932, 2873, 1457, 1379, 1250, 1216, 1164, 1106, 1047, 921, 872 cm^{-1}. MS (EI) *m/z* (%): 115 (41), 98 (24), 83 (20), 71 (80), 69 (58), 59 (21), 55 (26), 43 (100), 41 (50), 39 (25). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{22}O_4Na$: 265.1410, found: 265.1408.

Carboxylic Acid 124b. Water (7.6 µL, 0.42 mmol), TEMPO (2.0 mg, 13 µmol) and



bis-(acetoxy)iodobenzene (30 mg, 93 µmol) were added to a solution of alcohol **123b** (10.2 mg, 42.1 µmol) in acetonitrile (0.20 mL). After stirring for 16 h at ambient temperature the reaction was diluted with acetonitrile (0.2 mL) and quenched with pH 7 phosphate buffer (0.05 mL). After filtration through a short pad of Na_2SO_4 the filtrate was concentrated. The residue was dissolved in acetonitrile (5 mL) and washed with cyclohexane (5 mL). The cyclohexane phase was extracted with acetonitrile (3 mL). The combined acetonitrile phases were concentrated under reduced pressure. The yellow residual oil (10.7 mg, 99%) was used without further purification. $[\alpha]_D^{20}$ = +11,1 (c = 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (ddd, *J* = 17.1, 10.2, 8.3 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.29 (ddd, *J* = 10.1, 1.5, 0.8 Hz, 1H), 4.55 (dd, *J* = 7.7, 6.1 Hz, 1H), 4.19–4.09 (m, 2H), 4.04 (d, *J* = 8.8 Hz, 1H), 2.37 (ddp, *J* = 10.3, 8.7, 6.7 Hz, 1H), 2.21 (ddd, *J* = 12.5, 7.1, 5.3 Hz, 1H), 1.52 (s, 3H), 1.47–1.39 (m, 4H), 1.26 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 134.0, 119.5, 109.6, 82.8, 80.5, 79.4, 78.8, 39.5, 37.3, 27.6, 25.5, 17.5 ppm. IR (film) $\tilde{\nu}$ = 3476, 3369, 2984, 2935, 1731, 1379, 1249, 1216, 1047, 933,

872 cm^{-1}. MS (EI) *m/z* (%): 256 (1), 129 (30), 127 (40), 101 (49), 98 (71), 83 (74), 69 (91), 59 (41), 55 (43), 43 (100), 41 (54), 39 (26) 29 (22). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{20}O_5Na$: 279.1203, found: 279.1201.

5.3.2 Synthesis of Northern Fragments 139

1,5-Dichloropentane-2,4-dione (126). An oven-dried 3-necked flask equipped with a 250 ml dropping funnel and a reflux condenser, which was connected to two Drechsel bottles filled with 1 M NaOH solution, was charged with $AlCl_3$ (60 g, 0.45 mol). Nitrobenzene (76 mL, 0.74 mol) was added dropwise over 30 min, followed by the dropwise addition of 1,2-dichloroethane (90.0 mL, 1.14 mol) over 30 min. The mixture was stirred vigorously for 30 min before it was cooled to 0 °C. Next, acetyl acetone (46.2 mL, 450 mmol) was added dropwise over 30 min, followed by chloroacetyl chloride (79.2 mL, 994 mmol), which was added dropwise over 40 min. The resulting mixture was allowed to warm to rt, the reflux condenser was replaced by an internal thermometer, and the addition funnel was replaced by a distillation head, which was attached to the set of Drechsel bottles. The mixture was gently heated to 65 °C over the course of 2 h. Distillation of acetyl chloride (38–39 °C) was continued for 6 h, before the mixture was cooled to ambient temperature and poured into a mixture of ice and conc. HCl (65 mL). The resulting suspension was stirred vigorously at ambient temperature for 17 h before the phases were separated. The aq. phase was extracted with Et_2O (4 × 200 mL) and the combined organic phases were poured into sat. $Cu(OAc)_2$ solution (800 mL). The resulting biphasic mixture was stirred vigorously at ambient temperature for 24 h before it was filtered with suction. The collected precipitate was washed with Et_2O (200 mL) and triturated with Et_2O (250 mL). After filtration, the copper complex was obtained as green powdery solid, which was suspended in a mixture of Et_2O (400 mL) and 10% H_2SO_4 (250 mL). The mixture was stirred at ambient temperature for 24 h, the aq. phase was separated and extracted with Et_2O (250 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification by Kugelrohr distillation afforded the title compound (17.5 g, 23%) as a yellow oil that darkened over time. The product was detected as a mixture of keto-enol tautomers in the NMR: Enol: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.49 (s, 1H), 6.18 (s, 1H), 4.09 (s, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.5, 187.4, 96.9, 44.2 (2C) ppm. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (s, 4H), 3.98 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.4 (2C), 50.6, 48.4 (2C) ppm. IR (film): $\tilde{\nu}$ = 2937, 1727, 1604, 1397, 1321, 1227, 1191, 1123, 903, 723, 650, 574 cm^{-1}. MS (EI) *m/z* (%): 132 (14), 121 (33), 119 (100), 79 (10), 77 (32), 68 (12), 67 (19), 49 (12), 43 (26), 39 (16), 37 (13), 36 (17). HRMS (ESIpos): *m/z* calcd for $C_5H_6O_2Cl_2Na$: 190.9637; found: 190.9638. The analytical and spectroscopic data are in agreement with those reported in the literature.[496]

(2*R*,4*R*)-1,5-Dichloropentane-2,4-diol (127). Freshly distilled **126** (11.4 g, 67.5 mmol) was dissolved in methanol (70 mL) and the resulting solution was degassed by bubbling Ar through the mixture for 20 min. $[RuCl_2((S)\text{-BINAP})]_2{\cdot}Et_3N$ (65 mg, 73 µmmol) was added and the resulting mixture was cannulated into an oven-dried 100 mL autoclave, which was sealed and pressurized with H_2 (62 bar). The mixture was stirred at 75 °C (external temperature) for 18 h before it was cooled to ambient temperature and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 1:1 to 1:2) to afford the title compound as a yellow solid and THF-ring **128** (**127**/**128** = 6:1) as an orange oil. Recrystallization from CH_2Cl_2/hexane (3:2, 70 mL) afforded diol **127** (6.34 g, 54%, 97% *ee*, dr = >20:1) as colourless needles. m.p. [hexane] = 86–88 °C. $[\alpha]_D^{20}$ = +21.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (tdd, *J* = 6.8, 5.4, 4.1 Hz, 2H), 3.65 (dd, *J* = 11.1, 4.0 Hz, 2H), 3.53 (dd, *J* = 11.1, 6.9 Hz, 2H), 2.77 (brs, 2H), 1.75 (dd, *J* = 6.7, 5.3 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 68.7 (2C), 50.1 (2C), 37.6 ppm. IR (film): $\tilde{\nu}$ = 3361, 3285, 2959, 2890, 1433, 1402, 1326, 1294, 1215, 1186, 1102, 1072, 1052, 911, 709, 571 cm^{-1}. MS (ESIneg) *m/z* (%): 171.0 (100 (M–H)). HRMS (ESIneg): *m/z* calcd for $C_5H_9O_2Cl_2$ [M−H]$^-$: 170.9985; found: 170.9987. The analytical and spectroscopic data are in agreement with those reported in the literature.[496]

Spectral and analytical data for **(3*R*,5*R*)-5-(chloromethyl)tetrahydrofuran-3-ol** (**128**). $[\alpha]_D^{20}$ = −0.7 (c = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (ddt, *J* = 5.8, 3.7, 1.8 Hz, 1H), 4.21 (dq, *J* = 8.5, 5.2 Hz, 1H), 3.92 (dt, *J* = 9.8, 1.6 Hz, 1H), 3.78 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.71 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.67 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.32 (ddd, *J* = 14.0, 8.6, 6.1 Hz, 1H), 1.89 (ddt, *J* = 14.0, 5.0, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 78.0, 76.2, 72.1, 47.0, 38.4 ppm. IR (film): $\tilde{\nu}$ = 3395, 2951, 1722, 1430, 1333, 1259, 1051, 989, 865, 808, 744, 702 cm^{-1}. MS (ESIpos) *m/z* (%): 159.0 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_5H_9O_2ClNa$: 159.0183; found: 159.0185.

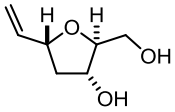
Mosher Ester Analysis of Diol 127. The enantiomeric excess of diol **127** was initially determined by a modified Mosher ester analysis as described by Rychnovsky and coworkers[228a] and for further batches of material by comparison of optical rotation values. To a solution of diol **53** (5.0 mg, 31 µmol) in CH_2Cl_2 (3 mL) was added Et_3N (26 µL, 0.19 mmol) followed by (*S*)-(+)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*S*)-MTPA-Cl) (25 µL, 0.13 mmol) and DMAP (0.5 mg, 4.1 µmol, 13 mol%). The mixture was stirred at ambient temperature for 2 h, before the reaction was quenched with sat. $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude diastereomeric mixture of (*R*)-MTPA-**53** was obtained as a colourless oil (17.5 mg, 47%). $[\alpha]_D^{20}$ = +82.5 (c = 2.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.55 (m, 4H), 7.47–7.41 (m, 6H), 5.05 (ddt, *J* = 7.6, 5.3, 4.1 Hz, 2H), 3.73 (dd, *J* = 12.3, 4.0 Hz, 2H), 3.633 (s, 3H), 3.630 (s, 3H), 3.49 (dd, *J* = 12.3, 4.2 Hz, 2H), 2.08 ppm (dd, *J* = 7.3, 5.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1 (2C), 132.2 (2C), 130.0 (2C), 128.8 (4C), 127.25 (2C), 127.24 (2C), 124.8 (2C), 121.9 (2C), 71.5 (2C), 56.0,

55.9, 45.2 (2C), 34.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2851, 1753, 1452, 1242, 1170, 1122, 1082, 1017, 819, 765, 719, 699 cm^{-1}. MS (ESIpos) *m/z* (%): 627.1 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{24}O_6F_6Cl_2Na$: 327.0746; found: 627.0750. The enantiomeric excess was determined based on ^1H NMR by integration of the central CH_2 signal of each derivative at 400 MHz in $CDCl_3$. The signal for the (*R*,*R*)-diol derivative appears at 2.08 ppm (dd, *J* = 7.3, 5.2 Hz, 2H) whereas the signal for the (*S*,*S*)-diol derivative appears at 2.20 ppm (dd, *J* = 7.3, 5.5 Hz, 0.03H). Hence, 98.5% of the (*R*,*R*)-diol and 1.5% of the (*S*,*S*)-diol were detected in the diastereomeric mixture, resulting in approx. 97% *ee* of diol **127**.

(*R*,*R*)-1,2:4,5-Diepoxypentane (130). Freshly powdered potassium hydroxide (12.1 g, 215 mmol) was added to a solution of diol **127** (3.72 g, 21.5 mmol) in diethylether (165 mL) at 0 °C. After stirring for 3 h at ambient temperature, the mixture was filtered through a plug of $MgSO_4$ and concentrated to afford the title compound as a courless oil (2.13 g, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.11 (tdd, *J* = 5.7, 4.0, 2.7 Hz, 2H), 2.83 (dd, *J* = 5.0, 4.0 Hz, 2H), 2.54 (dd, *J* = 5.0, 2.7 Hz, 2H), 1.76 (t, *J* = 5.7 Hz, 2H) ppm. The spectroscopic data are in agreement with those reported in the literature.[496]

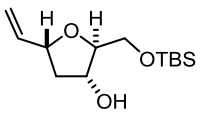
(3*R*,5*R*)-Hepta-1,6-diene-3,5-diol (129). A solution of *n*-BuLi (1.71 M in hexane, 174 mL, 297 mmol) was added dropwise over 10 min to a solution of Me_3SI (60.5 g, 297 mmol) in THF (250 mL) at –40 °C. The resulting mixture was agigated with a mechanically stirred steel paddle for 15 min before a freshly prepared solution of diol **127** (5.13 g, 29.7 mmol) in THF (25 mL) was added in one portion. The mixture was warmed up to ambient temperature over the course of 6 h (10 °C per h) and stirred for 12 h before it was poured into sat. NH_4Cl (200 mL). The aq. phase was extracted with EtOAc (3 × 250 mL). The combined organic phases were dried over Na_2SO_4, washed wit brine (200 ml), filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1) affording the title compound as a colourless oil (2.60 g, 68%) and THF-ring **128** as the major side product. $[\alpha]_D^{20}$ = –27.8 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 2H), 5.29 (dt, *J* = 17.2, 1.5 Hz, 2H), 5.15 (dt, *J* = 10.5, 1.4 Hz, 2H), 4.46 (tdd, *J* = 6.9, 5.4, 1.5 Hz, 2H), 2.42 (brs, 2H), 1.78 ppm (dd, *J* = 6.1, 5.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.5 (2C), 114.8 (2C), 70.6 (2C), 42.0 ppm. IR (film): $\tilde{\nu}$ = 3328, 3082, 2983, 2915, 1645, 1422, 1315, 1114, 1054, 991, 921, 824, 656 cm^{-1}. MS (EI) *m/z* (%): 57 (40), 56 (16), 55 (36), 54 (100), 43 (11), 39 (20), 29 (19), 27 (13). HRMS (ESIpos): *m/z* calcd for $C_7H_{12}O_2Na$: 151.0729; found: 151.0731. The analytical and spectroscopic data are in agreement with those reported in the literature.[229a]

(2*S*,3*R*,5*R*)-2-(Hydroxymethyl)-5-alkenyltetrahydrofuran-3-ol (131). Diol **129** (1.81 g, 14.1 mmol) in



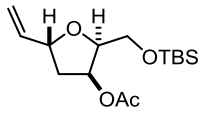
i-PrOH (150 mL) was added to a flask charged with $Co(nmp)_2$ (798 mg, 1.41 mmol). The pale red solution was purged with O_2 for 15 min before *t*-BuOOH (5.5 M in decane, 0.26 mL, 1.4 mmol) was added in one portion; the solution slowly turned green. The mixture was stirred at 55 °C under an oxygen atmosphere (balloon) for 5 h. After cooling to ambient temperature, the oxygen atmosphere was replaced by argon. The solvent was removed under reduced pressure, the residue was redissolved in EtOAc (10 mL) and the solution was filtered through a pad of silica (1 cm) over packed Celite® (3 cm), eluting with EtOAc (100 mL). The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexane/EtOAc 2:1 to 1:2) to yield the title compound as a pale yellow oil (1.59 g, 78%). $[\alpha]_D^{20}$ = −37.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (ddd, *J* = 17.0, 10.3, 6.4 Hz, 1H), 5.28 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.14 (dt, *J* = 10.3, 1.3 Hz, 1H), 4.52 (ddd, *J* = 7.0, 6.4, 1.0 Hz, 1H), 4.32 (q, *J* = 6.1 Hz, 1H), 3.92 (td, *J* = 5.0, 4.0 Hz, 1H), 3.74 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.64 (dd, *J* = 11.7, 4.9 Hz, 1H), 2.41 (ddd, *J* = 12.8, 6.8, 6.7 Hz, 1H), 2.32 (brs, 1H), 2.26 (brs, 1H), 1.84 (ddd, *J* = 13.2, 7.2, 6.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3, 115.8, 85.3, 79.3, 73.2, 62.8, 41.2 ppm. IR (film): $\tilde{\nu}$ = 3359, 2930, 2877, 1645, 1427, 1338, 1329, 1088, 1035, 989, 928, 887, 857, 670 cm^{-1}. MS (EI) *m/z* (%): 113 (43), 95 (32), 83 (27), 71 (11), 70 (19), 69 (10), 67 (53), 60 (11), 57 (29), 56 (28), 55 (100), 54 (16), 53 (11), 43 (30), 42 (12), 41 (37), 39 (23), 31 (20), 29 (24), 27 (14). HRMS (ESIpos): *m/z* calcd for $C_7H_{12}O_3Na$: 167.0679, found: 167.0680.

Alcohol 132. Et_3N (1.36 mL, 9.73 mmol), TBSCl (1.03 g, 6.81 mmol) and DMAP (39.6 mg, 0.32 mmol,



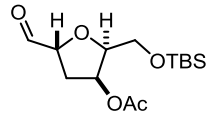
5 mol%) were sequentially added to a solution of diol **131** (935 mg, 6.49 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 7 h. The reaction was quenched with sat. $NaHCO_3$ (25 mL) and the aq. phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 15:1 to 9:1) to afford alcohol **132** as a colourless oil (1.35 g, 81%). $[\alpha]_D^{20}$ = –10.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (ddd, *J* = 16.9, 10.3, 6.3 Hz, 1H), 5.27 (ddd, *J* = 17.1, 1.5, 1.4 Hz, 1H), 5.11 (ddd, *J* = 10.3, 1.4, 1.2 Hz, 1H), 4.52 (tdt, *J* = 7.2, 6.2, 1,3 Hz, 1H), 4.34 (ddd, *J* = 6.6, 5.9, 4.4 Hz, 1H), 3.89 (dt, *J* = 6.5, 4.3 Hz, 1H), 3.81 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.58 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.42 (ddd, *J* = 12.7, 6.9, 6.7 Hz, 1H), 1.82 (ddd, *J* = 12.8, 6.9, 5.9 Hz, 1H), 1.79 (brs, 1H), 0.90 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.9, 115.4, 85.0, 79.5, 75.3, 64.7, 40.7, 26.0, 18.4, –5.3 (2C) ppm. IR (film): $\tilde{\nu}$ = 3431, 2954, 2929, 2857, 1472, 1361, 1255, 1131, 1091, 1005, 919, 836, 778, 673 cm^{-1}. MS (EI) *m/z* (%): 193 (17), 147 (14), 117 (52), 109 (11), 89 (14), 77 (10), 75 (100), 73 (20), 67 (13), 59 (14), 55 (18), 45 (10), 41 (14), 39 (13). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{26}O_3SiNa$: 281.1543, found: 281.1542.

Acetate 133. PPh_3 (2.70 g, 10.3 mmol) and DIAD (2.4 mL, 12 mmol) were added to a solution of



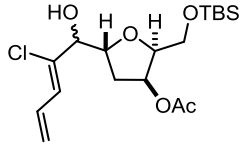
alcohol **132** (1.58 g, 6.11 mmol) in toluene (48 mL) at 0 °C. The ice bath was removed and the resulting mixture was stirred for 30 min at ambient temperature before dropwise addition of acetic acid (0.70 mL, 12 mmol). After stirring for 4.5 h at the same termperature, the mixture was diluted with *t*-butyl methyl ether (20 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 99:1) to yield the title compound as a colourless oil (1.63 g, 89%). $[\alpha]_D^{25}$ = +51.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddd, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.47–5.41 (m, 1H), 5.27 (ddd, *J* = 17.1, 1.4, 1.3 Hz, 1H), 5.11 (ddd, *J* = 10.1, 1.2, 1.0 Hz, 1H), 4.58 (dt, *J* = 9.4, 6.5 Hz, 1H), 4.11 (ddd, *J* = 7.1, 5.8, 3.8 Hz, 1H), 3.80–3.72 (m, 2H), 2.19 (ddd, *J* = 13.8, 6.2, 1.4 Hz, 1H), 2.08 (s, 3H), 1.96 (ddd, *J* = 14.1, 9.4, 5.0 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 138.4, 116.1, 81.1, 79.0, 74.4, 61.1, 39.6, 25.9, 21.3, 18.4, −5.2, −5.4 ppm. IR (film): $\tilde{\nu}$ = 3083, 2954, 2930, 2884, 2857, 1743, 1472, 1426, 1373, 1232, 1186, 1088, 1017, 987, 932, 836, 776, 726, 666, 624, 602 cm^{-1}. MS (ESIpos) *m/z* (%): 323.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{15}H_{28}O_4SiNa$: 323.1649, found: 323.1646.

Aldehyde 134. Ozone was bubbled through a solution of olefin **133** (864 mg, 2.88 mmol) in CH_2Cl_2



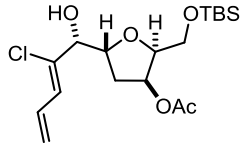
(160 mL) at –78 °C for 30 min, until the blue color persisted. Oxygen was bubbled through the mixture for approx. 10 min followed by argon until the solution was colourless. PPh_3 (1.51 g, 5.75 mmol) was added in one portion and the mixture was allowed to reach ambient temperature overnight. After stirring for 16 h, the mixture was washed with a 1:1 mixture of sat. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 100:1 to 10:1 to 2:1) to afford the title compound as a colourless oil (750 mg, 86%). $[\alpha]_D^{25}$ = +37.5 (c = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 1.8 Hz, 1H), 5.42 (td, *J* = 4.2, 3.0 Hz, 1H), 4.49 (td, *J* = 8.2, 1.8 Hz, 1H), 4.11 (ddd, *J* = 6.7, 5.6, 3.8 Hz, 1H), 3.83 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.79 (dd, *J* = 10.2, 6.4 Hz, 1H), 2.28 (dd, *J* = 3.6. 1.8 Hz, 1H), 2.26 (dd, *J* = 3.6. 2.2 Hz, 1H), 2.08 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.8, 170.2, 82.7, 81.6, 73.2, 61.0, 34.5, 25.9, 21.1, 18.4, –5.3, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2885, 2857, 1738, 1472, 1443, 1374, 1237, 1092, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 325.1 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{14}H_{26}O_5SiNa$: 325.1442, found: 325.1440.

Chlorodiene 137. A solution of 4,4,4-trichlorobutene (185 mg, 0.631 mmol) in pentane (5.0 mL) and a

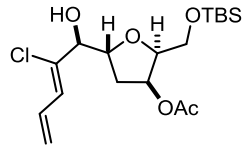


solution of aldehyde **134** (190 mg, 0.631 mmol) in THF (5.0 mL with rinses) were added to a suspension of chromium (II)-chloride (1.00 g, 5.07 mmol) in THF (5.0 mL). After stirring for 96 h the suspension turned from green to purple. The mixture was diluted with EtOAc (50 mL) and the reaction was quenched with pH

7.4 phosphate buffer (100 mL). The aq. phase was separated and extracted with EtOAc (100 mL). The combined organic phases were washed with water (3 × 150 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/NEt_3/EtOAc 90:1:10 to 85:1:15) to afford chlorodiene **137** as a yellow oil (127 mg, 51%, diastereomeric mixture, dr = 1.9:1).



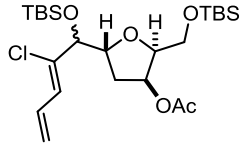
Spectral data for major diastereomer (*R*)-**137**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (dtd, *J* = 17.0, 10.2, 4.8 Hz, 1H), 6.47 (dd, *J* = 10.3, 1.1 Hz, 1H), 5.44–5.27 (m, 3H), 4.50 (ddd, *J* = 9.3, 6.1, 4.1 Hz, 1H), 4.46 (d, *J* = 4.2 Hz, 1H), 4.14 (td, *J* = 6.2, 3.9 Hz, 1H), 3.74 (d, *J* = 6.2 Hz, 2H), 2.48 (br s, 1H), 2.21 (ddd, *J* = 14.3, 9.2, 5.2 Hz, 1H), 2.06 (s, 3H), 1.95 (ddd, *J* = 14.0, 6.2, 1.6 Hz, 1H), 0.87 (s, 9H), 0.05–0.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 132.2, 131.0, 126.2, 120.9, 82.2, 78.7, 74.9, 74.2, 61.3, 32.5, 25.8, 21.0, 18.2, –5.4, –5.5.



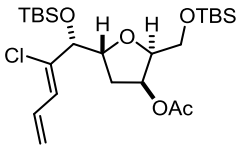
Analytical and spectral data for minor diastereomer minor (*S*)-**137**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (dtd, *J* = 17.0, 10.2, 4.8 Hz, 1H), 6.45 (dd, *J* = 10.3, 0.8 Hz, 1H), 5.44–5.27 (m, 3H), 4.41 (ddd, *J* = 8.6, 7.3, 5.5 Hz, 1H), 4.10 (ddd, *J* = 6.7, 5.9, 3.8 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 1H), 3.76 (d, *J* = 5.6 Hz, 2H), 2.76 (br s, 1H), 2.10 (dd, *J* = 7.5, 3.0 Hz, 1H), 2.08–2.06 (m, 4H), 0.87 (s, 9H), 0.05–0.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 133.1, 131.2, 127.4, 121.2, 81.7, 78.9, 77.1, 74.0, 61.0, 35.7, 25.8, 21.0, 18.2, –5.4, –5.5 ppm. IR (film): $\tilde{\nu}$ = 3458, 2954, 2930, 2885, 2858, 1743, 1472, 1374, 1251, 1092, 837, 777 cm^{-1}. MS (EI) *m/z* (%): 390 (2), 273 (27), 145 (78), 143 (42), 129 (32), 117 (59), 105 (26), 89 (100), 75 (63), 73 (71), 43 (31). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}O_5SiClNa$: 413.1521, found: 413.1520.

Absolute stereochemistry was assigned according to the preferential *anti*-diol formation during intermolecular NHK reactions with α-alkoxy aldehydes via a Felkin-Anh transition state.[97]

Compound 138. 2,6-Lutidine (64 µL, 0.55 mmol) and TBSOTf (0.11 mL, 0.48 mmol) were added to a solution of alcohol **137** (127 mg, 0.324 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After stirring for 12 h and allowing to warm to ambient temperature, the mixture was diluted with *t*-butyl methyl ether (25 mL) and the reaction was quenched with pH 7.4 phosphate buffer (25 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 99:1) to afford the title compound as a yellow oil (70.5 mg, 43%, diastereomeric mixture, dr = 2.4:1). For analytical analysis the diastereomeric mixture was separated by flash chromatography (fine silica, hexane/EtOAc 99:1) to afford major epimer (*R*)-**138** and minor epimer (*S*)-**138.**

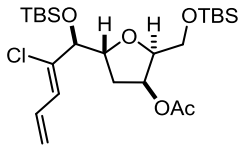


Analytical and spectral data for (*R*)-**138**: $[\alpha]_D^{20}$ = +98.6 (c = 0.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



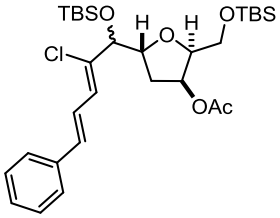
δ = 6.65 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.42 (dt, *J* = 10.3, 0.9 Hz, 1H), 5.37 (td, *J* = 3.5, 1.7 Hz, 1H), 5.33 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.25 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.47 (ddd, *J* = 8.8, 6.5, 3.2 Hz, 1H), 4.42 (d, *J* = 3.0 Hz, 1H), 4.07 (td, *J* = 6.1, 3.6 Hz, 1H), 3.71 (dd, *J* = 6.1, 0.8 Hz, 2H), 2.30 (ddd, *J* = 14.0, 8.8, 5.2 Hz, 1H), 2.05 (s, 3H), 1.88 (ddd, *J* = 13.9, 6.6, 1.5 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 134.1, 131.2, 126.0, 120.2, 82.0, 78.9, 76.7, 74.7, 61.4, 32.1, 25.8, 25.8, 21.1, 18.2, 18.2, –5.0, –5.1, –5.4, –5.5 ppm.

Analytical and spectral data for (*S*)-**138**: $[\alpha]_D^{20}$ = +14.2 (c = 0.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



δ = 6.68 (dt, *J* = 17.1, 10.3 Hz, 1H), 6.41 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.38–5.35 (m, 1H), 5.33 (dd, *J* = 9.6, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.36 (ddd, *J* = 8.7, 6.8, 4.7 Hz, 1H), 4.07 (dd, *J* = 4.8, 0.8 Hz, 1H), 4.03 (td, *J* = 6.3, 3.5 Hz, 1H), 3.73 (d, *J* = 6.2 Hz, 2H), 2.10 (ddd, *J* = 13.8, 8.7, 5.0 Hz, 1H), 2.05 (s, 3H), 2.01 (ddd, *J* = 14.1, 6.9, 1.7 Hz, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.05 (s, 2H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 134.1, 131.4, 127.0, 120.3, 81.6, 79.2, 78.2, 74.4, 61.0, 34.9, 25.8, 25.7, 21.1, 18.2, 18.2, −4.9, –5.0, –5.4, –5.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1744, 1472, 1374, 1251, 1093, 838, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 527.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{24}H_{45}O_5Si_2ClNa$: 527.2386, found: 527.2384.

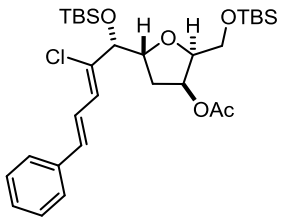
Styrene 142. A solution of 4,4,4-trichloromethylstyrene (25 mg, 0.11 mmol) in THF (0.2 mL) and a solution of aldehyde **134** (32 mg, 0.11 mmol) in THF (0.2 mL) were added to a turquoise suspension of chromium(II)-chloride (84 mg, 0.42 mmol) in THF (0.3 mL). After stirring for 96 h, the suspension was heated to 35 °C and stirred for another 48 h. After cooling to ambient temperature, the mixture was diluted with EtOAc (5 mL) and the reaction was quenched with water (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with water (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was filtered through a short pad of silica (EtOAc/NEt_3 = 99:1) to afford a diastereomeric mixture of allyl alcohol (26 mg, 52%, 2.6:1 dr) as a yellow oil, which degraded quickly and was thus subjected to the following TBS protection.



2,6-Lutidine (23 µL, 0.20 mmol) and TBSOTf (39 µL, 0.17 mmol) were added to a solution of the crude mixture (26 mg, 56 µmol) in CH_2Cl_2 (0.26 mL) at 0 °C. After stirring for 16 h and allowing to warm to ambient temperature, the mixture was diluted with *t*-butyl methyl ether (5 mL) and the reaction was quenched with pH 7 phosphate buffer (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried

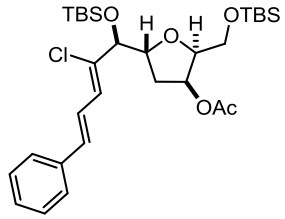
over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/NEt_3/EtOAc 97:1:2) to afford compounds (*R*)-**142** (17 mg, 28% over 2 steps) and (*S*)-**142** (7.2 mg, 11% over 2 steps) as a yellow oils

Analytical and spectral data for (*R*)-**142**: $[\alpha]_D^{20}$ = +40.9 (c = 1.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



δ = 7.47–7.43 (m, 2H), 7.36–7.31 (m, 2H), 7.29–7.23 (m, 1H), 7.08 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.57 (dt, *J* = 10.5, 0.9 Hz, 1H), 5.38 (ddd, *J* = 5.1, 3.6, 1.5 Hz, 1H), 4.53–4.45 (m, 2H), 4.09 (td, *J* = 6.1, 3.6 Hz, 1H), 3.72 (d, *J* = 6.1 Hz, 2H), 2.33 (ddd, *J* = 14.0, 8.5, 5.2 Hz, 1H), 2.06 (s, 3H), 1.90 (ddd, *J* = 14.0, 6.3, 1.5 Hz, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 136.8, 135.1, 134.0, 128.7, 128.1, 126.7, 125.7, 123.1, 82.0, 79.0, 76.9, 74.7, 61.4, 32.2, 25.8 (2C), 21.1, 18.2, 18.2, –5.0, −5.0, –5.4, –5.5 ppm.

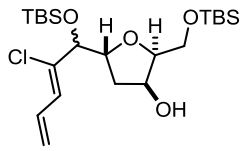
Analytical and spectral data for (*S*)-**142**: $[\alpha]_D^{20}$ = −19.5 (c = 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



δ = 7.49–7.42 (m, 2H), 7.37–7.29 (m, 2H), 7.29–7.22 (m, 1H), 7.11 (dd, *J* = 15.8, 10.5 Hz, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.61–6.54 (m, 1H), 5.37 (ddd, *J* = 4.9, 3.4, 1.5 Hz, 1H), 4.39 (ddd, *J* = 8.7, 6.8, 4.7 Hz, 1H), 4.14–4.10(m, 1H), 4.05 (td, *J* = 6.3, 3.5 Hz, 1H), 3.74 (d, *J* = 6.3 Hz, 2H), 2.13 (ddd, *J* = 13.8, 8.6, 5.0 Hz, 1H), 2.08–2.00 (m, 4H), 0.93 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H).ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2885, 2857, 1743, 1472, 1372, 1249, 1093, 837, 778 cm^{-1}. MS (EI) *m/z* (%): 580 (2), 307 (22), 273 (38), 213 (31), 145 (100), 89 (80), 73 (62). HRMS (ESIpos): *m/z* calcd for $C_{30}H_{49}O_5Si_2ClNa$: 603.2699, found: 603.2690.

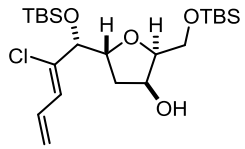
Absolute stereochemistry was assigned according to the preferential *anti*-diol formation during intermolecular NHK reactions with α-alkoxy aldehydes via a Felkin-Anh transition state.[97]

Alcohol 139. K_2CO_3 (39 mg, 0.28 mmol) was added to a solution of acetate **138** (70.5 mg, 140 µmol)



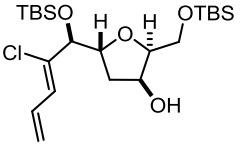
in methanol (2.5 mL). After stirring for 4 h at ambient temperature, the reaction was quenched with pH 7.0 phosphate buffer (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (fine silica, hexane/EtOAc 99:1 to 98:2 to 96:4) to afford alcohol major epimer (*R*)-**139** (25.1 mg, 39%) and minor epimer (*S*)-**139** (8.7 mg, 14%) as separable diastereomers.

Analytical and spectral data for (*R*)-**139**: $[\alpha]_D^{20}$ = +98.6 (c = 0.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



δ = 6.67 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.42 (dq, *J* = 10.3, 0.9 Hz, 1H), 5.33 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.25 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.54 (ddd, *J* = 9.6, 6.4, 3.4 Hz, 1H), 4.51–4.47 (m, 1H), 4.38 (dd, *J* = 3.5, 1.1 Hz, 1H), 3.95–3.88 (m, 3H), 3.29 (d, *J* = 4.5 Hz, 1H), 2.14 (ddd, *J* = 13.2, 8.6, 5.4 Hz, 1H), 1.84 (ddd, *J* = 13.2, 6.5, 2.1 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.5, 131.4, 125.8, 120.0, 81.4, 79.2, 77.0, 74.0, 62.9, 34.9, 25.8, 25.7, 18.2, 18.1, −5.0, −5.1, −5.5, −5.6 ppm.

Analytical and spectral data for (*S*)-**139**: $[\alpha]_D^{20}$ = +8.4 (c = 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



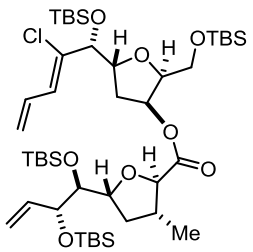
δ = 6.69 (dt, *J* = 17.1, 10.3 Hz, 1H), 6.40 (dd, *J* = 10.4, 0.9 Hz, 1H), 5.34 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.8 Hz, 1H), 4.49 (q, *J* = 3.7 Hz, 1H), 4.43 (ddd, *J* = 8.5, 6.9, 4.8 Hz, 1H), 4.29 (qd, *J* = 6.9, 3.6 Hz, 1H), 4.08 (dd, *J* = 4.9, 0.8 Hz, 1H), 3.95–3.89 (m, 3H), 1.98–1.92 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.11–0.07 (m, 9H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.5, 131.5, 126.7, 120.0, 80.8, 79.8, 78.4, 74.1, 62.8, 37.6, 25.8, 25.8, 18.2, 18.1, –4.9, –5.0, –5.5, –5.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1744, 1472, 1374, 1251, 1093, 838, 778 cm^{-1}. MS (EI) *m/z* (%): 273 (24), 145 (54), 143 (22), 115 (22), 105 (21), 89 (100), 75 (40), 73 (90). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{43}O_4Si_2ClNa$: 485.2281, found: 485.2278.

5.3.3 Fragment Assembly for RCM Precursors

General Procedure for Yamaguchi Esterification of Southern Fragments 124a and 124b with both Diastereomeric Northern Fragments 139.

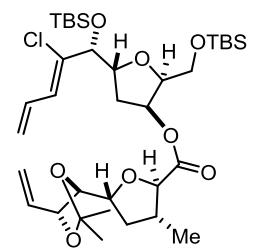
Et_3N (900 mol%) and 2,4,6-trichlorobenzoyl chloride (220 mol%) were added to a solution of carboxylic acid **124a** or **124b** (100 mol%) in THF (0.09 M). After stirring for 1 h at ambient temperature, a solution of the corresponding alcohol **139** (100 mol%) in toluene (0.04 M) and DMAP (500 mol%) were added to the solution of mixed Yamaguchi anhydride. After stirring for another 3 h, the reaction was quenched with sat. $NaHCO_3$ (5 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 99:2 to 96:4) to afford the title compound.

Ester (*R*)-**143.** According to General Procedure using carboxylic acid **124a** (5.8 mg, 13 µmol) and



alcohol (*R*)-**139** (6.0 mg, 13 µmol). Light yellow oil (2.9 mg, 25%). $[\alpha]_D^{20}$ = +13.4 (c = 0.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.42 (dd, *J* = 10.3, 1.0 Hz, 1H), 5.90 (ddd, *J* = 17.3, 10.4, 6.8 Hz, 1H), 5.43 (t, *J* = 3.9 Hz, 1H), 5.33 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.26 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.17–5.07 (m, 2H), 4.47 (ddd, *J* = 9.1, 6.5, 3.2 Hz, 1H), 4.43 (d, *J* = 3.2 Hz, 1H), 4.13–4.05 (m, 3H), 3.90 (d, *J* = 8.9 Hz, 1H), 3.72 (dd, *J* = 10.4, 5.9 Hz, 1H), 3.69 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.55 (dd, *J* = 6.0, 3.3 Hz, 1H), 2.36–2.25 (m, 2H), 2.03 (ddd, *J* = 12.1, 6.9, 5.3 Hz, 1H), 1.84 (ddd, *J* = 13.9, 6.5, 1.4 Hz, 1H), 1.47–1.37 (m, 1H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.90–0.88 (m, 18H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07–0.05 (m, 9H), 0.04–0.02 (m, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 138.8, 134.0, 131.3, 125.9, 120.2, 115.8, 82.6, 82.2, 81.6, 79.1, 79.0, 76.6, 76.1, 74.9, 61.5, 40.1, 37.2, 32.1, 26.1, 26.0, 25.8, 25.8, 18.4, 18.3, 18.2, 18.2, 17.3, −4.1, −4.2, −4.4, −4.7, −5.0, −5.1, −5.4, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2956, 2929, 2889, 2858, 1733, 1472, 1255, 1091, 995, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 911.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{85}O_8Si_4ClNa$: 911.4902, found: 911.4908.

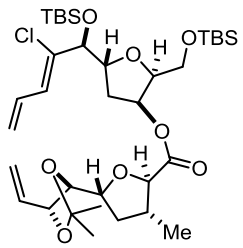
Ester (*R*)-**144.** According to General Procedure using carboxylic acid **124b** (16 mg, 62 µmol) and



alcohol (*R*)-**139** (29 mg, 62 µmol). Light yellow oil (13.5 mg, 31%). $[\alpha]_D^{20}$ = +79.7 (c = 0.32, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.42 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.1, 8.5 Hz, 1H), 5.41 (ddd, *J* = 5.1, 3.5, 1.4 Hz, 1H), 5.37–5.23 (m, 4H), 4.53 (dd, *J* = 8.3, 6.6 Hz, 1H), 4.48 (td, *J* = 6.5, 3.4 Hz, 1H), 4.44 (d, *J* = 2.9 Hz, 1H), 4.16 (dt, *J* = 9.6, 6.0 Hz, 1H), 4.12–4.03 (m, 3H), 3.74–3.76 (m, 2H), 2.39–2.27 (m, 2H), 2.15 (ddd, *J* = 12.7, 7.4, 5.7 Hz, 1H), 1.86 (ddd, *J* = 14.0, 6.6, 1.5 Hz, 1H), 1.52 (s, 3H), 1.39 (s, 3H), 1.36 (dt, *J* = 12.4, 9.5 Hz, 1H), 1.19

(d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 134.2, 133.9, 131.2, 125.9, 120.3, 119.6, 109.5, 83.5, 82.2, 80.5, 79.3, 79.2, 79.0, 76.6, 75.1, 61.6, 39.6, 36.9, 32.0, 27.6, 25.8, 25.8, 25.6, 18.3, 18.2, 18.2, −5.0, −5.1, −5.4, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2858, 1739, 1256, 1091, 997, 839, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 723.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{35}H_{61}O_8Si_2ClNa$: 723.3486, found: 723.3489.

Ester (*S*)-**144.** According to General Procedure using carboxylic acid **124b** (7.8 mg, 30 µmol) and

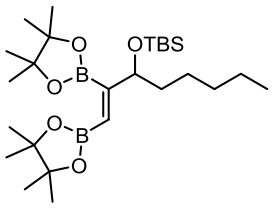


alcohol (*S*)-**139** (14 mg, 30 µmol). Light yellow oil (13.1 mg, 61%). which analyzed as follows: $[\alpha]_D^{20}$ = –1.0 (c = 0.63, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.67 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.41 (d, *J* = 10.4 Hz, 1H), 5.97 (ddd, *J* = 16.9, 10.2, 8.5 Hz, 1H), 5.41 (t, *J* = 3.7 Hz, 1H), 5.37–5.24 (m, 4H), 4.53 (dd, *J* = 8.5, 6.5 Hz, 1H), 4.37 (ddd, *J* = 8.6, 6.8, 4.6 Hz, 1H), 4.16 (dt, *J* = 9.6, 6.0 Hz, 1H), 4.11–4.03 (m, 4H), 3.72 (d, *J* = 6.2 Hz, 2H), 2.35 (dh, *J* = 9.6, 6.9 Hz, 1H), 2.18–2.08 (m, 2H), 2.00 (ddd, *J* = 14.1, 6.8, 1.4 Hz, 1H), 1.52 (s, 3H), 1.41–1.32 (m, 4H), 1.19 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.3, 134.2, 134.0, 131.4, 127.1, 120.3, 119.6, 109.5, 83.5, 81.8, 80.5, 79.3, 79.2, 79.2, 78.2, 74.8, 61.3, 39.6, 36.9, 35.0, 27.5, 25.8, 25.7, 25.6, 18.4, 18.2, 18.2, –4.9, –5.0, –5.3, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2858, 1739, 1256, 1091, 997, 839, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 723.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{35}H_{61}O_8Si_2ClNa$: 723.3486, found: 723.3489.

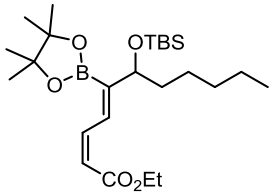
5.4 Synthesis of Macrocyclic Core 78 by Pd-catalyzed Cross Coupling

5.4.1 Model Studies

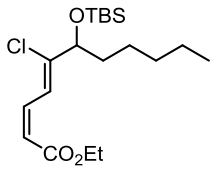
Bisboronate 176. A pressure Schlenk tube (Young tube) was charged with $Pt(PPh_3)_4$ (31 mg, 25 µmol) and B_2pin_2 (0.21 g, 0.83 mmol). A solution of alkyne **175b** (0.20 g, 0.83 mmol) in degassed DMF (1 mL) was added and the solution was stirred for 16 h at 80 °C. After cooling to ambient temperature, the mixture was diluted with *t*-butyl methyl ether (20 mL) and washed with brine (3 × 5 mL). The organic phase was dried over $MgSO_4$, filtered through a small pad of Celite® and concentrated. The crude mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 1.5 Hz, 1H), 4.19 (ddd, *J* = 6.6, 5.0, 1.5 Hz, 1H), 1.56–1.41 (m, 2H), 1.39–1.16 (m, 30H), 0.89–0.83 (m, 12H), 0.02 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 83.6, 83.4, 78.0, 37.9, 32.0, 26.2, 25.2, 25.1, 25.1, 24.9, 22.7, 18.5, 14.3, –4.1, –4.7 ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.1 ppm. IR (film) $\tilde{\nu}$ = 2977, 2956, 2929, 2857, 1621; 1464, 1402, 1371, 1335, 1310, 1255, 1215, 1140, 969, 835 cm^{-1}. MS (ESIpos) *m/z* (%): 517.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{52}O_5B_2SiNa$: 517.3662, found: 517.3664.



Dienylboronate 178. The crude bisboronate **176** (80 mg, 0.16 mmol) was dissolved in THF (1 mL) and water (43 µL, 2.4 mmol), $PdCl_2$(dppf) (3.6 mg, 4.9 µmol), K_3PO_4 (0.1 g, 0.5 mmol), and ethyl *Z*-3-iodoacrylate (**177**) (21 µL, 0.16 mmol) were added subsequently and the mixture was stirred at 60 °C for 16 h. The reaction was allowed to cool to ambient temperature and was dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography (hexane/EtOAc 9:1) to afford the title compound (52 mg, 69%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dt, *J* = 11.7, 1.2 Hz, 1H), 7.25 (t, *J* = 11.7 Hz, 1H), 5.69 (dd, *J* = 11.5, 1.1 Hz, 1H), 4.35 (td, *J* = 6.4, 1.2 Hz, 1H), 4.18 (qd, *J* = 7.1, 2.2 Hz, 2H), 1.53 (m, 2H), 1.34–1.20 (m, 21H), 0.92–0.83 (m, 12H), 0.07 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 142.8, 135.9, 119.0, 83.6, 75.9, 60.0, 38.4, 32.0, 26.1, 25.3, 25.2, 24.7, 22.7, 18.4, 14.5, 14.2, –4.2, –4.7 ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.1 ppm. IR (film) $\tilde{\nu}$ = 2956, 2929, 2857, 1719, 1580, 1464, 1380, 1309, 1255, 1181, 1142, 1086, 1059, 834, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 489.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{47}O_5BSiNa$: 489.3178, found: 489.3174.

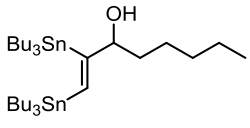


Chlorodiene 180. (Ph_3P)AuCl (5.3 mg, 11 µmol) was added to a suspension of dienylboronate **178**



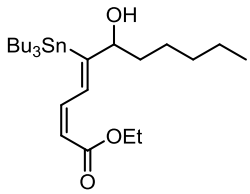
(5.0 mg, 11 µmol) and Cs_2CO_3 (3.5 mg, 11 µmol) in *i*-PrOH (0.5 mL) and the mixture was stirred at 50 °C for 1 h. The mixture was allowed to cool to ambient temperature and NCS (7.2 mg, 54 µmol) was added and stirred for 16 h. After filtration through a small pad of silica and rinsing with *t*-butyl methyl ether the filtrate was concentrated. The residue was purified by flash chromatography (hexane/EtOAc 1:0 to 50:1) to afford the title compound as a colourless oil (3.0 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dt, *J* = 11.2, 0.9 Hz, 1H), 7.00 (t, *J* = 11.3 Hz, 1H), 5.79 (dd, *J* = 11.5, 1.1 Hz, 1H), 4.26 (t, *J* = 6.0 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.70–1.61 (m, 2H), 1.33–1.22 (m, 9H), 0.93–0.85 (m, 12H), 0.07 (d, *J* = 0.7 Hz, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.2, 147.3, 138.0, 120.5, 120.0, 76.4, 60.3, 36.1, 31.8, 25.9, 24.8, 22.7, 18.3, 14.4, 14.2, –4.6, −4.9 ppm. IR (film) $\tilde{\nu}$ = 2956, 2930, 2858, 1718, 1630, 1464, 1417, 1257, 1186, 1143, 1093, 1033, 836, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 397.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{35}O_3ClSiNa$: 397.1936, found: 397.1932.

Bis(alkenyl)stannane 181. A solution of 1-octin-3-ol (**175a**) (58 µL, 0.4 mmol) in THF (1 mL) was



added to a solution of [(*t*BuNC)$_2$PdCl$_2$] (14 mg, 40 µmol) in THF (1 mL). Hexabutylditin (0.22 mL, 0.44 mmol) wasi added in one portion and the resulting mixture stirred at ambient temperature for 7 h. The solvent was evaporated and the residue purified by flash chromatography (hexane/Et_3N 200:1) to yield the title compound as a yellow oil (239 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 1.2 Hz, J_{SnH} = 179, 66.8 Hz, 1H), 4.05 (tdd, *J* = 6.5, 3.6, 1.1 Hz, 1H), 2.52 (q, *J* = 7.2 Hz, 1H), 1.52–1.44 (m, 15H), 1.37–1.30 (m, 17H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.92–0.87 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 9H), 0.89 (t, *J* = 7.2 Hz, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 140.3, 84.0, 37.3, 32.0, 29.5, 29.3, 27.8, 27.6, 25.7, 22.8, 14.2, 13.8, 13.8, 11.3, 11.0 ppm. ^{119}Sn NMR (112 MHz, $CDCl_3$): δ = –60.5, –65.5 ppm. IR (film): $\tilde{\nu}$ = 3464, 2955, 2921, 2871, 2854, 1463, 1376, 1340 1291, 1071, 1021, 961, 863, 826, 666, 594 cm^{-1}. MS (ESIpos) *m/z* (%): 731.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{32}H_{68}OSn_2Na$: 731.3205, found: 731.3212.

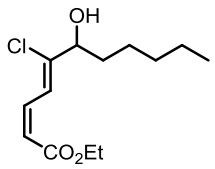
Dienylstannane 182. Tetrabutyl-ammonium diphenylphosphinate (52.1 mg, 11.3 mmol) was placed



in a Schlenk tube, which was evacuated and flame-dried. A solution of bisstannane **181** (50.0 mg, 70.8 µmol) in degassed DMF (0.5 mL) was added, followed by $Pd(PPh_3)_4$ (16.4 mg, 14.2 µmol). The resulting mixture was stirred at ambient temperature for 5 min before CuTC (20.2 mg, 106 µmol) was introduced, followed by a solution of ethyl (*Z*)-3-iodoacrylate (**177**) (17.0 mg, 76.3 µmol) in degassed DMF (0.5 mL). The resulting mixture was stirred at ambient temperature for 1 h before the reaction was quenched with water (3 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated.

The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether/Et_3N 95:5:0.5) to yield the title compound as a colourless oil (21.5 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 11.5 Hz, J_{SnH} = 113 Hz, 1H), 6.57 (t, J = 11.4 Hz, 1H), 5.70 (dd, J = 11.3, 1.1 Hz, 1H), 4.32 (t, J = 6.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.61 (brs, 1H), 1.52–1.44 (m, 6H), 1.40–1.22 (m, 18H), 1.05–0.97 (m, 5H), 0.89 (t, J = 7.2 Hz, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 144.9, 134.7, 130.2, 117.9, 79.9, 60.2, 37.5, 31.9, 29.3, 27.5, 25.6, 22.8, 14.5, 1.45, 13.8, 11.8 ppm. ^{119}Sn NMR (112 MHz, $CDCl_3$): δ = –53.6 ppm. IR (film): $\tilde{\nu}$ = 3483, 2956, 2925, 2855, 1716, 1613, 1561, 1463, 1179, 1027, 821, 671, 596 cm^{-1}. MS (ESIpos) *m/z* (%): 539.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{48}O_3SnNa$: 539.2517, found: 539.2522.

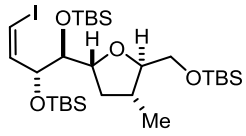
Ethyl (2*Z*,4*Z*)-5-chloro-6-hydroxyundeca-2,4-dienoate (179). Copper(II) chloride (6.5 mg, 49 µmol)



was added to a solution of dienylstannane **182** (10 mg, 19 µmol) in THF (0.2 mL) followed by 2,6-lutidine (2.3 µL, 19 µmol). After stirring for 72 h at ambient temperature, the mixture was diluted with *t*-butyl methyl ether (2 mL) and quenched with sat. $NaHCO_3$ (3 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 2 mL). The combined organic phases were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 9:1 to 6:1) to afford the title compound as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dt, J = 11.0, 0.8 Hz, 1H), 7.01 (dd, J = 11.4, 11.0 Hz, 1H), 5.84 (dd, J = 11.4, 1.1 Hz, 1H), 4.35–4.27 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.99 (br s, 1H), 1.78–1.63 (m, 2H), 1.37–1.28 (m, 9H), 0.88 (t, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 146.1, 137.8, 121.1, 120.7, 75.9, 60.5, 35.1, 31.7, 25.1, 22.6, 14.4, 14.1. IR (film) $\tilde{\nu}$ = 3460, 2956, 2928, 2859, 1715, 1629, 1464, 1417, 1386, 1285, 1186, 1137, 1029, 826 cm^{-1}. MS (ESIpos) *m/z* (%): 283.1 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{21}O_3ClNa$: 283.1071, found: 283.1071.

5.4.2 Synthesis of Southern Fragments for Cross Coupling

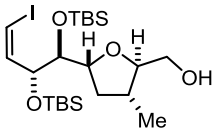
(*Z*)-Alkenyl Iodide 183. Iodomethyltriphenylphosphonium iodide (997 mg, 2.29 mmol) was added in



portions to a solution of NaHMDS (386 mg, 2.10 mmol) in THF (15 mL). The resulting yellow mixture was stirred at ambient temperature for 30 min before it was cooled to –78 °C. HMPA (0.80 mL, 4.57 mmol) was added, followed by a solution of aldehyde **120a** (500 mg, 0.91 mmol) in THF (3 mL). The resulting mixture was stirred at −78 °C for 7 h. The reaction was quenched with water (8 mL) and the aq. phase was extracted with *t*-butyl methyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 300:1) to afford the title compound as a colourless oil (596 mg, 97%, *Z*/*E* = >20:1). $[\alpha]_D^{20}$ = +6.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.40 (dd, J = 8.2, 7.7 Hz, 1H), 6.27 (dd, J = 7.7, 0.5 Hz, 1H), 4.31

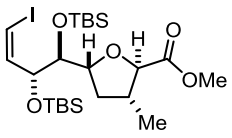
(ddd, *J* = 8.3, 1.9, 0.8 Hz, 1H), 3.75 (ddd, *J* = 9.8, 8.0, 5.7 Hz, 1H), 3.67–3.59 (m, 3H), 3.46 (dt, *J* = 9.2, 4.7 Hz, 1H), 2.29 (ddd, *J* = 12.3, 7.0, 5.7 Hz, 1H), 2.06 (ddt, *J* = 11.0, 8.8, 6.7 Hz, 1H), 1.31 (td, *J* = 11.6, 10.0 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.07 (s, 3H), 0.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.9, 84.9, 81.8, 80.7, 79.3, 76.7, 65.2, 38.7, 37.2, 26.3, 26.1, 26.1, 18.6, 18.5, 18.3, 17.2, −3.9, –4.0, –4.2, –4.5, –5.2 (2C) ppm. IR (film): $\tilde{\nu}$ = 2954, 2928, 2886, 2856, 1471, 1462, 1388, 1361, 1252, 1131, 1075, 1005, 959, 832, 774, 672, 594 cm^{-1}. MS (EI) *m/z* (%): 615 (13), 614 (28), 413 (69), 543 (13), 481 (15), 375 (17), 374 (25), 371 (27), 349 (12), 298 (15), 297 (100), 230 (13), 229 (73), 186 (16), 185 (97), 147 (12), 115 (12), 89 (13), 75 (16), 73 (91). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{59}O_4ISi_3Na$: 693.2658, found: 693.2657.

Alcohol S5. Pyridine (2.78 mL, 34.4 mmol) was slowly added to a Teflon® vial charged with



HF·pyridine (0.49 mL, 5.4 mmol) and the resulting mixture diluted with THF (3 mL). This solution was added dropwise to a solution of compound **183** (140 mg, 0.209 mmol) in THF (1 mL) in a second Teflon® vial. The resulting mixture was stirred at ambient temperature for 9 h. The mixture was diluted with EtOAc (5 mL) and the reaction was carefully quenched with sat. $NaHCO_3$ (10 mL). The phases were separated and the aq. phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 30:1) to afford the title compound as a colourless oil (105 mg, 91%). $[\alpha]_D^{20}$ = +5.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (ddd, *J* = 8.2, 7.7 Hz, 1H), 6.30 (d, *J* = 7.7 Hz, 1H), 4.32 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.81 (ddd, *J* = 10.0, 7.7, 5.6 Hz, 1H), 3.74–3.70 (m, 1H), 3.63 (dd, *J* = 7.7, 2.1 Hz, 1H), 3.54–3.47 (m, 2H), 2.33 (ddd, *J* = 12.1, 7.2, 6.2 Hz, 1H), 2.10 (ddqd, *J* = 13.3, 9.0, 6.5, 4.4 Hz, 1H), 1.91 (t, *J* = 6.1 Hz, 1H), 1.37 (td, *J* = 12.1, 11.2, 10.0 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.8, 84.9, 82.0, 80.7, 79.6, 76.9, 63.2, 38.6, 35.4, 26.2, 26.1, 18.6, 18.3, 16.4, −3.9, −4.1, −4.1, −4.2 ppm. IR (film): $\tilde{\nu}$ = 3447, 2954, 2928, 2856, 1462, 1388, 1361, 1252, 1145, 1077, 1055, 1005, 959, 833, 776, 674 cm^{-1}. MS (ESIpos) *m/z* (%): 579.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{45}O_4ISi_2Na$: 579.1793, found: 579.1794.

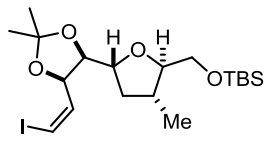
Ester 157. $NaHCO_3$ (38 mg, 0.45 mmol), PIDA (107 mg, 0.33 mmol) and TEMPO (4.7 mg, 30 µmol)



were sequentially added to a solution of alcohol **S5** (84 mg, 0.15 mmol) in MeCN/H_2O (1:1, 1.5 mL). After stirring for 20 h, the mixture was diluted with MeCN (5 mL) and the reaction was quenched with pH 5 phosphate buffer (0.5 mL). After filtration through a short pad of Na_2SO_4, the solvent was removed under reduced pressure. The residue was partitioned between MeCN (5 mL) and cyclohexane (5 mL). The cyclohexane phase was extracted with MeCN (3 × 8 mL). The combined MeCN-organic phases were

dried over Na_2SO_4, filtered and concentrated. The crude acid was used in the next step without further purification.

A solution of $TMSCHN_2$ (2 M in Et_2O, 0.14 mL, 0.27 mmol) was added to a solution of the crude acid (86 mg, 0.15 mmol) in THF (1.5 mL) at 0 °C. The resulting yellow mixture was stirred at 0 °C for 30 min before the reaction was carefully quenched with pH 5 phosphate buffer (2 mL). The phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 49:1) to yield the title compound as a colourless oil (58.0 mg, 66% over two steps). $[\alpha]_D^{20}$ = +16.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.29 (dd, *J* = 7.6, 0.7 Hz, 1H), 4.37 (ddd, *J* = 8.2, 2.3, 0.8 Hz, 1H), 4.03 (ddd, *J* = 10.3, 7.2, 5.3 Hz, 1H), 3.98 (d, *J* = 8.6 Hz, 1H), 3.74 (s, 3H), 3.71 (dd, *J* = 7.2, 2.3 Hz, 1H), 2.36 (dddq, *J* = 10.5, 8.5, 6.6, 6.5 Hz, 1H), 2.27 (ddd, *J* = 12.1, 6.9, 5.3 Hz, 1H), 1.44 (dt, *J* = 11.8, 10.5 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 141.9, 82.7, 82.3, 81.4, 79.5, 76.8, 52.0, 39.9, 37.7, 26.2, 26.1, 18.5, 18.3, 17.5, −3.9, −4.2 (2C), −4.3 ppm. IR (film): $\tilde{\nu}$ = 2954, 2928, 2888, 2956, 1759, 1738, 1611, 1472, 1462, 1389, 1361, 1253, 1201, 1146, 1078, 1005, 962, 835, 777, 674 cm^{-1}. MS (EI) *m/z* (%): 528 (18), 527 (59), 457 (12), 371 (22), 331 (35), 325 (20), 321 (12), 297 (38), 288 (13), 287 (60), 241 (12), 186 (12), 185 (73), 175 (36), 171 (23), 159 (10), 155 (77), 143 (39), 133 (15), 127 (19), 115 (87), 113 (10), 95 (14), 89 (149, 83 (13), 75 (21), 73 (100), 59 (10). HRMS (ESIpos): *m/z* calcd for $C_{23}H_{45}O_5ISi_2Na$: 607.1742, found: 607.1746.

(*Z*)-Alkenyl Iodide 184. 

Iodomethyltriphenylphosphonium iodide (1.82 g, 4.17 mmol) was added in portions to a solution of NaHMDS (753 mg, 4.11 mmol) in THF (25 mL). The resulting yellow mixture was stirred at ambient temperature for 30 min before it was cooled to –78 °C. HMPA (1.40 mL, 8.02 mmol) was added, followed by a solution of aldehyde **120b** (575 mg, 1.60 mmol) in THF (6 mL). The resulting mixture was stirred at –78 °C for 4 h. The reaction was quenched with water (15 mL) and the aq. phase was extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 70:1 to 40:1) to afford the title compound as a colourless oil (517 mg, 67% over two steps, *Z*/*E* > 20:1). $[\alpha]_D^{20}$ = –53.2 (c = 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.36 (dd, *J* = 8.6, 7.7 Hz, 1H), 4.82 (ddd, *J* = 8.6, 6.3, 0.6 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 1H), 3.89 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.72 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.65 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.56 (ddd, *J* = 8.9, 5.1, 3.9 Hz, 1H), 2.18 (ddq, *J* = 13.9, 10.1, 6.5 Hz, 1H), 2.07 (ddd, *J* = 13.0, 7.2, 5.9 Hz, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.33 (dt, *J* = 11.9, 10.1 Hz, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.04(s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6, 110.0, 86.0, 85.6, 81.1, 79.8, 77.2, 64.9, 38.1, 36.7, 27.8, 26.0,

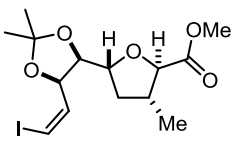
25.8, 18.4, 17.8, –5.2, –5.2 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1461, 1378, 1252, 1214, 1164, 1125, 1085, 1059, 999, 837, 777, 677 cm^{-1}. MS (EI) *m/z* (%): 483 (11), 482 (24), 467 (12), 426 (19), 425 (87), 367 (22), 337 (12), 293 (11), 243 (21), 230 (19), 229 (100), 186 (12), 185 (61), 171 (28), 157 (34), 149 (17), 117 (18), 93 (11), 75 (31), 73 (43). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{35}O_4ISiNa$: 505.1242, found: 505.1244.

Alcohol 198. Pyridine (5.5 ml, 68 mmol), and HF·pyridine (0.70 ml, 7.8 mmol) were successively added to a solution of compound **184** (241 mg, 0.500 mmol) in THF (12 mL) in a Teflon® vial. The resulting mixture was stirred at ambient temperature for 16 h. The mixture was diluted with EtOAc (10 mL) and the reaction carefully quenched with sat. $NaHCO_3$ (20 mL). The phases were separated and the aq. phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with a 1:3 mixture of sat. NH_4Cl and brine (50 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1 to 2:1) to afford the title compound as a colourless oil (220 mg, 99%). $[\alpha]_D^{20}$ = –50.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.34 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.82 (ddd, *J* = 8.6, 6.3, 1.0 Hz, 1H), 4.16 (t, *J* = 6.6 Hz, 1H), 3.94 (ddd, *J* = 9.7, 7.0, 5.7 Hz, 1H), 3.80 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.58 (ddd, *J* = 8.9, 3.9, 2.7 Hz, 1H), 3.50 (dd, *J* = 11.9, 4.0 Hz, 1H), 2.21–2.12 (m, 1H), 2.12–2.06 (m, 1H), 1.98 (brs, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.42–1.32 (m, 1H), 1.05 ppm (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.3, 110.1, 86.3, 85.8, 81.2, 79.7, 77.3, 62.4, 37.9, 34.7, 27.9, 25.7, 16.3 ppm. IR (film): $\tilde{\nu}$ = 3442, 2983, 2957, 2930, 2872, 1455, 1372, 1249, 1251, 1160, 1088, 1053, 926, 866, 816 cm^{-1}. MS (ESIpos) *m/z* (%): 391.0 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{21}O_4INa$: 391.0377, found: 391.0375.

Carboxylic Acid 185. Water (0.09 mL, 5 mmol), bis-(acetoxy)iodobenzene (348 mg, 1.08 mmol) and TEMPO (23 mg, 0.15 mmol) were added to a solution of alcohol **198** (180 mg, 0.489 mmol) in MeCN (2.4 mL). The pale orange solution was stirred for 19 h at ambient temperature. The reaction was quenched with aq. NaOH (5% w/w, 100 mL) and the aq. phase washed with *t*-butyl methyl ether (2 × 50 mL). The aq. solution was acidified with HCl (2 M) until pH 3 was reached; pH 3.5 phosphate buffer solution (50 mL) was added and the aq. phase was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with a 1:1 mixture of pH 5 phosphate buffer and brine (200 mL). After drying over Na_2SO_4 and filtration, the residue was concentrated under reduced pressure. The yellow residual oil (183 mg, 98%) was used without further purification. $[\alpha]_D^{20}$ = –64,5 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.45 (t, *J* = 7.9 Hz, 1H), 4.88 (ddd, *J* = 7.8, 6.6, 1.0 Hz, 1H), 4.22 (dd, *J* = 6.5, 5.6 Hz, 1H), 4.12 (dt, *J* = 9.9, 5.7 Hz, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 2.37 (ddp, *J* = 10.5, 8.7, 6.7 Hz, 1H), 2.17 (ddd, *J* = 12.7, 7.2, 5.8 Hz, 1H), 1.56–1.47 (m, 4H), 1.42 (s, 3H), 1.27 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.9, 137.6, 110.1, 85.8, 83.1, 79.9, 79.7, 79.1, 39.8, 37.5, 27.6, 25.6,

17.6 ppm. IR (film) $\tilde{\nu}$ = 3461, 3070, 2982, 2933, 1733, 1380, 1274, 1248, 1216, 1162, 1055, 866 cm^{-1}. MS (EI) *m/z* (%): 367 (21), 253 (13), 224 (100), 195 (68), 129 (36), 97 (43), 83 (25), 43 (22). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{19}O_5INa$: 405.0169, found: 405.0173.

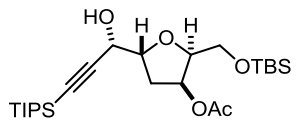
Ester 186. A solution of $TMSCHN_2$ (2 M in Et_2O, 0.23 mL, 0.46 mmol) was added to a solution of crude



185 (97.6 mg, 0.26 mmol) in THF (2.5 mL) at 0 °C. The resulting yellow mixture was stirred at 0 °C for 1 h before the reaction was carefully quenched with pH 5 phosphate buffer (3 mL). The phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 6:1) to yield the title compound as a colourless oil (73.2 mg, 72% over two steps). $[\alpha]_D^{20}$ = −62.5 (c = 0.80, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.51 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.45 (dd, *J* = 8.3, 7.7 Hz, 1H), 4.86 (ddd, *J* = 8.3, 6.3, 0.9 Hz, 1H), 4.18 (t, *J* = 6.3 Hz, 1H), 4.12 (dt, *J* = 9.4, 6.0 Hz, 1H), 4.06 (d, *J* = 7.7 Hz, 1H), 3.72 (s, 3H), 2.43–2.31 (m, 1H), 2.12 (ddd, *J* = 12.1, 7.4, 5.8 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.44–1.36 (m, 1H), 1.20 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.3, 137.5, 110.1, 85.8, 83.8, 80.1, 79.9, 78.9, 52.1, 39.6, 37.2, 27.6, 25.7, 18.2 ppm. IR (film): $\tilde{\nu}$ = 2981, 2961, 2933, 2875, 1753, 1615, 1437, 1379, 1274, 1249, 1212, 1164, 1130, 1086, 1057, 867 cm^{-1}. MS (ESIpos) *m/z* (%): 419.0 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{14}H_{21}O_5INa$: 419.0326, found: 419.0322.

5.4.3 Synthesis of Northern Fragment for Macrocyclic Core 78

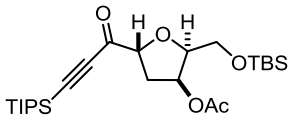
Propargyl Alcohol (*S*)-**187.** A solution of lanthanum(III) chloride bis(lithium chloride) complex (0.6 M



in THF, 2.7 mL, 1.6 mmol) was added to a solution of aldehyde **134** (470 mg, 1.55 mmol) in THF (13 mL). After stirring for 15 min, the premixed aldehyde solution was added to a solution of lithium TIPS-acetylide (0.44 M in THF, 4.2 mL, 1.85 mmol) at –78 °C over a period of 10 min and the flask was rinsed with THF (2 × 2.5 mL). After stirring for 2 h at the same temperature, the cold mixture was poured onto sat. NH_4Cl (30 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 25:1 to 25:2 to 25:4) to afford the title compound as a colourless oil (616 mg, 82%, 4:1 d.r.). ^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = $[\alpha]_D^{25}$ = +37 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.45 (ddd, *J* = 5.3, 3.6, 1.6 Hz, 1H), 4.49 (dd, *J* = 6.5, 2.9 Hz, 1H), 4.36 (ddd, *J* = 9.2, 6.7, 2.9 Hz, 1H), 4.23 (ddd, *J* = 6.7, 5.7, 3.7 Hz, 1H), 3.79–3.69 (m, 2H), 2.39 (ddd, *J* = 14.1, 8.9, 5.3 Hz, 1H), 2.32 (d, *J* = 6.6 Hz, 1H), 2.16–2.09 (m, 1H), 2.08 (s, 3H), 1.10–1.02 (m, 21H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 104.6, 87.9, 82.6, 80.5, 74.3, 65.1,

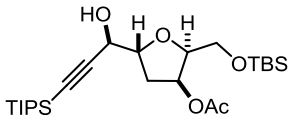
61.1, 33.9, 25.9, 21.2, 18.7, 18.3, 11.2, −5.3, −5.4 ppm. IR (film) $\tilde{\nu}$ = 3447, 2942, 2891, 2865, 2170, 1745, 1464, 1374, 1238, 1096, 883, 837, 777, 678 cm^{-1}; MS (ESIpos) *m/z* (%): 507.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{48}O_5Si_2Na$: 507.2933, found: 507.2934.

Ynone 188. A solution of propargyl alcohol (*S*)-**175** (683 mg, 1.41 mmol) in CH_2Cl_2 (8 mL) was added



over a period of 2 min to a suspension of $NaHCO_3$ (970 mg, 11.5 mmol) and DMP (896 mg, 2.11 mmol) in CH_2Cl_2 (30 mL). After addition of *t*-BuOH (0.20 mL, 2.1 mmol), the suspension was stirred at ambient temperature for 50 min. The reaction was quenched with sat. $NaHCO_3$ (25 mL) and the aq. phase was separated. After extracting with *t*-butyl methyl ether (3 × 25 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 100:6 to 92:8) to afford the title compound as a colourless oil (575 mg, 85%). $[\alpha]_D^{20}$ = +36.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (ddd, *J* = 4.9, 3.6, 2.5 Hz, 1H), 4.63 (td, *J* = 8.2, 0.7 Hz, 1H), 4.23 (ddd, *J* = 7.5, 5.2, 3.7 Hz, 1H), 3.83 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.77 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.39 (dd, *J* = 6.2, 1.8 Hz, 1H), 2.38 (dd, *J* = 8.0, 3.9 Hz, 1H), 2.08 (s, 3H), 1.19–1.08 (m, 21H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.1, 170.2, 101.9, 100.5, 82.8, 82.7, 73.3, 60.5, 36.7, 25.9, 21.1, 18.6, 18.3, 11.1, –5.3, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2946, 2867, 1747, 1682, 1464, 1373, 1230, 1097, 1069, 838, 778, 608 cm^{-1}. MS (EI) *m/z* (%): 427 (12), 426 (31), 425 (95), 366 (20), 365 (65), 213 (19), 209 (19), 173 (18), 163 (10), 159 (17), 157 (12), 146 (13), 145 (100), 133 (13), 131 (11), 130 (11), 129 (84), 119 (10), 117 (53), 115 (29), 103 (16), 91 (10), 89 (100), 87 (11), 75 (42), 73 (74), 59 (15), 43 (21). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{46}O_5Si_2Na$: 505.2776, found: 505.2778.

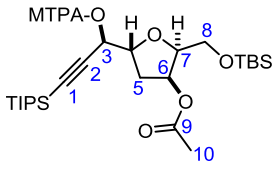
Propargyl Alcohol (*R*)-**187.** Formic acid-triethylamine complex (5:2, 2.0 mL, 24 mmol) and (*S*,*S*)-Teth-



TsDpen-RuCl (**Ru19**) (74 mg, 0.12 mmol) were added to a solution of ynone **176** (575 mg, 1.19 mmol) in CH_2Cl_2 (18 mL). After stirring for 50 min at ambient temperature, the reaction was quenched with sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 94:6 to 91:9 to 89:11) to afford the title compound as a colourless oil (560 mg, 97%, dr = >20:1). $[\alpha]_D^{20}$ = +40.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (ddd, *J* = 4.1, 3.9, 2.9 Hz, 1H), 4.34 (d, *J* = 6.7 Hz, 1H), 4.26 (dt, *J* = 7.7, 7.0 Hz, 1H), 4.10 (ddd, *J* = 6.6, 5.8, 3.6 Hz, 1H), 3.78–3.72 (m, 2H), 2.21–2.14 (m, 2H), 2.08 (s, 3H), 1.10–1.02 (m, 21H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 104.9, 87.7, 81.7, 81.0, 74.1, 66.0, 61.0, 35.5, 25.9, 21.2, 18.7, 18.3, 11.2, –5.3, –5.4 ppm. IR (film): $\tilde{\nu}$ = 3425, 2930, 2891, 2865, 1745, 1463, 1374, 1238, 1094, 1074, 837, 777, 678 cm^{-1}. MS (EI) *m/z* (%): 441 (12), 427 (25), 367 (23), 273 (14), 213 (22), 173 (14), 157 (24), 146 (13), 145 (100), 143 (22), 129 (15), 119 (17), 117

(24), 115 (32), 103 (10), 91 (13), 89 (66), 87 (15), 75 (33), 73 (46), 59 (15), 43 (11). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{48}O_5Si_2Na$: 507.2933, found: 507.2935.

Mosher Ester Analysis of Alcohol (*R*)-**187.** Et_3N (5.8 µL, 41 µmol) was added to a solution of alcohol



(*R*)-**187** (5.0 mg, 10 µmol) in CH_2Cl_2 (0.5 mL) followed by (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (3.9 µL, 21 µmol). The mixture was stirred at ambient temperature for 4 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 19:1 to 9:1) to give the corresponding (*S*)-Mosher ester **(*S*)-MTPA-**(*R*)-**187** (5.5 mg, 76%), which analyzed as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 2H), 7.41–7.36 (m, 3H), 5.68 (d, *J* = 6.3 Hz, 1H), 5.38 (ddd, *J* = 5.1, 3.5, 1.3 Hz, 1H), 4.34 (dt, *J* = 8.2, 6.6 Hz, 1H), 4.10 (ddd, *J* = 6.3, 6.1, 3.5 Hz, 1H), 3.74–3.70 (m, 1H), 3.70–3.67 (m, 1H), 3.57 (d, *J* = 1.2 Hz, 3H), 2.28 (ddd, *J* = 13.9, 8.3, 5.3 Hz, 1H), 2.10 (ddd, *J* = 14.4, 7.0, 1.4 Hz, 1H), 2.05 (s, 3H), 1.09–1.03 (m, 21H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. MS (EI) *m/z* (%): 657 (11), 276 (24), 275 (100), 233 (14), 189 (62), 183 (12), 173 (10), 145 (37), 117 (13), 115 (11), 89 (55), 73 (28). HRMS (ESIpos): *m/z* calcd for $C_{35}H_{55}O_7F_3Si_2Na$: 723.3331, found: 723.3336.

The same procedure was followed for the preparation of **(*R*)-MTPA-**(*R*)-**187** (4.6 mg, 63%), which analyzed as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 2H), 7.40–7.34 (m, 3H), 5.59 (d, *J* = 7.5 Hz, 1H), 5.42 (ddd, *J* = 5.0, 3.5, 1.6 Hz, 1H), 4.41 (dt, *J* = 8.4, 7.3 Hz, 1H), 4.12 (ddd, *J* = 6.7, 5.8, 3.5 Hz, 1H), 3.74 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.70 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.58 (d, *J* = 1.2 Hz, 3H), 2.27 (ddd, *J* = 13.5, 8.3, 5.1 Hz, 1H), 2.19 (ddd, *J* = 14.4, 7.0, 1.5 Hz, 1H), 2.07 (s, 3H), 1.04–1.01 (m, 21H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. MS (EI) *m/z* (%): 657 (11), 276 (24), 275 (100), 233 (14), 189 (62), 183 (12), 173 (10), 145 (37), 117 (13), 115 (11), 89 (55), 73 (28). HRMS (ESIpos): *m/z* calcd for $C_{35}H_{55}O_7F_3Si_2Na$: 723.3331, found: 723.3336.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-1. Mosher ester analysis for the assignment of the C(3) stereocenter; arbitrary numbering as shown in the insert.

Assignment	(*R*)-187	(*S*)-MTPA-(*R*)-187	(*R*)-MTPA-(*R*)-187	Δ (δ(S–R))
3	4.34	5.68	5.59	+0.09
4	4.26	4.34	4.41	–0.07
5a	2.19	2.28	2.27	+0.01
5b	2.16	2.10	2.19	–0.09
6	5.43	5.38	5.42	–0.04
7	4.10	4.10	4.12	–0.02
8a	3.76	3.72	3.74	–0.02
8b	3.74	3.69	3.70	–0.01
10	2.08	2.05	2.07	–0.02
TIPS-Me	1.05	1.06	1.02	+0.04

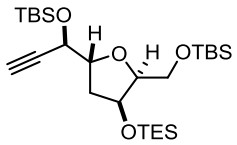
Terminal Alkyne 189. A solution of TBAF (0.5 M in THF, 2 × 0.56 mL; 0.42 mL, 0.77 mmol) was added dropwise and portionwise every 12 h to a solution of alkynol (*R*)-**187** (340 mg, 0.701 mmol) in THF (150 mL) at –40 °C. After stirring for 16 h, the reaction was quenched with sat. NH_4Cl (100 mL). The aq. phase was separated and extracted with EtOAc (5 × 100 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1) to yield the totle compound as a colourless oil (160 mg, 69%) along with the desilylated alcohol as a byproduct. $[\alpha]_D^{20}$ = +46.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (ddd, *J* = 4.1, 4.0, 2.8 Hz, 1H), 4.32–4.25 (m, 2H), 4.11 (ddd, *J* = 6.8, 5.7, 3.7 Hz, 1H), 3.81–3.74 (m, 2H), 2.46 (d, *J* = 2.1 Hz, 1H), 2.21–2.15 (m, 2H), 2.07 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 81.9, 81.6, 80.7, 74.3, 74.1, 65.0, 61.0, 35.2, 25.9, 21.2, 18.4, –5.3, −5.4 ppm. IR (film): $\tilde{\nu}$ = 3454, 2929, 2857, 1742, 1472, 1375, 1250, 1093, 838, 778 cm^{-1}. MS (EI) *m/z* (%): 271 (16), 213 (12), 212 (13), 211 (79), 193 (19), 169 (11), 167 (17), 159 (11), 145 (44), 143 (29), 129 (47), 119 (15), 117 (74), 91 (16), 89 (55), 81 (119, 75 (100), 73 (58), 43 (38). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{28}O_5SiNa$: 351.1598, found: 351.1599.

5.4.4 Suzuki Cross Coupling Attempt

Compound 190. Imidazole (12.4 mg, 0.18 mmol) and TBSCl (21 mg, 0.14 mmol) were added to a solution of **189** (30 mg, 91 µmol) in CH_2Cl_2 (1 mL). After stirring for 16 h, the reaction was quenched with sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by

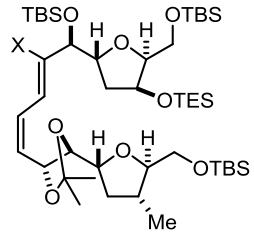
flash chromatography (hexane/EtOAc 15:1) to afford the title compound (40 mg, 96%) as a colourless oil. $[\alpha]_D^{25}$ = +17.6 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (ddd, *J* = 5.2, 3.5, 1.6 Hz, 1H), 4.45 (dd, *J* = 5.1, 2.1 Hz, 1H), 4.23 (ddd, *J* = 8.4, 6.8, 5.1 Hz, 1H), 4.14 (ddd, *J* = 7.1, 5.7, 3.5 Hz, 1H), 3.79–3.70 (m, 2H), 2.38 (d, *J* = 2.1 Hz, 1H), 2.32 (ddd, *J* = 13.9, 8.5, 5.2 Hz, 1H), 2.13 (ddd, *J* = 14.3, 6.8, 1.6 Hz, 1H), 2.07 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 82.6, 81.7, 80.2, 74.1, 73.6, 65.4, 60.8, 34.6, 25.8, 25.7, 21.1, 18.2 (2C), −4.7, −5.1, −5.4, −5.5 ppm. IR (film) $\tilde{\nu}$ = 3312, 2955, 2930, 2886, 2858, 1744, 1472, 1374, 1249, 1089, 836, 778 cm^{-1}. MS (EI) *m/z* (%): 385 (65), 325 (69), 193 (54), 141 (34), 117 (43), 89 (46), 73 (100). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{42}O_5Si_2Na$: 465.2463, found: 465.2460.

Compound 196. K_2CO_3 (38 mg, 0.27 mmol) was added to a solution of **190** (40 mg, 0.90 mmol) in



methanol (5 mL). After stirring for 3 h, the mixture was filtered through a small plug of Celite® that was rinsed with *t*-butyl methyl ether (10 mL). The combined filtrates were washed with a sat. NH_4Cl. The aq. phase was separated and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (0.5 mL) before adding imidazole (13 mg, 0.18 mmol) and TESCl (23 µL, 0.14 mmol). The resulting mixture was allowed to stir at ambient temperature for 1 h before adding sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography (hexane/EtOAc 15:1) to afford the title compound (47.5 mg, 99%) as a colourless oil. $[\alpha]_D^{25}$ = + 10.5 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46 (dd, *J* = 5.1, 2.1 Hz, 1H), 4.42 (ddd, *J* = 4.9, 3.2, 1.9 Hz, 1H), 4.28–4.21 (m, 1H), 3.90 (ddd, *J* = 6.6, 5.2, 3.2 Hz, 1H), 3.81 (dd, *J* = 10.1, 6.6 Hz, 1H), 3.71 (dd, *J* = 10.1, 5.3 Hz, 1H), 2.36 (d, *J* = 2.1 Hz, 1H), 2.12 (ddd, *J* = 13.2, 8.7, 4.7 Hz, 1H), 1.97 (ddd, *J* = 13.1, 6.5, 1.9 Hz, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.68–0.55 (m, 6H), 0.13 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 84.0, 83.0, 80.1, 73.2, 72.0, 65.6, 61.2, 37.4, 26.0, 25.7, 18.3, 18.2, 6.8, 4.8, −4.8, −5.1, −5.3, −5.3 ppm. IR (film) $\tilde{\nu}$ = 3313, 2954, 2929, 2879, 2857, 1471, 1463, 1361, 1252, 1079, 1006, 836, 777, 727 cm^{-1}. MS (EI) *m/z* (%): 457 (82), 325 (54), 299 (66), 195 (100), 145 (43), 115 (59), 78 (52), 73 (69). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{54}O_4Si_3Na$: 537.3222, found: 537.3219.

Dienylboronate 193 (X = Bpin) and Diene 194 (X = H). A pressure Schlenk tube (Young tube) was

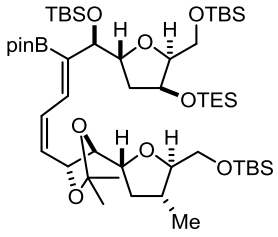


charged with $Pt(PPh_3)_4$ (0.2 mg, 0.2 µmol, 2.5 mol%) and B_2pin_2 (1.8 mg, 7.2 µmol) before adding a solution of alkyne **190** (2.9 mg, 6.5 µmol) in DMF (0.5 mL). After stirring for 16 h at 80 °C, the mixture was allowed to cool to ambient temperature and was diluted with *t*-butyl methyl ether (2 mL). The

organic phase was washed with brine (3 × 1 mL), dried over $MgSO_4$, filtered through a small pad of Celite® and concentrated. The residue was used in the next step without further purification.

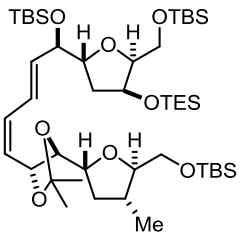
A Schlenk flask was charged with $Pd_2(dba)_3$ (0.7 mg, 0.8 µmol), Ph_3As (1.0 mg, 3.1 µmol) and Ag_2O (3.6 mg, 16 µmol) before adding a solution of crude bis(alkenyl)boronate **191** (5.0 mg, 6.5 µmol) and alkenyl iodide **184** (2.5 mg, 5.2 µmol) in THF (0.25 mL). After treatment with water (5.6 µL, 0.3 mmol), the mixture was stirred at 70 °C for 1 h. After cooling to ambient temperature, the mixture was dried over $MgSO_4$ and filtered through a small pad of Celite®. After rinsing with EtOAc (5 mL), the combined filtrates were concentrated and the residue was purified by flash chromatography (hexane/EtOAc 99:1 to 50:1 to 25:1) to afford dienylboronate **193** (1.7 mg, 32%) and diene **194** (2.4 mg, 52%) as colourless oil each.

Analytical and spectral data of **193**: $[\alpha]_D^{25}$ = +12.2 (c = 0.50, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.01



(d, *J* = 12.0 Hz, 1H), 6.76 (ddd, *J* = 12.1, 10.9, 1.1 Hz, 1H), 5.56 (ddd, *J* = 10.8, 9.8, 1.1 Hz, 1H), 5.12 (ddd, *J* = 9.9, 6.6, 1.3 Hz, 1H), 4.60 (dd, *J* = 5.9, 0.8 Hz, 1H), 4.32 (dt, *J* = 9.4, 6.0 Hz, 1H), 4.28 (q, *J* = 3.2, 2.2 Hz, 1H), 4.06 (t, *J* = 6.7 Hz, 1H), 3.96 (ddd, *J* = 9.7, 7.0, 5.7 Hz, 1H), 3.81 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.77 (ddd, *J* = 7.2, 4.7, 3.4 Hz, 1H), 3.75 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.64 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.63 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.55 (ddd, *J* = 7.9, 5.5, 3.9 Hz, 1H), 2.15 (dq, *J* = 10.2, 7.2 Hz, 1H), 2.07 (ddd, *J* = 12.5, 7.3, 5.8 Hz, 1H), 1.75–1.64 (m, 2H), 1.52 (s, 3H), 1.38 (s, 3H), 1.27 (s, 6H), 1.26 (s, 6H), 1.27–1.18 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.58 (q, *J* = 8.0 Hz, 6H) 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.1, 134.4, 130.7, 128.2, 109.4, 85.9, 83.7, 83.5, 81.8, 80.8, 77.7, 75.6, 72.7, 71.9, 65.1, 61.5, 38.3, 36.9, 36.5, 28.0, 26.1, 26.1, 26.0, 25.7, 25.4, 24.7, 18.5, 18.5, 18.4, 17.8, 7.0, 5.0, –4.6, –4.7, –5.2, –5.2, –5.2 (2C) ppm. IR (film) $\tilde{\nu}$ = 2954, 2929, 2881, 2857, 1732, 1589, 1462, 1378, 1305, 1252, 1143, 1093, 1006, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 1019.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{51}H_{101}BO_{10}Si_4Na$: 1019.6457, found: 1019.6457.

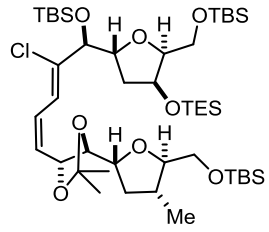
Analytical and spectral data of **194**: $[\alpha]_D^{25}$ = +15.5 (c = 0.13, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$):



δ = 6.51 (ddt, *J* = 15.0, 11.5, 1.3 Hz, 1H), 6.16 (t, *J* = 11.1 Hz, 1H), 5.82 (dd, *J* = 15.1, 5.6 Hz, 1H), 5.48 (t, *J* = 10.4 Hz, 1H), 5.02 (ddd, *J* = 9.7, 6.2, 0.9 Hz, 1H), 4.32 (q, *J* = 3.2 Hz, 1H), 4.27 (td, *J* = 5.3, 1.3 Hz, 1H), 4.19 (td, *J* = 7.7, 5.1 Hz, 1H), 4.06 (dd, *J* = 7.2, 6.4 Hz, 1H), 3.94 (ddd, *J* = 9.7, 7.2, 5.8 Hz, 1H), 3.80 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.76 (td, *J* = 6.2, 5.1, 3.2 Hz, 1H), 3.74 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.69 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.65 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.56 (ddd, *J* = 7.8, 5.4, 3.7 Hz, 1H), 2.22–2.11 (m, 1H), 2.04 (ddd, *J* = 12.3, 7.2, 5.9 Hz, 1H), 1.82–1.77 (m, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.20 (dt, *J* = 11.9, 10.1 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.89 (s, 9H),

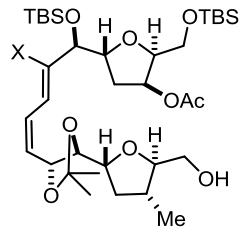
0.88 (s, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.0, 131.5, 126.8, 125.4, 109.5, 85.9, 84.0, 81.9, 80.7, 77.8, 74.6, 73.0, 72.3, 65.1, 61.7, 38.2, 37.1, 36.9, 28.1, 26.1, 26.1, 26.0, 25.8, 18.5, 18.4, 18.4, 17.9, 7.0, 5.0, –4.4, −4.6, –5.1, –5.2, –5.2, –5.2 ppm. IR (film) $\tilde{\nu}$ = 2955, 2928, 2883, 2856, 1462, 1378, 1255, 1093, 1007, 837, 777, 738 cm^{-1}. MS (ESIpos) *m/z* (%): 888.6 (100 (M+NH_4)). HRMS (ESIpos): *m/z* calcd for $C_{45}H_{90}O_8Si_4Na$: 893.5605, found: 893.5606.

Chlorodiene 195. (Ph_3P)AuCl (1.7 mg, 3.4 µmol) was added to a suspension of dienylboronate **193**



(3.5 mg, 3.5 µmol) and Cs_2CO_3 (1.1 mg, 3.4 µmol) in *i*-PrOH (0.5 mL). The mixture was stirred at 50 °C for 1 h before adding additional (Ph_3P)AuCl (3.4 mg, 6.8 µmol) and Cs_2CO_3 (2.2 mg, 6.8 µmol). After stirring for 2 h at 50 °C, the mixture was allowed to cool to ambient temperature. NCS (2.8 mg, 21 µmol) was added and the mixture was stirred for 16 h. The resulting mixture was filtrated through a small pad of SiO_2, rinsed with CH_2Cl_2 (5 mL) and the combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc 100:0 to 98:2) to afford the title compound (2.1 mg, 66%) as a colourless oil. $[\alpha]_D^{25}$ = +15.5 (c = 0.12, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 11.0 Hz, 1H), 6.52 (td, *J* = 11.0, 1.1 Hz, 1H), 5.69 (ddd, *J* = 10.8, 9.8, 1.0 Hz, 1H), 4.95 (ddd, *J* = 9.8, 6.5, 1.2 Hz, 1H), 4.40–4.32 (m, 2H), 4.08 (d, *J* = 5.0 Hz, 1H), 4.06 (t, *J* = 6.7 Hz, 1H), 3.94 (ddd, *J* = 9.8, 7.0, 5.7 Hz, 1H), 3.82–3.76 (m, 2H), 3.73 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.68 (dd, *J* = 12.3, 7.5 Hz, 1H), 3.65 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.55 (ddd, *J* = 7.8, 5.2, 3.8 Hz, 1H), 2.21–2.11 (m, 1H), 2.01 (ddd, *J* = 12.8, 7.2, 5.7 Hz, 1H), 1.87–1.77 (m, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 1.21 (dt, *J* = 12.0, 10.0 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.09 (s, 3H), 0.05 (s, 6H), 0.05 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 137.9, 129.7, 126.2, 120.3, 109.6, 85.9, 83.8, 81.6, 79.2, 78.9, 77.4, 73.1, 72.2, 64.9, 61.6, 37.9, 37.9, 36.6, 27.8, 25.9, 25.9, 25.8, 25.6, 18.3, 18.3, 18.2, 17.7, 6.8, 4.8, −4.9 (2C), −5.3, −5.4, −5.4, −5.4 ppm. IR (film) $\tilde{\nu}$ = 2955, 2928, 2883, 2856, 1462, 1378, 1255, 1093, 1007, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 927.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{45}H_{89}O_8ClSi_4Na$: 927.5215 found: 927.5217.

Dienylboronate 199 (X = Bpin) and Diene 200 (X = H). **<u>Procedure A:</u>** A pressure Schlenk tube (Young



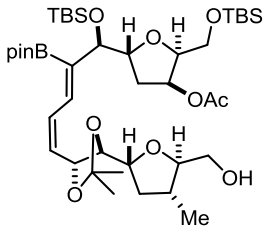
tube) was charged with $Pt(PPh_3)_4$ (0.8 mg, 0.6 µmol, 2.5 mol%) and B_2pin_2 (7.0 mg, 28 µmol) before adding a solution of **196** (11 mg, 25 µmol,) in DMF (1 mL). After stirring for 16 h at 80 °C, the mixture was allowed to cool to ambient temperature and diluted with *t*-butyl methyl ether (5 mL). The organic phase was washed with brine (3 × 2 mL), dried over $MgSO_4$, filtered through a small pad of Celite® and concentrated. The crude mixture was used in the next step without further purification.

A Schlenk flask was charged with $Pd_2(dba)_3$ (1.8 mg, 2.0 µmol, 10 mol%), Ph_3As (2.4 mg, 7.9 µmol) and Ag_2O (14 mg, 6.0 µmol) before adding a solution of crude bis(alkenyl)boronate **197** (17 mg, 25 µmol) and alkenyl iodide **198** (7.3 mg, 20 µmol) in THF (0.5 mL). After treatment with water (21 µL, 1.2 mmol), the mixture was stirred at ambient temperature for 1 h. After adding $MgSO_4$, the mixture was filtered through a small pad of Celite®, rinsed with EtOAc (2 mL) and the combined filtrates were concentrated. The crude mixture was purified by flash chromatography (hexane/EtOAc 90:10) to afford diene **200** (6.5 mg, 48%) and dienylboronate **199** (2.0 mg, 12%) as colourless oil each.

Procedure B: A pressure Schlenk tube (Young tube) was charged with $Pt(PPh_3)_4$ (0.9 mg, 0.7 µmol) and B_2pin_2 (7.8 mg, 31 µmol) before adding a solution of alkyne **196** (12 mg, 28 µmol,) in DMF (1 mL). After stirring for 16 h at 80 °C, the mixture was allowed to cool to ambient temperature before diluting with *t*-butyl methyl ether (5 mL). The mixture was washed with brine (3 × 2 mL), dried over $MgSO_4$, filtered through a small pad of Celite©, rinsed with *t*-butyl methyl ether (5 mL) and the combined filtrates were concentrated. The crude mixture was used in the next step without further purification.

A Schlenk flask was charged with $Pd_2(dba)_3$ (1.9 mg, 2.1 µmol, 7.5 mol%), Ph_3As (2.6 mg, 8.4 µmol, 30 mol%) and Ag_2O (19 mg, 84 µmol) before adding a solution of crude bis(alkenyl)boronate **197** (20 mg, 28 µmol) and alkenyl iodide **198** (10 mg, 28 µmol) in THF (0.75 mL). After treatment with water H_2O (30 µL, 1.7 mmol), the mixture was stirred at ambient temperature for 30 min before adding additional $Pd_2(dba)_3$ (0.5 mg, 0.5 µmol, 2.0 mol%). After stirring for 30 min, $MgSO_4$ was added and the resulting mixture was filtered through a small pad of Celite®, rinsed with EtOAc (2 mL) and the combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc 50:1 to 25:1) to afford dienylboronate **199** (15 mg, 66%) as a colourless oil.

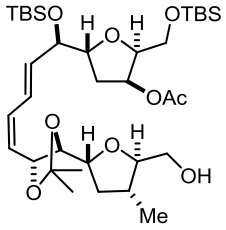
Analytical and spectral data for **199:** $[\alpha]_D^{25}$ = +16.7 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$):



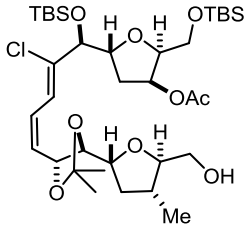
δ = 7.07 (dt, *J* = 12.3, 1.3 Hz, 1H), 6.82 (ddd, *J* = 12.1, 10.9, 1.1 Hz, 1H), 5.59 (ddd, *J* = 10.9, 9.8, 1.0 Hz, 1H), 5.29 (ddd, *J* = 5.0, 3.6, 1.6 Hz, 1H), 5.12 (ddd, *J* = 9.8, 6.4, 1.1 Hz, 1H), 4.54 (dd, *J* = 5.9, 1.4 Hz, 1H), 4.24 (dt, *J* = 9.1, 6.2 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 1H), 4.06–3.94 (m, 2H), 3.80 (d, *J* = 11.9 Hz, 1H), 3.75–3.64 (m, 2H), 3.58 (ddd, *J* = 8.8, 4.0, 2.7 Hz, 1H), 3.55–3.45 (m, 1H), 2.19–2.12 (m, 1H), 2.13–2.06 (m, 1H), 2.03 (s, 3H), 2.00 – 1.95 (m, 1H), 1.86 (ddd, *J* = 14.0, 6.5, 1.7 Hz, 1H), 1.61 (s, 1H), 1.53 (s, 3H), 1.40 (s, 3H), 1.29–1.21 (m, 1H), 1.27 (s, 6H), 1.26 (s, 6H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 6H), 0.01 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 135.6, 130.5, 128.5, 109.3, 86.1, 83.4, 81.6, 81.0, 80.9, 77.6, 75.4, 74.0, 72.3, 62.3, 60.8, 37.7, 34.5, 33.8, 27.9, 25.9, 25.8, 25.8, 25.5, 25.1, 24.8, 24.6, 21.1, 18.2, 18.2, 16.1, −4.7, −4.9, −5.5,

−5.6 ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 39.4 ppm. IR (film) $\tilde{\nu}$ = 3480, 2955, 2930, 2883, 2858, 1743, 1588, 1472, 1372, 1306, 1250, 1143, 1092, 1052, 837, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 833.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{41}H_{75}O_{11}BSi_2Na$: 833.4833, found: 833.4842.

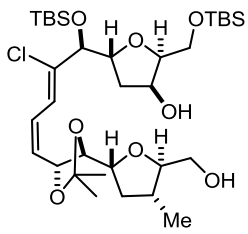
Spectral data for **200:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.52 (ddt, *J* = 15.1, 11.3, 1.2 Hz, 1H), 6.17 (t, *J* = 11.1 Hz, 1H), 5.82 (dd, *J* = 15.1, 5.7 Hz, 1H), 5.48 (t, *J* = 10.5 Hz, 1H), 5.35–5.29 (m, 1H), 5.01 (ddd, *J* = 9.9, 6.3, 1.0 Hz, 1H), 4.26–4.21 (m, 1H), 4.15 (ddd, *J* = 8.5, 6.8, 4.9 Hz, 1H), 4.09 (dd, *J* = 7.3, 6.2 Hz, 1H), 4.03–3.96 (m, 2H), 3.81 (br. d, *J* = 11.9 Hz, 1H), 3.73 (d, *J* = 6.2 Hz, 2H), 3.58 (ddd, *J* = 9.0, 3.9, 2.7 Hz, 1H), 3.51 (dd, *J* = 11.8, 6.2 Hz, 1H), 2.21–2.12 (m, 1H), 2.11–2.07 (m, 1H), 2.05 (s, 3H), 2.00–1.92 (m, 3H), 1.53 (s, 3H), 1.42–1.40 (m, 3H), 1.27 (d, *J* = 5.7 Hz, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 134.6, 130.4, 125.7, 124.4, 108.5, 85.1, 80.7, 80.5, 79.8, 76.6, 73.5, 73.2, 71.7, 36.7, 33.4, 33.1, 27.0, 24.8, 24.8, 24.8, 24.6, 23.8, 20.1, 17.2, 17.2, 15.1, −5.5, −5.8, −6.4, −6.5 ppm.



Chlorodiene 201. (Ph_3P)AuCl (5.7 mg, 12 µmol) was added to a suspension of dienylboronate **199** (7.5 mg, 9.2 µmol), Cs_2CO_3 (3.8 mg, 12 µmol) and 3 Å molecular sieves in *i*-PrOH (0.5 mL) and the mixture was stirred at 40 °C for 1 h. NCS (6.2 mg, 46 µmol) was added and the mixture was stirred for 2 h. After filtration of the resulting mixture through a small pad of silica and rinsing with CH_2Cl_2 (5 mL), the combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc 80:20) to afford the title product (2.2 mg, 33%) as a colourless oil. $[\alpha]_D^{20}$ = +12.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (dt, *J* = 11.1, 0.9 Hz, 1H), 6.53 (td, *J* = 11.0, 1.1 Hz, 1H), 5.69 (ddd, *J* = 10.9, 9.8, 1.0 Hz, 1H), 5.39–5.32 (m, 1H), 4.95 (ddd, *J* = 9.8, 6.4, 1.1 Hz, 1H), 4.36 (ddd, *J* = 8.6, 7.0, 4.5 Hz, 1H), 4.13–4.07 (m, 2H), 4.05–3.95 (m, 2H), 3.81 (dt, *J* = 11.2, 4.1, 2.4 Hz, 1H), 3.73 (dt, *J* = 5.9, 1.8 Hz, 2H), 3.58 (ddd, *J* = 9.0, 4.0, 2.7 Hz, 1H), 3.51 (ddd, *J* = 11.6, 7.2, 4.2 Hz, 1H), 2.20–2.13 (m, 1H), 2.05 (s, 3H), 2.08–2.02 (m, 3H), 1.94 (t, *J* = 6.5 Hz, 1H), 1.53 (s, 3H), 1.41 (s, 3H), 1.26–1.21 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 137.6, 129.8, 126.4, 120.5, 109.8, 86.3, 81.7, 81.7, 79.2, 78.6, 77.6, 77.4, 74.4, 73.1, 62.5, 61.1, 37.8, 35.1, 34.7, 28.1, 25.9, 25.9, 25.7, 21.2, 18.3, 16.3, −4.7, −4.8, −5.2, −5.4 ppm. IR (film) $\tilde{\nu}$ = 3474, 2955, 2930, 2884, 2857, 1742, 1462, 1373, 1250, 1092, 1054, 838, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 741.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{35}H_{63}O_9ClSi_2Na$: 741.3591, found: 741.3583.

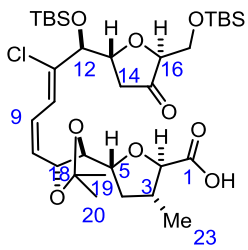


Diol 202. K_2CO_3 (4.0 mg, 29 µmol, 3 equiv.) was added to a solution of acetate **201** (7.0 mg, 9.7 µmol)



in methanol (1 mL). After stirring for 3 h, the mixture was filtered through a small plug of Celite®, which was rinsed with EtOAc (5 mL). After adding sat. NH_4Cl (2 mL), the aq. phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (hexane/EtOAc 80:20 to 60:40) to afford the title compound (5.9 mg, 90%) as a colourless oil. $[\alpha]_D^{20}$ = +6.6 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (dt, *J* = 11.1, 1.0 Hz, 1H), 6.54 (td, *J* = 10.9, 1.1 Hz, 1H), 5.67 (td, *J* = 10.5, 0.6 Hz, 1H), 4.95 (ddd, *J* = 9.8, 6.4, 1.1 Hz, 1H), 4.53–4.45 (m, 1H), 4.42 (ddd, *J* = 8.9, 6.4, 5.0 Hz, 1H), 4.13–4.08 (m, 2H), 3.99 (ddd, *J* = 9.8, 7.2, 5.7 Hz, 1H), 3.95–3.87 (m, 3H), 3.81 (dt, *J* = 11.6, 2.4 Hz, 1H), 3.57 (ddd, *J* = 9.0, 4.0, 2.7 Hz, 1H), 3.55–3.47 (m, 2H), 2.19–2.12 (m, 1H), 2.10–2.01 (m, 1H), 1.97–1.88 (m, 3H), 1.53 (s, 3H), 1.40 (s, 3H), 1.25–1.21 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.9, 129.4, 126.3, 120.0, 109.6, 86.1, 81.6, 80.8, 79.8, 78.7, 77.4, 74.0, 73.0, 62.8, 62.3, 37.6 (2C), 34.5, 27.9, 25.7 (2C), 25.6, 18.2, 18.1, 16.2, −4.8, −4.9, −5.5, −5.6 ppm. IR (film) $\tilde{\nu}$ = 3453, 2954, 2928, 2856, 1462, 1380, 1371, 1253, 1090, 1052, 1006, 835, 804, 777, 756 cm^{-1}. MS (ESIpos) *m/z* (%): 699.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{33}H_{61}O_8ClSi_2Na$: 699.3486, found: 699.3487.

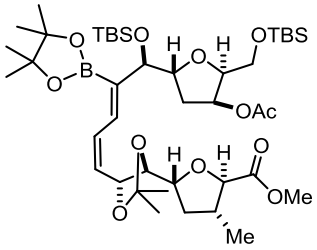
Ketone 203. Bis-(acetoxy)iodobenzene (3.1 mg, 9.7 µmol) TEMPO (2.1 mg, 1.3 µmol, 30 mol%) and



water (3.2 µL, 0.18 mmol) were added to a solution of diol **202** (3.0 mg, 4.4 µmol), in MeCN (0.1 mL). After stirring for 24 h, the mixture was dilutedwith MeCN (0.5 ml) and the reaction was quenched by the addition of a solution of pH 7 phosphate buffer (50 µL). After filtration through a short pad of Na_2SO_4 the filtrate was concentrated. The residue was dissolved in MeCN (5 ml) and washed with cyclohexane (5 ml). The nonpolar cyclohexane phase was extracted with additional MeCN (3 ml). The combined organic phases were concentrated and the crude mixture was purified by flash chromatography (hexane/EtOAc/AcOH 60:40:0 to 0:100:0 to 0:99.5:0.5) to afford the title compound (1.3 mg, 43%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 11.1, 1H, 10-H), 6.59 (td, *J* = 11.1, 1.3, 1H, 9-H), 5.74 (dd, *J* = 11.0, 9.0, 1H, 8-H), 5.01 (ddd, *J* = 8.9, 6.8, 1.3, 1H, 7-H), 4.77 (ddd, *J* = 8.6, 3.4, 2.6, 1H, 13-H), 4.19 (d, *J* = 2.4, 1H, 12-H), 4.16 (dt, *J* = 10.4, 5.5, 1H, 5-H), 4.10 (dd, *J* = 6.7, 5.6, 1H, 6-H), 4.01 (d, *J* = 9.2, 1H, 2-H), 4.00 (t, *J* = 2.3, 1H, 16-H), 3.84 (dd, *J* = 11.1, 2.3, 1H, 17'-H), 3.74 (dd, *J* = 11.1, 2.3, 1H, 17''-H), 2.57 (dd, *J* = 17.6, 8.6, 1H, 14'-H), 2.39–2.30 (m, 1H, 3), 2.33 (dd, *J* = 17.5, 3.4, 1H, 14''-H), 2.14 (dt, *J* = 12.4, 6.4, 1H, 4'-H), 1.52 (s, 3H, 19-H), 1.49–1.42 (m, 1H, 4''-H), 1.39 (s, 3H, 20-H), 1.26 (d, *J* = 6.5, 3H, 23-H), 0.90 (s, 9H, OSi*t*Bu), 0.85 (s, 9H, OSi*t*Bu), 0.09 (s, 3H, OSiMe), 0.03 (s, 3H, OSiMe), 0.03 (s, 3H, OSiMe), 0.01 (s, 3H, OSiMe) ppm. ^{13}C

NMR (151 MHz, $CDCl_3$): δ = 213.6 (15), 172.8 (1), 136.7 (11), 129.3 (8), 126.5 (9), 120.3 (10), 109.7 (18), 82.8 (2), 81.7 (16), 80.2 (6), 79.3 (12), 79.3 (5), 76.3 (13), 73.4 (7), 63.5 (17), 39.8 (14), 39.5 (3), 37.4 (4), 27.5 (19), 25.8 (OSi*t*Bu), 25.7 (OSi*t*Bu), 25.3 (20), 18.2 (OSi*t*Bu), 18.0 (OSi*t*Bu), 17.3 (23), −4.9 (OSiMe), −5.3 (OSiMe), −5.5 (OSiMe), −5.7 (OSiMe) ppm. IR (film): $\tilde{\nu}$ = 2954, 2928, 2857, 1762, 1729, 1462, 1378, 1253, 1216, 1125, 1005, 836, 778, 733 cm^{-1}. MS (ESIpos) *m/z* (%): 711.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{33}H_{57}O_9ClSi_2Na$: 711.3122, found: 711.3125.

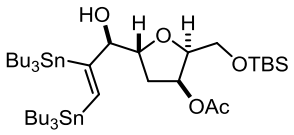
Dienylboronate 204. A pressure Schlenk tube (Young tube) was charged with $Pt(PPh_3)_4$ (1.4 mg, 1.1 µmol, 2.5 mol%) and B_2pin_2 (12 mg, 48 µmol) before adding a solution of **196** (20 mg, 44 µmol,) in DMF (1 mL). After stirring for 16 h at 80 °C, the mixture was cooled to ambient temperature and diluted with *t*-butyl methyl ether (5 mL). The organic phase was washed with brine (3 × 2 mL). dried over $MgSO_4$, filtered through a small pad of Celite® and concentrated. The crude mixture was used in the next step without further purification.



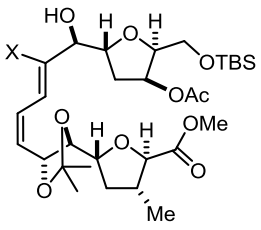
A Schlenk flask was charged with $Pd_2(dba)_3$ (3.2 mg, 3.5 µmol, 10 mol%), Ph_3As (4.3 mg, 14 µmol, 40 mol%), Ag_2O (25 mg, 0.11 µmol) before adding a solution of crude bis(alkenyl)boronate **197** (31 mg, 44 µmol) and alkenyl iodide **186** (14 mg, 35 µmol) in THF (1.5 mL). After adding water (38 µL, 2.1 mmol), the mixture was stirred at ambient temperature for 1 h. After adding $MgSO_4$, the resulting mixture was filtered through a small pad of Celite® and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (Hexane/EtOAc: 90/10) to afford the title compound (22 mg, 26 µmol, 75%) as a colourless oil. $[\alpha]_D^{25}$ = +15.9 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (dt, *J* = 12.1, 1.3 Hz, 1H), 6.85 (ddd, *J* = 12.1, 11.0, 1.1 Hz, 1H), 5.65 (ddd, *J* = 10.9, 9.8, 1.0 Hz, 1H), 5.29 (ddd, *J* = 5.2, 3.7, 1.7 Hz, 1H), 5.15 (ddd, *J* = 9.7, 6.5, 1.1 Hz, 1H), 4.55 (dd, *J* = 5.9, 1.4 Hz, 1H), 4.27–4.16 (m, 2H), 4.09 (t, *J* = 6.5 Hz, 1H), 4.05 (d, *J* = 7.8 Hz, 1H), 3.98 (ddd, *J* = 7.4, 5.6, 3.7 Hz, 1H), 3.73 (s, 3H), 3.72–3.67 (m, 2H), 2.44–2.28 (m, 1H), 2.12 (ddd, *J* = 12.7, 7.4, 5.8 Hz, 1H), 2.03 (s, 3H), 1.96 (ddd, *J* = 14.1, 9.1, 5.1 Hz, 1H), 1.85 (ddd, *J* = 14.0, 6.5, 1.7 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H), 1.27 (s, 6H), 1.33–1.19 (m, 1H), 1.26 (s, 6H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 170.1, 135.6, 130.9, 128.3, 109.4, 83.6, 83.4, 81.0, 80.9 (2C), 79.2, 75.3, 74.0, 72.4, 60.8, 51.9, 39.5, 37.1, 33.8, 27.7, 25.8, 25.8, 25.4, 25.1, 24.6, 21.1, 18.2, 18.2, 17.9, −4.7, −4.9, −5.5, −5.6 ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 27.2 ppm. IR (film) $\tilde{\nu}$ = 2954, 2929, 2898, 2857, 1742, 1462, 1372, 1248, 1143, 1089, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 861.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{75}O_{12}BSi_2Na$: 861.4782, found: 861.4791.

5.4.5 Stille Cross Coupling Approach

Bis(alkenyl)stannane 206. A solution of alkyne **189** (33 mg, 0.10 mol) in THF (0.8 mL with rinses) was added to a solution of [(*t*BuNC)$_2$PdCl$_2$] (3.5 mg, 10 µmol) in THF (0.2 mL). Hexabutylditin (81 µL, 0.16 mmol) was added in one portion and the resulting mixture was stirred at ambient temperature for 21 h. The solvent was evaporated and the residue purified by flash chromatography (hexane/*t*-butyl methyl ether/Et$_3$N 100:1:1) to yield the title compound as a colourless oil (69 mg, 76%). $[\alpha]_D^{20}$ = +15.8 (c = 1.00, CHCl$_3$). ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 7.02 (d, *J* = 1.2 Hz, J_{SnH} = 177, 67.4 Hz, 1H), 5.42 (ddd, *J* = 5.3, 3.6, 1.6 Hz, 1H), 4.33–4.26 (m, 1H), 4.02–3.89 (m, 2H), 3.85–3.79 (m, 2H), 2.77 (br s, 1H), 2.01 (ddd, *J* = 14.0, 6.4, 1.6 Hz, 1H), 1.90–1.82 (m, 1H), 1.79–1.70 (m, 6H), 1.68 (s, 3H), 1.70–1.62 (m, 6H), 1.54–1.39 (m, 12H), 1.27–1.19 (m, 6H), 1.18–1.10 (m, 6H), 1.03–0.97 (m, 18H), 0.97 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, C$_6$D$_6$): δ = 169.7, 169.2, 144.2, 87.8, 81.6, 81.1, 74.5, 61.6, 36.0, 29.9, 29.8, 28.1, 27.9, 26.0, 20.6, 18.5, 14.0, 14.0, 12.1, 11.5, −5.2, −5.3 ppm. ^{119}Sn NMR (150 MHz, C$_6$D$_6$): δ = −59.3, −67.3 ppm. IR (film): $\tilde{\nu}$ = 3498, 2955, 2925, 2855, 1746, 1463, 1375, 1232, 1071, 938, 837, 777, 667, 595 cm^{-1}. MS (ESIpos) *m/z* (%): 933.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{40}H_{82}O_5SiSn_2Na$: 933.3866, found: 933.3874.



Dienylstannane 208a (X = SnBu3) and Diene 208b (X = H). Procedure A: *DMF was carefully degassed by three freeze-pump-thaw cycles prior to use.* Tetrabutylammonium diphenylphosphinate (23.3 mg, 50.7 µmol) was placed in a Schlenk tube, which was evacuated and flame-dried. A solution of bisstannane **195** (41.9 mg, 46.1 µmol) in degassed DMF (0.7 mL) was added, followed by Pd(PPh$_3$)$_4$ (21.3 mg, 18.4 µmol, 40 mol%). The resulting mixture was stirred at ambient temperature for 5 min before CuTC (9.2 mg, 48 µmol) was introduced, followed by a solution of alkenyl iodide **186** (10.4 mg, 46.1 µmol) in degassed DMF (0.5 mL). The resulting mixture was stirred at ambient temperature for 30 min before the reaction was quenched with water (3 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 9:1 to 4:1) to yield the title dienylstannane **208a** (16.2 mg, 40%, 1.7:1 r.r.) and its regioisomer **209** (9.7 mg, 24%) as a colourless oil each and diene **208b** (1.4 mg, 5%) as a light yellow oil; **209** was fully characterized at the more stable alkenyl chloride stage **S6** (*vide infra*).



Procedure B: *NMP was carefully degassed by three freeze-pump-thaw cycles prior to use.* A solution of bisstannane **206** (75 mg, 0.083 mmol) in NMP (0.5 mL) was added to a solution of alkenyl iodide **186** (22 mmol, 55 µmol) and LiCl (7.9 mg, 0.19 mmol) in NMP (2.0 mL). After subsequent addition of a

solution of tetrabutylammonium diphenylphosphinate (25 mg, 22 µmol) in NMP (0.1 mL) and a solution of Pd(*t*-$Bu_3P)_2$ (2.8 mg, 5.5 µmol) in NMP (0.1 mL), the reaction flask was placed in a preheated oil bath and stirred for 4 h at 45 °C. After cooling to ambient temperature, the mixture was diluted with *t*-butyl methyl ether (5 mL) and the reaction was quenched with pH 7 phosphate buffer (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc/NEt_3 95:5:1 to 89:10:1 to 80:20:1) to recover bisstannane **206** (30.3 mg, 82.5 µmol) and afford the dienylstannane **208a** (31.7 mg, 65%, >20:1 r.r.) as a yellow oil. Analytical and spectral data for **208a**: $[\alpha]_D^{20}$ = +32.0 (c = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.03 (d, *J* = 11.4 Hz, J_{SnH} = 111 Hz, 1H), 6.17 (td, *J* = 11.2, 1.0 Hz, 1H), 5.59 (t, *J* = 10.5 Hz, 1H), 5.37 (ddd, *J* = 5.6, 3.8, 1.9 Hz, 1H), 5.10 (dd, *J* = 9.7, 5.5 Hz, 1H), 4.13–4.01 (m, 5H), 3.99 (d, *J* = 7.9 Hz, 1H), 3.74 (d, *J* = 6.1 Hz, 2H), 3.71 (s, 3H), 2.62 (d, *J* = 2.1 Hz, 1H), 2.31 (dq, *J* = 10.0, 7.4 Hz, 1H), 2.08–2.04 (m, 1H), 2.03 (s, 3H), 1.99–1.87 (m, 2H), 1.52–1.45 (m, 6H), 1.49 (s, 3H), 1.38 (s, 3H), 1.35–1.28 (m, 9H), 1.25–1.21 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.03–0.98 (m, 6H), 0.91–0.89 (m, 6H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 173.4, 170.3, 154.9, 135.2, 132.4, 128.5, 109.7, 83.8, 83.5, 81.7, 81.4, 81.2, 79.5, 74.5, 73.0, 61.6, 52.1, 39.8, 37.5, 36.0, 29.5, 28.0, 27.7, 26.0, 25.8, 21.2, 18.5, 18.1, 13.9, 12.0, –5.3, –5.4 ppm. IR (film): $\tilde{\nu}$ = 3507, 2957, 2928, 2856, 1743, 1462, 1375, 1259, 1093, 1020, 799 cm^{-1}. MS (ESIpos) *m/z* (%): 911.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{76}O_{10}SiSnNa$: 911.4121, found: 911.4119.

(*Z*,*Z*)-Chlorodiene 213. 2,6-Lutidine (30 µL, 0.26 mmol) and copper(II) chloride (23.5 mg, 175 µmol) were added to a solution of dienylstannane **208a** (33.5 mg, 37.7 µmol) in THF (0.50 mL). After stirring the brown suspension for 48 h in the dark, additional copper(II) chloride (14 mg, 104 µmol) and DMSO (0.5 mL) were added and the resulting mixture was stirred for 24 h in the dark at ambient temperature. The reaction was diluted with *t*-butyl methyl ether (2.5 mL) and quenched with sat. $NaHCO_3$ (3 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 2:1 to 1:1 to 1:2) to yield the title compound as a light yellow oil (20.4 mg, 86%). $[\alpha]_D^{20}$ = +8.2 (c = 0.44, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-2.* ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-2.* IR (film): $\tilde{\nu}$ = 3397, 2960, 2926, 2854, 1740, 1669, 1456, 1377, 1260, 1091, 1019, 798 cm^{-1}. MS (ESIpos) *m/z* (%): 655.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{30}H_{49}O_{10}ClSiNa$: 655.2676, found: 655.2672.

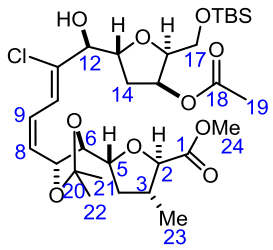
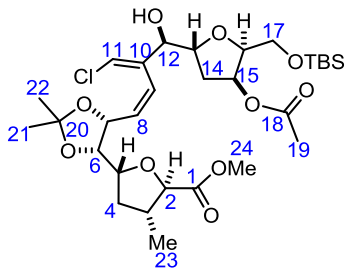


Table S-2. NMR data of chlorodiene **213**; arbitrary numbering scheme as shown in the insert.*

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (150 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	-	-	-	-	-	173.4	(2), (3), 23
2	4.05	d	7.8	3	4b, 23	83.8	(4a), 23
3	2.37	dq	9.9, 6.9	2, 4, 23	2, 5, 19, 23, (24)	39.6	2, 23
4a 4b	2.06 1.28	m m	- -	(3), 4b, 5 3, 4a, 5	3, 4b, 5, (23) 2, 4a, (5), 6, (7)	37.2	23
5	4.17	dt	9.8, 6.2	4a(b), 6	3, 4a(b), 8,	79.14	4b, (7)
6	4.10	m	-	5, 7	4b, 7, 15, 22	80.8	4b
7	5.00	dd	9.8, 6.4	8	6, 8, 10, 22	73.2	9
8	5.81	dd	11.0, 9.8	7,9	5, (7), 21	130.4	6, 10
9	6.57	t	11.0	8, 10	8	126.5	7
10	6.74	d	11.0	9	2, 12, (13), 21	121.0	8
11	-	-	-	-	-	136.5	9, 10, (13)
12	4.08	t	4.6	12-OH, 13	10, 13, 14, 21	77.5	10
12-OH	2.84	d	4.6	12	-	-	-
13	4.41	ddd	8.4, 7.0, 5.6	12, 14	12, 14, 21	79.06	12, 14a
14a 14b	2.08	m	-	13, 15	12, 15	35.8	-
15	5.43	ddd	5.6, 5.1, 2.6	14, (16)	14, 16, 17, 19	74.1	(14), 17
16	4.10	m	-	15, 17	4b, 7, 15, (22)	82.0	17
17a 17b	3.75	d	6.4	16	15, 16, 17-TBS	61.2	-
18	-	-	-	-	-	170.2	19
19	2.07	s	-	-	(23), 17-TBS	21.2	-
20	-	-	-	-	-	110.0	21, 22
21	1.53	s	-	22	(2), 8, 22	27.8	-
22	1.41	s	-	21	6, 7, 21	25.8	-
23	1.19	d	6.6	3	2, 3, 4a, (19), (24)	18.2	2
24	3.73	s	-	-	2	52.1	-

* The signals of the TBS group are not listed and appear as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.9, 18.4, –5.2, –5.3 ppm.

Chlorodiene S6. A solution of dienylstannane **209** (9.7 mg, 11 µmol) in THF (0.15 mL) was added to a



suspension of copper(II) chloride (7.3 mg, 55 µmol) and 2,6-lutidine (5.3 µL, 45.6 µmol) in THF (0.15 mL). After stirring for 20 h at ambient temperature, the mixture was diluted with *t*-butyl methyl ether (2.5 mL) and the reaction quenched with sat. $NaHCO_3$ (3 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether

(3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 5:1 to 2:1) to yield the title as a colourless oil (3.5 mg, 51%). $[\alpha]_D^{20}$ = –18.3 (c = 0.06, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-3.* ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-3.* IR (film): $\tilde{\nu}$ = 3433, 2959, 2926, 2873, 2855, 1736, 1439, 1373, 1258, 1183, 1069, 1047, 798, 758 cm^{-1}. MS (ESIpos) *m/z* (%): 655.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{30}H_{49}O_{10}ClSiNa$: 655.2676, found: 655.2672.

Table S-3. NMR data of chlorodiene **S6**; arbitrary numbering scheme as shown in the insert.*

atom n°	**^{1}H NMR** (600 MHz, $CDCl_3$)					**^{13}C NMR** (150 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	173.6	(2), 24
2	4.05	d	7.8	3	14, 21, 23, 24	83.8	(4a), 23
3	2.35	dq	9.8, 7.1	4, 23	2, 4a, 5, 23	39.5	2, 23
4a	2.14	ddd	12.1, 7.4, 6.1	(3), 4b	3, 4b, 5	37.1	23
4b	1.49	ddd	12.1, 9.9, 9.9	3, 4a	4a, (5), 6, 23		
5	4.25	ddd	9.8, 5.8, 4.6	4, 6	3, 4a(b), 6, 8	79.2	4b, (2)
6	4.13	dd	6.4, 4.5	5, 7	4b, 5, 7, 22	79.3	5, 21
7	4.72	dd	9.9, 6.6	6, 8	6, (8), 12, 22	73.8	9
8	6.05	dd	11.5, 9.9	7,9	5, (7), 21	131.3	9
9	6.13	dd	11.6, 1.5	8	13	127.6	11
10	-	-	-	-	-	137.9	8, 11
11	6.38	dd	1.5, 0.8	-	12, 12-OH	119.5	9
12	4.07	m	-	12-OH	7, 11, 12-OH, 14	77.1	11
12-OH	2.67	d	4.1	12	(11), 12, (13)	-	-
13	4.16	ddd	9.2, 6.4, 6.4	12, 14	9, (11), 12, 14	80.2	14a
14a	2.07	ddd	14.1, 6.4, 1.4	14b	13	35.4	-
14b	1.97	ddd	14.1, 9.2, 5.0	14a	12, 15		
15	5.38	ddd	5.0, 3.6, 1.2	14, (16)	14, 16, 17	74.4	14, 17
16	4.06	td	6.4, 3.7	15, 17	14b, 15, 17	81.7	14, 17
17a 17b	3.74	m	-	16	15, 16, 17-TBS	61.1	-
18	-	-	-	-	-	170.2	19
19	2.05	s	-	-	(12), 15, 17-TBS	21.2	-
20	-	-	-	-	-	109.4	21, 22
21	1.48	s	-	22	2, 6, (5), 22	27.5	-
22	1.35	s	-	21	6, 7, 21	25.6	21
23	1.18	d	6.8	3	2, 3, 4a	18.0	2
24	3.73	s	-	-	2	52.0	-

* The signals of the TBS group are not listed and appear as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.9, 18.4, –5.2, –5.3 ppm.

Compound S7. 2,6-Lutidine (35 µL, 0.30 mmol) and TBSOTf (50 µL, 0.22 mmol) were added to a solution of alcohol **213** (20 mg, 32 µmol) in CH_2Cl_2 (0.25 mL) at 0 °C. The resulting mixture was stirred for 10 min before removing the ice bath. After stirring for 4 h at ambient temperature, the mixture was diluted with *t*-butyl methyl ether (3 mL) and the reaction was quenched with sat. NH_4Cl (3 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 4:1) to yield the title compound as a colourless oil (18.9 mg, 80%). $[\alpha]_D^{20}$ = +4.8 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 11.1 Hz, 1H), 6.55 (td, *J* = 11.0, 1.1 Hz, 1H), 5.77 (ddd, *J* = 10.8, 9.6, 1.0 Hz, 1H), 5.36 (ddd, *J* = 5.2, 3.6, 1.8 Hz, 1H), 4.99 (ddd, *J* = 9.6, 6.4, 1.1 Hz, 1H), 4.36 (ddd, *J* = 8.6, 6.9, 4.5 Hz, 1H), 4.17 (dt, *J* = 9.6, 6.1 Hz, 1H), 4.13–4.07 (m, 2H), 4.05 (d, *J* = 7.7 Hz, 1H), 4.02 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.73 (s, 3H), 3.73–3.70 (m, 2H), 2.37 (dq, *J* = 9.5, 7.1 Hz, 1H), 2.13–2.06 (m, 2H), 2.05 (s, 3H), 2.03–1.98 (m, 1H), 1.53 (s, 3H), 1.39 (s, 3H), 1.30–1.27 (m, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4, 170.4, 137.5, 129.6, 126.7, 120.5, 109.8, 83.8, 81.7, 80.9, 79.2, 79.1, 78.5, 74.4, 73.3, 61.1, 52.1, 39.6, 37.1, 35.0, 27.8, 25.9, 25.9, 25.7, 21.2, 18.3, 18.2 (2C), −4.7, −4.8, −5.2, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2885, 2857, 1741, 1462, 1371, 1248, 1087, 393, 836, 777, 666 cm^{-1}. MS (ESIpos) *m/z* (%): 769.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{36}H_{63}O_{10}ClSi_2Na$: 769.3541, found: 769.3538.

***Seco*-Acid 214.** K_2CO_3 (35 mg, 0.25 mmol) was added to a solution of **S7** (15.6 mg, 20.9 µmol) in a 0.6:0.9:1 mixture of water (0.30 mL), methanol (0.45 mL) and CH_2Cl_2 (0.50 mL). After stirring for 3 d, the reaction was diluted with EtOAc and quenched with pH 5 phosphate buffer (3 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with a 1:3 mixture of pH 5 phosphate buffer and brine, dried over Na_2SO_4, filtered and concentrated. The colourless residual oil (14 mg, 97%) was clean by NMR and used without further purification in the macrolactonization. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 11.1 Hz, 1H), 6.58 (td, *J* = 10.9, 1.1 Hz, 1H), 5.70 (dd, *J* = 10.7, 9.3 Hz, 1H), 5.02 (ddd, *J* = 9.2, 6.4, 1.2 Hz, 1H), 4.54–4.47 (m, 1H), 4.42 (ddd, *J* = 8.6, 6.6, 4.6 Hz, 1H), 4.13 (ddd, *J* = 15.6, 9.5, 5.0 Hz, 3H), 4.02 (d, *J* = 8.9 Hz, 1H), 3.91 (p, *J* = 4.6, 3.7 Hz, 3H), 2.35 (ddt, *J* = 10.6, 8.8, 6.7 Hz, 1H), 2.12 (ddd, *J* = 12.5, 7.1, 5.4 Hz, 1H), 2.00–1.88 (m, 2H), 1.52 (s, 3H), 1.47–1.37 (m, 4H), 1.25 (d, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.10–0.08 (m, 6H), 0.08 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4, 138.4, 129.1, 126.9, 120.1, 109.8, 83.0, 81.1, 80.5, 79.8, 79.4, 78.7, 74.1, 73.4, 62.9, 39.7, 37.8, 37.5,

27.7, 25.9 (2C), 25.5, 18.3, 18.3, 17.5, −4.7, −4.8, −5.3, −5.4 ppm. MS (ESIneg) *m/z* (%): 689.3 (100 (M–H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{58}O_9ClSi_2$ $[M-H]^-$: 689.3313, found: 689.3321.

Macrolactone 78. A solution of *seco*-acid **214** (9.3 mg, 14 µmol) in CH_2Cl_2 (4.0 mL with rines) was added over a period of 3 h to a suspension of 2-bromo-1-ethylpyridinium tetrafluoroborate (106 mg, 387 µmol) and $NaHCO_3$ (0.34 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 80 °C. After stirring for 2.5 h at the same temperature, the temperature was ramped up to 95 °C for 21 h and to 100 °C for 3 h. After cooling to ambient temperature, the reaction was quenched with pH 5 phosphate buffer (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 98:2 to 95:5 to 90:10) to afford the title compound **78** and THP-ring **215** as a colourless oil (**78**/**215** = 4:1, 2.1 mg, 23%). [Conditions for LC-MS: ZORBAX Eclipse Plus C-18, 1.8 µm, 50 × 4.6 mm, MeCN/H_2O = 90:10, v = 0.8 mL/min, λ = 250 nm, 35 °C, 121 bar, t(*seco*-acid) = 2.79 min, t(macrocycle) = 18.49 min]. Spectral and analytical data for **78**: ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-4*. ^{13}C NMR (101 MHz, $CDCl_3$): *see Table S-4*. MS (ESIpos) *m/z* (%):695.3 (100 (M+Na)) *see Figures S-1–S-2.* HRMS (ESIpos): *m/z* calcd for $C_{33}H_{57}O_8ClSi_2Na$ $[M+Na^+]$: 695.3173, found: 695.3172.

Figure S-1. MS (ESIpos) analysis of a clean sample of macrocycle **78** *m/z* = 695.3 $[M+Na]^+$, *m/z* = 1367.6 $[2M+Na]^+$.

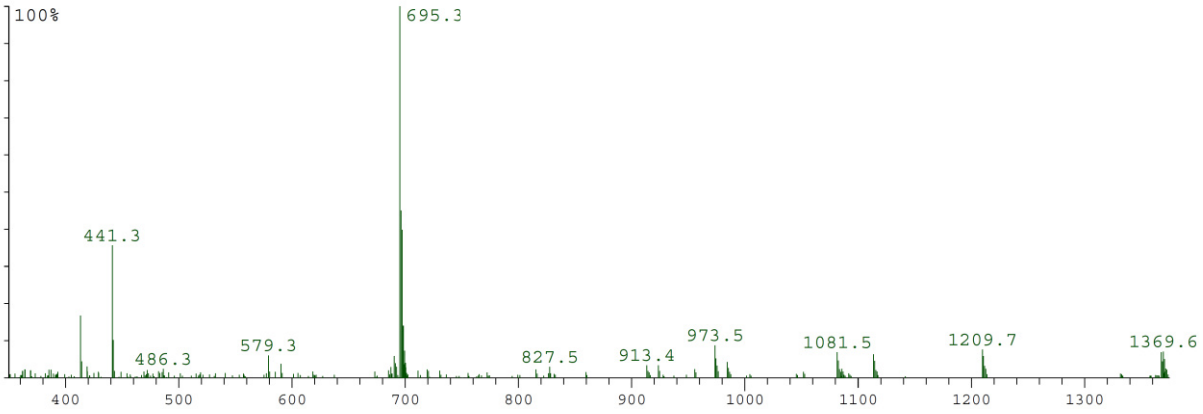
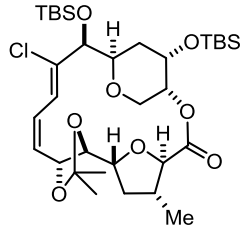


Table S-4. NMR data of chlorodiene **macrolactone 78**; arbitrary numbering scheme as shown in the insert.*

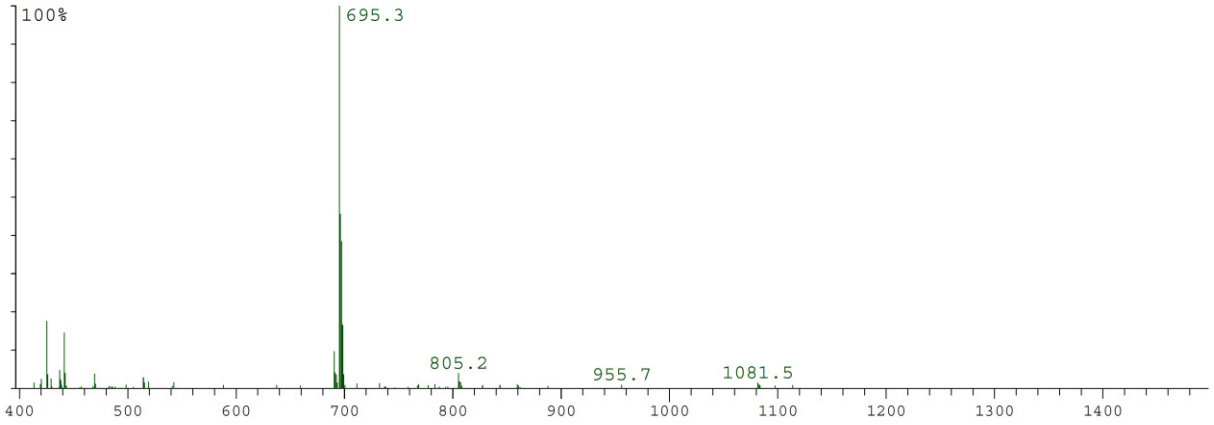
atom	**^{1}H NMR** (600 MHz, $CDCl_3$)					**^{13}C NMR** (150 MHz, $CDCl_3$)	
n°	**δ** [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	170.2	15
2	3.89	d	9.2	3	(4b), 15, 23	80.5	23
3	2.80	ddq	9.0, 6.6, 6.2	2, 4(a)b, 23	(2), (4a), 5, 23	37.6	(2), 23
4a	2.16	ddd	12.0, 6.6, 5.1	3, 4b, 5	(3), 4b, 5	36.8	(6), 23
4b	1.57	m	-	3, 4a, 5	(2), 4a, 8, (23)		
5	4.15	m	-	4(a)b, (6)	3, 4a, 6	81.3	4b, (7)
6	4.65	m	7.0, 3.6	(5), 7	5, 7, 10, (22)	78.0	4b
7	5.19	m	-	6, 8	(8), 10, 22	75.4	9
8	5.88	dd	11.0, 5.3	7,9	4b, (7), 9	130.5	(7), 10
9	6.56	td	11.1, 2.3	8, 10	8	123.4	(10)
10	6.69	d	11.6	9	6, 7, (14a)	123.0	(8)
11	-	-	-	-	-	135.7	12, 13
12	4.40	d	4.1	13	-	75.3	(10), 14b
13	4.37	dd	8.6, 4.2	14b	14b, 12-TBS	82.1	14b
14a	2.52	dd	12.5, 7.8	14b, 15	10, 14b, 15	31.6	12
14b	2.26	ddd	12.0, 10.3, 5.2	13, 14a, 15	13, 14a, (17)		
15	4.92	dt	10.3, 7.9	14, 16	2, (6), 14a, 16	76.1	14(a)b, (13)
16	4.05	m	-	15, 17	15, 17	78.8	14a
17a	3.73	m	-	16	17-TBS	63.0	15
17b							
20	-	-	-	-	-	107.8	21, 22
21	1.48	s	-	-	(8), 22	27.1	-
22	1.34	s	-	-	(6), 7, 21	24.2	-
23	1.12	d	6.4	3	2, 3, (4b)	16.9	2

* The signals of the TBS groups are not listed and appear as follows: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.92 (s, 9H), 0.90 (s, 9H), 0.083 (s, 3H), 0.082 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.1, 25.7, 18.5, 18.0, –4.8, –5.0, –5.2, –5.3 ppm.

Spectral and analytical data for **215.** 

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 11.2 Hz, 1H), 6.45 (t, *J* = 11.4 Hz, 1H), 5.45–5.43 (m, 1H), 5.29–5.24 (m, 1H), 4.88 (t, *J* = 6.1 Hz, 1H), 4.30–4.24 (m, 2H), 4.15–4.13 (m, 1H), 4.13–4.10 (m, 1H), 4.09–4.07 (m, 1H), 3.95 (ddd, *J* = 11.5, 8.5, 2.7 Hz, 1H), 3.83–3.80 (m, 1H), 3.78 (d, *J* = 7.0 Hz, 1H), 2.70 (dt, *J* = 12.8, 6.8 Hz, 1H), 1.95 (dt, *J* = 13.0, 8.0, 7.5 Hz, 1H), 1.74–1.71 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H), 1.20–1.19 (m, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07–0.06 (m, 12H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6, 135.5, 127.3, 125.2, 124.9, 109.3, 84.5, 81.7, 81.3, 79.5, 78.5, 76.0, 75.2, 68.8, 62.0, 36.8, 36.8, 30.6, 26.6, 26.1, 25.8, 24.5, 18.5, 18.0, 14.0, −4.8, −5.0, −5.2, −5.3 ppm. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)) *see Figures S-1–S-2.* HRMS (ESIpos): *m/z* calcd for $C_{33}H_{57}O_8ClSi_2Na$ [M+Na$^+$]: 695.3173, found: 695.3172.

Figure S-2. MS (ESIpos) analysis of a clean sample of macrocycle **215** *m/z* = 695.3 [M+Na]$^+$.

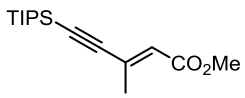


Comparison of ionization pattern of **78** and **215** differs in dimeric adduct formation, *m/z* = 1367.6 [2M+Na]$^+$, which is present exclusively in **78** (Figure S-1).

5.5 Synthesis of Complete epi-C15-Northern Fragment 237

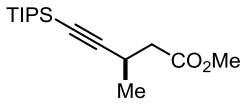
5.5.1 Synthesis of Side Chain 77

Methyl-(*E*)-3-methyl-5-(triisopropylsilyl)pen*t*-2-en-4-ynoate (226). Methyl-2-butynoate (**224**)



(980 mg, 10.0 mmol) and TIPS-acetylene (2.80 mL, 12.5 mmol) were added to a solution of $Pd(OAc)_2$ (67.3 mg, 0.30 mmol, 3 mol%) and TDMPP (**225**) (133 mg, 0.30 mmol, 3 mol%) in toluene. The resulting mixture was stirred at ambient temperature for 20 h before it was diluted with CH_2Cl_2/Et_2O (1:1, 10 mL) and filtered through a plug of Florisil®. The filter cake was washed with CH_2Cl_2/Et_2O (1:1, 30 mL) and Et_2O (50 mL). The filtrates were concentrated and the residue purified by flash chromatography (pentane/Et_2O 20:1) to afford the title compound as a pale yellow oil (2.56 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (q, J = 1.5 Hz, 1H), 3.71 (s, 3H), 2.30 (d, J = 1.5 Hz, 3H), 1.10–1.07 (m, 21H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 138.3, 124.3, 108.7, 96.5, 51.4, 20.1, 18.7, 11.3 ppm . IR (film): $\tilde{\nu}$ = 2945, 2866, 1721, 1615, 1463, 1341, 1240, 1150, 999, 882, 678, 624 cm^{-1}. MS (EI) *m/z* (%): 280 (10), 238 (22), 237 (100), 209 (21), 195 (14), 181 (14), 167 (21), 89 (12). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{28}O_2SiNa$: 303.1751, found: 303.1752. The analytical and spectroscopic data are in agreement with those reported in the literature.[498]

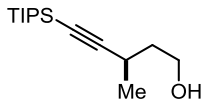
Methyl-(*R*)-3-methyl-5-(triisopropylsilyl)pen*t*-4-ynoate (227). A solution of $Cu(OAc)_2$ (193 mg,



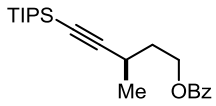
1.06 mmol) and (S,S_{FC})-WalPhos (987 mg, 1.06 mmol) in toluene (10 mL) was stirred at ambient temperature for 30 min. Methyldiethoxysilane (3.4 mL, 21 mmol) was added and the resulting mixture stirred at ambient temperature for 30 min before cooling to 0 °C. After addition of a solution of enyne **226** (2.97 g, 10.6 mmol) in toluene (3.5 mL), *t*-BuOH (2.0 mL, 21 mmol) was added to the bronce reation mixture at 0 °C and the temperature was ramped to 4 °C. After stirring for 44 h at 4 °C, the mixture was filtered through a pad of Florosil© and the filter cake was washed with Et_2O (50 mL). The combined filtrates were concentrated. The residue was purified by fractional distillation under reduced pressure, collecting the fraction that distilled from 70–75 °C at 8 mbar, to afford the title compound as a pale yellow oil (2.84 g, 95%, 98% *ee*). $[\alpha]_D^{20}$ = –25.6 (c = 1.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H), 2.99 (tq, J = 7.4, 6.9 Hz, 1H), 2.55 (dd, J = 15.2, 7.4 Hz, 1H), 2.41 (dd, J = 15.2, 7.4 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H), 1.07–1.00 (m, 21H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 111.6, 80.7, 51.8, 41.9, 24.1, 21.1, 18.7, 11.3 ppm. IR (film): $\tilde{\nu}$ = 2943, 2865, 2166, 1743, 1463, 1437, 1356, 1249, 1169, 1065, 997, 882, 675, 660, 627 cm^{-1}. MS (EI) *m/z* (%): 240 (11), 239 (63), 209 (22), 198 (15), 197 (100), 169 (64), 167 (13), 155 (15), 145 (26), 141 (58), 127 (17), 117 (17), 99 (13), 95 (11), 91 (15), 89 (30), 75 (29), 59 (23). HRMS (ESIpos): *m/z* calcd for $C_{16}H_{30}O_2SiNa$: 305.1907, found: 305.1909.

The enantiomeric excess was determined by chiral HPLC of the benzoate derivative, which was prepared in analytical quantities by the following two-step protocol:

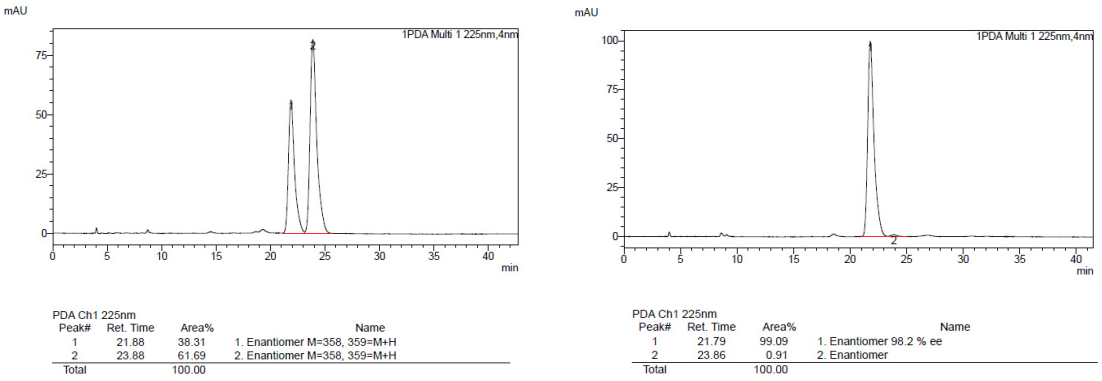
(*R*)-3-Methyl-5-(triisopropylsilyl)pen*t*-4-yn-1-ol (S8). $LiAlH_4$ (7.86 mg, 0.21 mmol) was added to a solution of methyl ester **226** (27.2 mg, 0.10 mmol) in THF (10 mL) at 0 °C. The suspension was stirred at 0 °C for 20 min, then at ambient temperature for 1 h. The mixture was diluted with *t*-butyl methyl ether (10 mL) and the reaction was quenched with sat. Rochelle salt solution (10 mL). The biphasic mixture was stirred for 16 h, the phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 20:1 to 10:1) to afford the title compound as a colourless oil (20.2 mg, 82%). $[\alpha]_D^{20}$ = –57.5 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86–3.77 (m, 2H), 2.66 (dqd, *J* = 9.4, 6.9, 5.1 Hz, 1H), 1.81 (br s, 1H), 1.79–1.61 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.08–1.02 (m, 21H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 113.2, 81.1, 61.6, 39.7, 24.2, 21.7, 18.8, 11.3 ppm. IR (film): $\tilde{\nu}$ = 3318, 2941, 2891, 2865, 2165, 1463, 1382, 1326, 1243, 1134, 1078, 1052, 996, 883, 675, 660, 620 cm^{-1}. MS (EI) *m/z* (%): 211 (55), 169 (58), 167 (13), 157 (19), 155 (37), 141 (33), 139 (28), 131 (28), 129 (16), 127 (44), 125 (21), 123 (12), 115 (55), 114 (13), 113 (37), 111 (23), 109 (16), 103 (53), 101 (21), 99 (18), 97 (20), 95 (16), 87 (56), 85 (26), 83 (18), 81 (11), 79 (14), 77 (14), 75 (85), 73 (82), 71 (14), 69 (18), 67 (13), 61 (43), 59 (100), 55 (16), 53 (14), 45 (40), 43 (29), 42 (27), 41 (58), 40 (12), 39 (33), 29 (89), 27 (11). HRMS (ESIpos): *m/z* calcd for $C_{15}H_{30}OSiNa$: 277.1958, found: 277.1956.



(*R*)-3-Methyl-5-(triisopropylsilyl)pen*t*-4-yn-1-yl benzoate (229). Pyridine (20 µL, 0.24 mmol) and benzoyl chloride (28 µL, 0.24 mmol) were sequentially added to a solution of alcohol **S8** (20 mg, 79 µmol) in CH_2Cl_2 (0.8 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 1.5 h. The reaction was quenched with water (1.5 mL) and the aq. phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with HCl (2 M, 10 mL), sat. $NaHCO_3$ (10 mL) and aq. half-sat. brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 25:1) to afford the title compound as a colourless oil (22.6 mg, 80%). $[\alpha]_D^{20}$ = –29.3 (c = 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.02 (m, 2H), 7.59–7.52 (m, 1H), 7.47–7.41 (m, 2H), 4.56–4.42 (m, 2H), 2.74 (dqd, *J* = 9.1, 6.9, 5.5 Hz, 1H), 2.00–1.81 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.10–1.03 (m, 21H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 132.8, 130.4, 129.5, 128.3, 112.1, 80.9, 63.1, 35.8, 24.0, 21.3, 18.6, 11.2 ppm. IR (film): $\tilde{\nu}$ = 2942, 2865, 2164, 1723, 1452, 1384, 1272, 1115, 1070, 921, 771, 676, 661, 619 cm^{-1}. MS (EI) *m/z* (%): 316 (10), 315 (41), 236 (19), 235 (100), 105 (31), 77 (11). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{34}O_2SiNa$: 381.2220, found: 381.2220. The *ee* was determined



by HPLC (Chiralcel OJ-3R, 3 µm, 150 × 4.6 mm, MeOH/H_2O 85:15, v = 0.5 mL/min, λ = 225 nm, 35 °C, 132 bar): minor enantiomer t_R = 21.8 min; major enantiomer t_R = 23.9 min.



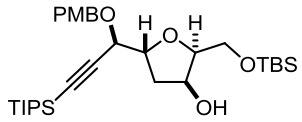
Methyl-(*R*)-3-methylpen*t*-4-ynoate (77). TBAF trihydrate (3.37 g, 10.7 mmol) was added to a solution of TIPS alkyne **226** (2.32 g, 8.21 mmol) in Et_2O (10 mL). After stirring for 14 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (25 mL). The aq. phase was separated and extracted with pentane (2 x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated carefully until aprox. a 20 mL solution remained. The residue was distilled under reduced pressure, collecting the fractions that distilled at 58-64 °C at 200 mbar, to afford the title compound as a colourless volatile liquid (648 mg, 58%). $[\alpha]_D^{20}$ = –22.3 (c = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 2.96 (hd, *J* = 7.1, 2.4 Hz, 1H), 2.57 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.42 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9, 87.2, 68.9, 51.9, 41.3, 22.7, 20.7 ppm. IR (film) $\tilde{\nu}$ = 3300, 2943, 2894, 2867, 1739, 1463, 1438, 1361, 1280, 1252, 1172, 1112, 1053, 1006, 883, 811, 671, 647. MS (EI) *m/z* (%): 126 (2), 125 (18), 111 (89), 98 (30), 97 (37), 95 (61), 84 (20), 83 (44), 74 (25), 68 (21), 67 (100), 66 (41), 65 (58), 59 (37), 53 (67), 51 (44) 43 (77), 41 (87), 39 (70). HRMS (ESIpos): *m/z* calcd for $C_7H_{10}O_2Na$: 149.0573, found: 149.0575.

5.5.2 Synthesis of Aldehydes 231 and 238

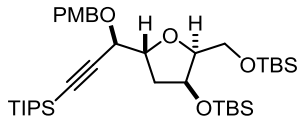
PMB-Ether S9. Scandium(III) triflate (24 mg, 50 µmol) and PMB-trichloroacetimidate (0.41 mL, 2.0 mmol) were added to a solution of propargyl alcohol (*R*)-**187** (480 mg, 990 µmol) in toluene (10 mL) at 0 °C. After stirring for 1 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$ (15 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 95:5) to afford the title compound (512 mg, 86%) as a colourless amorphous solid. $[\alpha]_D^{20}$ = –39.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–

7.25 (m, 2H), 6.89–6.84 (m, 2H), 5.42 (ddd, *J* = 5.0, 3.5, 1.4 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.32 (ddd, *J* = 8.5, 6.3 Hz, 1H), 4.24 (d, *J* = 5.7 Hz, 1H), 4.14 (ddd, *J* = 7.2, 5.6, 3.5 Hz, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.72 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.36 (ddd, *J* = 13.9, 8.6, 5.2 Hz, 1H), 2.17 (ddd, *J* = 14.3, 6.6, 1.5 Hz, 1H), 2.05 (s, 3H), 1.15–1.05 (m, 21H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 159.3, 129.8, 129.6, 113.8, 103.6, 89.0, 81.6, 78.8, 74.0, 71.2, 70.0, 60.7, 55.3, 35.4, 25.7, 21.0, 18.6, 18.1, 11.1, –5.5, –5.6.ppm. IR (film): $\tilde{\nu}$ = 2942, 2889, 2865, 1744, 1613, 1514, 1463, 1373, 1248, 1092, 1078, 1038, 837, 777, 678 cm^{-1}. MS (ESIpos) *m/z* (%): 622.4 (100 (M+NH_4)). HRMS (ESIpos): *m/z* calcd for $C_{33}H_{56}O_6Si_2Na$: 627.3508, found: 627.3510.

Alcohol 230. K_2CO_3 (234 mg, 1.69 mmol) was added to a solution of acetate **S9** (512 mg, 0.847 mmol) in a 1:1 mixture of THF (4.5 mL) and methanol (4.5 mL) at 0 °C. After stirring for 13 h and allowing the mixture to reach ambient temperature, the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 5:1 to 4:1) to afford the title compound as a colourless oil (429 mg, 90%). $[\alpha]_D^{20}$ = –112.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.57–4.49 (m, 2H), 4.42 (dt, *J* = 8.4, 6.3 Hz, 1H), 4.17 (d, *J* = 6.0 Hz, 1H), 4.00 (dt, *J* = 6.0, 3.8 Hz, 1H), 3.99–3.87 (m, 2H), 3.80 (s, 3H), 3.41 (d, *J* = 4.0 Hz, 1H), 2.26–2.08 (m, 2H), 1.14–1.05 (m, 21H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 129.7, 113.7, 103.9, 88.5, 81.2, 79.3, 73.7, 71.5, 69.9, 62.6, 55.2, 38.1, 25.7, 18.6, 18.6, 18.1, 11.2, –5.5, –5.6 ppm. IR (film): $\tilde{\nu}$ = 3468, 2941, 2865, 1612, 1514, 1463, 1303, 1250, 1173, 1073, 1038, 883, 837, 779, 679 cm^{-1}. MS (ESIpos) *m/z* (%): 585.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{54}O_5Si_2Na$: 585.3402, found: 585.3403.

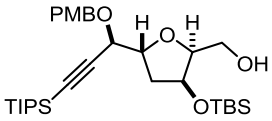


Compound S10. Imidazole (234 mg, 3.44 mmol) and TBSCl (449 mg, 2.98 mmol) were added to a solution of alcohol **229** (429 mg, 0.762 mmol) in CH_2Cl_2 (7.5 mL). After stirring for 18 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (10 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 30:1 to 20:1) to afford the title compound as colourless oil (479 mg, 93%). $[\alpha]_D^{20}$ = –31.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2H), 6.89–6.84 (m, 2H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.40–4.31 (m, 2H), 4.22 (d, *J* = 6.1 Hz, 1H), 3.92 (ddd, *J* = 7.1, 5.3, 3.1 Hz, 1H), 3.82–3.75 (m, 4H), 3.69 (dd, *J* = 10.0, 5.3 Hz, 1H), 2.17–2.00 (m, 2H), 1.12–1.07 (m, 21H), 0.88 (s, 9H), 0.88 (s, 9H), 0.08–0.05 (m, 6H), 0.05–0.02 (m, 6H) ppm. ^{13}C NMR

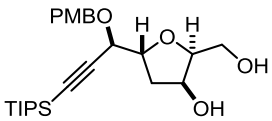


(101 MHz, $CDCl_3$): δ = 159.2, 129.8, 129.8, 113.7, 104.1, 88.4, 84.2, 78.8, 72.0, 71.9, 70.0, 61.1, 55.2, 38.5, 25.9, 25.7, 18.6, 18.3, 18.1, 11.2, −4.8, −5.1, −5.3, −5.3 ppm. IR (film): $\tilde{\nu}$ = 2929, 2892, 2864, 1613, 1514, 1463, 1361, 1251, 1076, 1043, 836, 776, 679 cm^{-1}. MS (ESIpos) *m/z* (%): 699.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{68}O_5Si_3Na$: 699.4267, found: 699.4271.

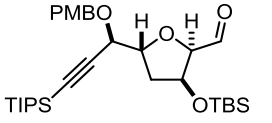
Alcohol 231. (±)-CSA (49 mg, 0.21 mmol) was added to a solution of bis-silyl ether **S10** (475 mg, 0.701 mmol) in a 1:1 mixture of methanol (6.0 mL) and THF (6.0 mL) at 0 °C. After stirring for 5 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 4:1 to 1:2) to afford the diol **S11** (40.7 mg, 13%) and title compound as colourless oil (303 mg, 77%). Analytical and spectral data for **231**: $[\alpha]_D^{20}$ = –58.1 (c = 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2H), 6.89–6.84 (m, 2H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.56–4.48 (m, 2H), 4.40 (dt, *J* = 8.3, 6.3 Hz, 1H), 4.19 (d, *J* = 6.0 Hz, 1H), 4.06 (dt, *J* = 5.5, 4.5 Hz, 1H), 3.83–3.76 (m, 4H), 3.72 (dd, *J* = 9.4, 3.0 Hz, 1H), 2.31–2.15 (m, 2H), 2.05 (ddd, *J* = 13.3, 6.5, 2.5 Hz, 1H), 1.12–1.06 (m, 21H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 129.9, 129.6, 113.8, 103.9, 88.7, 82.7, 79.0, 73.7, 71.6, 70.1, 62.5, 55.3, 38.6, 25.7, 18.6, 17.9, 11.2, −4.7, –5.2 ppm. IR (film): $\tilde{\nu}$ = 3479, 2941, 2892, 2864, 1613, 1514, 1463, 1250, 1174, 1111, 1070, 1013, 883, 835, 776, 678 cm^{-1}. MS (ESIpos) *m/z* (%): 585.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{54}O_5SiNa$: 585.3402, found: 585.3406.



Analytical and spectral data for diol **S11:** $[\alpha]_D^{20}$ = –82.6 (c = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 2H), 6.90–6.84 (m, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.50 (dddd, *J* = 3.6, 2.2 Hz, 1H), 4.46 (dt, *J* = 8.6, 6.7 Hz, 1H), 4.15 (d, *J* = 6.5 Hz, 1H), 4.03–3.90 (m, 3H), 3.80 (s, 3H), 3.45 (br s, 1H), 2.48 (br s, 1H), 2.18 (ddd, *J* = 13.6, 6.5, 2.1 Hz, 1H), 2.16 (ddd, *J* = 13.9, 8.4, 4.1 Hz, 1H), 1.12–1.07 (m, 21H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 129.9, 129.5, 113.8, 103.4, 89.0, 81.2, 79.5, 74.2, 71.6, 70.1, 61.7, 55.3, 38.9, 18.6, 11.1 ppm. IR (film): $\tilde{\nu}$ = 3417, 2941, 2864, 1612, 1514, 1463, 1303, 1248, 1173, 1065, 1035, 882, 820, 675 cm^{-1}. MS (ESIpos) *m/z* (%): 471.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{40}O_5SiNa$: 471.2537, found: 471.2539.



Aldehyde S12. Hünig's base (0.11 mL, 0.32 mmol) was added to a solution of alcohol **230** (64.6 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) at –20 °C. In a second flask, sulfur trioxide pyridine complex (51 mg, 0.32 mmol) was suspended in DMSO (90 µL, 1.2 mmol) and CH_2Cl_2 (0.3 mL). After stirring for 10 min at ambient temperature, the suspension was added to the alcohol solution at –20 °C and the flask was rinsed with CH_2Cl_2 (0.8 mL). The resulting mixture was stirred at –20 °C for 45 min. The mixture was diluted



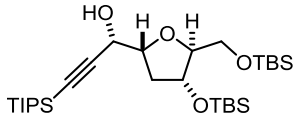
with *t*-butyl methyl ether (5 mL) and the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 9:1) to afford the title compound as a colourless oil (58.6 mg, 91%). $[\alpha]_D^{20}$ = –25.2 (c = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 2.2 Hz, 1H), 7.33–7.28 (m, 2H), 6.91–6.85 (m, 2H), 4.80 (d, *J* = 11.4 Hz, 1H), 4.73 (td, *J* = 4.0, 1.8 Hz, 1H), 4.66 (dt, *J* = 9.4, 6.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.29–4.22 (m, 2H), 3.80 (s, 3H), 2.15–2.07 (m, 2H), 1.12–1.08 (m, 21H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 159.4, 129.9, 129.4, 113.8, 103.4, 89.1, 87.6, 81.3, 75.5, 71.3, 70.2, 55.3, 39.0, 25.5, 18.6, 17.9, 11.1, –4.8, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2942, 2894, 2864, 1737, 1612, 1514, 1463, 1362, 1303, 1251, 1174, 1113, 1076, 1041, 994, 883, 832, 778, 679 cm^{-1}. MS (ESIpos) *m/z* (%): 583.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{52}O_3Si_2Na$: 583.3246, found: 583.3251.

Compound S13. Imidazole (2.11 g, 31.0 mmol) and TBSCl (3.82 g, 25.3 mmol) were added to a solution of diol **131** (1.47 g, 9.39 mmol) in CH_2Cl_2 (120 mL). After stirring for 40 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (100 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 100 mL). The combined organic phases were washed with brine (250 mL), dried over Na_2SO_4 and concentrated to a colourless liquid. The residual oil was purified using flash chromatography /hexane/*t*-butyl methyl ether = 99:1) to give the product as a colourless oil (3.54 g, 93%). $[\alpha]_D^{20}$ = −21.8 (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.99 (ddd, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.16 (ddd, *J* = 17.2, 1.7, 1.0 Hz, 1H), 5.04 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 1H), 4.44 (qt, *J* = 6.9, 0.9 Hz, 1H), 4.39 (ddd, *J* = 6.3, 5.3, 4.0 Hz, 1H), 3.86 (q, *J* = 4.5, 3.9 Hz, 1H), 3.64 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.60 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.28 (ddd, *J* = 12.5, 7.1, 6.4 Hz, 1H), 1.73 (ddd, *J* = 12.3, 6.7, 5.3 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07–0.06 (m, 6H), 0.06–0.05 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.9, 115.0, 86.3, 80.1, 73.3, 63.4, 41.4, 25.9, 25.7, 18.3, 17.9, –4.7, –4.8, –5.4, –5,5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2886, 2857, 1472, 1463, 1252, 1111, 1077, 1005, 986, 834, 775, 672 cm^{-1}. MS (ESIpos) *m/z* (%): 395.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{40}O_3Si_2Na$: 395.2408, found: 395.2413.

Aldehyde 240. Ozone was bubbled through a solution of olefin **S13** (864 mg, 2.87 mmol) in CH_2Cl_2 (160 mL) at −78 °C for 30 min, until the blue color persisted. Oxygen was bubbled through the mixture for 10 min followed by argon for 5 min, until the solution was colourless. PPh_3 (1.51 g, 5.75 mmol) was added in one portion and the mixture was allowed to reach ambient temperature over 16 h. The mixture was washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 10:1 to 5:1 to 2:1) to afford the title compound as a colourless oil (750 mg, 86%). $[\alpha]_D^{20}$ = –7.4

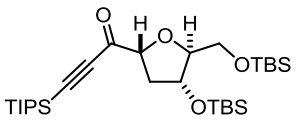
(c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 1.5 Hz, 1H), 4.37–4.31 (m, 2H), 4.06 (dd, *J* = 6.7, 4.0 Hz, 1H), 3.64 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.42 (dd, *J* = 10.8, 6.7 Hz, 1H), 2.30 (dddd, *J* = 13.7, 9.4, 4.3, 0.6 Hz, 1H), 2.03 (dt, *J* = 13.0, 1.8 Hz, 1H), 0.89 (s, 9H), 0.85 (s, 9H), 0.07–0.05 (m, 9H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.4, 88.7, 82.9, 72.8, 63.6, 38.5, 25.9, 25.6, 18.3, 17.8, −4.9 (2C), −5.5 (2C) ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2858, 1735, 1472, 1362, 1256, 1093, 1093, 1043, 836, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 397.2 (100 (M+Na)). MS (ESIpos) *m/z* (%): 577.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{38}O_4Si_2Na$: 577.3535, found: 577.3536.

Propargyl Alcohol (*S*)-**239.** A solution of lanthanum(III) chloride bis(lithium chloride) complex (0.6 M



in THF, 7.5 mL, 4.5 mmol) was added to a solution of aldehyde **240** (1.60 g, 4.27 mmol) in THF (30 mL). After stirring for 15 min, the premixed aldehyde solution was added to a solution of lithium TIPS-acetylide (0.39 M in THF, 13.0 mL, 5.07 mmol) at −78 °C in one portion and rinsed with THF (2 × 10 mL). After stirring for 1.5 h at the same temperature, the cold mixture was poured onto sat. NH_4Cl (150 mL). The aq. phase was separated and extracted with EtOAc (3 × 250 mL). The combined organic phases were washed with brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 25:1 to 25:2 to 25:4) to afford the title compound as a colourless oil (2.27 g, 96%, 1.8:1 d.r.). The diastereomeric mixture was oxidized to the ynone **S14**. Spectral and analytical data for (*S*)-**239**: $[\alpha]_D^{20}$ = +10.7 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (dd, *J* = 7.5, 3.4 Hz, 1H), 4.42–4.34 (m, 2H), 4.09 (d, *J* = 7.5 Hz, 1H), 4.05 (ddd, *J* = 6.0, 3.8, 1.8 Hz, 1H), 3.60 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.46 (dd, *J* = 10.8, 6.2 Hz, 1H), 2.37–2.26 (m, 1H), 2.21 (ddd, *J* = 13.8, 3.6, 2.3 Hz, 1H), 1.08–1.03 (m, 21H), 0.90 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07–0.04 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 106.9, 88.4, 86.4, 81.9, 73.4, 64.8, 63.6, 35.3, 25.9, 25.7, 18.6, 18.3, 17.9, 11.1, –4.9, –5.0, –5.5, −5.5 ppm. IR (film): $\tilde{\nu}$ = 3418, 2929, 2893, 2864, 1463, 1253, 1115, 1075, 1047, 996, 883, 835, 776, 675 cm^{-1}. MS (ESIpos) *m/z* (%): 579.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{29}H_{60}O_4Si_3Na$: 579.3691, found: 579.3698.

Ynone S14. A solution of the diastereomeric mixture of propargyl alcohol **239** (532 mg, 955 µmol) in



CH_2Cl_2 (6 mL) was added over a period of 2 min to a suspension of $NaHCO_3$ (658 mg, 7.83 mmol) and DMP (607 mg, 1.43 mmol) in CH_2Cl_2 (20 mL). After addition of *t*-BuOH (0.14 mL, 1.5 mmol), the suspension was stirred at ambient temperature for 1 h. The reaction was quenched with sat. $NaHCO_3$ (20 mL) and the aq. phase was separated. After extracting with *t*-butyl methyl ether (3 × 20 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 50:3 to 23:1) to afford the title compound as a colourless oil (430 mg, 81%). $[\alpha]_D^{20}$ = –17.2 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (dd, *J* = 6.7, 5.2 Hz, 1H), 4.32 (td, *J* = 3.8, 2.0 Hz, 1H), 4.06 (ddd, *J* = 5.7, 3.5, 2.0 Hz, 1H), 3.66 (dd, *J* = 10.9,

3.6 Hz, 1H), 3.50 (dd, *J* = 10.9, 5.8 Hz, 1H), 2.36–2.29 (m, 2H), 1.14–1.08 (m, 21H), 0.89 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04–0.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.6, 102.4, 99.1, 88.2, 84.0, 72.6, 63.2, 38.8, 25.9, 25.6, 18.5, 18.3, 17.8, 11.0, –4.9, –5.0, –5.4, –5.5 ppm. IR (film): $\tilde{\nu}$ = 2929, 2863, 1678, 1463, 1253, 1096, 882, 834, 776, 677 cm^{-1}. MS (ESIpos) *m/z* (%): 577.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{29}H_{58}O_4Si_3Na$: 577.3535, found: 577.3536.

Propargyl Alcohol (*R*)-**239.** Formic acid-triethylamine complex (5:2, 1.3 mL, 15 mmol) and (*S*,*S*)-Teth-TsDpen-RuCl (**Ru19**) (48 mg, 77 µmol) were added to a solution of ynone **S14** (429 mg, 773 µmol) in CH_2Cl_2 (12 mL). After stirring for 1 h at ambient temperature, the reaction was quenched with sat. $NaHCO_3$ (5 mL). The aq. phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 200:1 to 50:1) to afford the title compound as a colourless oil (403 mg, 94%, dr = >20:1). $[\alpha]_D^{20}$ = +8.7 (c = 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (dd, *J* = 8.2, 3.2 Hz, 1H), 4.33 (dt, *J* = 5.7, 2.6 Hz, 1H), 4.11 (td, *J* = 8.2, 3.5 Hz, 1H), 3.91 (ddd, *J* = 6.1, 3.8, 2.4 Hz, 1H), 3.62 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.48 (dd, *J* = 10.8, 5.8 Hz, 1H), 2.54 (d, *J* = 3.2 Hz, 1H), 2.25 (ddd, *J* = 13.8, 8.2, 5.9 Hz, 1H), 1.97 (dt, *J* = 13.3, 3.2 Hz, 1H), 1.09–1.04 (m, 21H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06–0.04 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 105.6, 87.6, 86.6, 83.0, 73.3, 66.3, 63.5, 37.2, 25.9, 25.7, 18.6, 18.3, 17.9, 11.1, –4.9, –4.9, –5.4, –5.5 ppm. IR (film): $\tilde{\nu}$ = 3428, 2929, 2893, 2863, 1463, 1387, 1362, 1254, 1115, 1068, 1004, 883, 836, 777, 677 cm^{-1}. MS (ESIpos) *m/z* (%): 579.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{29}H_{60}O_4Si_3Na$: 579.3691, found: 579.3693.

Mosher Ester Analysis of Alcohol (*R*)-**239.** Et_3N (17 µL, 0.12 mmol) was added to a solution of alcohol (*R*)-**239** (9.5 mg, 17 µmol) in CH_2Cl_2 (1.5 mL) followed by (*S*)-(−)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*S*)-MTPA-Cl) (12 µL, 64 µmol). The mixture was stirred at ambient temperature for 72 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 60:1) to give the corresponding (*R*)-Mosher ester **(*R*)-MTPA-**(*R*)-**329** (11.1 mg, 85%), which analyzed as follows: $[\alpha]_D^{20}$ = –6.4 (c = 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 2H), 7.39–7.33 (m, 3H), 5.95 (d, *J* = 9.0 Hz, 1H), 4.33 (dt, *J* = 5.5, 2.6 Hz, 1H), 4.28 (ddd, *J* = 9.0, 8.0, 3.1 Hz, 1H), 3.94–3.89 (m, 1H), 3.64 (d, *J* = 1.2 Hz, 3H), 3.60 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.47 (dd, *J* = 11.0, 5.4 Hz, 1H), 2.23 (ddd, *J* = 13.7, 8.1, 5.8 Hz, 1H), 2.09 (dt, *J* = 13.4, 2.9 Hz, 1H), 1.05–1.00 (m, 21H), 0.92 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2952, 2894, 2864, 1756, 1464,

1256, 1187, 1171, 1123, 1079, 1019, 837, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 795.4 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{39}H_{67}O_6F_3Si_3Na$: 795.4090, found: 795.4087.

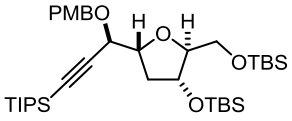
The same procedure was followed for the preparation of **(*S*)-MTPA-**(*R*)-**239** (6.5 mg, 85%), which analyzed as follows: $[\alpha]_D^{20}$ = –48.8 (c = 0.65, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 2H), 7.40–7.33 (m, 3H), 6.01 (d, *J* = 8.7 Hz, 1H), 4.32 (dt, *J* = 5.8, 2.9 Hz, 1H), 4.21 (ddd, *J* = 8.7, 7.9, 3.4 Hz, 1H), 3.90 (ddd, *J* = 5.3, 3.6, 2.7 Hz, 1H), 3.62–3.56 (m, 4H), 3.46 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.23–2.14 (m, 1H), 2.08 (dt, *J* = 13.4, 3.2 Hz, 1H), 1.09–1.04 (m, 21H), 0.91 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2952, 2894, 2864, 1756, 1464, 1256, 1187, 1171, 1123, 1079, 1019, 837, 778 cm^{-1}. MS (ESIpos) *m/z* (%): 795.4 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{39}H_{67}O_6F_3Si_3Na$: 795.4090, found: 795.4087.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-5. Mosher ester analysis for the assignment of the C(3) stereocenter; arbitrary numbering as shown in the insert.

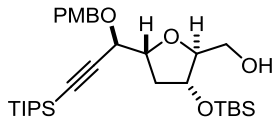
Assignment	(*R*)-239 [ppm]	(*S*)-MTPA-(*R*)-239	(*R*)-MTPA-(*R*)-239	Δ (δ(*S*–*R*)) [ppm]
3	4.50	6.01	5.95	+0.06
4	4.38	4.21	4.28	–0.07
5a	2.33	2.18	2.23	–0.05
5b	2.21	2.08	2.09	–0.01
6	4.38	3.90	3.91	–0.01
7	4.05	4.32	4.33	–0.01
8a	3.60	3.59	3.60	–0.01
8b	3.46	3.46	3.47	–0.01
TIPS-Me	1.06	1.06	1.03	+0.03

PMB-Ether S15. PMB-trichloroacetimidate (0.98 mL, 4.7 mmol) and scandium(III) triflate (65 mg, 0.13 mmol) were added to a solution of propargyl alcohol (*R*)-**239** (1.47 g, 2.64 mmol) in toluene (20 mL) at 0 °C. After stirring for 5 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$ (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 25 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 100:1 to 50:1) to afford the title compound (1.39 g, 86%) as a colourless oil. $[\alpha]_D^{20}$ = –81.6 (c = 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2H), 6.87–6.81 (m, 2H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.27 (dt, *J* = 5.9, 3.4 Hz, 1H), 4.20 (td, *J* = 7.9, 4.2 Hz, 1H), 3.86 3.81 (m, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.47 (dd, *J* = 10.8, 5.8 Hz, 1H), 2.22 (ddd, *J* = 13.5, 7.8, 5.9 Hz, 1H), 2.09 (dt, *J* =



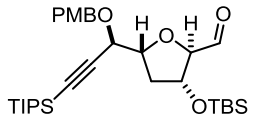
13.2, 4.0 Hz, 1H), 1.10–1.06 (m, 21H), 0.88 (s, 9H), 0.80 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 130.0, 129.8, 113.7, 104.6, 88.1, 87.1, 80.6, 72.9, 72.0, 69.9, 63.3, 55.2, 37.3, 25.9, 25.6, 18.6, 18.3, 17.7, 11.2, –4.9, –5.0, –5.4, –5.4 ppm. IR (film): $\tilde{\nu}$ = 2929, 2862, 1613, 1513, 1463, 1362, 1302, 1249, 1173, 116, 1075, 882, 835, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 699.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{68}O_5Si_3Na$: 699.4267, found: 699.4270.

Primary Alcohol 241. (±)-CSA (102 mg, 0.439 mmol) was added to a solution of compound **S15**



(1.00 g, 1.48 mmol) in methanol (12 mL) and THF (13 mL) at 0 °C. After stirring for 3.5 h at the same temperature, the reaction was quenched with sat. $NaHCO_3$ (15 mL). The aq. phase was separated and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 9 :1 to 6:1 to 3:1 to 1:1) to recover bis-silyl ether **S15** (164 mg, 16%) and afford the title compound as a colourless oil (627 mg, 75%). $[\alpha]_D^{20}$ = –103.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 2H), 6.88–6.84 (m, 2H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 4.25–4.18 (m, 2H), 3.81–3.75 (m, 4H), 3.73 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.51 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.28 (dt, *J* = 12.8, 6.9 Hz, 1H), 2.07 (dt, *J* = 12.8, 6.0 Hz, 1H), 1.12–1.07 (m, 21H), 0.82 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 129.9, 129.6, 113.8, 103.9, 88.7, 85.5, 80.0, 71.9, 71.6, 70.1, 62.1, 55.2, 38.0, 25.6, 18.6, 17.8, 11.2, –4.8, –5.0 ppm. IR (film): $\tilde{\nu}$ = 3479, 2941, 2892, 2864, 1613, 1514, 1463, 1250, 1174, 1111, 1070, 1013, 883, 835, 776, 678 cm^{-1}. MS (ESIpos) *m/z* (%): 585.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{54}O_5SiNa$: 585.3402, found: 585.3407.

Aldehyde 238. Hünig's base (0.97 mL, 5.6 mmol) was added to a solution of alcohol **241** (625 mg,

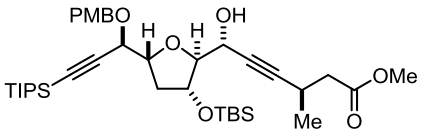


1.11 mmol) in CH_2Cl_2 (15 mL) at –35 °C. In a second flask, sulfur trioxide pyridine complex (461 mg, 2.89 mmol) was suspended in DMSO (0.82 mL, 11.5 mmol) and stirred for 10 min at ambient temperature, before the suspension was added to the alcohol solution at –25 °C and the flask was rinsed with CH_2Cl_2 (2.0 mL). The resulting mixture was allowed to reach –20 °C and stirred for 2.5 h. The mixture was diluted with *t*-butyl methyl ether (15 mL) and the reaction was quenched with sat. NH_4Cl (25 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 25 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residual light yellow oil (588 mg, 95%) was used without further purification in the next step. $[\alpha]_D^{20}$ = –75.7 (c = 1.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.5 Hz, 1H), 7.33–7.29 (m, 2H), 6.88–6.84 (m, 2H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.43–4.33 (m, 3H), 4.17 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.79 (s, 3H), 2.22–2.15 (m, 2H), 1.11–1.08 (m, 21H), 0.81 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.4, 159.3, 129.9, 129.5, 113.8, 103.7, 90.6, 89.0, 81.6, 73.4, 71.5,

70.1, 55.2, 37.9, 25.5, 18.6, 17.7, 11.1, –5.1, –5.1 ppm. IR (film): $\tilde{\nu}$ = 2942, 2892, 2864, 1735, 1612, 1513, 1463, 1249, 1173, 1110, 1071, 1017, 882, 836, 777, 674 cm^{-1}. MS (ESIpos) *m/z* (%): 583.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{52}O_3Si_2Na$: 583.3246, found: 583.3248.

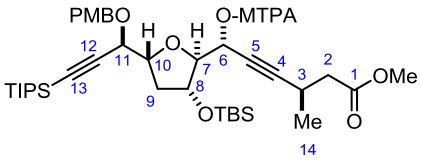
5.5.3 Completion of C-15 *epi* Northern Fragment Synthesis

Propargyl Alcohol 242. A Schlenk tube was charged with $Zn(OTf)_2$ (dried at 120 °C under high vacuum



for 24 h, 292 mg, 0.803 mmol) and (–)-NME (151 mg, 0.842 mmol), which had been dried by applying high vacuum and purging with argon. After the addition of toluene (2.0 mL), Hünig's base (0.15 mL, 0.86 mmol) was added and the suspension stirred for 1.5 h at ambient temperature before adding a solution of alkyne **77** (110 mg, 0.873 mmol) in toluene (1.0 mL with rinses). After stirring for 45 min at ambient temperature, the crude aldehyde **238** (241 mg, 430 µmol) in toluene (7.0 mL with rinses) was added quickly to the milky suspension. After stirring for 18 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (10 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 5:1) to provide the title compound as a yellow oil (199 mg, 67%, pure isomer, dr = 5.5:1). $[\alpha]_D^{20}$ = −71.6 (c = 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 2H), 6.88–6.83 (m, 2H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.30–4.23 (m, 2H), 4.14 (dd, *J* = 6.1, 1.8 Hz, 1H), 3.83 (dd, *J* = 6.2, 3.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 2.98 (dpd, *J* = 8.5, 6.8, 1.7 Hz, 1H), 2.57 (dd, *J* = 15.5, 6.4 Hz, 1H), 2.38 (dd, *J* = 15.6, 8.2 Hz, 1H), 2.24 (ddd, *J* = 13.6, 7.9, 5.9 Hz, 1H), 2.13 (dt, *J* = 13.4, 4.0 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.11–1.07 (m, 21H), 0.80 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.7, 159.2, 129.8, 129.7, 113.8, 104.1, 89.0, 88.8, 88.5, 81.1, 78.8, 72.7, 71.8, 70.1, 62.7, 55.2, 51.7, 41.0, 37.6, 25.6, 22.7, 20.5, 18.6, 17.7, 11.1, −4.8, −4.9 ppm. IR (film) $\tilde{\nu}$ = 3451, 2942, 2865, 1741, 1613, 1514, 1463, 1362, 1250, 1173, 1072 cm^{-1}. MS (ESIpos) *m/z* (%): 709.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{38}H_{62}O_7Si_2Na$: 709.3926, found: 709.3930.

Mosher Ester Analysis of Alcohol 242. Et_3N (15 µL, 0.11 mmol) was added to a solution of alcohol



242 (4.0 mg, 5.8 µmol) in CH_2Cl_2 (0.6 mL) followed by (*S*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*S*)-MTPA-Cl) (12.5 µL, 67 µmol) and DMAP (2.5 mg, 21 µmol). The mixture was stirred at ambient temperature for 4 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 19:1) to give the corresponding (*R*)-Mosher ester

(*R*)-MTPA-242 (4.6 mg, 88%), which analyzed as follows: $[\alpha]_D^{20}$ = –33.0 (c = 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.53 (m, 2H), 7.38–7.34 (m, 3H), 7.31–7.27 (m, 2H), 6.87–6.80 (m, 2H), 5.44 (dd, *J* = 7.2, 1.9 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 4.31–4.22 (m, 2H), 4.00 (dd, *J* = 7.2, 2.0 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.56 (d, *J* = 1.1 Hz, 3H), 2.95 (dqd, *J* = 8.6, 7.0, 1.9 Hz, 1H), 2.50 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.39–2.26 (m, 2H), 2.13 (dt, *J* = 13.6, 3.0 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.10–1.06 (m, 21H), 0.78 (s, 9H), –0.02 (s, 3H), –0.06 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2944, 2938, 2865, 1754, 1514, 1463, 1251, 1172, 1123, 1109, 1077, 1015 cm^{-1}. MS (ESIpos) *m/z* (%): 925.4 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{48}H_{69}O_9F_3Si_2Na$: 925.4324, found: 925.4328.

The same procedure was followed for the preparation of **(*S*)-MTPA-242** (3.5 mg, 67%), which analyzed as follows: $[\alpha]_D^{20}$ = –78.9 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2H), 7.37–7.33 (m, 3H), 7.30–7.25 (m, 2H), 6.87–6.80 (m, 2H), 5.51 (dd, *J* = 5.7, 2.0 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.30 (d, *J* = 8.2 Hz, 1H), 4.24 (dd, *J* = 8.0, 3.8 Hz, 1H), 4.22 (dt, *J* = 5.7, 2.7 Hz, 1H), 3.92 (dd, *J* = 5.8, 2.3 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.58 (d, *J* = 1.1 Hz, 3H), 2.99 (hd, *J* = 7.0, 2.0 Hz, 1H), 2.52 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.38 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.25 (ddd, *J* = 13.6, 8.0, 5.8 Hz, 1H), 2.09 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.11–1.07 (m, 21H), 0.75 (s, 9H), −0.02 (s, 3H), −0.11 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2944, 2938, 2865, 1754, 1514, 1463, 1251, 1172, 1123, 1109, 1077, 1015 cm^{-1}. MS (ESIpos) *m/z* (%): 925.4 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{48}H_{69}O_9F_3Si_2Na$: 925.4324, found: 925.4335.

Both products were analyzed according to Hoye and co-workers:[497]

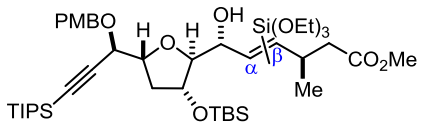
Table S-6. Mosher ester analysis for the assignment of the C(6) stereocenter; arbitrary numbering as shown in the insert.

Assignment	242 [ppm]	(*S*)-MTPA-242 [ppm]	(*R*)-MTPA-242 [ppm]	Δ (δ(*S*–*R*)) [ppm]
2a	2.57	2.52	2.50	+0.02
2b	2.38	2.38	2.32	+0.04
3	2.98	2.99	2.95	+0.04
6	4.14	5.51	5.44	+0.07
7	3.83	3.92	4.00	–0.08
8	4.26	4.22	4.28	–0.06
9a	2.24	2.25	2.32	–0.07
9b	2.13	2.09	2.13	–0.04
10	4.26	4.24	4.28	–0.04
11	4.34	4.30	4.34	–0.04
14	1.21	1.21	1.18	+0.03

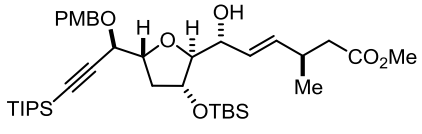
Alkenylstannane 246. A solution of [Cp*RuCl] (0.9 mg, 3.3 µmol) in CH_2Cl_2 (0.25 mL) was added to a solution of propargyl alcohol **242** (19.3 mg, 28.1 µmol) in CH_2Cl_2 (0.55 mL). After stirring for 1 min at ambient temperature, the purple solution was cooled to –30 °C. A solution of tributylstannane (11.1 µL, 40.2 µmol) in CH_2Cl_2 (0.30 mL) was added over a period of 1 h at the same temperature. After warming to –20 °C, the mixture was stirred for another 1 h. After removal of the cold bath, the mixture was concentrated and the residue was purified by flash chromatography ((hexane/NEt_3 99:1)/*t*-butyl methyl ether 98:2 to 96:4 to 94:6) to afford the title compound as a colourless oil (21.2 mg, 77%, *Z/E* >20:1, >20:1 r.r.). $[\alpha]_D^{20}$ = –58.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2H), 6.89–6.81 (m, 2H), 5.96 (dd, *J* = 10.2 Hz, J_{SnH} = 119.5 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.33 (d, *J* = 8.1 Hz, 1H), 4.25 (tt, *J* = 8.1, 4.3 Hz, 1H), 4.15 (dt, *J* = 3.6, 2.0 Hz, 1H), 3.79 (s, 3H), 3.75–3.64 (m, 5H), 2.72 (d, *J* = 3.2 Hz, 1H), 2.68–2.56 (m, 1H), 2.36 (dd, *J* = 14.9, 4.7 Hz, 1H), 2.28–2.16 (m, 2H), 2.11 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.55–1.45 (m, 6H), 1.33 (h, *J* = 7.3 Hz, 6H), 1.11–1.06 (m, 21H), 1.04–0.95 (m, 9H), 0.89 (t, *J* = 7.3 Hz, 9H), 0.77 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 159.2, 146.4, 145.2, 129.8, 129.6, 113.7, 104.3, 89.3, 88.4, 81.0, 79.2, 72.5, 72.4, 70.1, 55.2, 51.4, 41.7, 37.3, 35.8, 29.2, 27.5, 25.6, 20.7, 18.6, 17.6, 13.6, 11.5, 11.2, –4.7, –4.7 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = −54.1 ppm. IR (film) $\tilde{\nu}$ = 3503, 2955, 2928, 2866, 1741, 1613, 1513, 1463, 1250, 1076, 838, 674, 666 cm^{-1}. MS (EI) *m/z* (%): 922 (45), 921 (82, M–*t*-Bu), 919 (60), 121 (100). HRMS (ESIpos): *m/z* calcd for $C_{50}H_{90}O_7Si_2SnNa$: 1001.5139, found: 1001.5146.

THP 248. Tetrabutylammonium diphenylphosphinate (12.5 mg, 27.2 mmol) and copper(I) thiophene-2-carboxylate (5.0 mg, 26 mmol) were added to a solution of alkenylstannane **246** (21 mg, 22 mmol) in DMF (0.2 mL). After stirring for 2.5 h, the mixture was diluted with EtOAc (1 mL) and the reaction was quenched with water (1 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 3:1) to afford the title compound as a colourless oil (10 mg, 83%). $[\alpha]_D^{20}$ = –98.5 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 2H), 6.90–6.82 (m, 2H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.31–4.16 (m, 3H), 3.84–3.69 (m, 5H), 3.56–3.47 (m, 1H), 2.28 (dt, *J* = 12.8, 6.9 Hz, 1H), 2.06 (dt, *J* = 12.8, 6.0 Hz, 1H), 1.86 (s, 1H), 1.14–1.04 (m, 21H), 0.82 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 129.9, 129.6, 113.8, 103.9, 88.7, 85.5, 80.0, 71.9, 71.6, 70.1, 62.1, 55.2, 38.0, 25.6, 18.6, 17.8, 11.2, −4.8, −5.0 ppm. IR (film) $\tilde{\nu}$ = 3460, 2943, 2864, 1612, 1514, 1463, 1250, 1173, 1104, 1070, 883, 836, 777, 678 cm^{-1}. MS (ESIpos) *m/z* (%): 585.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{54}O_5Si_2Na$: 585.3402, found: 585.3399.

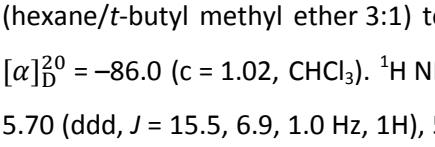
(*Z*)-Alkenylsilane 249. Triethoxysilane (18 µL, 98 µmol) and a solution of [Cp*RuCl] (1.1 mg, 4.0 µmol) in CH_2Cl_2 (0.20 mL) were added to a solution of propargyl alcohol **242** (55 mg, 80 µmol) in CH_2Cl_2 (0.70 mL). After stirring for 1 h at ambient temperature, the mixture was concentrated. The residue was used in the next step without further purification (*prox*-**242**/*dist*-**242** = 2.2:1).



(*E*)-Alkene 247. A solution of TBAF (0.2 M in THF, 0.42 mL, 84 µmol) was added to a solution of the crude **249** in THF (1.5 mL) at –40 °C. After stirring for 30 min and allowing the mixture to warm to –30 °C, the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 3:1) to afford the title compound as a colourless oil (27.6 mg, 50%). $[\alpha]_D^{20}$ = –86.0 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 2H), 6.89–6.83 (m, 2H), 5.70 (ddd, *J* = 15.5, 6.9, 1.0 Hz, 1H), 5.50 (ddd, *J* = 15.5, 6.7, 1.2 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.31 (d, *J* = 7.8 Hz, 1H), 4.23 (td, *J* = 7.7, 4.8 Hz, 1H), 4.16 (dt, *J* = 6.1, 4.2 Hz, 1H), 3.84 (q, *J* = 5.6 Hz, 1H), 3.79 (s, 3H), 3.68 (dd, *J* = 5.7, 3.7 Hz, 1H), 3.65 (s, 3H), 2.70 (hept, *J* = 6.9 Hz, 1H), 2.43–2.32 (m, 2H), 2.29–2.18 (m, 2H), 2.10 (dt, *J* = 13.2, 4.6 Hz, 1H), 1.12–1.07 (m, 21H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.80 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 159.2, 137.4, 129.8, 129.7, 128.2, 113.8, 104.1, 88.7, 88.5, 80.5, 72.5, 72.2, 71.7, 70.1, 55.2, 51.5, 41.2, 37.7, 33.2, 25.6, 19.7, 18.6, 17.7, 11.1, –4.8, –4.9 ppm. IR (film) $\tilde{\nu}$ = 3414, 2945, 2892, 2864, 1738, 1513, 1462, 1249, 1172, 1119, 1039, 1007, 883, 836, 776, 674 cm^{-1}. MS (ESIpos) *m/z* (%): 711.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{38}H_{64}O_7Si_2Na$: 711.4083, found: 711.7089.

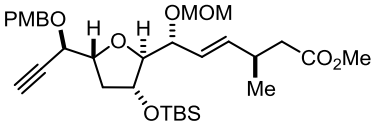


MOM-Ether S16. Tetrabutylammonium iodide (9.2 mg, 25 µmol) was added to a solution of allylic alcohol **247** (29 mg, 42 µmol) in CH_2Cl_2 (0.8 mL) causing a colour change to yellow. After cooling to 0 °C, Hünig's base (0.29 mL, 1.7 mmol) and MOMCl (0.05 mL, 0.7 mmol) were added dropwise. After stirring for 10 min at 0 °C, the ice bath was removed and the mixture was stirred for 14 h at 30 °C. After cooling the orange solution to ambient temperature, the mixture was diluted with EtOAc (5 mL) and the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 85:15) to afford the title compound as a colourless oil (23.0 mg, 75%). $[\alpha]_D^{20}$ = –112.3 (c = 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2H), 6.87–6.81 (m, 2H), 5.62 (ddd, *J* = 15.5, 7.3, 0.8 Hz, 1H), 5.41 (ddd, *J* = 15.6, 7.9, 1.1 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.33 (d, *J* = 7.9

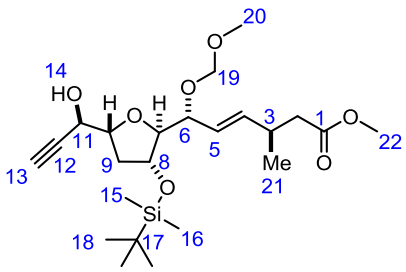


Hz, 1H), 4.28–4.18 (m, 2H), 4.01 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.84 (dd, *J* = 4.2, 3.1 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.34 (s, 3H), 2.71 (heptd, *J* = 6.5, 1.1 Hz, 1H), 2.33 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.28 (dd, *J* = 14.9, 7.3 Hz, 1H), 2.15 (ddd, *J* = 13.5, 7.6, 6.1 Hz, 1H), 2.08 (dt, *J* = 13.1, 4.0 Hz, 1H), 1.11–1.06 (m, 21H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 172.7, 159.1, 139.2, 129.9, 129.8, 125.6, 113.7, 104.6, 93.5, 88.6, 88.1, 80.8, 75.8, 72.7, 71.5, 69.9, 55.5, 55.2, 51.4, 41.4, 38.1, 33.5, 25.6, 20.1, 18.6, 17.7, 11.2, −4.8, –5.0 ppm. IR (film): $\tilde{\nu}$ = 2944, 2892, 2864, 1740, 1514, 1463, 1250, 1076, 1037, 837, 776, 679 cm^{-1}. MS (ESIpos) *m/z* (%): 755.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{40}H_{68}O_8Si_2Na$: 755.4345, found: 755.4347.

Terminal Alkyne 250. A solution of TBAF (0.1 M in THF, 0.44 mL, 44 µmol) was added dropwise to a solution of TIPS alkyne **S16** (31.0 mg, 42 µmol) in THF (0.85 mL) at −20 °C. After stirring for 15 min at the same temperature, the mixture was diluted with *t*-butyl methyl ether (5 mL) and the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 85:15 to 4:1) to afford the title compound as a light yellow oil (19.0 mg, 78%). $[\alpha]_D^{20}$ = −120.6 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2H), 6.88–6.81 (m, 2H), 5.63 (ddd, *J* = 15.5, 7.3, 0.8 Hz, 1H), 5.41 (ddd, *J* = 15.6, 8.0, 1.1 Hz, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 6.7 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 4.29 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.30–4.19 (m, 2H), 4.01 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.83 (dd, *J* = 4.3, 2.8 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.34 (s, 3H), 2.71 (hept, *J* = 7.1 Hz, 1H), 2.43 (d, *J* = 2.0 Hz, 1H), 2.34 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.27 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.15 (ddd, *J* = 13.6, 7.6, 6.2 Hz, 1H), 2.00 (dt, *J* = 12.9, 3.4, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 172.7, 159.2, 139.3, 129.7, 129.7, 125.5, 113.7, 93.5, 88.9, 81.0, 75.9, 74.9, 72.9, 72.9, 70.7, 70.2, 55.5, 55.2, 51.5, 41.3, 38.0, 33.5, 25.6, 20.1, 17.7, –4.8, –4.9 ppm. IR (film): $\tilde{\nu}$ = 2953, 2929, 2857, 1738, 1514, 1249, 1173, 1151, 1077, 1035, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 599.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{48}O_8SiNa$: 599.3011, found: 599.3014.



Propargyl Alcohol 251. DDQ (23 mg, 0.10 mmol) was added to an emulsion of PMB-ether **250** (18.0 mg, 31.2 µmol) in a 4:1 mixture of CH_2Cl_2 (0.40 mL) and pH 7.4 phosphate buffer (0.10 mL). After stirring for 4 h at ambient temperature, the mixture was diluted with CH_2Cl_2 (2 mL) and the reaction was quenched with a 1:1 mixture of sat. $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ (2 mL). The aq. phase was separated and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash



chromatography (hexane/EtOAc 3:2) to afford the title compound as a light yellow oil (11.0 mg, 77%). $[\alpha]_D^{20}$ = −89.4 (c = 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *see Table S-7*. ^{13}C NMR (126 MHz, $CDCl_3$): *see Table S-7*. ^{29}Si NMR (99 MHz, $CDCl_3$) δ = 20.5 ppm. IR (film): $\tilde{\nu}$ = 3459, 2954, 2930, 2887, 2857, 1737, 1254, 1151, 1100, 1035, 978, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 479.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{23}H_{40}O_7SiNa$: 479.2436, found: 479.2438.

Table S-7. NMR data of terminal alkyne **251**; arbitrary numbering scheme as shown in the insert

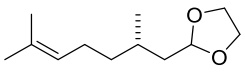
atom n°	**^{1}H NMR** (500 MHz, $CDCl_3$)					**^{13}C NMR** (126 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	172.6	2, 3, 22
2a	2.34	dd	14.9, 7.3	3	4, 21	41.3	3, 21
2b	2.30	dd	14.7, 6.9				
3	2.72	hept	7.0	2, 4	21	33.5	2, 4, 5, 21
4	5.65	ddd	15.6, 7.4, 0.6	3, 5	2ab, 3, 5, 6, 7, 21	139.9	2, 3, 7, 21
5	5.38	ddd	15.6, 7.8, 1.2	4, 6	3, 7, 8, 21	125.2	3
6	3.96	dd	7.7, 5.1	5	4, 5, 8, 19ab, 20	76.0	4, 19
7	3.98	dd	5.1, 1.8	(8)	4, 5, 8, 19ab, 20	89.7	(6)
8	4.31	dt	5.9, 1.8	9ab	6, 7, 3a, 15/16	73.5	(7)
9a	2.24	ddd	13.8, 8.5, 5.9	8, 9b, 10	8, 9b, 10	37.7	-
9b	1.89	ddd	13.7, 3.0, 2.0	9a	8, 9a, 11		
10	4.21	ddd	8.6, 7.0, 3.1	9ab, 11	9a	82.8	8, 9a, 11
11	4.48	dd	6.8, 2.0	10, 13, 14	7, 9b	65.3	9a
12	-	-	-	-	-	82.1	11, 13
13	2.42	d	2.2	(11)	-	73.4	-
14-OH	3.11	br s	-	-	-	-	-
15	0.07	s	-	-	-	–4.8◘	-
16	0.08	s	-	-	8	–4.8	-
17	-	-	-	-	-	17.8	15, 16, 18
18	0.88	s	-	-	8, 11	25.7	-
19a	4.64	d	6.7	19b	6, 7, 20	93.3	22
19b	4.50	d	6.7	19a	7, 20		
20	3.35	s	-	-	19b	55.5	19ab
21	1.06	d	6.8	3	2ab, 3, 4, 5, 15/16	20.0	2ab, 3, 4
22	3.65	s	-	-	-	51.5	-

Bis(alkenyl)stannane 237. A solution of alkyne **251** (6.0 mg, 13 µmol) in THF (0.3 mL with rinses) was added to a solution of [(*t*BuNC)$_2$PdCl$_2$] (0.9 mg, 2.6 µmol) in THF (0.1 mL). Hexabutylditin (10 µL, 20 µmol) was added in one portion and the resulting mixture was stirred at ambient temperature for 15.5 h. The solvent was evaporated and the residue was purified by flash chromatography (hexane/*t*-butyl methyl ether/Et_3N 100:1:2 to 100:1:4) to yield the title compound as a yellow oil (69 mg, 76%). $[\alpha]_D^{20}$ = −39.7 (c = 0.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CHCl_3$): δ = 7.02 (d, *J* = 0.7 Hz, J_{SnH} = 177.1, 68.0 Hz, 1H), 5.63 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.40 (ddd, *J* = 15.5, 8.1, 1.1 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.28 (dt, *J* = 6.5, 2.5 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 4.00–3.92 (m, 2H), 3.89 (dd, *J* = 4.9, 2.5 Hz, 1H), 3.65 (s, 3H), 3.36 (s, 3H), 3.10 (s, 1H), 2.72 (hept, *J* = 7.0 Hz, 1H), 2.39–2.25 (m, 2H), 2.03 (ddd, *J* = 13.4, 8.3, 6.5 Hz, 1H), 1.77 (dt, *J* = 13.4, 3.0 Hz, 1H), 1.53–1.41 (m, 12H), 1.35–1.27 (m, 12H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.95–0.86 (m, 39H), 0.07–0.05 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CHCl_3$): δ = 172.6, 169.0, 145.1, 139.7, 125.6, 93.3, 89.0, 86.8, 82.5, 76.1, 73.8, 55.5, 51.5, 41.3, 37.0, 33.5, 29.3, 29.2, 27.6, 27.4, 25.8, 20.0, 17.9, 13.7, 13.7, 11.5, 10.9, −4.7, −4.8 ppm. ^{119}Sn NMR (150 MHz, $CHCl_3$): δ = –60.1, –67.2 ppm. IR (film): $\tilde{\nu}$ = 3464, 2955, 2927, 2871, 2855, 1742, 1463, 1376, 1251, 1214, 1152, 1062, 1036, 921, 860, 839, 777, 671, 596 cm^{-1}. MS (ESIpos) *m/z* (%): 1061.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{47}H_{94}O_7SiSn_2Na$: 1061.4710, found: 1061.4710.

5.6 Total Synthesis of the Putative Structure of Chagosensine

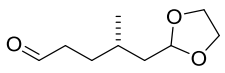
5.6.1 Synthesis of Complete Northern Fragment 256

(*S*)-2-(2,6-Dimethylhept-5-en-1-yl)-1,3-dioxolane (S17). Triethylorthoformate (69 mL, 0.42 mol) and



ethylene glycol (117 mL, 2.09 mol) were added to a solution of CSA (1.62 g, 6.99 mmol) in CH_2Cl_2 (1.0 L). Neat (*S*)-citronellal (**252**) (25.2 mL, 139 mmol) was added dropwise *via* syringe over 10 min. The colourless solution was stirred at ambient temperature for 20 min before the reaction was quenched with sat. $NaHCO_3$ (300 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with brine (2 × 200 mL), dried over Na_2SO_4 and concentrated to a colourless liquid. This liquid can be purified by flash chromatography (hexane/*t*-butyl methyl ether 70:30) to give the title compound as a colourless liquid (27.1 g, 98%). More conveniently, the crude mixture was distilled under high vacuum, discarding the fore-run but collecting the fraction distilling between 66–69 °C at 1.6×10^{-2} mbar. The product **S17** was isolated as a colourless liquid in a slightly reduced yield (23.1 g, 84%). $[\alpha]_D^{20}$ = –4.3 (c = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (tq, *J* = 7.1, 2.2 Hz, 1H), 4.90 (dd, *J* = 5.2, 4.7 Hz, 1H), 4.02–3.91 (m, 2H), 3.89–3.80 (m, 2H), 2.08–1.88 (m, 2H), 1.76–1.62 (m, 5H), 1.60 (s, 3H), 1.54–1.44 (m, 1H), 1.44–1.32 (m, 1H), 1.28–1.13 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.2, 124.7, 103.8, 64.7, 64.6, 40.9, 37.5, 29.1, 25.7, 25.4, 19.8, 17.6 ppm. IR (film): $\tilde{\nu}$ = 2960, 2915, 2877, 1454, 1409, 1378, 1130, 1040, 945 cm^{-1}. MS (EI) *m/z* (%): 136 (10), 113 (28), 69 (20), 41 (35). HRMS (ESIpos) *m/z* calcd for $C_{12}H_{23}O_2$ $[M+H^+]$: 199.1693, found: 199.1692. The analytical and spectroscopic data are in agreement with those reported in the literature.[499]

(*S*)-5-(1,3-dioxolan-2-yl)-4-methylpentanal (258). Sudan Red III (5-10 mg) was added to a solution of



ketal **S17** (22.5 g, 114 mmol) in CH_2Cl_2 (500 mL). The solution was cooled to −78 °C before ozone was bubbled (35-40 g/Nm^3, 420 min) through the mixture until a colour change from red/pink to pale yellow was observed. After purging with oxygen for 30 min, dimethyl sulfide (17 mL, 0.23 mol) was added and the mixture was allowed to reach ambient temperature over 12 h. The mixture was concentrated to give a yellow oil. After dissolving the residue in pentane (300 mL), the solution was washed with brine (3 × 200 mL). The combined brine washes were back-extracted with pentane (200 mL) and the combined pentane phases were dried over Na_2SO_4 and concentrated to a yellow oil. This residue was purified by flash chromatography (hexane/EtOAc 100:0 to 80:20) to yield the title compound as a colourless liquid (19 g, 97%). Alternatively, the crude product can be purified by distillation under high vacuum, collecting the fraction distilling between 72-75 °C at 6×10^{-2} mbar; in this case, the title compound was isolated as a colourless liquid in a deminished yield (10.3 g, 53 %). $[\alpha]_D^{20}$ = –5.9 (c = 1.36, $CHCl_3$). ^{1}H NMR

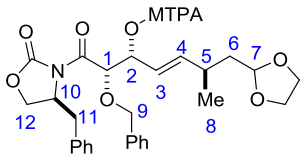
(400 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.8 Hz, 1H), 4.89 (dd, *J* = 5.4, 4.6 Hz, 1H), 3.99–3.92 (m, 2H), 3.86–3.80 (m, 2H), 2.52–2.37 (m, 2H), 1.79–1.60 (m, 3H), 1.58–1.48 (m, 2H), 0.96 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 103.6, 64.9, 64.8, 41.7, 40.7, 30.0, 29.1, 19.9 ppm. IR (film): $\tilde{\nu}$ = 2955, 2880, 2722, 1722, 1411, 1137, 1034, 948 cm^{-1}. MS (EI) *m/z* (%): 113 (3), 73 (100), 55 (6), 45 (20). HRMS (ESIpos) *m/z* calcd for $C_9H_{16}O_3Na$: 195.0992, found: 195.0993. The analytical and spectroscopic data are in agreement with those reported in the literature.[500]

(*R*,*E*)-5-(1,3-dioxolan-2-yl)-4-methylpent-2-enal (253). Diethyl allyl phosphate (12.7 mL, 71.3 mmol) was added to a solution of aldehyde **258** (10.2 g, 59.4 mmol) in THF (48 mL). $Pd(OAc)_2$ (530 mg, 2.36 mmol) and $NaHCO_3$ (6.00 g, 71.4 mmol) were introduced and the orange heterogeneous mixture was placed in a pre-heated oil bath at 86 °C. The mixture was stirred at reflux temperature under a stream of argon for 60 h, causing a gradual color change to pale green/brown. The mixture was allowed to cool and partitioned between *t*-butyl methyl ether (200 mL) and deionized water (100 mL). The aq. phase was separated and extracted *t*-butyl methyl ether (2 × 100 mL). The combined organic phases were washed with sat. NH_4Cl (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated. The resulting orange oil was first purified by flash chromatography (hexane/*t*-butyl methyl ether 50:50) giving the product as a colourless liquid contaminated with the corresponding allyl enol ether. This material was further purified by Kugelrohr distillation, collecting the fraction that distilled between 80–90 °C at 2 × 10^{-2} mbar, to give the title compound as a pale-yellow pungent oil (5.87 g, 58%). $[\alpha]_D^{20}$ = –59.5 (c = 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 15.6, 7.6 Hz, 1H), 6.10 (ddd, *J* = 15.7, 7.8, 1.2 Hz, 1H), 4.87 (t, *J* = 4.8 Hz, 1H), 4.02–3.89 (m, 2H), 3.88–3.80 (m, 2H), 2.81–2.65 (m, 1H), 1.89–1.67 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.4, 163.2, 131.3, 102.9, 65.1, 65.0, 39.9, 33.2, 19.8 ppm. IR (film): $\tilde{\nu}$ = 2965, 2882, 1688, 1410, 1130, 1029, 977 cm^{-1}. MS (EI) *m/z* (%): 113 (3), 73 (100), 55 (3), 45 (15). HRMS (ESIpos) *m/z* calcd for $C_9H_{14}O_3Na$: 193.0835, found: 193.0837.

Aldol 358. Et_3N (5.4 mL, 39 mmol) was added to a solution of (*S*)-4-benzyl-3-(2-(benzyloxy)acetyl)oxazolidin-2-one (**259**) (9.68 g, 29.8 mmol) in CH_2Cl_2 (100 mL). The mixture was cooled to –78 °C before a solution of *n*-Bu_2BOTf (1 M solution in CH_2Cl_2, 30 mL, 30 mmol) was added at such a rate as to keep the internal temperature below –65 °C. The mixture was allowed to reach 0 °C over 1.25 h. At this point the mixture was re-cooled to –78 °C before a solution of enal **253** (4.22 g, 24.8 mmol) in CH_2Cl_2 (5 mL) was added at such a rate as to keep the internal temperature below –65 °C. The mixture was stirred at –78 °C for 20 min and allowed to reach 0 °C over 1.5 h. The reaction was quenched with methanol (140 mL) followed by pH 7 buffer (80 mL). Aq. hydrogen peroxide (35%, 40 mL) was added cautiously ensuring that the temperature remained below 10 °C. The mixture was

stirred for an additional h at 0 °C and the aq. phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with sat. $Na_2S_2O_3$ (200 mL, CAUTION: EXOTHERM!) and brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 40:60) to give the *syn*-aldol adduct **342** as a colourless syrup (9.84 g, 80%, dr = 12:1). $[\alpha]_D^{20}$ = +17.9 (c = 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 8H), 7.22–7.17 (m, 2H), 5.71 (ddd, *J* = 15.6, 7.4, 1.1 Hz, 1H), 5.56 (ddd, *J* = 15.5, 6.3, 1.0 Hz, 1H), 5.24 (d, *J* = 4.2 Hz, 1H), 4.84 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.66 – 4.57 (m, 2H), 4.37 (d, *J* = 5.4 Hz, 1H), 4.24–4.13 (m, 2H), 4.00–3.87 (m, 2H), 3.84–3.75 (m, 2H), 3.20 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.66 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.59 (s, 1H), 2.48–2.36 (m, 1H), 1.67 (ddd, *J* = 13.8, 7.8, 4.4 Hz, 1H), 1.58 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 170.6, 153.4, 139.1, 137.1, 135.2, 129.5, 129.1, 128.7, 128.6, 128.4, 127.6, 126.6, 103.3, 80.2, 73.7, 73.5, 66.9, 64.8, 64.8, 55.7, 40.7, 37.9, 32.7, 20.7 ppm. IR (film): $\tilde{\nu}$ = 3467, 2957, 1776, 1707, 1389, 1210, 1110, 1028, 974 cm^{-1}. MS (EI) *m/z* (%): 1013.4 (30), 518.2 (100), 327.1 (2). HRMS (ESIpos) *m/z* calcd for $C_{28}H_{33}NO_7Na$: 518.2149, found: 518.2154.

Mosher Ester Analysis of Alcohol 358. Et_3N (14 µL, 0.1 mmol) and DMAP (0.8 mg, 0.01 mmol) were



added to a solution of alcohol **358** (17 mg, 0.034 mmol) in CH_2Cl_2 (2 mL) followed by (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (7.6 µL, 0.04 mmol). The mixture was stirred at ambient temperature for 2 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 70:30) to give the corresponding (*S*)-Mosher ester (*S*)-**MTPA-358** (19.1 mg, 79%) as a pale yellow oil. $[\alpha]_D^{20}$ = +6.7 (c = 1.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.53 (m, 2H), 7.41–7.25 (m, 11H), 7.19–7.13 (m, 2H), 5.87 (dd, *J* = 15.5, 7.8 Hz, 1H), 5.81 (dd, *J* = 8.2, 5.6 Hz, 1H), 5.61 (ddd, *J* = 15.5, 8.2, 1.0 Hz, 1H), 5.45 (d, *J* = 5.6 Hz, 1H), 4.76 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.50 (d, *J* = 1.6 Hz, 2H), 4.49–4.39 (m, 1H), 4.23–4.08 (m, 2H), 3.93–3.86 (m, 2H), 3.79–3.70 (m, 2H), 3.53 (d, *J* = 1.2 Hz, 3H), 3.13 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.54 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.49–2.34 (m, 1H), 1.66–1.54 (m, 2H), 0.99(d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2957, 2878, 1779, 1749, 1709, 1454, 1390, 1246, 1169, 1109, 1019, 979, 699 cm^{-1}. MS (EI) *m/z* (%): 1445.5 (25), 734.3 (100), 478.2 (3), 375.6 (5). HRMS (ESIpos) *m/z* calcd for $C_{38}H_{40}NO_9F_3Na$: 734.2547, found: 734.2548.

The corresponding Mosher ester (*R*)-**MTPA-358** (17.6 mg, 76%) was prepared analogously: $[\alpha]_D^{20}$ = +46.1 (c = 1.73, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.51 (m, 2H), 7.39– 7.27 (m, 11H), 7.21–7.14 (m, 2H), 5.82 (ddd, *J* = 7.6, 4.7, 0.8 Hz, 1H), 5.72 (ddd, *J* = 15.6, 7.8, 0.9 Hz, 1H), 5.55–5.47 (m, 1H), 5.44 (d, *J* = 4.7 Hz, 1H), 4.76–4.63 (m, 2H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.53–4.46 (m, 1H), 4.24 (dd, *J* = 9.0, 7.7 Hz, 1H), 4.15 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.95–3.80 (m, 2H), 3.77–3.66 (m, 2H), 3.60 (d, *J*

= 1.2 Hz, 3H), 3.18 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.65 (dd, *J* = 13.5, 9.7 Hz, 1H), 2.44–2.28 (m, 1H), 1.68–1.46 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2957, 2878, 1779, 1749, 1709, 1454, 1390, 1246, 1169, 1109, 1019, 979, 699 cm^{-1}. MS (EI) *m/z* (%): 1445.5 (25), 734.3 (100), 478.2 (3), 375.6 (5). HRMS (ESIpos) *m/z* calcd for $C_{38}H_{40}NO_9F_3Na$: 734.2547, found: 734.2549.

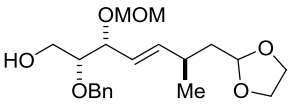
Both products were analyzed according to Hoye and co-workers:[497]

Table S-8. Mosher ester analysis for the assignment of the C(2) stereocenter; arbitrary numbering as shown in the insert.

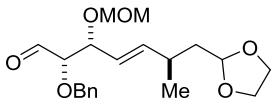
Assignment	358 [ppm]	(*S*)-MTPA-358 [ppm]	(*R*)-MTPA-358 [ppm]	Δ (δ (S–R)) [ppm]
1	5.24	5.45	5.44	+0.01
2	4.37	5.81	5.82	–0.01
3	5.56	5.61	5.51	+0.10
4	5.71	5.87	5.72	+0.15
5	2.41	2.42	2.36	+0.06
6	1.63	1.60	1.55	+0.05
7	4.84	4.76	4.68	+0.08
8	1.02	0.99	0.95	+0.04
9a	4.71	4.50	4.67	–0.12
9b	4.60	4.50	4.57	–0.07
10	4.63	4.45	4.49	–0.04
11a	3.20	3.13	3.18	–0.05
11b	2.66	2.54	2.65	–0.11
12a	4.18	4.16	4.24	–0.08
12b	4.18	4.12	4.15	–0.03

MOM-Ether 260. Tetrabutylammonium iodide (73 mg, 0.20 mmol) was added to a solution of alcohol **358** (9.78 g, 19.7 mmol) in CH_2Cl_2 (60 mL), whereupon the solution turned yellow. The solution was cooled to 0 °C before Hünig's base (24 mL, 0.14 mol) was added dropwise, causing the yellow colour to disappear. MOMCl (6.0 mL, 79 mmol) was added dropwise with vigorous stirring at such as rate as to keep the internal temperature ≤ +10 °C. Once the addition was complete, the mixture was allowed to reach ambient temperature and stirring was continued for 12 h. The reaction was quenched with sat. NH_4Cl (100 mL) and the phases were separated. The aq. phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 50:50) to give the title compound as a colourless syrup (10.7 g, quant.). $[\alpha]_D^{20}$ = –18.5 (c = 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.41–7.37 (m, 2H), 7.36–7.27 (m, 6H), 7.21–7.17 (m, 2H), 5.69 (dd, *J* = 15.5, 7.8 Hz, 1H), 5.51 (ddd, *J* = 15.6, 7.9, 1.0 Hz, 1H), 5.33 (d, *J* = 4.7 Hz, 1H), 4.82 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.66–4.53 (m, 4H), 4.41 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.20–4.12 (m, 2H), 3.96–3.88 (m,

2H), 3.82–3.75 (m, 2H), 3.29 (s, 3H), 3.21 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.69 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.48–2.36 (m, 1H), 1.70–1.54 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 170.2, 153.3, 141.8, 137.6, 135.3, 129.6, 129.1, 128.5, 128.5, 128.1, 127.6, 123.9, 103.4, 94.0, 79.8, 77.2, 73.7, 66.8, 64.9, 64.8, 55.8, 55.6, 40.8, 37.8, 32.9, 20.8 ppm. IR (film): $\tilde{\nu}$ = 2954, 1779, 1709, 1389, 1210, 1105, 1032, 978 cm^{-1}. MS (EI) *m/z* (%): 1101.5 (30), 562.2 (100), 478.2 (8). HRMS (ESIpos) *m/z* calcd for $C_{30}H_{37}NO_8Na$: 562.2411, found: 562.2416.

(2*R*,3*R*,6*R*,*E*)-2-(Benzyloxy)-7-(1,3-dioxolan-2-yl)-3-(methoxymethoxy)-6-methylhept-4-en-1-ol (S18). 

Water (395 µL, 21.9 mmol) was added to a solution of oxazolidinone **260** (10.7 g, 19.8 mmol) in Et_2O (400 mL). The reaction was cooled to 0 °C before a solution of lithium borohydride (4 M in THF, 5.45 mL, 21.8 mmol) was added cautiously, causing evolution of hydrogen gas. After the addition was complete stirring was continued at 0 °C for 50 min. The reaction was quenched with NaOH (1 M, 10 mL), the mixture was diluted with *t*-butyl methyl ether (100 mL) and stirred until clean phase separation was reached. The aq. phase was extracted with *t*-butyl methyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (*t*-butyl methyl ether) to give the title compound as a colourless syrup (6.42 g, 88%). $[\alpha]_D^{20}$ = –67.5 (c = 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 67.5, 11.9 Hz, 5H), 5.68 (ddd, *J* = 15.6, 7.7, 0.8 Hz, 1H), 5.41 (ddd, *J* = 15.6, 8.0, 1.1 Hz, 1H), 4.83 (dd, *J* = 5.6, 4.6 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.20 (ddd, *J* = 8.1, 5.6, 0.9 Hz, 1H), 3.99–3.90 (m, 2H), 3.87–3.77 (m, 2H), 3.72 (ddd, *J* = 10.9, 7.1, 3.9 Hz, 1H), 3.64–3.51 (m, 2H), 3.37 (s, 3H), 2.54–2.37 (m, 1H), 2.26–2.12 (m, 1H), 1.80–1.56 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.2, 138.5, 128.6, 128.1, 127.9, 124.6, 103.5, 93.9, 81.4, 77.6, 73.5, 64.8 (2C), 62.1, 55.7, 40.8, 33.0, 20.9 ppm. IR (film): $\tilde{\nu}$ = 3489, 2955, 2885, 1454, 1406, 1098, 1028, 977 cm^{-1}. MS (EI) *m/z* (%): 755.4 (45), 389.2 (100), 305.2 (6). HRMS (ESIpos) *m/z* calcd for $C_{20}H_{30}O_6Na$: 389.1935, found: 389.1933.

(2*S*,3*R*,6*R*,*E*)-2-(Benzyloxy)-7-(1,3-dioxolan-2-yl)-3-(methoxymethoxy)-6-methylhept-4-enal (261). 

Sulfur trioxide pyridine complex (5.6 g, 35 mmol) was suspended in CH_2Cl_2 (100 mL) and the resulting mixture was cooled to –30 °C. After adding DMSO (11.2 mL, 158 mmol), a solution of alcohol **S18** (6.42 g, 17.5 mmol) and Hünig's base (12.2 mL, 70.0 mmol) in CH_2Cl_2 (50 mL) was added at –30 °C. The mixture was allowed to reach 0 °C over 2 h and the reaction was quenched with sat. NH_4Cl (50 mL). The aq. phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The resulting yellow oil was purified by flash chromatography (*t*-butyl methyl ether) to give the title compound as a colourless syrup (6.29 g, 98%, dr = 13:1). $[\alpha]_D^{20}$ = –145.0 (c = 1.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (d, *J* = 1.6 Hz, 1H),

7.40–7.29 (m, 5H), 5.72 (ddd, *J* = 15.6, 7.6, 0.6 Hz, 1H), 5.54 (ddd, *J* = 15.6, 8.2, 1.0 Hz, 1H), 4.90–4.77 (m, 2H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.44 (dd, *J* = 8.2, 3.6 Hz, 1H), 4.03–3.93 (m, 2H), 3.88–3.78 (m, 3H), 3.29 (s, 3H), 2.53–2.41 (m, 1H), 1.76–1.60 (m, 2H), 1.04 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 202.9, 142.1, 136.9, 128.5, 128.3, 128.2, 123.4, 103.3, 93.3, 85.4, 76.3, 73.5, 64.7, 64.6, 55.7, 40.5, 32.9, 20.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2887, 1733, 1149, 1096, 1027, 978 cm^{-1}. MS (EI) *m/z* (%): 751.4 (40), 419.2 (3), 387.2 (100). HRMS (ESIpos) *m/z* calcd for $C_{20}H_{28}O_6Na$: 387.1778, found: 387.1779.

(4*S*,5*R*,6*R*,9*R*,*E*)-5-(Benzyloxy)-10-(1,3-dioxolan-2-yl)-6-(methoxymethoxy)-9-methyldeca-1,7-dien-4-ol (262). Magnesium bromide diethyl etherate (8.90 g, 34.5 mmol) was added to a solution of the aldehyde **261** (6.29 g, 17.3 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The suspension became instantly yellow and was stirred at 0 °C for 1 h. Allyl trimethylsilane (5.5 mL, 35 mmol) was added in one portion and stirring continued at ambient temperature for 16 h before the reaction was quenched with sat. NH_4Cl (50 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to a yellow oil, which was purified by flash chromatography (*t*-butyl methyl ether) to give the title compound as a pale yellow syrup (6.47 g, 92%, dr = 14:1). $[\alpha]_D^{20}$ = –65.9 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.37–7.27 (m, 5H), 5.85–5.68 (m, 2H), 5.42 (ddd, *J* = 15.6, 8.1, 1.1 Hz, 1H), 5.09–5.06 (m, 1H), 5.06–5.01 (m, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 4.83 (dd, *J* = 5.6, 4.6 Hz, 1H), 4.72 (d, *J* = 6.6 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.30 (ddd, *J* = 8.1, 6.3, 0.8 Hz, 1H), 3.99–3.90 (m, 2H), 3.84–3.78 (m, 2H), 3.78–3.72 (m, 1H), 3.38–3.32 (m, 4H), 2.50–2.39 (m, 1H), 2.35 (dd, *J* = 7.0, 0.7 Hz, 1H), 2.33–2.27 (m, 2H), 1.75–1.60 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 141.3, 138.4, 135.0, 128.6, 128.3, 128.0, 125.2, 117.5, 103.5, 93.9, 82.7, 78.0, 77.4, 75.1, 70.6, 64.9 (2C), 55.8, 40.8, 39.0, 33.1, 20.9 ppm. IR (film): $\tilde{\nu}$ = 3477, 2929, 2886, 1454, 1401, 1212, 1097, 1028, 917 cm^{-1}. MS (EI) *m/z* (%): 835.5 (30), 629.3 (3), 429.2 (100), 345.2 (5). HRMS (ESIpos) *m/z* calcd for $C_{23}H_{34}O_6Na$: 429.2248, found: 429.2247.

Mosher Ester Analysis of Alcohol 262. Et_3N (21 µL, 0.15 mmol) and DMAP (1 mg, 0.01 mmol) were added to a solution of alcohol **261** (21 mg, 0.051 mmol) in CH_2Cl_2 (2 mL), followed by (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (14.2 µL, 0.08 mmol). The mixture was stirred at ambient temperature for 2 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 70:30) to give the corresponding (*S*)-Mosher ester (*S*)-**MTPA-262** (24.5 mg, 78%). $[\alpha]_D^{20}$ = –64.2 (c = 2.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.54 (d, *J* = 7.4 Hz, 2H),

7.39–7.24 (m, 8H), 5.68 (dddd, *J* = 16.8, 10.6, 7.8, 6.4 Hz, 1H), 5.56 (dd, *J* = 15.5, 7.8 Hz, 1H), 5.48–5.32 (m, 2H), 5.06 (d, *J* = 1.2 Hz, 1H), 5.02 (dd, *J* = 8.9, 1.8 Hz, 1H), 4.80 (dd, *J* = 5.6, 4.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 6.7 Hz, 1H), 4.19 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.99–3.89 (m, 2H), 3.86–3.75 (m, 2H), 3.57 (t, *J* = 5.4 Hz, 1H), 3.51 (s, 3H), 3.34 (s, 3H), 2.62 (dddd, *J* = 13.3, 6.7, 3.4, 1.5 Hz, 1H), 2.53–2.33 (m, 2H), 1.74–1.55 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2953, 2888, 1746, 1453, 1250, 1169, 1122, 1026, 698 cm^{-1}. MS (EI) *m/z* (%): 1267.5 (20), 645.3 (100), 501.3 (2). HRMS (ESIpos) *m/z* calcd for $C_{33}H_{41}O_8F_3Na$: 645.2646, found: 645.2645.

The corresponding ester (*R*)-**MTPA-262** (11.7 mg, 46%) was prepared analogously: $[\alpha]_D^{20}$ = –34.4 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.55 (m, 2H), 7.40–7.23 (m, 8H), 5.73 (dddd, *J* = 16.9, 10.5, 7.5, 6.4 Hz, 1H), 5.50 (ddd, *J* = 15.5, 8.0, 0.7 Hz, 1H), 5.35–5.28 (m, 1H), 5.22 (ddd, *J* = 15.6, 8.3, 1.0 Hz, 1H), 5.12–5.10 (m, 1H), 5.07 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.79 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 4.07 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.97–3.90 (m, 2H), 3.83–3.77 (m, 2H), 3.56–3.48 (m, 4H), 3.29 (s, 3H), 2.65 (dddd, *J* = 12.0, 6.6, 3.5, 1.5 Hz, 1H), 2.57–2.45 (m, 1H), 2.41–2.30 (m, 1H), 1.72–1.54 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2954, 2886, 1746, 1453, 1254, 1168, 1124, 1026, 920, 721, 698 cm^{-1}. MS (EI) *m/z* (%): 1267.5 (15), 1123.5 (3), 645.3 (100), 501.3 (4). HRMS (ESIpos) *m/z* calcd for $C_{33}H_{41}O_8F_3Na$: 645.2646, found: 645.2647.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-9. Mosher ester analysis for the assignment of the C(4) stereocenter; arbitrary numbering as shown in the insert.

Assignment	262 [ppm]	(*S*)-MTPA-262 [ppm]	(*R*)-MTPA-262 [ppm]	Δ (δ (S–R)) [ppm]
1a	5.07	5.06	5.11	–0.05
1b	5.04	5.02	5.07	–0.05
2	5.79	5.68	5.73	–0.05
3a	2.36	2.62	2.65	–0.03
3b	2.30	2.42	2.50	–0.08
4	3.75	5.37	5.30	+0.07
5	3.35	3.57	3.53	+0.04
6	4.30	4.19	4.07	+0.12
7	5.43	5.37	5.22	+0.15
8	5.70	5.56	5.50	+0.06
9	2.44	2.42	2.35	+0.07
10	1.05	0.99	0.98	+0.01
11ab	1.66	1.63	1.61	+0.02
12	4.83	4.80	4.79	+0.01
13a	4.90	4.74	4.69	+0.05
13b	4.63	4.62	4.53	+0.09
14a	4.72	4.68	4.62	+0.06
14b	4.56	4.52	4.48	+0.04
15	3.33	3.34	3.29	+0.05

Compound S19. 2,6-Lutidine (3.7 mL, 32 mmol) and *t*-butyl dimethylsilyltriflate (5.44 mL, 23.7 mmol) were added to a solution of alcohol **261** (6.42 g, 15.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h before the reaction was quenched with sat. NH_4Cl (50 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 80:20) to give the title compound as a colourless syrup (7.21 g, 88%). $[\alpha]_D^{20}$ = –68.4 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.22 (m, 5H), 5.89–5.73 (m, 1H), 5.56 (dd, *J* = 15.6, 7.7 Hz, 1H), 5.43 (ddd, *J* = 15.6, 8.3, 0.9 Hz, 1H), 5.08–5.04 (m, 1H), 5.02 (d, *J* = 1.3 Hz, 1H), 4.81 (dd, *J* = 5.8, 4.5 Hz, 1H), 4.72–4.67 (m, 3H), 4.53 (d, *J* = 6.7 Hz, 1H), 4.24 (dd, *J* = 8.2, 4.3 Hz, 1H), 3.97–3.91 (m, 2H), 3.92–3.87 (m, 1H), 3.82–3.76 (m, 2H), 3.35 (s, 3H), 3.34–3.30 (m, 1H), 2.60–2.45 (m, 1H), 2.45–2.27 (m, 2H), 1.80–1.58 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.2, 138.9, 135.8, 128.4, 128.2, 127.6, 126.1, 117.0, 103.6, 93.6, 83.5, 76.4, 74.6, 72.6, 64.9, 64.8, 56.0, 40.8, 37.8, 33.1, 26.1, 20.8, 18.3, –4.2, –4.2 ppm. IR (film): $\tilde{\nu}$ = 2954, 2884, 1472,1255, 1147, 1098, 1028, 916, 835 cm^{-1}. MS (EI) *m/z* (%):

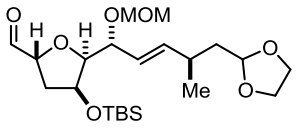
1063.6 (30), 543.3 (100), 459.3 (13), 351.2 (3). HRMS (ESIpos) *m/z* calcd for $C_{29}H_{48}O_6SiNa$: 543.3112, found: 543.3111.

Alcohol 254. DDQ (233 mg, 1.00 mmol) was added in a single portion to a pre-heated solution of the benzyl ether **S19** (134 mg, 0.257 mmol) in a mixture of 1,2-dichloroethane (1.5 mL) and pH 7.4 buffer solution (1.5 mL) at 50 °C. The mixture was stirred at this temperature for 50 min before allowing the reaction to reach ambient temperature. The mixture was diluted with *t*-butyl methyl ether (20 mL) and the separated organic phase was washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (hexane/EtOAc 70:30) to give the title compound as a colourless syrup (77.1 mg, 70%). $[\alpha]_D^{20}$ = –72.4 (c = 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.64 (ddd, *J* = 15.6, 8.0, 0.7 Hz, 1H), 5.34 (ddd, *J* = 15.6, 8.5, 1.1 Hz, 1H), 5.13–5.04 (m, 2H), 4.83 (dd, *J* = 5.6, 4.7 Hz, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.04 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.97–3.92 (m, 2H), 3.85–3.79 (m, 3H), 3.47 (td, *J* = 6.4, 3.5 Hz, 1H), 3.38 (s, 3H), 2.57 (d, *J* = 6.4 Hz, 1H), 2.52–2.41 (m, 2H), 2.30–2.21 (m, 1H), 1.75–1.60 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.8, 134.2, 125.1, 117.7, 103.4, 93.4, 77.2, 77.0, 74.5, 71.6, 64.7 (2 x), 55.5, 40.7, 38.5, 33.2, 25.9, 20.9, 18.1, –3.8, –4.4 ppm. IR (film): $\tilde{\nu}$ = 3494, 2954, 2929, 2885, 2857, 1472, 1408, 1361, 1253, 1147, 1094, 1030, 917, 836, 776 cm^{-1}. MS (EI) *m/z* (%): 883.5 (40), 453.3 (100), 369.2 (22), 237.1 (3). HRMS (ESIpos) *m/z* calcd for $C_{22}H_{42}O_6SiNa$: 453.2643, found: 453.2645.

Alcohol 255. $Co(nmp)_2$ (355 mg, 0.628 mmol) was added to a solution of alcohol **254** (2.63 g, 6.12 mmol) in *i*-PrOH (61 mL). The solution was degassed by 3 freeze-pump-thaw cycles and back-filled with oxygen. After adding *t*-BuOOH (5 M in decane, 122 µL, 0.612 mmol), a balloon of oxygen was fitted to the flask which was placed in a pre-heated oil bath at 55 °C. The mixture turned green within 5 min of heating and stirring was continued for 16 h. After reaching ambient temperature, the mixture was concentrated to a green oil, which was purified by flash chromatography (hexane/EtOAc 20:80) to give the title product as a colourless syrup (1.89 g, 69%). $[\alpha]_D^{20}$ = –19.7 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (ddd, *J* = 15.7, 7.6, 1.1 Hz, 1H), 5.44 (ddd, *J* = 15.7, 6.7, 1.1 Hz, 1H), 4.84 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.43–4.34 (m, 1H), 4.31 (q, *J* = 3.2 Hz, 1H), 4.27 (ddd, *J* = 7.7, 6.6, 0.9 Hz, 1H), 4.00–3.90 (m, 2H), 3.87–3.74 (m, 4H), 3.49 (dd, *J* = 11.6, 5.7 Hz, 1H), 3.39 (s, 3H), 2.43 (dddd, *J* = 14.4, 7.7, 6.7, 1.1 Hz, 1H), 2.07–1.97 (m, 1H), 1.94–1.88 (m, 2H), 1.71 (ddd, *J* = 13.7, 7.7, 4.6 Hz, 1H), 1.66–1.56 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.0, 125.2, 103.5, 94.3, 86.5, 78.6, 75.4, 73.4, 64.9, 64.8, 64.7, 55.5, 40.8, 37.1, 33.1, 26.0, 20.9, 18.1, –3.9, –4.6 ppm. IR (film): $\tilde{\nu}$ = 3467,

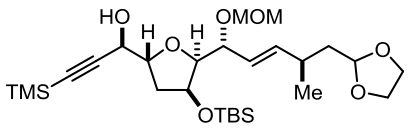
2954, 2927, 2885, 2856, 1472, 1361, 1255, 1131, 1035, 942, 836, 775 cm^{-1}. MS (EI) *m/z* (%): 915.5 (30), 469.3 (100), 385.2 (10). HRMS (ESIpos) *m/z* calcd for $C_{22}H_{42}O_7SiNa$: 469.2592, found: 469.2597.

Aldehyde S20. Hünig's base (2.8 mL, 16 mmol) was added at –30 °C to a solution of alcohol **262**



(1.13 g, 2.53 mmol) in CH_2Cl_2 (16 mL) and the resulting mixture was stirred for 5 min at this temperature. In a second flask a suspension of sulfur trioxide pyridine complex (1.26 g, 7.92 mmol) in CH_2Cl_2 (2.0 mL) was treated with DMSO (2.3 mL, 27 mmol) and the resulting mixture was stirred for 15 min at ambient temperature. This suspension was added to the alcohol solution at –30 °C, rinsing the flask with CH_2Cl_2 (5.0 mL). The mixture was allowed to slowly reach –20 °C over 1 h and stirring was continued for another 0.5 h at this temperature. The mixture was diluted with *t*-butyl methyl ether (20 mL) and the reaction was quenched with pH 7 phosphate buffer (50 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 50 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude aldehyde **S20** as a yellow oil which was used in the next step without further purification. An aliquot was purified for analytical purposes by flash chromatography (EtOAc/hexane 1:1). $[\alpha]_D^{20}$ = –0.4 (c = 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (d, *J* = 2.5 Hz, 1H), 5.77 (ddd, *J* = 15.6, 7.6, 1.0 Hz, 1H), 5.44 (ddd, *J* = 15.7, 6.9, 1.1 Hz, 1H), 4.84 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.54 (ddd, *J* = 9.6, 7.2, 2.5 Hz, 1H), 4.35–4.25 (m, 2H), 3.98–3.92 (m, 2H), 3.86 (dd, *J* = 7.6, 3.3 Hz, 1H), 3.83–3.78 (m, 2H), 3.39 (s, 3H), 2.50–2.37 (m, 1H), 2.18 (ddd, *J* = 13.0, 7.2, 2.3 Hz, 1H), 2.00 (ddd, *J* = 13.3, 9.4, 4.5 Hz, 1H), 1.71 (ddd, *J* = 13.9, 7.7, 4.6 Hz, 1H), 1.65–1.58 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.1, 140.6, 124.8, 103.5, 94.2, 87.5, 82.1, 74.9, 72.3, 64.9, 64.8, 55.6, 40.8, 37.2, 33.1, 25.9, 20.9, 18.1, −3.9, –4.6 ppm. IR (film) $\tilde{\nu}$ = 2956, 2928, 2884, 2858, 1733, 1472, 1258, 1128, 1097, 1028, 976, 939, 924, 833, 802, 775, 755, 733 cm^{-1}. MS (ESIpos) *m/z* (%): 467.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{40}O_7SiNa$: 467.2436, found: 467.2439.

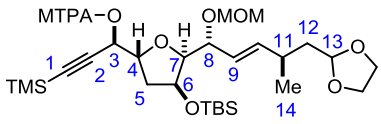
Propargyl Alcohol 263. A Schlenk tube was charged with $Zn(OTf)_2$ (dried at 120 °C under high vacuum



for 24 h, 2.25 mg, 6.18 mmol) and (–)-*N*-methylephedrine (dried aceotriopically by distilling toluene off the compound (3x), 1.18 g, 6.60 mmol). After the addition of toluene (6.0 mL), Hünig's base (1.2 mL, 6.9 mmol) was added and the resulting suspension was stirred for 2 h at ambient temperature before ethynyltrimethylsilane (0.91 mL, 6.3 mmol) was introduced. After stirring for another 1.5 h at ambient temperature, a solution of aldehyde **S20** (1.09 g, 2.45 mmol) in toluene (15.0 mL with rinses) was added in one portion to the milky suspension. After stirring for 18 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (50 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 50 mL). The combined organic phases were

dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/ EtOAc 7:3) to provide the title compound as a yellow oil (0.96 g, 65% over 2 steps, dr = 10.7:1). $[\alpha]_D^{20}$ = –163 (c = 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (ddd, *J* = 15.7, 7.6, 1.0 Hz, 1H), 5.43 (ddd, *J* = 15.7, 6.6, 1.2 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.36–4.22 (m, 4H), 3.983.91 (m, 2H), 3.85–3.79 (m, 2H), 3.76 (dd, *J* = 7.8, 3.3 Hz, 1H), 3.39 (s, 3H), 2.65 (br s, 1H), 2.42 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1H), 2.05 (ddd, *J* = 13.1, 6.1, 2.0 Hz, 1H), 1.91 (ddd, *J* = 13.2, 9.1, 4.5 Hz, 1H), 1.70 (ddd, *J* = 13.7, 7.7, 4.6 Hz, 1H), 1.60 (ddd, *J* = 13.1, 6.1, 6.1 Hz 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.9, 124.0, 102.7, 102.5, 93.2, 89.6, 85.7, 80.1, 74.1, 72.1, 65.0, 63.9, 63.8, 54.6, 39.8, 37.1, 32.1, 25.0, 19.9, 17.2, -1.1, -4.9, -5.6 ppm. IR (film) $\tilde{\nu}$ = 3432, 2956, 2929, 2886, 2858, 1472, 1408, 1361, 1251, 1129, 1099, 1036, 949, 841, 775 cm^{-1}. MS (ESIpos) *m/z* (%): 565.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{27}H_{50}O_7Si_2Na$: 565.2987, found: 565.2987.

Mosher Ester Analysis of Propargyl Alcohol 263. Hünig's base (9.0 µL, 52 µmol) was added to a solution of alcohol **263** (10.9 mg, 17 µmol) in CH_2Cl_2 (0.35 mL) followed by (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (6.0 µL, 32 µmol). After stirring for 17 h at ambient temperature, the mixture was diluted with CH_2Cl_2 (3 mL) and the reaction was quenched with sat. $NaHCO_3$ (3 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 4:1) to give the corresponding (*S*)-Mosher ester (*S*)-**MTPA-263** (10 mg, 76%). $[\alpha]_D^{20}$ = –38.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2H), 7.39 (tdd, *J* = 3.5, 2.3, 1.1 Hz, 3H), 5.72 (ddd, *J* = 15.8, 7.6, 1.1 Hz, 1H), 5.62 (d, *J* = 6.2 Hz, 1H), 5.43 (ddd, *J* = 15.6, 6.7, 1.1 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.64–4.59 (m, 2H), 4.41 (dt, *J* = 8.4, 6.5 Hz, 1H), 4.29 (ddd, *J* = 3.9, 3.3, 2.8 Hz, 1H), 4.21 (dd, *J* = 7.7, 6.6 Hz, 1H), 3.98–3.91 (m, 2H), 3.83–3.79 (m, 2H), 3.78 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.57 (d, *J* = 1.1 Hz, 3H), 3.32 (s, 3H), 2.47–2.35 (m, 1H), 2.05–1.96 (m, 2H), 1.70 (ddd, *J* = 13.8, 7.7, 4.6 Hz, 1H), 1.60 (dt, *J* = 13.5, 5.9 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. IR (film) $\tilde{\nu}$ = 2956, 2930, 2886, 2858, 1757, 1251, 1185, 1170, 1124, 1035, 844, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 781.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{57}O_9Si_2F_3Na$: 781.3385, found: 781.3392.



The corresponding Mosher ester (*R*)-**MTPA-263** (13.7 mg, 92%) was prepared analogously using (*S*)-(−)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride. $[\alpha]_D^{20}$ = –26.0 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2H), 7.42–7.35 (m, 3H), 5.73 (ddd, *J* = 15.7, 7.5, 1.0 Hz, 1H), 5.51–5.40 (m, 2H), 4.83 (dd, *J* = 5.8, 4.5 Hz, 1H), 4.63 (s, 2H), 4.47 (ddd, *J* = 8.8, 7.4, 6.4 Hz, 1H), 4.32 (dq, *J* = 4.6, 2.5 Hz, 1H), 4.26–4.19 (m, 1H), 4.00–3.90 (m, 2H), 3.86–3.77 (m, 3H), 3.65–3.57 (m, 3H), 3.31 (s, 3H), 2.48–2.36 (m, 1H), 2.11 (ddd, *J* = 13.1, 6.5, 2.4 Hz, 1H), 1.98 (ddd, *J* = 13.3, 8.9, 4.7 Hz, 1H), 1.70

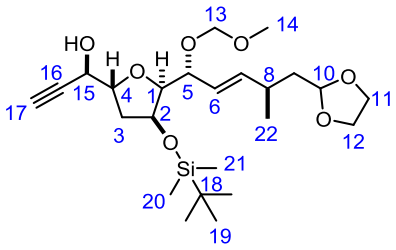
(ddd, *J* = 13.8, 7.7, 4.6 Hz, 1H), 1.62 (dt, *J* = 13.6, 6.3, 5.8 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. IR (film) $\tilde{\nu}$ = 2956, 2930, 2886, 2858, 1757, 1251, 1185, 1170, 1124, 1035, 844, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 781.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{57}O_9Si_2F_3Na$: 781.3385, found: 781.3396.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-10. Mosher ester analysis for the assignment of the C(3) stereocenter; arbitrary numbering as shown in the insert.

Assignment	263 [ppm]	(*S*)-MTPA-263 [ppm]	(*R*)-MTPA-263 [ppm]	Δ (δ (S–R)) [ppm]
3	4.23	5.62	5.48	+0.19
4	4.31	4.41	4.47	–0.06
5a	2.04	2.02	2.11	–0.09
5b	1.92	1.99	1.98	+0.01
6	4.31	4.29	4.32	–0.03
7	3.76	3.78	3.81	–0.03
8	4.27	4.21	4.22	–0.01
9	5.43	5.43	5.44	–0.01
10	5.73	5.72	5.73	–0.02
11	2.42	2.41	2.42	+0.01
12a	1.70	1.70	1.70	0
12b	1.61	1.60	1.62	–0.02
13	4.83	4.83	4.83	0
14	1.05	1.05	1.05	0
TMS-Me	0.15	0.17	0.12	+0.05

Terminal Alkyne S21. K_2CO_3 (350 mg, 2.53 mmol) was added to a solution of TMS-alkyne **263**

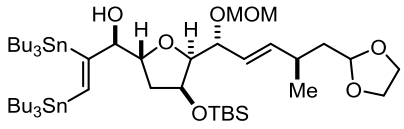


(890 mg, 1.64 mmol) in dry methanol (16 mL) at 0 °C. The suspension was allowed to warm to ambient temperature, while it was vigoroursly stirred for 2 h. The mixture was diluted with *t*-butyl methyl ether (20 mL) and the reaction was quenched with sat. NH_4Cl (5 mL). The organic phase was separated and the aq. phase was extracted with *t*-butyl methyl ether (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 60:40 to 40:60) to provide the title compund as a colourless syrup (698 mg, 85%, dr = 16:1). $[\alpha]_D^{20}$ = –20.7 (c = 2.26, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *see Table S-11;* ^{13}C NMR (126 MHz, $CDCl_3$): *see Table S-11*. ^{29}Si NMR (99 MHz, $CDCl_3$) δ = 19.00 ppm. IR (film): $\tilde{\nu}$ = 3420, 3309, 2955, 292, 2885, 2857, 1472, 1361, 1254, 1127, 1099, 1063, 947, 835, 775 cm^{-1}. MS (EI) *m/z* (%): 963.5 (13), 493.3 (100). HRMS (ESIpos) *m/z* calcd for $C_{24}H_{42}O_7SiNa$: 493.2592, found: 493.2594.

Table S-11. NMR data of terminal alkyne **S21**; arbitrary numbering scheme as shown in the insert

atom n°	^{1}H NMR (500 MHz, $CDCl_3$)					^{13}C NMR (126 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	3.76	dd	7.8, 3.3	(2), 5	(3b)	86.6	3, (4), 5, 6
2	4.32–4.29	m	-	(1),(3a)	(21), (22), (19), (6)	73.0	(1), 3b, (5)
3a	2.06	ddd	13.1, 6.4, 2.0	3b, 4	4	37.9	(4)
3b	1.93	ddd	13.2, 8.9, 4.5	2, 3a, 4	(1), 15		
4	4.35	dt	8.9, 6.2	3ab, (15)	3b, 15-OH	80.9	3a, (15)
5	4.27	t	7.2	1, 6	7, 13ab, (14)	75.2	6, 7, 13ab
6	5.43	dd	15.7, 6.6	5, 7	(2), 8, (22)	125.0	5, 8
7	5.73	dd	15.6, 7.6	6, 8	5, (22)	140.0	5, 8, 9ab, 22
8	2.42	sept	7.0	9a, 7, 22	6, 22	33.1	6, 7, 10, 9ab
9a	1.70	ddd	13.8, 7.8, 4.6	9b, 8, (10)	9b	40.8	6, 7, 8
9b	1.60	dt	13.9, 6.2	9a, (10)	9a, 22		
10	4.83	t	5.2	(9ab)	(22)	103.5	11ab,12ab
11a	3.98–3.91	m	-	11b	11b, 12ab	64.9	12ab
11b	3.84–3.78	m	-	11a	11a, 12ab		
12a	3.98–3.91	m	-	12b	11ab, 12b	64.8	11ab
12b	3.84–3.78	m	-	12a	11ab, 12a		
13a	4.70	d	6.6	13b	5, 13b, 14ab	94.3	5, 8, 9ab, 14
13b	4.64	d	6.6	13a	2, 6-TBS, 14a		
14	3.39	s	-	-	13ab, (5)	55.6	13ab
15	4.24	d	6.2	4, (17)	(15-OH), 3a	65.3	3a(b), 17
16	-	-	-	-	-	82.1	4, (15), (15-OH), 17
17	2.42	d	2.1	15	-	73.8	-
18	-	-	-	-	-	18.1	19, 20 , 21
19	0.90	s	-	-	20, 21, (2)	26.0	-
20	0.09	s	-	-	19, (2)	–3.9	21
21	0.07	s	-	-	19, (2)	–4.6	20
22	1.05	d	6.8	8	(6), (7), 8, 9b, (10)	20.9	7, 8, 9ab
15-OH	2.91	s	-	15	(4), (15)	-	-

Bis(alkenyl)stannane 256. [(*t*BuNC)$_2$PdCl$_2$] (21 mg, 61 µmol) was added to a solution of alkyne **S21** (284 mg, 0.603 mmol) in THF (2.0 mL) at ambient temperature. After dropwise addition of hexabutyldistannane (0.45 mL, 0.89 mmol) to the orange suspension, the mixture turned into a dark red solution, which colour intensity increased over time. After stirring for 20 h at ambient temperature, the mixture was concentrated under reduced pressure. The residual oil was purified by flash chromatography ((hexane/NEt_3 99:1)/*t*-butyl methyl ether 9:1 to 8:1) to afford the title

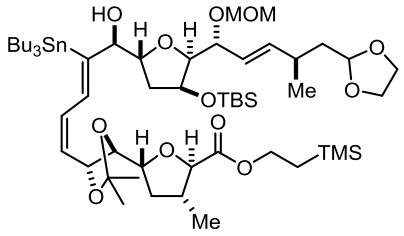


compound as a yellow-orange oil (588 mg, 93%). $[\alpha]_D^{20}$ = –8.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (ddd, *J* = 1.2 Hz, J_{SnH} = 178.0, 63.6 Hz, 1H), 5.74 (ddd, *J* = 15.7, 7.6, 1.1 Hz, 1H), 5.43 (ddd, *J* = 15.7, 6.3, 1.1 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.29–4.23 (m, 2H), 4.13 (ddd, *J* = 9.2, 7.9, 6.0 Hz, 1H), 3.99–3.91 (m, 2H), 3.87–3.76 (m, 3H), 3.71 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.38 (s, 3H), 2.82 (d, *J* = 2.0 Hz, 1H), 2.42 (ddt, *J* = 13.8, 6.3, 6.3 Hz, 1H), 1.82 (ddd, *J* = 13.1, 6.2, 1.7 Hz, 1H), 1.76–1.66 (m, 2H), 1.61 (ddd, *J* = 13.8, 6.6, 5.8 Hz, 1H), 1.55–1.38 (m, 12H), 1.31 (tt, *J* = 7.2, 7.2 Hz, 12H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.99–0.82 (m, 39H), 0.06 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 144.3, 139.5, 125.2, 103.5, 94.4, 87.8, 86.3, 80.4, 75.2, 73.4, 64.9, 64.8, 55.5, 40.8, 38.7, 33.1, 29.4, 29.3, 27.7, 27.5, 26.0, 20.9, 18.1, 13.8, 13.8, 11.5, 11.0, –3.8, –4.6 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = −59.2, –66.6 ppm. IR (film) $\tilde{\nu}$ = 3476, 2955, 2927, 2871, 2855, 1464, 1376, 1256, 1124, 1101, 1041, 951, 835, 775, 670 cm^{-1}. MS (ESIpos) *m/z* (%): 1073.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{48}H_{96}O_7SiSn_2Na$: 1075.4860, found: 1075.4879.

5.6.2 Completion of the Total Synthesis

Ester 219. DMAP (36.5 mg, 0.299 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (411 mg, 2.14 mmol) and 2-(trimethylsilyl)-ethanol (0.56 mL, 3.9 mmol) were added to a solution of carboxylic acid **185** (600 mg, 1.49 mmol) in CH_2Cl_2 (7.5 mL). After stirring for 4 h at ambient temperature, the mixture was diluted with EtOAc (10 mL) and the reaction was quenched with sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 96:4 to 94:6 to 92:8) to yield the title compound as a colourless oil (512 mg, 71%). $[\alpha]_D^{20}$ = –56.3 (c = 1.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (d, *J* = 7.9 Hz, 1H), 6.46 (t, *J* = 7.8 Hz, 1H), 4.86 (dd, *J* = 7.9, 6.3 Hz, 1H), 4.24–4.09 (m, 4H), 4.01 (d, *J* = 7.5 Hz, 1H), 2.35 (ddq, *J* = 12.0, 9.5, 6.8 Hz, 1H), 2.11 (ddd, *J* = 12.0, 7.5, 5.8 Hz, 1H), 1.51 (s, 3H), 1.45–1.37 (m, 4H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.02–0.97 (m, 2H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 137.6, 110.1, 85.7, 83.9, 80.0, 79.9, 78.9, 63.2, 39.6, 37.2, 27.6, 25.7, 18.3, 17.5, -1.4 ppm. IR (film) $\tilde{\nu}$ = 2956, 2897, 1748, 1731, 1456, 1371, 1274, 1250, 1215, 1175, 1131, 1086, 1059, 860, 838 cm^{-1}. MS (EI) *m/z* (%): 467 (13), 279 (21), 224 (100), 195 (41), 173 (61), 97 (41), 73 (90). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}O_5ISiNa$: 505.0877, found: 505.0878.

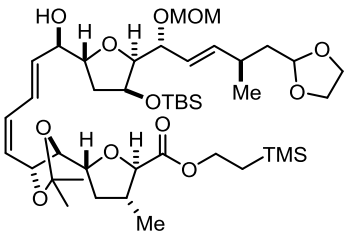
Dienylstannane 264. A solution of bis(alkenyl)stannane **256** (204 mg, 0.194 mmol) in degassed NMP



(1.0 mL, with rinses) was added to a suspension of (*t*-$Bu_3P)_2Pd$ (15 mg, 29 µmol), tetrabutylammonium diphenylphosphinate (115 mg, 0.250 mmol) and LiCl (27 mg, 0.64 mmol) in degassed NMP (0.5 mL). The dark mixture was placed in a preheated oil bath at 60 °C. A solution of alkenyl iodide **219** (114 mg, 0.236 mmol) in degassed NMP (1.0 mL) was added via syringe pump over a period of 3 h to the suspension at 60 °C. After stirring for additional 14 h at 60 °C, the brown mixture was cooled to ambient temperature and the reaction was quenched with pH 7 phosphate buffer (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 30 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography ((hexane/NEt_3=99:1)/*t*-butyl methyl ether = 9:1 to 4:1 to 3:1 to 3:2 to 1:1 to 1:2) to afford the title compound as a pale yellow oil (109 mg, 50%); additional fractions contained the destannylated diene **265** (18 mg, 11%), alkenyl chloride **S22** (11 mg, 12%) and a 7.6:1 mixture of homocoupled alkenyl iodide **S23** and starting bis(alkenyl)stannane **256** (20 mg, 20%).

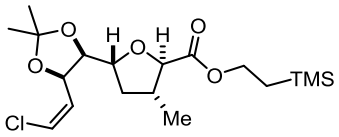
Analytical and spectral data for dienylstannane **264**: $[\alpha]_D^{20}$ = –11.5 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 109.2, 11.1 Hz, 1H), 6.18 (t, *J* = 11.5, 10.8 Hz, 1H), 5.74 (ddd, *J* = 15.7, 7.6, 1.0 Hz, 1H), 5.62 (t, *J* = 10.9, 10.1 Hz, 1H), 5.43 (ddd, *J* = 15.6, 6.3, 1.1 Hz, 1H), 5.12 (dd, *J* = 10.0, 6.3 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.29–4.17 (m, 5H), 4.14–4.06 (m, 2H), 4.02–3.91 (m, 4H), 3.85–3.77 (m, 2H), 3.70 (dd, *J* = 8.2, 2.9 Hz, 1H), 3.38 (s, 3H), 2.89 (brs, 1H), 2.43 (dp, *J* = 13.8, 6.8 Hz, 1H), 2.32 (dp, *J* = 13.7, 9.1, 6.6, 6.1 Hz, 1H), 2.07 (ddd, *J* = 12.7, 7.4, 5.7 Hz, 1H), 1.78 (ddd, *J* = 13.2, 6.2, 1.5 Hz, 1H), 1.69 (dddd, *J* = 36.6, 13.7, 7.6, 4.4 Hz, 1H), 1.65–1.57 (m, 2H), 1.53 (s, 3H), 1.51–1.42 (m, 6H), 1.41 (s, 3H), 1.35–1.26 (m, 7H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.02–0.96 (m, 8H), 0.92–0.83 (m, 18H), 0.06 (s, 6H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 154.7, 139.7, 134.8, 132.7, 127.6, 125.0, 109.7, 103.5, 94.4, 86.2, 84.5, 83.9, 81.2, 80.8, 79.2, 75.2, 73.4, 72.6, 64.9, 64.8, 63.2, 55.5, 40.8, 39.6, 38.8, 37.2, 33.1, 29.2, 27.9, 27.5, 26.0, 25.8, 20.9, 18.3, 18.1, 17.5, 13.8, 11.7, –1.4, –3.8, –4.6 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –50.8 ppm. IR (film) $\tilde{\nu}$ = 3482, 2955, 2928, 2857, 1749, 1731, 1463, 1378, 1251, 1215, 1178, 1127, 1099, 1048, 945, 860, 836, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5667, found: 1139.5679.

Analytical and spectral data for diene **265.** $[\alpha]_D^{20}$ = –23.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):



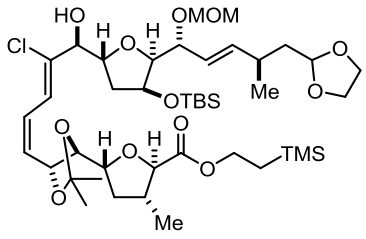
δ = 6.60 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.19 (t, *J* = 11.2 Hz, 1H), 5.80–5.69 (m, 2H), 5.62 (t, *J* = 10.5 Hz, 1H), 5.44 (ddd, *J* = 15.7, 6.4, 1.1 Hz, 1H), 5.07 (dd, *J* = 9.9, 6.2 Hz, 1H), 4.84 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.30–4.06 (m, 7H), 4.03–3.91 (m, 4H), 3.87–3.79 (m, 2H), 3.73 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.39 (s, 3H), 2.68 (br s, 1H), 2.49–2.28 (m, 2H), 2.12–2.04 (m, 1H), 1.91 (ddd, *J* = 13.0, 6.2, 1.8 Hz, 1H), 1.82–1.67 (m, 2H), 1.61 (ddd, *J* = 13.8, 6.6, 5.7 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.34–1.27 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.03–0.97 (m, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 139.8, 134.6, 131.9, 127.2, 126.4, 125.0, 109.6, 103.5, 94.4, 86.4, 83.9, 81.0, 80.8, 79.2, 75.4, 75.3, 73.2, 72.8, 64.9, 64.8, 63.2, 55.6, 40.8, 39.5, 38.1, 37.1, 33.1, 27.8, 26.0, 25.8, 20.9, 18.4, 18.1, 17.5, –1.4, –3.8, –4.6. ppm. IR (film) $\tilde{\nu}$ = 3486, 2956, 2930, 2891, 1747, 1462, 1379, 1251, 1214, 1131, 1100, 1048, 951, 861, 836, 809, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 849.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{74}O_{12}Si_2Na$: 849.4611, found: 849.4617.

Analytical and spectral data for (*Z*)-alkenyl chloride **S22.** $[\alpha]_D^{20}$ = –3.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400



MHz, $CDCl_3$): δ = 6.27 (dd, *J* = 13.3, 0.7 Hz, 1H), 6.08 (dd, *J* = 13.3, 8.8 Hz, 1H), 4.55 (dd, *J* = 8.9, 6.4 Hz, 1H), 4.25–4.11 (m, 3H), 4.08 (t, *J* = 6.3 Hz, 1H), 4.01 (d, *J* = 7.5 Hz, 1H), 2.39 (dtq, *J* = 9.6, 6.9, 6.9 Hz, 1H), 2.12 (ddd, *J* = 12.0, 7.5, 5.7 Hz, 1H), 1.50 (s, 3H), 1.39–1.31 (m, 4H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.05–0.98 (m, 2H), 0.03 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 129.9, 123.0, 109.9, 83.9, 80.4, 79.1, 77.5, 77.2, 76.8, 76.3, 63.3, 39.4, 37.0, 27.6, 25.6, 18.4, 17.5, -1.4 ppm. IR (film) $\tilde{\nu}$ = 2956, 2898, 1746, 1729, 1629, 1456, 1379, 1249, 1214, 1175, 1129, 1084, 1056, 942, 857, 842, 695, 517 cm^{-1}. MS (ESIpos) *m/z* (%): 413.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}O_5SiClNa$: 413.1522, found: 413.1525.

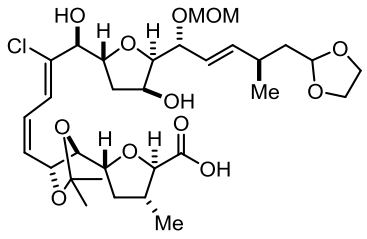
Chlorodiene 266. 2,6-Lutidine (115 µL, 0.987 mmol) and copper(II) chloride (125 mg, 0.930 mmol)



were added to a solution of dienylstannane **264** (174 mg, 0.156 mmol) in THF (3.2 mL). The resulting purple suspension was stirred for 20 h at ambient temperature, while the colour of the mixture gradually turned brown. After filtration through a short plug of silica, which was rinsed with *t*-butyl methyl ether (25 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 2:3 to 1:1 to 3:2) to afford the title compound as a colourless oil (105 mg, 78%). $[\alpha]_D^{20}$ = –28.3 (c = 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 11.0 Hz, 1H), 6.57 (td, *J* = 11.0, 1.0 Hz, 1H), 5.82 (t, *J* = 10.3 Hz, 1H), 5.75 (ddd, *J* = 15.7, 7.6, 1.1 Hz, 1H), 5.43 (ddd,

J = 15.7, 6.3, 1.1 Hz, 1H), 5.00 (dd, *J* = 9.7, 6.4 Hz, 1H), 4.83 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.47 (dt, *J* = 9.5, 5.9 Hz, 1H), 4.32–4.13 (m, 5H), 4.09 (t, *J* = 6.3 Hz, 1H), 4.05 (t, *J* = 4.9, 1.8 Hz, 1H), 4.01 (d, *J* = 7.5 Hz, 1H), 3.98 – 3.91 (m, 2H), 3.84–3.78 (m, 2H), 3.74 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.37 (s, 3H), 3.06 (br s, 1H), 2.48–2.29 (m, 2H), 2.06 (ddd, *J* = 12.6, 7.4, 5.7 Hz, 1H), 1.97 (ddd, *J* = 13.1, 6.0, 1.6 Hz, 1H), 1.81 (ddd, *J* = 13.3, 9.6, 4.2 Hz, 1H), 1.70 (ddd, *J* = 13.7, 7.7, 4.6 Hz, 1H), 1.61 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.34–1.27 (m, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.97 (m, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 139.8, 136.9, 130.2, 126.6, 124.9, 121.0, 109.9, 103.5, 94.5, 86.9, 83.9, 80.7, 79.3, 79.0, 78.1, 75.2, 73.2, 73.1, 64.9, 64.8, 63.2, 55.6, 40.8, 39.5, 38.6, 37.1, 33.1, 27.8, 26.0, 25.8, 20.9, 18.4, 18.1, 17.5, –1.4, –3.8, –4.6 ppm. IR (film) $\tilde{\nu}$ = 3447, 2955, 2931, 2859, 1730, 1463, 1379, 1252, 1214, 1132, 1102, 1045, 941, 861, 838, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4231.

***Seco*-Acid 267.** A solution of TBAF trihydrate (29 mg, 93 µmol) in THF (0.15 mL) was added dropwise



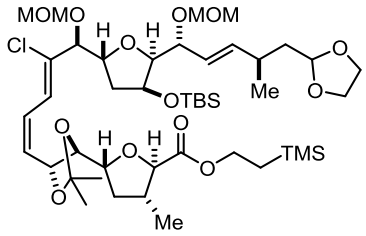
at 0 °C to a solution of compound **266** (10 mg, 12 µmol) in THF (0.05 mL). After stirring for 17 h at 0°C, the mixture was slowly warmed to ambient temperature, before it was diluted with EtOAc (5 mL) and sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with a 1:3 mixture of sat. NH_4Cl and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/AcOH 99:1) to afford the title compound as a colourless oil (6.0 mg, 80%). $[\alpha]_D^{20}$ = –34.8 (c = 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, *J* = 11.0 Hz, 1H), 6.58 (td, *J* = 11.0, 1.1 Hz, 1H), 5.94 (dd, *J* = 15.7, 6.7 Hz, 1H), 5.73 (ddd, *J* = 10.5, 9.6, 1.0 Hz, 1H), 5.40 (ddd, *J* = 15.7, 8.8, 1.3 Hz, 1H), 5.02 (dd, *J* = 9.4, 5.7 Hz, 1H), 4.85 (t, *J* = 4.8 Hz, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.5 Hz, 1H), 4.52 (dt, *J* = 9.5, 5.9 Hz, 1H), 4.37–4.27 (m, 2H), 4.19–4.08 (m, 2H), 4.07 (d, *J* = 5.7 Hz, 1H), 4.01 (d, *J* = 8.9 Hz, 1H), 4.01–3.90 (m, 2H), 3.90 (dd, *J* = 7.2, 3.1 Hz, 1H), 3.87–3.76 (m, 2H), 3.37 (s, 3H), 2.50 (ddq, *J* = 14.2, 7.6, 7.0 Hz, 1H), 2.43–2.26 (m, 1H), 2.17 – 2.00 (m, 2H), 1.93 (ddd, *J* = 13.6, 9.6, 4.8 Hz, 1H), 1.79 (dt, *J* = 14.0, 5.1 Hz, 1H), 1.67 (ddd, *J* = 14.0, 8.5, 4.6 Hz, 1H), 1.52 (s, 3H), 1.45–1.38 (m, 4H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.1, 142.3, 137.2, 129.8, 126.7, 123.8, 120.8, 109.9, 103.5, 93.6, 85.2, 83.2, 80.5, 79.7, 79.3, 77.8, 77.0, 73.3, 72.8, 64.9, 64.8, 55.6, 41.0, 39.6, 38.0, 37.5, 32.1, 27.7, 25.6, 19.8, 17.6 ppm. IR (film) $\tilde{\nu}$ = 3448, 2958, 2928, 1733, 1380, 1259, 1215, 1100, 1031, 869 cm^{-1}. MS (ESIneg) *m/z* (%): 645.3 (100 (M+Na)). HRMS (ESIneg): *m/z* calcd for $C_{31}H_{46}O_{12}Cl$ $[M-H]^-$: 645.2683, found: 645.2687.

Lactone 268. $NaHCO_3$ (217 mg, 2.58 mmol) was added to a suspension of 2-bromo-1-ethyl-pyridinium tetrafluoroborate (**216**) (74 mg, 0.27 mmol) and *seco*-acid **267** (5.5 mg, 8.5 µmol) in 1,2-dichloroethane (17 mL) in a sealed tube. The tube was placed in a pre-heated oil bath at 80 °C and the mixture was stirred for 22 h. The light purple suspension was cooled to ambient temperature before the reaction was quenched with pH 7 phosphate buffer (10 mL). The aq. phase was separated and extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc/AcOH 1:1:0 to 1:2:0 to 100:0:0 to 99:0:1) to provide the title compound as a colourless oil (1.6 mg, 30%); a second fraction contained recovered starting material **267** (3.1 mg, 56%) [Conditions for LC-MS: ZORBAX Eclipse Plus C-18, 1.8 µm, 50 × 4.6 mm, MeCN/H_2O = 70:30, v = 0.8 mL/min, λ = 250 nm, 35 °C, 181 bar, t(carboxylate) = 1.0 min, t(carboxylic acid) = 1.1 min, t(lactone) = 11.6 min]. $[\alpha]_D^{20}$ = –83.3 (c = 0.15, $CHCl_3$). λ_{max} (MeCN) = 249 nm. ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-5;* ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-5*. IR (film): $\tilde{\nu}$ = 3455, 2959, 2923, 1747, 1651, 1456, 1379, 1365, 1260, 1215, 1149, 1096, 1030, 870, 847, 800 cm^{-1}. MS (ESIpos) *m/z* (%): 651.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{31}H_{45}O_{11}ClNa$: 651.2542, found: 651.2548.

Table S-12. NMR data of 13-membered lactone **268**; numbering scheme as shown in the insert

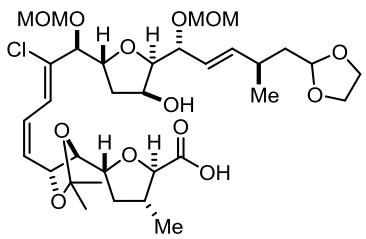
atom n°	^{1}H NMR (500 MHz, $CDCl_3$)					^{13}C NMR (126 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	170.5	2
2	4.04	d	5.4	3, 4a	(4a), 23	82.7	4, 23
3	2.84–2.74	m	-	2, (4a), 4b, 23	5, 4a, 23	32.3	23
4a	1.93	ddd	11.4, 7.4, 4.2	(2), 3, 4b, 5	3, 5, 4b	39.0	23
4b	1.52	td	11.5, 10.3	3, 4a, 5	4a, (23)		
5	3.31	dd	11.7, 4,2	4ab, (6)	4a, 6, 10	75.8	2, 7
6	4.06	d	5.5	7, (5), (8)	5, 7	77.4	7
7	4.75	dd	7.2, 5.4	(4), 7, 8	6, 8, 26	76.6	8, (9)
8	5.61	ddd	11.8, 7.1, 0.9	7,9, (10)	7, 9	125.2	7, 9
9	6.67	dd	11.8, 11.2	8, 10	8, 10	130.7	7
10	7.78	dt	11.2, 0.8	(8), 9, (12)	9, 13, 5, (25)	124.9	(8), 12
11	-	-	-	-	-	131.6	9, 10, 12
12	5.09	d	7.3	13, (10)	13	81.4	(10), (13)
13	4.57	ddd	9.6, 7.3, 6.2	12, 14a, 14b	10, 12, 14b	78.4	12
14a	2.14	ddd	13.2, 9.4, 4.6	13, 14b, (15)	12, 14b, 15	37.3	12, (16)
14b	2.08	ddd	13.2, 6.3, 1.7	13, 14a, 15	13, 14a, (15)		
15	4.40–4.36	m	-	16, 15-OH	16, 14a, (15-OH), (14b)	72.8	14b
16	3.94	dd	6.4, 3.3	15, 17	15, 17, 18	84.6	(14b), (17)
17	4.34	dd	8.8, 6.2	16, 18, (19)	16, 19, 29	76.8	19, 29ab
18	5.48	ddd	15.7, 8.8, 1.2	17, 19	16, 31, (20)	124.4	(20)
19	5.87	dd	15.7, 7.0	18, (17)	17, (20)	141.9	17, 20
20	2.49	tq	8.1, 6.9	19, 21b, 31	(18), 19, 31	32.4	31
21a	1.75	dt	13.9, 5.3	22, 21b	20	41.0	(22), 31
21b	1.67	ddd	13.9, 8.4, 4.5	20, 21a, (22)	32		
22	4.84	dd	5.1, 4.5	21a, 21b	28a, 29a	103.5	28b, 29b
23	1.13	d	6.9	3, (4a)	2, 3	18.8	2
24	-	-	-	-	-	109.7	6, 24, 25
25	1.67	s	-	26, (6)	(2), 26	25.8	26
26	1.40	s	-	25	7, 8	26.0	25
27a	3.98–3.92	m	-	27b, 28ab	28a, 28b	64.9	-
27b	3.86–3.78	m	-	27a, 28ab	28a, 28b		
28a	3.98–3.92	m	-	27ab, 28b	27a, 27b	64.8	-
28b	3.86–3.78	m	-	27ab, 28a	27a, 27b		
29a	4.74	d	6.6	29b	(17), 29b, (30)	93.7	30, (17)
29b	4.63	d	6.6	(17), 29a	(17), 29a, 30		
30	3.39	s	-	-	29b	55.8	29a, 29b
31	1.08	d	6.8	20	20, (21a), (21b)	20.1	20
15-OH	3.18	d	4.2	15	15	-	-

Compound 269. Hünig's base (0.55 mL, 3.2 mmol), tetrabutylammonium iodide (11 mg, 30 µmol) and



MOMCl (0.14 mL, 1.8 mmol) were added to a solution of alcohol **266** (103 mg, 120 µmol) in 1,2-dichloroethane (1.2 mL). The dark orange mixture was stirred for 4 h at 50 °C. After reaching ambient temperature, the mixture was diluted with *t*-butyl methyl ether (10 mL) and sat. $NaHCO_3$ (15 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 7:3 to 3:2 to 1:1 to 1:2) to afford the title compound as a yellow oil (99.5 mg, 92%). $[\alpha]_D^{20}$ = –50.8 (c = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65–6.52 (m, 2H), 5.84 (t, *J* = 9.9 Hz, 1H), 5.74 (ddd, *J* = 15.6, 7.6, 1.1 Hz, 1H), 5.47 (ddd, *J* = 15.7, 6.1, 1.0 Hz, 1H), 4.99 (dd, *J* = 9.8, 6.3 Hz, 1H), 4.83 (dd, *J* = 5.9, 4.5 Hz, 1H), 4.73–4.61 (m, 4H), 4.53 (dt, *J* = 9.8, 6.4 Hz, 1H), 4.27–4.07 (m, 7H), 4.01 (d, *J* = 7.5 Hz, 1H), 3.98–3.90 (m, 2H), 3.86-3.77 (m, 2H), 3.72 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 2.47–2.28 (m, 2H), 2.04 (ddd, *J* = 12.7, 7.4, 5.6 Hz, 1H), 1.92 (ddd, *J* = 13.0, 6.0, 1.6 Hz, 1H), 1.74-1.64 (m, 2H), 1.64–1.56 (m, 1H), 1.52 (s, 3H), 1.41 (s, 3H), 1.35–1.29 (m, 1H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.98 (m, 2H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 139.1, 134.9, 130.8, 126.3, 125.4, 123.0, 110.0, 103.5, 95.0, 94.1, 86.8, 83.9, 82.1, 80.8, 79.1, 78.8, 75.6, 73.1, 72.8, 64.9, 64.8, 63.3, 55.7, 55.5, 40.8, 39.5, 38.3, 37.0, 33.1, 27.8, 26.0, 25.8, 21.0, 18.4, 18.1, 17.6, –1.4, –3.8, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2894, 1748, 1458, 1379, 1251, 1216, 1137, 1101, 1047, 919, 862, 836 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4493.

***Seco*-Acid 270.** A solution of TBAF (1 M in THF, 0.55 mL, 0.55 mmol) was added dropwise to a solution



of ester **269** (99 mg, 0.11 mmol) in THF (0.7 mL) at 0 °C. After stirring for 2 h at 0 °C, the ice bath was removed and stirring was continued for 2.5 h at ambient temperature. After cooling to 0 °C, additional TBAF (1 M in THF, 0.05 mL, 0.05 mmol) was added and the solution was stirred for another 1 h at ambient temperature. After quenching of the reaction with sat. $NaHCO_3$ (5 mL), the aq. phase was washed with methyl *t*-butyl ether (2 × 5 mL). The aq. phase was acidified with HCl (2 M, 0.1 mL) until pH 4 was reached and extracted with EtOAc (3 × 10 mL). The combined EtOAc phases were washed with a 3:1 mixture of brine and pH 4 phosphate buffer (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The yellow residual oil (75.5 mg, 99%) was used in the next step without further purification. $[\alpha]_D^{20}$ = –65.6 (c = 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.63 (d, *J* = 11.0 Hz, 1H), 6.55 (td, *J* = 10.8, 1.1 Hz, 1H), 5.85 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.75 (t, *J* = 10.2 Hz, 1H), 5.47 (ddd, *J* = 15.6, 8.6, 1.2 Hz, 1H), 4.99 (dd, *J*

= 9.6, 5.7 Hz, 1H), 4.83 (t, *J* = 4.9 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.66–4.52 (m, 4H), 4.34-4.28 (m, 2H), 4.18–4.07 (m, 3H), 4.02 (d, *J* = 8.5 Hz, 1H), 3.97–3.90 (m, 2H), 3.86–3.77 (m, 3H), 3.40 (s, 3H), 3.36 (s, 3H), 3.30 (brs, 1H), 2.52–2.40 (m, 1H), 2.40–2.29 (m, 1H), 2.13–2.04 (m, 1H), 2.00 (ddd, *J* = 13.3, 6.4, 1.4 Hz, 1H), 1.80 (ddd, *J* = 13.7, 9.4, 4.8 Hz, 1H), 1.75–1.61 (m, 2H), 1.51 (s, 3H), 1.42–1.33 (m, 4H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5, 141.5, 135.1, 130.4, 126.4, 124.4, 122.8, 110.0, 103.4, 94.1, 93.8, 84.5, 83.1, 81.7, 80.7, 79.3, 78.9, 76.8, 73.2, 72.8, 64.9, 64.8, 55.7, 55.6, 40.9, 39.6, 37.8, 37.3, 32.4, 27.7, 25.6, 20.1, 17.7 ppm. IR (film): $\tilde{\nu}$ = 3477, 2957, 2932, 2894, 1735, 1380, 1250, 1216, 1151, 1101, 1032, 918, 869 cm^{-1}. MS (ESIpos) *m/z* (%): 713.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{33}H_{51}O_{13}ClNa$: 713.2910, found: 713.2917.

Macrolactone 257. Hünig's base (45 µL, 26 µmol) and 2,4,6-trichlorobenzoyl chloride (34 µL, 22 µmol) were added to a solution of *seco*-acid **270** (30 mg, 43 µmol) in THF (0.87 mL) at 0 °C. After stirring for 2 h at this temperature, the solvent was removed under reduced pressure and the residue was redissolved in toluene (9.0 mL). The resulting solution of the mixed anhydride was added via syringe pump over a period of 20 h to a solution of DMAP (132 mg, 1.08 mmol) in toluene (85 mL) at 110 °C. Once the addition was complete, stirring was continued for additional 2 h at the same temperature. The mixture was cooled to ambient temperature and the reaction was quenched with sat. NH_4Cl (100 mL). The aq. phase was separated and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 3:2 to 4:1 to 9:1) to provide the title compound as a light yellow oil (12 mg, 40%); additional fractions contained an epimerized macrolactone **S24** (1.8 mg, 6%) and the cyclic head-to-tail dimer **S25** (3.9 mg, 13%) [Conditions for LC-MS: ZORBAX Eclipse Plus C-18, 1.8 µm, 50 × 4.6 mm, MeCN/H_2O = 70:30, v = 0.8 mL/min, λ = 250 nm, 35 °C, 158 bar, t (epimerized macrolactone) = 2.7 min, t (macrolactone) = 3.4 min, t (dimer) = 16.0 min]. Analytical and spectral data of compound **257**: $[\alpha]_D^{20}$ = –25.9 (c = 0.80, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 2 main conformers, ratio 1:0.8, major conformer): *see Table S-13*. ^{13}C NMR (150 MHz, $CDCl_3$, 2 main conformers, ratio 1:0.8, major conformer): *see Table S-13*. ^{1}H NMR (600 MHz, $CDCl_3$, minor conformer): *see Table S-14*. ^{13}C NMR (150 MHz, $CDCl_3$, minor conformer): *see Table S-14*. IR (film): $\tilde{\nu}$ = 2958, 2933, 2892, 1741, 1454, 1381, 1256, 1213, 1151, 1099, 1031, 960 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)) *see Figures S-1 – S-3.* HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2811.

Table S-13. NMR data of the major conformer of macrolactone **257**; numbering scheme as shown in the insert.

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)						^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**ROESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-		170.1	2, 15, (3)
2	3.90	d	9.2	3	2*	23	80.3	3, 23
3	2.81	ddd q	12.2, 9,2, 6.5, 6.5	2, 23, (4b)	3*	-	37.6	2, 4ab, 23
4a	2.17	ddd	11.8, 6.3, 5.1	4b, 5, (3)	4a*	-	37.0	6, 23
4b	1.55–1.59	m	-	4a, 5	4b*	23		
5	4.16–4.13	m	-	4b, (4a), (6)	5*	-	81.4	4b, 7
6	4.74–4.65	m	-	(5), 7	6*	-	77.9	4b, 5, 7, 8
7	5.20	ddd	6.2, 5.4, 1.7	6, 8	7*	-	75.3	5, 8
8	5.92–5.86	m	-	7, 9, 10	8*	-	130.8	7, 9, 10
9	6.61–6.55	m	-	8	9*	-	123.4	7
10	6.61–6.55	m	-	8	10*	-	122.9	8, 12
11	-	-	-	-	-		133.9	9, 10, 13
12	4.49	d	4.9	13	12*	-	78.3	14ab, 27ab
13	4.57–4.54	m	-	12	13*	-	81.1	12, 14ab
14a 14b	2.50–2.42	m	-	13, 15	14a* 14b*	-	32.2	12, 16
15	4.95	q	8.7	14ab, 16	15*	-	76.2	13,
16	4.05	dd	7.9, 1.3	15	16*	-	80.7	(15), (14)
17	4.22–4.13	m	-	18	-	-	75.2	15, 19, 13, 29ab
18	5.58	dd	15.6, 8.6	17, 19, 20	18*	-	125.5	17, 19, 20
19	5.63	dd	15.6, 7.3	18, 20	19*	-	141.3	17, 18, 20, 21ab
20	2.45	dq	7.4, 7.4	19, 31, (21ab)	20*	-	33.1	18, 19, 21ab, 22, 31
21a	1.74–1.58	m	-	(20), 21b, 22	21a*b*	-	40.9	19, 20, 22, 31
21b				21a, 22	21a*b*			
22	4.83	dd	5.9, 4.4	21ab	22*	-	103.6	28b, 29b
23	1.11	d	6.5	3	23*	(2), (4b)	16.8	2, 4b
24	-	-	-	-	-	-	107.9	6, 25, 26
25	1.48	s	-	26	25*	-	27.2	-
26	1.38	s	-	25	26*	-	24.8	-
27a	4.66	d	6.5	27b	27a*	-	95.1	12, 28
27b	4.59	d	6.6	27a	27b*	-		
28	3.38	s	-	-	-	-	56.1	27ab
29a	4.72	d	6.6	29b	29ba*	-	93.8	17, 30
29b	4.67	d	6.7	29a	29ab*	-		
30	3.42	s	-	-	-	-	55.5	29ab
31	1.04	d	6.8	20	31*	-	20.8	20, 21ab
32a	3.96–3.91	m	-	-	-	-	64.8	33ab
32b	3.83–3.78	m						

33a 33b	3.96–3.91 3.83–3.78	m m	-	-	-	-	64.9	32ab

NOESY displays fast exchange with minor conformer (*).

Table S-14. NMR data of the minor conformer of macrolactone **257;** numbering scheme as shown in the Insert.

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)						^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	ROESY	δ [ppm]	HMBC
1	-	-	-	-	-		170.8	3
2	4.09	d	7.0	3	2*	23	87.4	(3), 4a, 23
3	2.58	ddd q	9.7, 7.6, 7.0, 6.7	2, (4b), 23	3*	-	35.5	2, 4ab, 23
4a	2.33	ddd	12.8, 7.6, 6.0	4b, 5	4a*	-	39.4	(5), 6, 23
4b	1.93	dt	12.2, 9.9	4a, 5	4b*	23		
5	4.48	dd	9.8, 6.0	4ab	5*	-	77.8	2, 4b, 6
6	4.23–4.12	m	-	7	6*	-	80.0	4b, 5
7	4.91	ddd	7.2, 5.5, 1.7	6, 8	7*	-	75.7	6, 9
8	5.70	d	11.0, 7.4	7, 9	8*	-	134.3	6, (10)
9	6.34	td	11.3, 1.6	8, 10	9*, 10, 12	-	124.3	7
10	6.63	d	11.7	9	9, 10*	-	122.8	6, 8
11	-	-	-	-	-		134.1	6, 9, 10, 13
12	4.23–4.12	m	-	13	12*	-	81.6	(10), 27ab
13	3.96–3.90	m	-	10, 12, 14b	13*	-	84.6	12
14a	1.82	td	12.8, 3.3	13, 14b, 15	14a*	-	38.1	-
14b	1.74-1.57	m	-	14a	14b*			
15	5.30	td	3.5, 1.0	16	15*	-	75.0	(14b), (2)
16	4.23–4.12	m	-	15	16*	-	84.3	12, (15), 17
17	4.23–4.12	m	-	7	17*	-	75.5	16, 18, 19, 29a
18	5.27	dd	15.5, 7.5	17, 19	18*, 19, 19*	-	124.2	20
19	5.60	dd	15.6, 7.3	18, 20	19*	-	141.7	20, 21ab, 31
20	2.38	dq	7.1, 7.1	19, 31, (21ab)	20*	-	33.3	18, 19, 21ab, 22, 31
21a 21b	1.74–1.58	m	-	22	21a*b*	-	40.6	19, 20, 22, 31
22	4.77	dd	5.6, 4.6	21ab	22*	-	103.4	20, 32ab, 33ab
23	1.16	d	6.7	3	23*	(2), (4b)	17.8	4b
24	-	-	-	-	-	-	108.4	7, 25, 26
25	1.57	s	-	26	25*	-	28.1	-
26	1.38	s	-	25	26*	-	26.2	-
27a	4.72	d	6.5	27b	27a*	-	95.4	12, 28
27b	4.69	d	6.6	-	27b*	-		
28	3.38	s	-	-	-	-	56.0	27ab

29a	4.72	d	6.6	29b, 29b*	29ba*	-	93.5	16, 17, 30
29b	4.55	d	6.6	29a	29ab*	-		
30	3.44	s	-	-	-	-	56.3	29ab
31	0.97	d	6.8	20	31*	-	21.3	20, 21ab
32a 32b	3.96–3.91 3.83–3.78	m m	-	-	-	-	64.9	33ab
33a 33b	3.96–3.91 3.83–3.78	m m	-	-	-	-	64.9	32ab

NOESY displays fast exchange with major conformer (*).

The cyclic monomer **257** and the head-to-tail dilactone (lactide) **S25** could be unambiguously distinguished by MS-MS fragmentation experiments, see below

Figure S-3. MS (ESIpos) analysis of macrocycle **257** *m/z* = 695.3 $[M+Na]^+$, *m/z* = 1367.6 $[2M+Na]^+$.

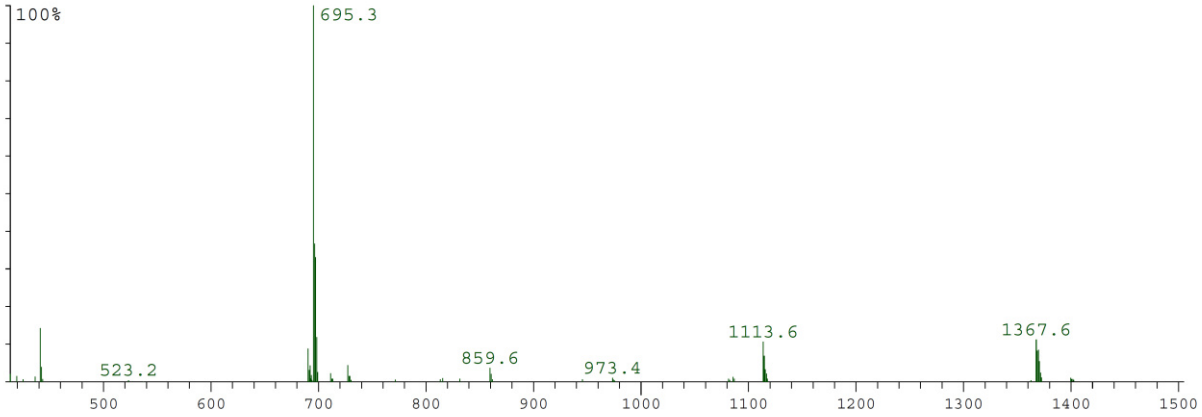


Figure S-4. MS-MS-Fragmentation of macrolactone **257** with *m/z* = 695.3 $[M+Na]^+$ as the precursor with increasing normalized collision energy (NCE).

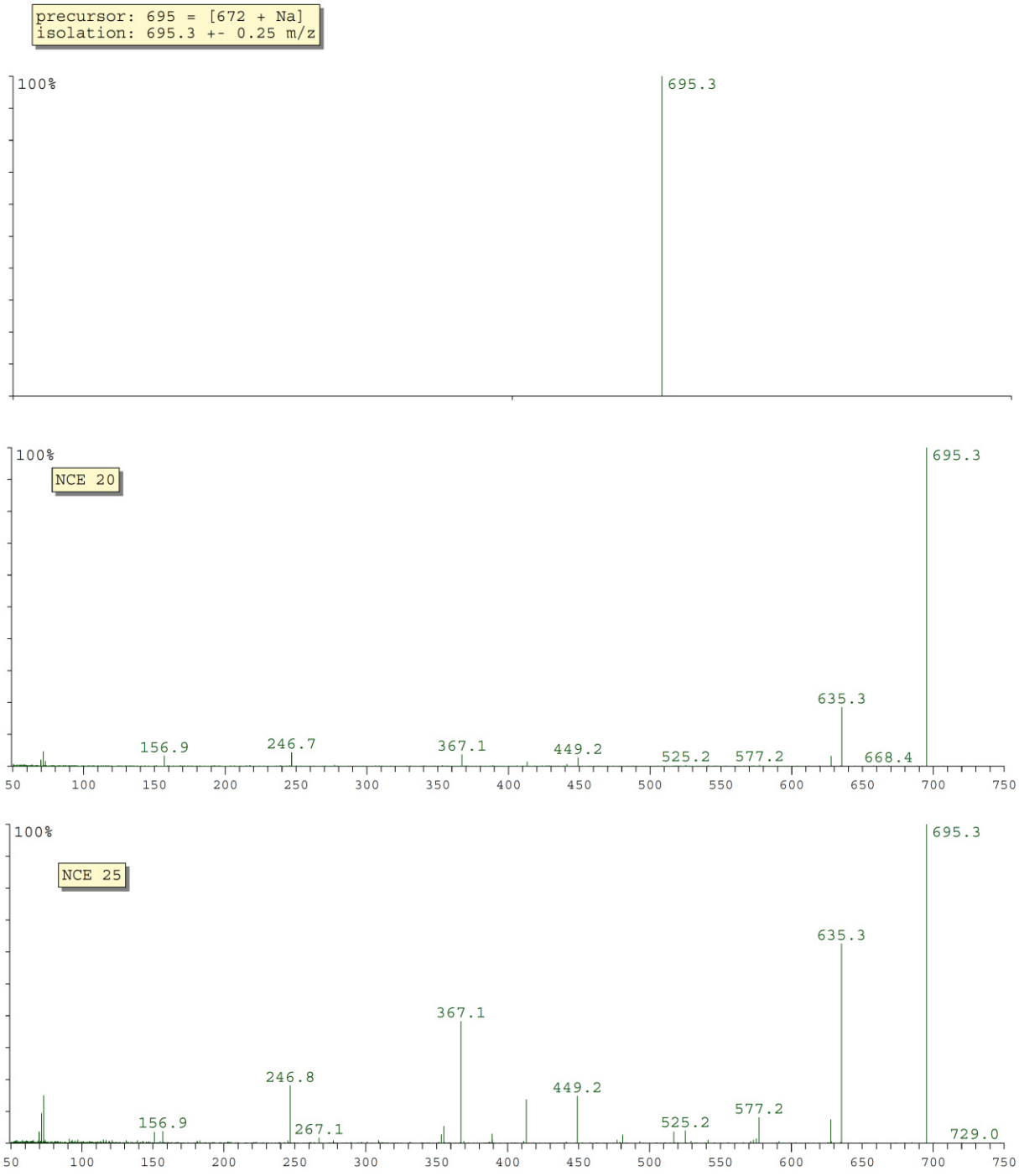
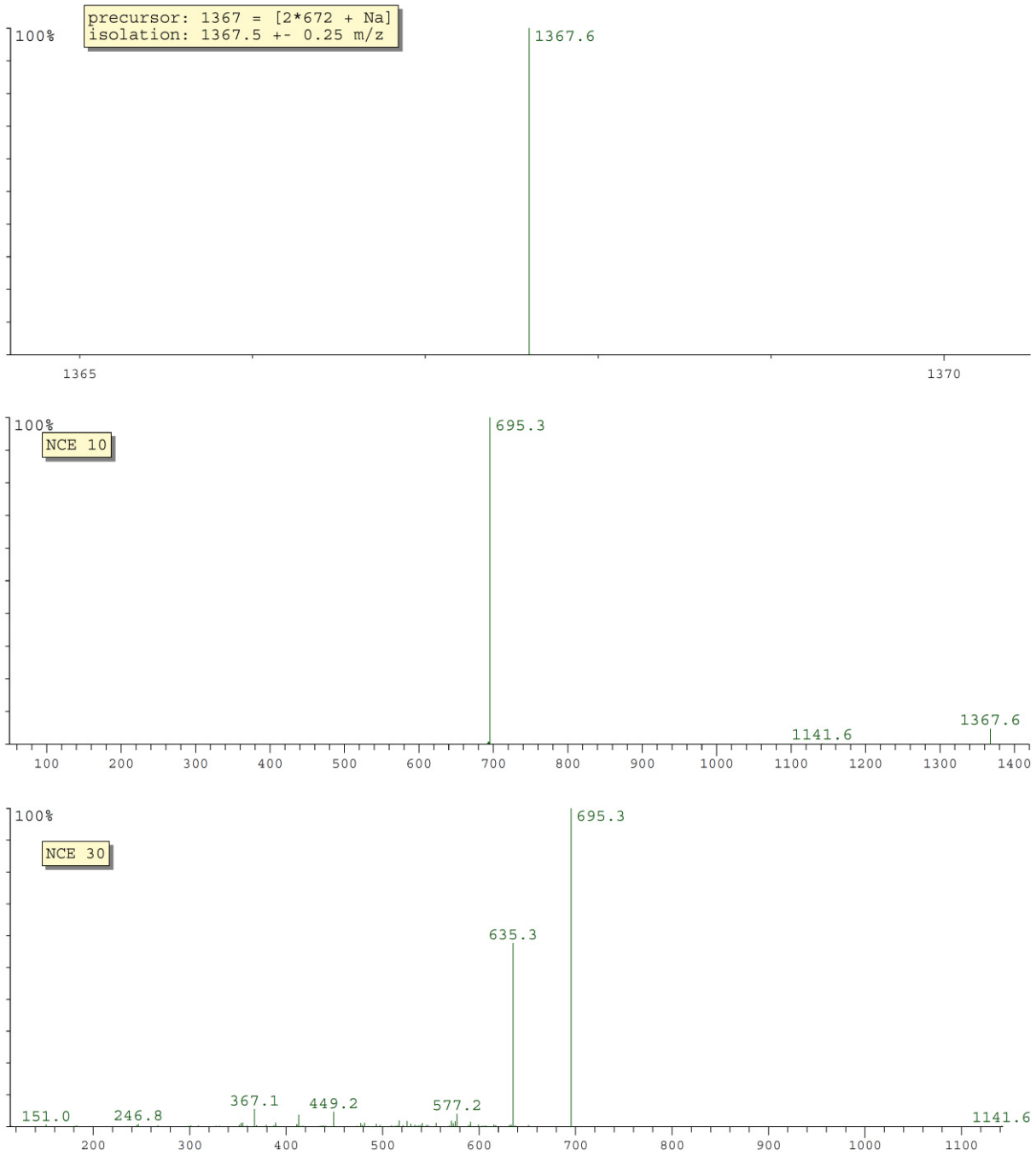


Figure S-5. MS-MS-Fragmentation of macrolactone **257** with *m/z* = 1367.6 $[2M+Na]^+$ as the precursor with increasing normalized collision energy (NCE).



After isolation of *m/z* = 1367.6 for the MS-MS-fragmentation analysis, a small NCE of 10 induces immediate fragmentation of the dimeric adduct [2M+Na] to the monomeric characteristic ion [M+Na]. Increasing the NCE to 30, the fragmentation pattern also matches with MS-MS-fragmentation analysis of [M+Na] in Figure S-4. These results clearly indicate that **257** is the monomeric species, although a dimeric adduct was observed in the ESI-MS experiment (see Figure S-3).

Analytical and spectral data of the epimeric macrolactone **S24** $[\alpha]_D^{20}$ = –7.6 (c = 0.17, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$,): *see Table S-8;* ^{13}C NMR (126 MHz, $CDCl_3$,): *see Table S-8;* IR (film): $\tilde{\nu}$ = 2957, 2926, 2854, 1732, 1666, 1458, 1379, 1260, 1216, 1152, 1098, 1031, 867, 800 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2809.

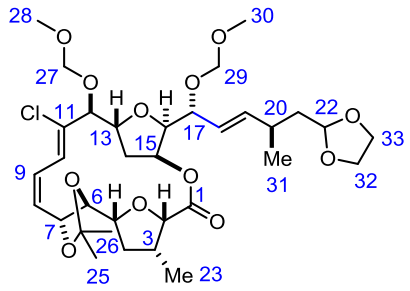
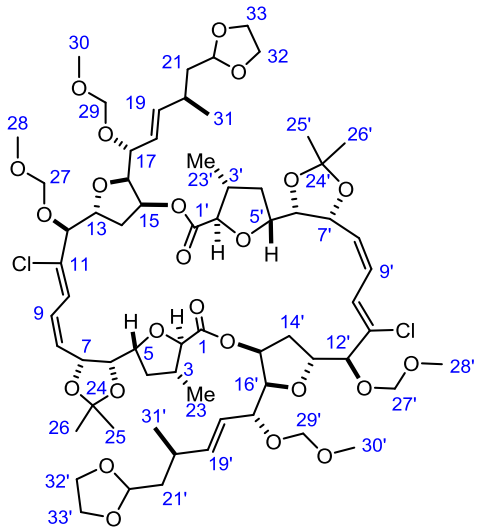


Table S-15. NMR data of epimerized macrolactone **S24**; numbering scheme as shown in the insert

atom n°	^{1}H NMR (500 MHz, $CDCl_3$)					^{13}C NMR (126 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	-	-	-	-	-	170.7	-
2	4.40	d	9.0	3	3, 5, 7	80.3	23
3	2.59–2.46	m	-	2, 6	2/6, 4a, 5, 23	39.6	23
4a	1.89	ddd	12.2, 5.6, 4.8	4b, (5)	3, 4b, 5, (7)	36.1	23
4b	1.02–0.98	m	-	3, 4a, 5	2/6, 4a		
5	4.06	ddd	13.2, 8.2, 4.7	2/6, 4b	2/6, 4a, 25, (3)	82.6	(7)
6	4.41	dd	8.0, 5.8	5, 7	3, 5, 7, 10	82.4	-
7	5.18	td	5.9, 2.4	2/6, 8	2/6, 8, 10, 24	75.8	(9)
8	5.86	ddd	10.9, 5.9, 1.0	7, 9	7, 9	129.9	-
9	6.44	td	10.9, 2.4	8, 10	8	125.4	-
10	6.78	dd	10.9, 1.0	9	6, 7, 13, (28/30)	124.5	-
11	-	-	-	-	-	134.1	12
12	4.19	d	9.5	13	14a, (28/30)	81.4	27ab
13	4.04	ddd	12.0, 9.6, 2.5	12, 14a	2/6, 10	83.8	(12)
14a	1.79	ddd	12.4, 11.6, 3.6	13, (15)	12, 14b, 15, 16	40.0	-
14b	1.70–1.64	m	-	14a	14a, 15		
15	5.78	t	3.7	16	14a, (14b), 16	74.5	-
16	4.26–4.21	m	-	15	14a, 15, 18, 19, 29ab, 28/30	84.3	(17)
17	4.26–4.21	m	-	18	15, 29ab	75.1	29ab
18	5.28	dd	15.5, 6.5	17, 19	16, 20	124.0	(20)
19	5.69	dd	15.5, 7.9	18, (20)	16, (31)	142.0	31
20	2.40	sept	7.0	19, 31	18, 31	33.2	31
21a	1.67	ddd	13.6, 7.8, 4.6	21b, 22	21b, 31	40.8	22
21b	1.60–1.56	m	-	21a, 22	21a, 31		
22	4.83	dd	5.7, 4.6	(21ab)	21b, (31), 32a, 33a	103.6	(21ab)
23	0.93	d	7.0	3	3, (14b)	14.5	-
24	-	-	-	-	-	108.9	25, 26
25	1.58	s	-	-	5, 26	28.8	-
26	1.47	s	-	-	7, 25	26.3	-
27a	4.75	d	6.7	27b	12, 28	95.5	28

27b	4.73	d	6.7	27a	12, 28		
28	3.39	s	-	-	27ab	56.0	27ab
29a	4.70	d	6.5	29b	30	94.4	17, 30
29b	4.68	d	6.5	29a	30		
30	3.39	s	-	-	29ab	55.4	29ab
31	1.00	d	6.8	20	(18), (19), 20, 21ab	20.5	-
32a	3.96–3.89	m	-	-	-	64.8	33ab
32b	3.85–3.78	m					
33a	3.96–3.91	m	-	-	-	64.8	32ab
33b	3.83–3.78	m					



Analytical and spectral data of lactide **S25.** $[\alpha]_D^{20}$ = –47.7 (c = 0.39, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, major conformer): *see Table S-9*. ^{13}C NMR (151 MHz, $CDCl_3$, major conformer, broad signals indicate time-averaged chemical shift): *see Table S-9;* IR (film): $\tilde{\nu}$ = 2956, 2927, 2855, 1740, 1462, 1379, 1259, 1214, 1150, 1099, 1029, 835 cm^{-1}. MS (ESIpos) *m/z* (%): 1367.6 (100 (M+Na)) *see Figure S-4 – S-6;* HRMS (ESIpos): *m/z* calcd for $C_{66}H_{98}O_{24}Cl_2Na$: 1367.5717, found: 1367.5728.

Table S-16. NMR data of cyclic dimer **S25**; numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1/1’	-	-	-	-	-	171.6	-
2/2’	4.07	d	6.2	3	(23)	83.0	23
3/3’	2.25–2.19	m	-	2, (4ab), 23	(4b)	39.6	23
4a/4a’	1.96	ddd	13.4, 7.6, 5.8	3, 4b, 5	-	37.0	2, 23
4b/4b’	1.19–1.16	m	-	(3), 4a, 5	(3)		
5/5’	4.19–4.10	m	-	4ab	-	79.3	2, (4b), (7)
6/6’	4.19–4.10	m	-	7	(25)	81.3	(4b)
7/7’	4.89	ddd	8.6, 6.0, 0.9	6	10, (25)	74.1	9
8/8’	5.66	ddd	11.4, 8.6, 0.9	7, 9	9	129.7	(6)
9/9’	6.50	td	11.3, 0.9	8, 10	8, (10)	125.8	(7)
10/10’	6.98	d	10.9	9	7	122.5	-
11/11’	-	-	-	-	-	134.1	9
12/12’	4.19–4.10	m	-	-	(26)	81.6	27ab
13/13’	4.19–4.10	m	-	14ab	-	80.8	(12)
14a/14a’	2.13	ddd	14.2, 9.7, 4.1	13, 14b, 15	14b	36.8	-
14b/14b’	1.91	dd	14.2, 5.6	13, 14a	14a		
15/15’	5.33	dd	4.2, 3.1	14a, 16	(16)	75.0	14b, 16

16/16’	3.98	dd	8.5, 2.9	15, 17	(15), (18)	83.6	17
17/17‘	4.18	ddd	8.6, 7.5, 0.9	16, 18	16, (29ab)	75.7	16, 18, 19, 29ab
18/18‘	5.26	ddd	15.5, 7.5, 0.9	17, 19	(31)	124.1	17, 20
19/19’	5.64	ddd	15.5, 8.2, 0.6	18, 20	(31)	141.4	17, 20, 21ab, 31
20/20‘	2.38	sept	7.0	19, 21ab, 31	22, 31	33.2	18, 19, 21ab, 22, 31
21a/21a‘	1.65	ddd	13.8, 8.1, 4.6	20, 21b, 22	(31)	40.7	19, (20), 22, 31
21b/21b’	1.59	ddd	13.8, 6.2, 5.7	20, 21a, 22	(31)		
22/22‘	4.78	dd	5.6, 4.6	21ab	20, 31, 32a, 33a	103.5	21ab, 32ab, 33ab
23/23’	1.18	d	6.8	3	2	19.7	(2)
24/24’	-	-	-	-	-	110.0	25, 26
25/25’	1.54	s	-	-	(26)	27.8	-
26/26‘	1.39	s	-	-	(25)	25.4	-
27a/27a’	4.67	d	6.7	-	(12)	94.5	12, 28
27b/27b’	4.66	d	6.7	-	(12)		
28/28’	3.43	s	-	-	27ab	55.8	27ab
29a/29a’	4.65	d	6.5	29b	30	94.4	17, 30
29b/29b‘	4.64	d	6.5	29a	30		
30/30‘	3.36	s	-	-	29ab	55.5	29ab
31/31‘	0.99	d	6.8	20	(18), (19), 20, 22	21.0	19, (20), 21ab
32a/32a‘	3.96–3.90	m	-	32b, 33b	-	64.8	33ab
32b/32b‘	3.84–3.79	m		32a, 33a			
33a/33a‘	3.96–3.90	m	-	32b, 33b	-	64.8	32ab
33b/33b‘	3.84–3.79	m		32a, 33a			

Figure S-6: MS (ESIpos) analysis of lactide **S25**. *m/z* = 1367.6 $[M+Na]^+$, *m/z* = 695.3 $[M+2Na]^{2+}$.

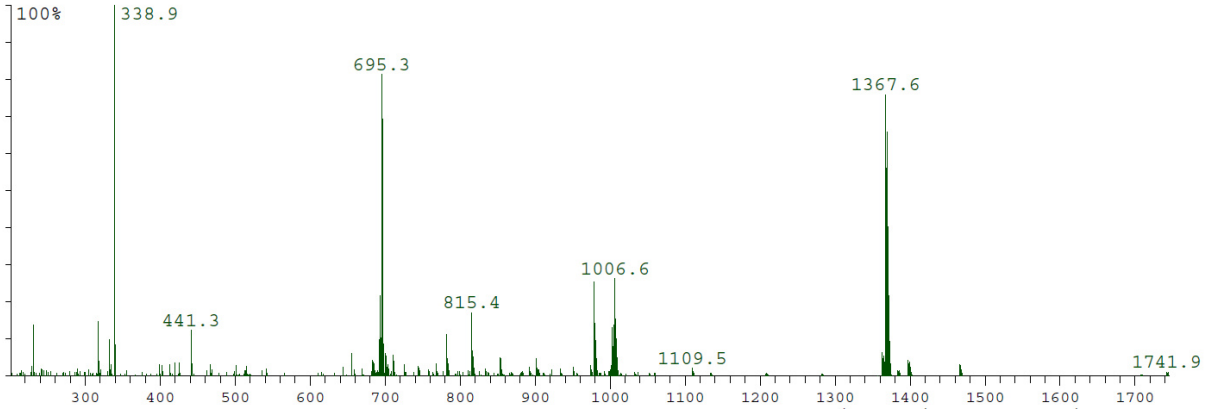


Figure S-7. MS-MS-Fragmentation of lactide **S25** with *m/z* = 1367.6 $[M+Na]^+$ with increasing normalized collision energy (NCE).

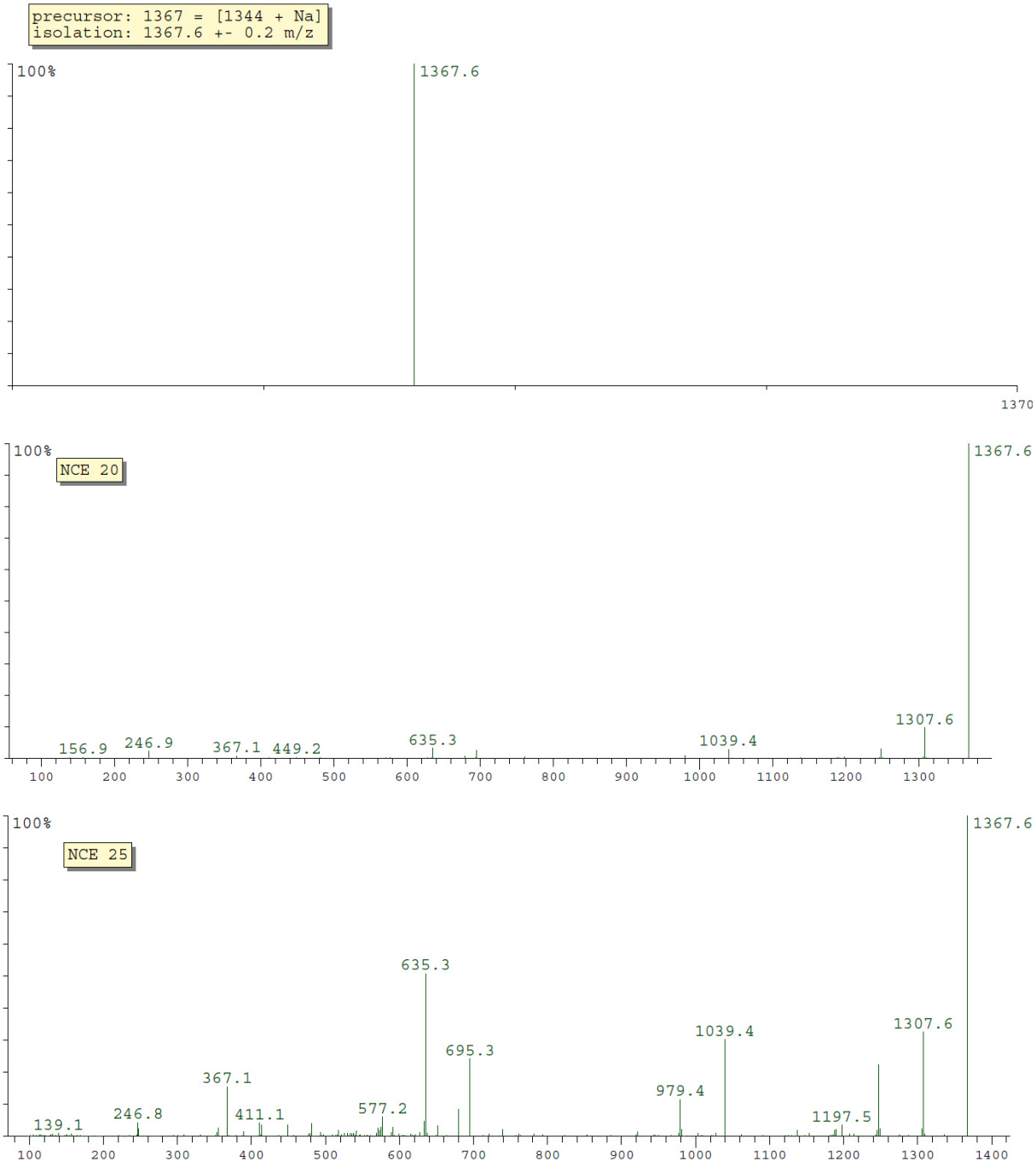
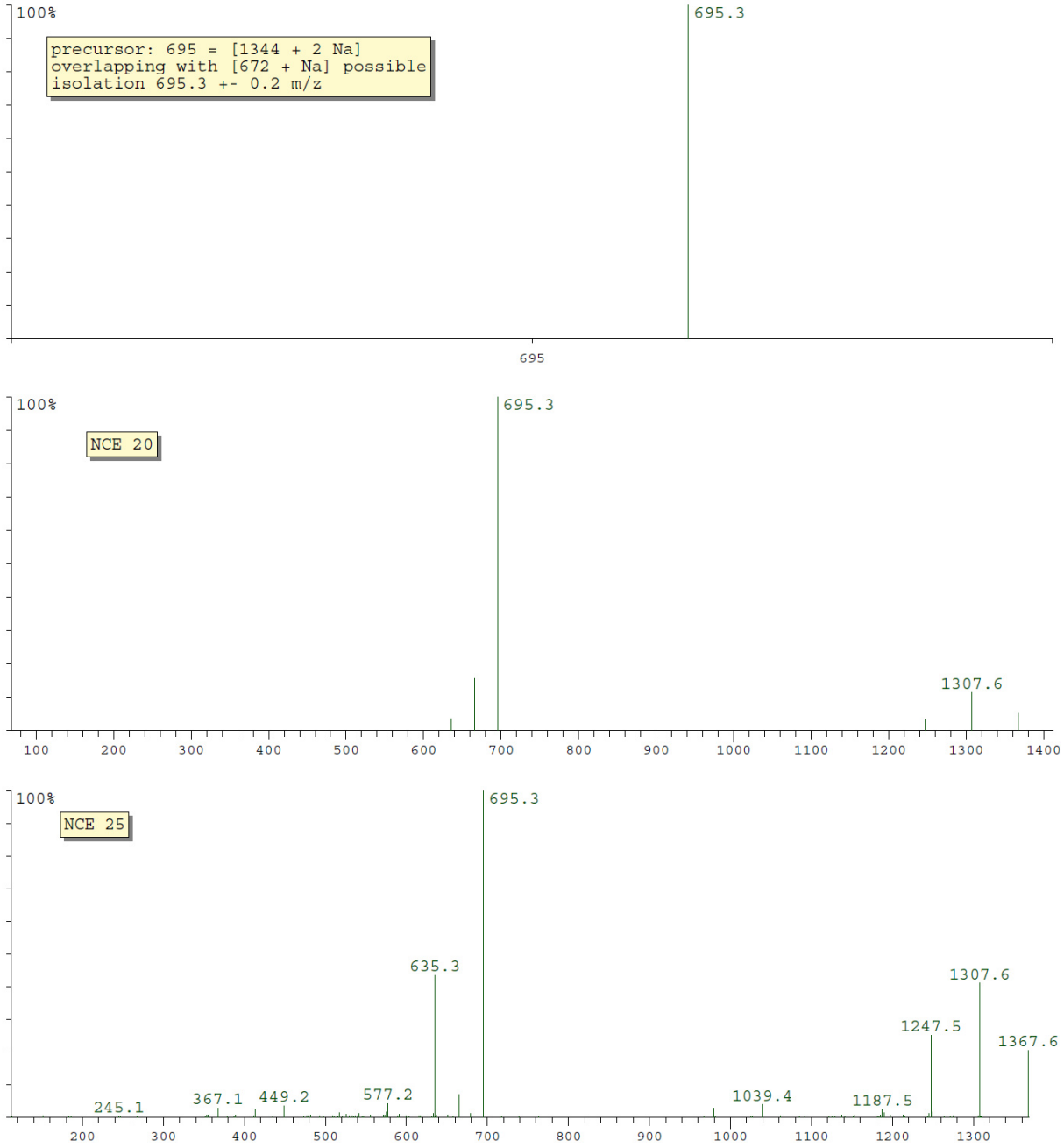
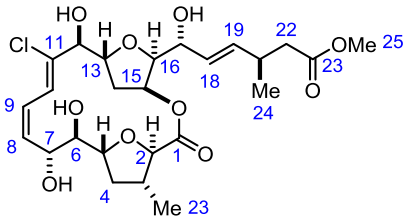


Figure S-8. MS-MS-Fragmentation of lactide **S25** with *m/z* = 695.3 $[M+2Na]^{2+}$ with increasing normalized collision energy (NCE).



After isolation of *m/z* = 695.3 for the MS-MS-fragmentation analysis, a NCE of 20 induces fragmentation with higher mass *m/z* = 1307.6 in the area of $[M+Na]^+$. Increasing the NCE to 30, the fragmentation pattern at higher molecular weight *m/z* > 1000 shows the characteristic ion $[M+Na]^+$ of **S25** and its fragmentation products from MS-MS-fragmentation analysis in Figure S-7. These results clearly indicate that **S25** is the lactide, although a double charged adduct $[M+2Na]^{2+}$ was observed in the ESI-MS experiment (see Figure S-6).

Methyl Ester 273. A solution of Me_2BBr (0.5 M in CH_2Cl_2, 0.30 mL, 0.15 mmol) was added dropwise to a solution of macrolactone **257** (2.5 mg, 3.7 µmol) in CH_2Cl_2 (0.4 mL) at −78 °C. After stirring for 30 min at –78 °C, the yellow mixture was poured into a solution of pH 7 phosphate buffer (0.15 ml), rinsing the flask with CH_2Cl_2 (1.5 mL). The emulsion was concentrated under reduced pressure to yield the crude aldehyde, which was used in the next step without further purification.



2-Methyl-2-butene (0.04 mL, 0.4 mmol) was added to a solution of crude aldehyde in THF (0.20 mL) and *t*-BuOH (0.20 mL). A solution of sodium chlorite (2.7 mg, 30 µmol) and sodium dihydrogen phosphate (4.3 mg, 36 µmol) in water (0.05 mL) was added at 0 °C to the mixture with a glass pipette. After stirring for 30 min at 0 °C, the reaction was quenched with sodium thiosulfate pentahydrate (11.5 mg, 46 mmol). After removing the ice bath, the mixture was stirred for 5 min before adding sodium sulfate (390 mg) in small poritons. The mixture was diluted with CH_2Cl_2 (2 mL), filtered through a short pad of sodium sulfate, rinsing with CH_2Cl_2 (15 mL in total). The combined filtrates were evaporated under reduced pressure at ambient temperature and the resulting crude acid was used in the next step without further purification.

A freshly prepared solution of diazomethane in diethyl ether (ca. 0.1 mL) was added dropwise to a solution of the crude carboxylic acid in CH_2Cl_2 (0.2 mL) at ambient temperature until a yellow colour presisted. After stirring for 5 min, the reaction was quenched with formic acid (10 µL, 0.27 mmol), causing the yellow colour to disappear. After concentrating under reduced pressure at ambient temperatue, the residue was purified by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 30 mm, MeCN/H_2O = 30:70, v = 20 mL/min, λ = 250 nm, 35 °C, 95 bar, t(methyl ester) = 4.53 min) to yield the title compound as a colourless amorphous solid (0.4 mg, 20% over 3 steps) [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeOH/H_2O = 40:60, v = 1.0 mL/min, λ = 250 nm, 35 °C, 153 bar, t(aldehyde) = 10.6 min, t(carboxylic acid) = 8.6 min, t(methyl ester) = 25.2 min]. $[\alpha]_D^{20}$ = +32.5 (c = 0.04, $CHCl_3$). ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-10;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-10*. IR (film): $\tilde{\nu}$ = 3386, 2958, 2922, 2852, 1736, 1455, 1259, 1095, 1063, 1039, 1010, 970, 876, 799, 758 cm^{-1}. MS (ESIpos) *m/z* (%): 553.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found: 553.1809.

Table S-17. NMR data of putative chagosensine methyl ester **273**; numbering scheme as shown in the insert

atom n°	**^{1}H NMR** (600 MHz, $CD_3OD/[D_5]$-pyridine 1:1 (v/v), referenced on CD_2HOD)					**^{13}C NMR** (151 MHz, $CD_3OD/[D_5]$-pyridine 1:1)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	171.3	-
2	4.09	d	4.2	(3)	(3), 23	87.1	23
3	2.58–2.50	m	-	2, (4ab)	(2), 4a, 23	36.4	(4ab), 23
4a	2.22	ddd	12.3, 7.5, 7.5	(3), 4b, (5)	3, 4b, 5	38.9	23
4b	1.35	ddd	12.3, 8.4, 6.0	4a, 5	4b, 6, 23		
5	3.77	ddd	8.4, 7.5, 6.5	4ab, 6,	4a, (6), 7, (10), (13)	81.7	(4b), (7)
6	4.02	d	6.5	5	4b, 5, 7	81.8	-
7	4.66	d	8.8	8	(4b), 5, 6, (8), 10	71.5	(6), 9
8	6.07	ddd	11.3, 8.8, 0.9	7, 9	(7), 9	137.2	(6), (7), 9, 10
9	6.35	ddd	11.2, 11.2, 1.1	8, 10	8	123.6	7
10	6.93	dd	10.9, 0.9	9	(5), 7, 13	123.2	(8), (12)
11	-	-	-	-	-	137.1	9, 10, 12
12	4.32	d	9.0	13	14a	79.5	(10), (13)
13	4.28	ddd	11.5, 9.1, 3.1	12, 14a, (14b)	(4a), (5), 10, 14b	85.5	12, (14a), (15)
14a	1.73	ddd	12.6, 11.4, 3.1	13, 14b, (15)	(12), (15), (16)	39.0	-
14b	1.67	ddd	12.8, 3.0, 0.6	(13), 14a	(5), (13), (15)		
15	5.41-5.39	m	-	(14a), 16	(14ab), 16	76.4	(14b)
16	4.20	dd	8.7, 3.7	(15), 17	15, (18)	86.9	(14b), 17
17	4.54	dd	8.7, 6.8	16, 18	(18), 19, (20)	72.1	(16), (18), 19
18	5.55	ddd	15.5, 6.8, 1.1	17, 19	(16), 17, 20, (24)	128.9	(17)
19	5.81	dd	15.5, 7.3, 1.1	18, (20)	17, (24)	138.0	17, (20), 21ab, 24
20	2.58–2.50	m	-	(19), 21ab, 24	(18), (19), 24	34.0	(18), 19, 21ab, 24
21a	2.18	dd	15.1, 7.5	20	(19), 20, 24	41.8	24
21b	2.15	dd	15.1, 6.9				
22	-	-	-	-	-	173.2	21ab, 25
23	0.83	d	7.0	3	2, 3	19.5	(2), (3), (4)
24	0.85	d	6.8	20	20, (18), (19)	20.4	21ab
25	3.46	s	-	-	-	51.8	-

5.7 Diverted Total Synthesis Approach

5.7.1 Synthesis of Four Diastereomeric Southern Fragments

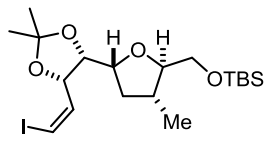
5.7.1.1 Testing the Original Route for Structural Confirmation

Acetonide 118c. PTSA·H_2O (50.5 mg, 0.27 mmol) was added to a solution of diol **117c** (887 mg, 2.55 mmol) in 2,2-dimethoxypropane (26 mL). The resulting mixture was stirred at ambient temperature for 14 h. The reaction was quenched with sat. $NaHCO_3$ (20 mL), the phases were separated and the aq. phase extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/methyl *t*-butyl ether 9:1) to afford the title compound as a colourless oil (474 mg, 48%). $[\alpha]_D^{20}$ = −7.0 (c = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, *J* = 6.8 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H), 3.99 (ddd, *J* = 9.4, 6.9, 5.6 Hz, 1H), 3.74 (s, 3H), 3.62 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.58 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.52 (dt, *J* = 7.7, 4.6 Hz, 1H), 2.17–2.05 (m, 2H), 1.57 (d, *J* = 0.7 Hz, 3H), 1.54–1.45 (m, 1H), 1.37 (d, *J* = 0.7 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.05–0.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 110.6, 86.2, 80.4, 76.5, 76.0, 64.7, 52.1, 38.1, 36.3, 27.0, 25.9, 25.5, 18.3, 17.4, −5.4, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 1758, 1461, 1381, 1252, 1204, 1165, 1129, 1089, 1006, 837, 777, 669, 514 cm^{-1}. MS (ESIpos) *m/z* (%): 411.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{36}O_6SiNa$: 411.2173, found: 411.2176.

Alcohol 119c. A solution of $LiAlH_4$ (51 mg, 1.34 mmol) in THF (5.0 mL) was added to a solution of ester **118c** (474 mg, 1.22 mmol) in THF (6.5 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 3 h. The mixture was cooled to 0 °C and the reaction was carefully quenched with methanol until gas evolution ceased. The mixture was then poured via cannula into sat. Rochelle salt (10 mL), the flask rinsed with *t*-butyl methyl ether (5 mL) and the emulsion vigorously stirred at ambient temperature overnight. The phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to afford the title compound **119c** as a colourless oil (275 mg, 63%). $[\alpha]_D^{20}$ = +13.5 (c = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (ddd, *J* = 8.6, 5.6, 5.0 Hz, 1H), 4.05 (td, *J* = 9.3, 5.4 Hz, 1H), 3.98 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.83 (ddd, *J* = 11.7, 8.6, 4.6 Hz, 1H), 3.76 (ddd, *J* = 11.8, 9.7, 5.0 Hz, 1H), 3.70–3.64 (m, 1H), 3.61–3.55 (m, 2H), 3.47 (dd, *J* = 9.8, 4.8 Hz, 1H), 2.34 (ddd, *J* = 12.4, 6.9, 5.3 Hz, 1H), 2.19–2.05 (m, 1H), 1.49 (ddd, *J* = 12.4, 11.0, 9.2 Hz, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 108.3, 86.8, 80.5, 77.6, 76.4, 64.3,

60.5, 40.3, 35.4, 27.8, 25.8, 25.3, 18.2, 17.0, –5.5, –5.5 ppm. IR (film): $\tilde{\nu}$ = 3486, 2956, 2930, 2886, 2858, 1472, 1462, 1380, 1370, 1253, 1217, 1166, 1129, 1057, 1005, 868, 838, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 383.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{36}O_5SiNa$: 383.2224, found: 383.2226.

(*Z*)-Alkenyl Iodide 184c. Hünig's base (0.38 mL, 2.18 mmol) was added to a solution of alcohol **119c**



(157 mg, 0.435 mmol) in CH_2Cl_2 (2.0 mL) at –20 °C. In a second flask, sulfur trioxide pyridine complex (177 mg, 1.09 mmol) was suspended in DMSO (0.31 mL, 4.4 mmol) and the mixture was stirred for 10 min at ambient temperature, before it was added to the alcohol solution at –25 °C and the flask was rinsed with CH_2Cl_2 (2 mL). The resulting mixture was stirred at –20 °C for 45 min. The mixture was poured into pH 7 phosphate buffer (5 mL) and *t*-butyl methyl ether (5 mL), the phases were separated and the aq. phase was extracted with *t*-butyl methyl ether (3 × 3 mL). The combined organic phases were washed with pH 7 phosphate buffer (20 mL), followed by brine (20 mL), dried over Na_2SO_4, filtered and concentrated under high vacuum to yield crude aldehyde (145 mg, 93%) as a pale yellow oil, which was subjected to olefination without further purification.

Iodomethyltriphenylphosphonium iodide (397 mg, 910 µmol) was added in portions to a solution of NaHMDS (150 mg, 818 µmol) in THF (1.0 mL). The resulting yellow mixture was stirred at ambient temperature for 1.5 h before it was cooled to –78 °C. HMPA (0.37 mL, 2.1 mmol) was added, followed by a solution of the crude aldehyde (145 mg, 404 µmol) in THF (3.0 mL). The resulting mixture was stirred at –78 °C for 4 h. The reaction was quenched with water (3 mL) and the aq. phase was extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine (3 × 5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 50:1 to 40:1) to afford the title compound as a colourless oil (94.6 mg, 45% over two steps, *Z*/*E* > 20:1). $[\alpha]_D^{20}$ = +54.2 (c = 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.37 (t, *J* = 7.9 Hz, 1H), 4.89 (ddd, *J* = 7.8, 6.5, 1.1 Hz, 1H), 4.26 (t, *J* = 6.3 Hz, 1H), 3.96 (dt, *J* = 9.1, 5.7 Hz, 1H), 3.65 (dd, *J* = 10.7, 4.3 Hz, 1H), 3.61 (td, *J* = 11.2, 10.8, 4.1 Hz, 1H), 3.52 (dt, *J* = 8.2, 4.2 Hz, 1H), 2.21–2.08 (m, 2H), 1.56–1.51 (m, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.06–0.03 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 108.8, 86.0, 85.4, 79.8, 79.8, 76.9, 64.5, 38.0, 36.0, 27.5, 25.9, 25.2, 18.3, 17.3, −5.3, −5.3 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1461, 1380, 1251, 1217, 1163, 1129, 1080, 1055, 1006, 837, 809, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 505.1 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{35}O_4ISiNa$: 505.1242, found: 505.1247.

Alcohol 198c. Pyridine (2.2 ml, 27 mmol) and HF·pyridine (0.26 ml, 2.9 mmol) were added to a solution of compound **184c** (93 mg, 0.19 mmol) in THF (4.5 mL) in a Teflon® vial. The resulting mixture was stirred at ambient temperature for 16 h. The mixture was diluted with EtOAc (5 mL) and the reaction was carefully quenched with sat. $NaHCO_3$ (5 mL). The phases were separated and the aq. phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with a 1:3 mixture of sat. NH_4Cl and brine (10 ml), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 4:1 to 2:1 to 1:1) to afford the title compound as a colourless oil (70 mg, quant.). $[\alpha]_D^{20}$ = +75.1 (c = 1.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.50 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.34 (t, *J* = 7.9 Hz, 1H), 4.91 (ddd, *J* = 7.9, 6.5, 1.2 Hz, 1H), 4.26 (t, *J* = 6.5 Hz, 1H), 3.99–3.91 (m, 1H), 3.69 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.58 (ddd, *J* = 8.7, 5.6, 2.8 Hz, 1H), 3.46 (dd, *J* = 11.6, 5.6 Hz, 1H), 2.19 (ddd, *J* = 12.0, 7.2, 5.9 Hz, 1H), 2.12–2.02 (m, 1H), 1.89 (br s, 1H), 1.57 (ddd, *J* = 12.0, 10.8, 9.3 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.7, 109.2, 86.0, 84.9, 80.2, 80.1, 76.7, 63.3, 38.4, 35.1, 27.5, 25.2, 16.4 ppm. IR (film): $\tilde{\nu}$ = 3457, 2931, 2873, 1455, 1380, 1245, 1214, 1162, 1049, 870, 513 cm^{-1}. MS (EI) *m/z* (%): 759.1 (23), 659.3 (2), 572.1 (4), 467.0 (2), 391.0 (100). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{21}IO_4Na$: 391.0377, found: 391.0378.

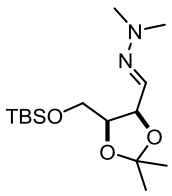
5.7.1.2 Homocrotylations Reactions

Boronate 283. Following the literature-known procedure, the homocrotylboration reagent **270** was synthesized in 11% over 5 steps (190 mg, 1.23 mmol) from *Z*-propenylboronic acid.[393] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (t, *J* = 5.3 Hz, 4H), 1.96 (p, *J* = 5.3 Hz, 2H), 0.98 (d, *J* = 5.9 Hz, 3H), 0.77–0.65 (m, 3H), 0.65–0.57 (m, 2H), −0.42 (q, *J* = 4.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 61.0, 26.7, 12.6, 12.5, 9.9, 8.5 ppm (2C). IR (film): $\tilde{\nu}$ = 3461, 2954, 2929, 2886, 2857, 1472, 1462, 1388, 1361, 1252, 1129, 1075, 1004, 832, 773, 672 cm^{-1}. ^{13}C NMR (128 MHz, $CDCl_3$): δ = 28.6 ppm. MS (EI) *m/z* (%): 154 (30), 111 (30), 68 (92), 67 (98), 55 (60), 41 (100), HRMS (EI): *m/z* calcd for $C_8H_{15}O_2B$: 154.1165, found: 154.1163. The analytical and spectroscopic data are in agreement with those reported in the literature.[393]

Lactol 277. $NaBH_4$ (3.4 g, 89.87 mmol) was added cautiously to a solution of 2,3-O-isopropylidene-D-ribofuranose (4.3 g, 22.62 mmol) in methanol (22 mL) at 4 °C. After stirring for 4 h at ambient temperature, acetic acid (6.73 mL, 89.87 mmol) was added dropwise and the mixture was stirred for 10 min until the excess borohydride had decomposed. Sodium periodate (5.3 g, 24.78) was added portionwise over 10 min and the reaction was then stirred for 1 h at ambient temperature. The resulting mixture was filtered through Celite®, which was rinsed with CH_2Cl_2 (200 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were washed with brine and dried over Na_2SO_4, filtered and concentrated to give a

colourless residue. The residue was purified by flash chromatography (hexane/EtOAc 1:1) to give the title compound as a colourless syrup (3.02 g, 83%, α/β = 9:1). $[\alpha]_D^{20}$ = +66 (c = 1.19, $CHCl_3$). Spectral data for α-**277:** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.42 (d, *J* = 1.4 Hz, 1H), 4.84 (dd, *J* = 5.9, 3.5 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.11–4.00 (m, 2H), 2.69 (br s, 1H), 1.47 (d, *J* = 0.7 Hz, 3H), 1.32 (d, *J* = 0.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 112.3, 101.8, 85.1, 79.9, 72.0, 26.2, 24.7 ppm. Spectral and analytical data for β-**264**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.99 (ddd, *J* = 11.5, 3.7, 0.7 Hz, 1H), 4.76 (ddd, *J* = 6.2, 3.8, 0.9 Hz, 1H), 4.49 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.98 (dd, *J* = 11.0, 0.8 Hz, 1H), 3.88 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.54 (dd, *J* = 11.0, 3.7 Hz, 1H), 1.54 (d, *J* = 0.7 Hz, 3H), 1.38 (d, *J* = 0.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 113.4, 97.4, 79.6, 78.2, 67.6, 26.0, 24.9 ppm. IR (film): $\tilde{\nu}$ = 3420, 2942, 1375, 1209, 1162, 1066, 987, 856 cm^{-1}. MS (EI) *m/z* (%): 145 (100), 99 (8), 85 (55), 71 (5), 59 (19), 43 (34). HRMS (ESIpos): *m/z* calcd for $C_7H_{12}O_4Na$: 183.0628, found: 183.0629. The analytical and spectroscopic data are in agreement with those reported in the literature.[405]

Hydrazone 292. 1,1-Dimethylhydrazine (1.10 mL, 14.5 mmol) was added to a solution of the lactol



277 (1.96 g, 12.2 mmol) in abs. EtOH (23 mL). The mixture was heated to reflux for 2.5 h. The mixture was allowed to cool and concentrated to give the crude hydrazone **291** as a pale yellow oil which was used directly in the next step.

Imidazole (1.10 g, 16.2 mmol) and TBSCl (2.00 g, 13.3 mmol) were added to a solution of crude hydrazone **291** in CH_2Cl_2 (45 mL) at 0 °C. The mixture was allowed warming to ambient temperature over 16 h and the reaction was quenched with sat. NH_4Cl (100 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a pale yellow residue. The residue was purified by flash chromatography (hexane/ EtOAc 4:1) to give the title compound as a colourless syrup. (3.5 g, 90%). $[\alpha]_D^{20}$ = +28.2 (c = 1.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.52 (d, *J* = 7.3 Hz, 1H), 4.74 (dd, *J* = 7.3, 6.7 Hz, 1H), 4.20 (ddd, *J* = 6.7, 5.8, 4.8 Hz, 1H), 3.73 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.62 (dd, *J* = 11.0, 4.8 Hz, 1H), 2.81 (s, 6H), 1.48 (d, *J* = 0.7 Hz, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 130.6, 108.5, 78.4, 78.3, 62.3, 42.6, 27.6, 25.9, 25.2, 18.2, −5.3, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2930, 2857, 1472, 1379, 1251, 1214, 1094, 1014, 837, 777 cm^{-1}. MS (EI) *m/z* (%): 655.4 (15), 570.4 (4), 431.2 (6), 339.2 (100), 259.2 (28). HRMS (ESIpos): *m/z* calcd for $C_{15}H_{32}N_2O_3SiNa$: 339.2074, found: 339.2077. The analytical and spectroscopic data are in agreement with those reported in the literature.[405]

Aldehyde 293. Ozone was bubbled through a solution of hydrazone **292** (3.10 g, 9.79 mmol) and Sudan Red III (10 mg) in CH_2Cl_2 (100 mL) at −78 °C until the colour of the indicator had faded from red to yellow. Argon was bubbled through the mixture for 30 min at which point dimethylsulfide (3.62 mL, 49.0 mmol) was added and the mixture was allowed to reach ambient temperature over 4 h. The mixture was concentrated to a yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to give the title compound as a colourless liquid (1.87 g, 69%). Boiling Point: 75-80 °C at 1 x 10^{-3} mbar. $[\alpha]_D^{20}$ = −43.9 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (d, *J* = 2.0 Hz, 1H), 4.47 (ddd, *J* = 7.9, 3.9, 2.8 Hz, 1H), 4.42 (dd, *J* = 7.9, 2.0 Hz, 1H), 3.78 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.69 (dd, *J* = 11.4, 2.8 Hz, 1H), 1.57 (d, *J* = 0.8 Hz, 3H), 1.38 (d, *J* = 0.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.2, 110.6, 80.8, 79.7, 60.5, 26.8, 25.7, 25.0, 18.2, −5.5, −5.7 ppm. IR (film): $\tilde{\nu}$ = 2931, 2858, 1732, 1381, 1254, 1214, 1146, 1091, 1015, 837, 778 cm^{-1}. MS (EI) *m/z* (%): 199 (5), 187 (3), 171 (6), 159 (32), 145 (3), 129 (70), 117 (100), 101 (32), 89 (30), 75 (100), 59 (19). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{27}O_4Si$ [M+H$^+$]: 275.1673, found: 275.1677. The analytical and spectroscopic data are in agreement with those reported in the literature.[405]

Phosphoramidite (*S,R,R*)-295. Phosphorus trichloride (0.14 mL, 1.62 mmol) was added to a solution of (*R*)-bis-1-(2-methoxyphenyl)ethylamine (462 mg, 1.62 mmol) and Et_3N (1.13 mL, 8.09 mmol) in THF (25 mL) at −78 °C. The mixture was allowed to reach ambient temperature and stirred for 4 h. (*S*)-BINOL (464 mg, 1.62 mmol) was then added in a single portion. The cloudy mixture was stirred for 16 h before it was filtered through Celite®, which was rinsed with EtOAc (50 mL). The combined filtrates were concentrated to give a pale yellow residue, which was purified by flash chromatography (hexane/EtOAc 9:1) to give the product as a white foam. The foam was triturated with cold *t*-butyl methyl ether to give the the title compound as a white solid (796 mg, 82%). $[\alpha]_D^{20}$ = +237.7 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.89 (m, 4H), 7.61–7.53 (m, 2H), 7.44–7.30 (m, 6H), 7.28–7.21 (m, 2H), 6.93 (td, *J* = 7.8, 1.7 Hz, 2H), 6.66 (td, *J* = 7.5, 1.1 Hz, 2H), 6.44–6.38 (m, 2H), 5.07–4.97 (m, 2H), 3.50 (s, 6H), 1.57 (s, 3 H), 1.56 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 150.7, 150.6, 150.1, 133.0, 132.9, 132.9, 132.2, 131.3, 130.4, 130.2, 129.4, 128.3, 128.1, 127.4, 127.4, 127.2, 127.2, 125.9, 125.7, 124.6, 124.4, 124.3, 124.2, 122.8, 122.4, 122.4, 121.7, 121.7, 119.4, 109.2 (2C), 54.6 (2C), 48.3, 48.2, 22.4, 22.2 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 151.4 ppm. IR (film): $\tilde{\nu}$ = 3055, 2967, 2834, 1589, 1491, 1463, 1328, 1233, 1204, 1097, 1070, 1032, 948, 823, 749, 626 cm^{-1}. MS (EI) *m/z* (%): 901.4 (18), 745.5 (8), 600.2 (19), 504.4 (5), 387.1 (3), 286.2 (100), 241.2 (3). HRMS (ESIpos): *m/z* calcd for $C_{38}H_{35}NO_4P$ [M+H$^+$]: 600.2298, found: 600.2303.

Alcohol 284a. Phosphoramidite (*S,S,S*)-**295** (10.8 mg, 18.2 µmol) was added to a solution of $Ni(cod)_2$ (5.0 mg, 18 µmol) in toluene (1.9 mL) and the mixture was stirred for 10 min during which time the pale yellow solution to became orange. To this mixture was added sequentially and rapidly; isoprene (0.15 mL, 1.5 mmol), aldehyde *ent*-**293** (100 mg, 0.364 mmol) and triethylborane (1 M in hexane, 0.88 mL, 0.88 mmol). The resulting dark orange/red mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. NH_4Cl (50 mL) and methyl *t*-butylether (50 mL). The aq. phase was separated and extracted with methyl *t*-butylether (2 x 50 mL). The combined organic phases were washed with brine and dried over Na_2SO_4, filtered and concentrated to give a pale green/yellow oil. The diastereomeric mixture ((3*S,*5*S*)/(3*R,*5*R*)/(*3R,*5*S*) = 2:1:1) was purified by flash chromatography (toluene/methyl *t*-butylether 95:5) to give the (3*S,*5*S*)-**288a** (37.5 mg, 30%) and (3*S,*5*S*)-**284a** (19 mg, 15%) a colourless oil.

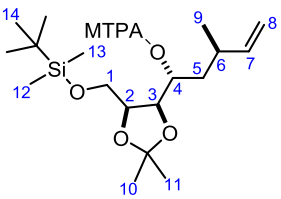
Spectral and analytical data for **288a**: $[\alpha]_D^{20}$ = –5.8 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.01 (ddd, *J* = 17.2, 1.9, 1.3 Hz, 1H), 4.90 (ddd, *J* = 10.3, 1.9, 1.1 Hz, 1H), 4.22 (ddd, *J* = 10.1, 5.3, 3.4 Hz, 1H), 4.00 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.93–3.86 (m, 1H), 3.85–3.83 (m, 1H), 3.82–3.76 (m, 1H), 3.58 (ddd, *J* = 10.3, 3.4, 0.7 Hz, 1H), 2.64–2.47 (m, 1H), 1.67–1.54 (m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3, 111.8, 108.3, 81.2, 77.2, 66.7, 62.0, 40.7, 33.3, 28.1, 25.7, 25.4, 18.8, 18.2, −5.6, −5.7 ppm. IR (film): $\tilde{\nu}$ = 3489, 2933, 1471, 1370, 1255, 1219, 1082, 1004, 837, 780 cm^{-1}. MS (EI) *m/z* (%): 711.5 (4), 435.5 (3), 367.2 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{36}O_4SiNa$: 367.2275, found: 367.2275.

Spectral data for **284a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.78 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 4.98 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.91 (ddd, *J* = 10.3, 1.8, 1.0 Hz, 1H), 4.15 (td, *J* = 6.8, 4.3 Hz, 1H), 4.02 (dd, *J* = 6.5, 3.0 Hz, 1H), 3.94 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.89 (dddd, *J* = 8.9, 5.7, 3.6, 2.2 Hz, 1H), 3.74 (dd, *J* = 10.7, 4.3 Hz, 1H), 2.76 (d, *J* = 5.7 Hz, 1H), 2.42 (tdd, *J* = 8.2, 6.6, 3.6 Hz, 1H), 1.76–1.62 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H) ppm.

Alcohol 296a. To a solution of $Ni(cod)_2$ (100 mg, 0.36 mmol) in toluene (38 mL) was added phosphoramidite (*S,R,R*)-**295** (222 mg, 0.37 mmol) and the mixture was stirred for 10 min during which time the pale yellow solution became orange. To this mixture were added, sequentially and rapidly; isoprene (3.0 mL, 30 mmol), aldehyde **293** (1.94 g, 7.05 mmol) and triethylborane (1 M in hexane, 17 mL, 17 mmol). The resulting dark orange/red mixture was stirred at ambient temperature for 16 h. The

reaction was quenched with sat. NH_4Cl (50 mL) and the mixture diluted with methyl *t*-butylether (50 mL). The aq. phase was separated and extracted with methyl *t*-butylether (2 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a pale green/yellow oil. The diastereomeric mixture ((3*R*,5*R*)/(3*S*,5*S*)/(3*S*,5*R*) = 5.2:1:0.52) was purified by flash chromatography (toluene/methyl *t*-butylether 95:5) to give the title compound as a colourless oil (1.45 g, 60%, contaminated with 10% of the (3*S*,5*R*)-configured diastereomer **296c**). Spectral and analytical data for **296a**: $[\alpha]_D^{20}$ = +6.6 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 4.89 (ddd, *J* = 17.2, 1.9, 1.3 Hz, 1H), 4.78 (ddd, *J* = 10.3, 1.9, 1.1 Hz, 1H), 4.10 (ddd, *J* = 10.1, 5.3, 3.4 Hz, 1H), 3.88 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.80–3.73 (m, 1H), 3.72 (br s, 1H), 3.70–3.64 (m, 1H), 3.46 (ddd, *J* = 10.3, 3.4, 0.7 Hz, 1H), 2.48–2.35 (m, 1H), 1.57–1.41 (m, 2H), 1.24 (s, 3H), 1.20 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.2, 111.6, 108.2, 81.1, 77.2, 66.5, 61.8, 40.5, 33.2, 28.0, 25.6, 25.2, 18.7, 18.0, −5.7, −5.8 ppm. IR (film): $\tilde{\nu}$ = 3489, 2933, 1471, 1370, 1255, 1219, 1082, 1004, 837, 780 cm^{-1}. MS (EI) *m/z* (%): 711.5 (4), 435.5 (3), 367.2 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{36}O_4SiNa$: 367.2275, found: 367.2275.

Mosher Ester Analysis of Homoallyl Alcohol 296a. Et_3N (13 µL, 0.091 mmol) and DMAP (0.4 mg, 0.003 mmol) were added to a solution of homoallyl acohol **283a** (10.5 mg, 0.031 mmol) in CH_2Cl_2 (1 mL) followed by (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (8.6 µL, 0.046 mmol). The resulting mixture was stirred at ambient temperature for 16 h. After quenching with sat. $NaHCO_3$ (3 mL), the aq. phase was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/methyl *t*-butylether 95:5) to give the corresponding (*S*)-Mosher ester **(*S*)-MTPA-296a** (10.2 mg, 60%). $[\alpha]_D^{20}$ = −15.4 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.53 (m, 2H), 7.43–7.36 (m, 3H), 5.72 (ddd, *J* = 17.4, 10.3, 7.4 Hz, 1H), 5.52 (ddd, *J* = 8.5, 5.3, 3.9 Hz, 1H), 4.98–4.93 (m, 1H), 4.93–4.90 (m, 1H), 4.19 (dd, *J* = 6.5, 5.3 Hz, 1H), 4.11–4.04 (m, 1H), 3.68 (dd, *J* = 11.1, 4.9 Hz, 1H), 3.58–3.52 (m, 4H), 2.24–2.14 (m, 1H), 1.87 (ddd, *J* = 14.3, 8.5, 5.6 Hz, 1H), 1.66 (ddd, *J* = 14.7, 9.0, 3.9 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2932, 1749, 1463, 1380, 1254, 1169, 1104, 1019, 838, 778, 719 cm^{-1}. MS (EI) *m/z* (%): 1143.5 (40), 860.9 (5), 583.3 (100), 543.2 (8). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{43}F_3O_6SiNa$: 583.2673, found: 583.2674.



The same procedure using (*S*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride was followed (reaction time 48 h) for the preparation of **(*R*)-MTPA-296a** (4.8 mg, 26%). $[\alpha]_D^{20}$ = +25.6 (c = 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.55 (m, 2H), 7.43–7.35 (m, 3H), 5.66 (ddd, *J* = 16.9, 10.5, 7.5 Hz, 1H), 5.49 (dt, *J* = 8.4, 4.0 Hz, 1H), 4.90–4.87 (m, 1H), 4.85 (d, *J* = 1.0 Hz, 1H), 4.29 (dd, *J* = 6.6,

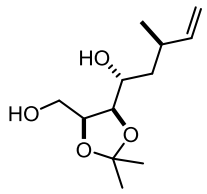
4.2 Hz, 1H), 4.21–4.11 (m, 1H), 3.70 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.62 (dd, *J* = 11.0, 6.1 Hz, 1H), 3.56 (s, 3H), 2.11– 1.99 (m, 1H), 1.85 (ddd, *J* = 14.5, 8.8, 5.6 Hz, 1H), 1.61–1.51 (m, 1H), 1.45 (s, 3H), 1.33 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2931, 1748, 1463, 1381, 1254, 1169, 1106, 1020, 837, 779, 719 cm^{-1}. MS (EI) *m/z* (%): 1143.5 (20), 860.4 (4), 583.3 (100), 543.2 (3). HRMS (ESIpos) *m/z* calcd for $C_{28}H_{43}F_3O_6SiNa$: 583.2673, found: 583.2675.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-20. Mosher ester analysis for the assignment of the C(4) stereocenter; arbitrary numbering as shown in the insert.

Assignment	296a	(*S*)-MTPA-296a	(*R*)-MTPA-296a	Δ (δ (S–R)) [ppm]
1a	3.67	3.68	3.70	-0.03
1b	3.46	3.56	3.62	-0.06
2	4.10	4.08	4.16	-0.08
3	3.88	4.19	4.29	-0.10
4	3.76	5.52	5.49	+0.03
5a	1.47	1.87	1.85	+0.02
5b	1.47	1.66	1.55	+0.10
6	2.42	2.19	2.05	+0.14
7	5.72	5.72	5.66	+0.06
8a	4.89	4.95	4.88	+0.07
8b	4.78	4.91	4.85	+0.06
9	0.91	1.04	0.98	+0.06
10	1.24	1.36	1.45	-0.09
11	1.20	1.29	1.33	-0.04
12	0.07	0.07	0.04	+0.03
13	0.06	0.06	0.05	+0.01
14	0.79	0.90	0.89	+0.01

Diol 278b. A solution of TBAF (1 M in THF, 4.4 mL, 4.4 mmol) was added dropwise to a solution of

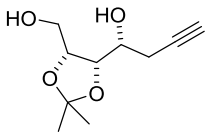


homoallyl alcohol **296a** (1.45 g, 4.20 mmol, contaminated with 10% of the 1,3-*syn* diastereoisomers **296c**) in THF (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min before it was poured into a solution of sat. NH_4Cl. (50 mL) and diluted with EtOAc (50 mL). The organic phase was separated and the aq. phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to a colourless residue. The residue was purified twice by flash chromatography (hexane/EtOAc 1:1) to yield the diol **278b** (950 mg, 98%, contaminated with 10% of the 1,3-*syn* diastereoisomers from **296c**). $[\alpha]_D^{20}$ = +2.9 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 5.84 (ddd, *J* = 17.2, 10.2, 7.9 Hz, 1H), 5.09 (dt, *J* = 17.3, 1.4 Hz, 1H), 4.97 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 4.28 (ddd, *J* = 8.0, 5.2, 4.4 Hz, 1H), 3.98–3.85 (m, 2H), 3.83 (d, *J* = 7.9 Hz, 1H), 3.72 (dd, *J* =

11.4, 4.5 Hz, 1H), 2.95 (br s, 2H), 2.43 (dtd, *J* = 13.8, 6.9, 1.0 Hz, 1H), 1.83–1.73 (m, 1H), 1.55–1.45 (m, 1H), 1.42–1.39 (m, 3H), 1.34 (d, *J* = 0.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.4, 113.3, 108.2, 80.1, 77.4, 69.1, 61.0, 41.0, 35.4, 28.0, 25.4, 20.1 ppm. IR (film): $\tilde{\nu}$ = 3458, 2954, 2929, 2857, 1740, 1461, 1440, 1388, 1253, 1128, 1080, 1004, 836, 777, 647 cm^{-1}. MS (EI) *m/z* (%): 215 (30), 141 (15), 137 (12), 131 (25), 123 (23), 119 (8), 113 (33), 109 (11), 99 (33), 95 (43), 91 (12), 85 (24), 83 (36), 81 (32), 79 (15), 74 (31), 73 (22), 59 (100), 43 (43), 41 (27). HRMS (ESIpos): *m/z* calcd for $C_{12}H_{22}O_4Na$: 253.1410, found: 253.1413.

5.7.1.3 Synthesis of Diol 278a

Diol 299. Preparation of allenyl Grignard reagent: To a 250 mL 3-necked round-bottomed flask fitted



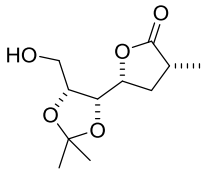
with a condenser, pressure equalizing dropping funnel and thermometer were added magnesium turnings (6.08 g, 250 mmol), ether (100 mL) and $HgCl_2$ (250 mg). The suspension was stirred for 30 min at ambient temperature before cooling to 0 °C. A small portion of a solution of propargyl bromide was added to intitate the reaction (2.28 mL). Once initiated (20 min, internal temperature reached 14 °C), the mixture was cooled to −20 °C and the remaining propargyl bromide (20 mL, 200 mmol, 80% soln.) was added dropwise over 30 min in order to maintain the temperature between −1 and +1 °C. After stirring for 45 min at 0 °C, the pale grey/green mixture was filtered through Celite® into to a graduated Schlenk tube and diluted to 200 mL with Et_2O. The clear pale yellow solution was titrated to be 0.745 M versus iodine (75% yield). The solution of allenyl Grignard reagent was stored at −20 °C for months without loss of activity.

To a solution of (−)-2,3-O-Isopropylidene-D-erythronolactone (19.9 g, 126 mmol) in THF (500 mL) at −78 °C was added the solution of allenyl Grignard reagent (185 mL, 0.745 M in Et_2O, 138 mmol) dropwise, not letting the internal temperature rise above −70 °C. The colourless homogenous reaction was stirred at −78 °C for 1 h. The reaction was quenched with sat. NH_4Cl (100 mL, added while keeping the temperature below −65 °C) and the mixture was allowed to reach ambient temperature. Distilled water was added dropwise until a clear bisphasic mixture was observed. The aq. phase was extracted with *t*-butyl methyl ether (3 x 500 mL) and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to give the crude lactol **301** contaminated with small amounts of allene **302** as a colourless oil which was immediately used in the next step.

A solution of lactol **301** (25.0 g, 126 mmol) in THF (250 mL with rinses) was added dropwise to a solution of Dibal-H (90 mL, 51 mmol) in THF (250 mL, Caution! Dissolution of Dibal-H is extremely exothermic) at −78 °C, not letting the temperature rise above −70 °C. The mixture was allowed to warm to 10 °C overnight before being cooled to 4 °C and the reaction was quenched cautiously with

methanol (20 mL). This mixture was poured onto a 1:1 mixture of sat. Rochelle's (500 mL) and EtOAc (500 mL) and stirred overnight. The organic phase was separated and the aq. phase was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to a colourless oil which solidified on standing. This solid represents a mixture of products (*syn*/*anti* = 95:5) and 4% allene deriving from **302**. The crude solid was cyrstallized four times from boiling toluene (50 mL; 40 mL x 3) to give the title compound as colourless needles (25.1 g, 80% over 2 steps). The product is the pure *syn* diastereomer and contains ca. 0.2% allene by ^{1}H-NMR analysis. $[\alpha]_D^{20}$ = –24.2 (c = 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35–4.22 (m, 2H), 3.94–3.79 (m, 3H), 3.11 (br d, *J* = 6.1 Hz, 1H), 2.68–2.60 (m, 1H), 2.59–2.45 (m, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.52 (s, 3H), 1.39 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 108.5, 80.4, 77.1, 77.0, 70.6, 68.0, 60.9, 26.9, 24.8, 24.8 ppm. IR (film): $\tilde{\nu}$ = 3267, 3200, 2985, 2933, 2887, 1470, 1382, 1386, 1220, 1134, 1091, 1013, 841, 670 cm^{-1}. MS (EI) *m/z* (%): 185 (4), 131 (10), 103 (8), 85 (13), 73 (10), 67 (8), 59 (100), 55 (15), 43 (55), 39 (18). HRMS (ESIpos): *m/z* calcd for $C_{10}H_{16}O_4Na$: 223.0941, found: 223.0942. Single crystals were grown by cooling the ethanol solution confirming absolute stereochemistry of **299** (see Appendix 8.1).

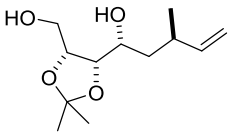
Lactone 297. A 100 mL autoclave was charged with $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), PTSA·H_2O (125 mg, 0.66 mmol), diphenyl-(6-methyl-2-pyridyl)-phosphine (273 mg, 0.98 mmol), BHT (724 mg, 3.29 mmol) and NMP (10 mL). The red mixture was stirred until a homogenous solution was obtained (around 10 min) before adding the diol **299** (6.58 g, 32.9 mmol). The autoclave apparataus was assembled and the mixture was stirred under high-vacuum for 2 h. The autoclave was pressurized with CO (60 bar) and the mixture was stirred at 45 °C for 16.5 h. The mixture was allowed to cool to ambient temperature before it was filtered through a pad of Florisil® (100 g), which was rinsed with EtOAc (500 mL). The filtrate containing α,β-unsaturated ester **298** was concentrated. The residue was diluted with EtOAc (250 mL) before adding Pd/C (10 wt.-%, 1.75 g, 1.64 mmol, 5 mol%). The flask was purged and back-filled with H_2 gas three times before the mixture was stirred for 1 h under balloon pressure of H_2. The catalyst was removed by filtration of the mixture through Celite®. The filtrate was concentrated to a pink oil, which was purified by flash chromatography (hexane/EtOAc 4:1) giving a mixture of lactone **297** and butenolide **304** (**297**/**304** = 0.45:1) as a colourless oil.



The crude mixture was redissolved in EtOAc (150 mL) before adding Pd/C (10 wt.-%, 1.75 g, 1.64 mmol, 5 mol%). The flask was purged and back-filled with H_2 gas three times before the mixture was stirred for 16 h under balloon pressure of H_2. After filtration through Celite® and rinsing with EtOAc, the combined filtrates were concentrated to a colourless oil affording the title comound as a single isomer (6.94 g, 92% over 2 steps). $[\alpha]_D^{20}$ = –43.5 (c = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (ddd, *J* = 9.7, 6.5, 3.4 Hz, 1H), 4.35 (td, *J* = 6.5, 5.1 Hz, 1H), 4.15–4.09 (m, 1H), 3.93–3.78 (m,

2H), 2.73–2.60 (m, 1H), 2.46 (ddd, *J* = 12.5, 9.3, 6.5 Hz, 1H), 2.11–2.05 (m, 1H), 1.87 (ddd, *J* = 12.4, 11.1, 9.6 Hz, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.1, 109.4, 77.6, 76.9, 75.4, 61.3, 34.7, 32.8, 26.9, 25.3, 15.2 ppm. IR (film): $\tilde{\nu}$ = 3457, 2983, 2937, 1765, 1456, 1381, 1215, 1167, 1035, 932, 856, 520 cm^{-1}. MS (EI) *m/z* (%): 215 (100), 199 (30), 181 (10), 155 (20), 137 (25), 131 (75), 109 (100), 99 (45), 85 (60), 81 (50), 59 (100), 43 (65). HRMS (ESIpos): *m/z* calcd for $C_{11}H_{18}O_5Na$: 253.1046, found: 253.1046.

Diol 278a. A solution of Dibal-H (1 M in CH_2Cl_2, 50 mL, 50 mmol) was added dropwise over 30 min to a



mechanically stirred solution of lactone **285** (5.52 g, 24.0 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The resulting thick foamy mixture was mechanically agigated by a steel paddle at −78 °C for an additional 30 min. The reaction was quenched by sequential, and cautious, addition of *t*-butanol (15 mL) and water (15 mL). Silica gel (24 g) was added in one portion and the mixture was allowed to come to ambient temperature and stirred for 1 h until homogenous. The reaction slurry was filtered and the cake was washed with EtOAc (500 mL). The combined filtrates were dried over Na_2SO_4, filtered and concentrated to give the crude lactol **305** as a colourless oil, which was used in the next step without further purification.

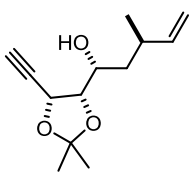
A solution of crude lactol **305** in toluene (50 + 20 mL) was added dropwise to a suspension of methylenetriphenylphosphorane (13.25 g, 47.96 mmol) in toluene (100 mL) at −78 °C, ensuring the internal temperature never rose above −70 °C. The mixture was allowed warming to ambient temperature over 16 h during which time the yellow suspension became homogenous. The mixture was cooled to 4 °C and the reaction was quenched cautiously with sat. NH_4Cl (100 mL). The organic phase was separated, and the aq. phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine and dried over Na_2SO_4, filtered and concentrated to give a cloudy pale yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 1:1) to give the product as a colourless oil which solidified on standing to a waxy solid (5.01 g, 91% over 2 steps). $[\alpha]_D^{20}$ = +9.4 (c = 2.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (m, 1H), 4.98 (dd, *J* = 17.3, 1.6 Hz, 1H), 4.91 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.22–4.15 (m, 1H), 4.04–3.99 (m, 1H), 3.82–3.68 (m, 3H), 2.83 (br s, 2H), 2.38 (hept, *J* = 6.8 Hz, 1H), 1.75–1.64 (m, 1H), 1.48 (s, 3H), 1.41–1.31 (m, 1H), 1.35 (s, 3H) 1.01 (dd, *J* = 6.7, 1.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.4, 112.7, 108.2, 79.1, 77.3, 67.0, 61.0, 41.3, 34.1, 27.2, 25.0, 19.3 ppm. IR (film): $\tilde{\nu}$ = 3406, 2935, 1640, 1372, 1215, 1038, 996, 862, 515 cm^{-1}. MS (EI) *m/z* (%): 483.3 (23), 253.1 (100), 231.1 (10). HRMS (ESIpos): *m/z* calcd for $C_{12}H_{22}O_4Na$: 253.1410, found: 253.1411.

5.7.1.4 **Diverted Synthesis of Alkynes 279a-d**

Compound S26a. TESCl (3.7 mL, 22.04 mmol) and DMAP (100 mg, 0.82 mmol) were added to a solution of diol **278a** (1 g, 4.34 mmol) in pyridine (20 mL). The resulting cloudy mixture was stirred at ambient temperature for 16 h. The mixture was partitioned between water (50 mL) and methyl *t*-butylether (50 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to a colourless residue. The residue was purified by flash chromatography (hexane/methyl *t*-butylether 95:5) to afford the title compound as a colourless oil (2.0 g, 100%). $[\alpha]_D^{20}$ = +25.8 (c = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 4.97 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.90 (ddd, *J* = 10.3, 1.8, 1.1 Hz, 1H), 4.04 (q, *J* = 5.5 Hz, 1H), 4.01–3.96 (m, 1H), 3.92 (td, *J* = 7.7, 4.2 Hz, 1H), 3.72 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.55 (dd, *J* = 10.7, 5.3 Hz, 1H), 2.49–2.36 (m, 1H), 1.51–1.45 (m, 2H), 1.43 (s, 3H), 1.32 (s, 3H), 1.02–0.93 (m, 21H), 0.70–0.57 (m, 12H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.9, 112.1, 107.8, 80.9, 78.1, 68.7, 62.1, 40.6, 33.2, 27.9, 25.4, 18.8, 7.0, 6.7, 5.5, 4.3 ppm. IR (film): $\tilde{\nu}$ = 2955, 2877, 1458, 1370, 1103, 1004, 911, 739 cm^{-1}. MS (EI) *m/z* (%): 939.6 (28), 573.3 (7), 481.3 (100), 345.2 (4). HRMS (ESIpos): *m/z* calcd for $C_{24}H_{50}O_4Si_2Na$: 481.3140, found: 481.3138.

Compound S26b. TESCl (3.46 mL, 20.6 mmol) and DMAP (100 mg, 0.82 mmol) were added to a solution of diol **278b** (950 g, 4.13 mmol) in pyridine (20 mL). The resulting cloudy mixture was stirred at ambient temperature for 16 h. The mixture was partitioned between water (50 mL) and methyl *t*-butylether (50 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to a colourless residue. The residue was purified by flash chromatography (hexane/methyl *t*-butylether 95:5) to afford the title compound as a colourless oil (1.88 g, 99%, contaminated with 10% of the 1,3-*syn*-diastereoisomers from **296c**). $[\alpha]_D^{20}$ = −14.8 (c = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddd, *J* = 17.4, 10.3, 7.4 Hz, 1H), 4.98 (ddd, *J* = 17.2, 1.8, 1.2 Hz, 1H), 4.93 (ddd, *J* = 10.3, 1.8, 0.9 Hz, 1H), 4.18 (ddd, *J* = 7.6, 6.5, 4.2 Hz, 1H), 4.09 (dd, *J* = 6.5, 4.2 Hz, 1H), 4.03 (ddd, *J* = 7.0, 5.1, 4.0 Hz, 1H), 3.84 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.68 (dd, *J* = 11.0, 7.6 Hz, 1H), 2.41–2.29 (m, 1H), 1.64 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.46 (s, 3H), 1.44–1.39 (m, 1H), 1.33 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 18H), 0.65–0.59 (m, 12H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6, 112.6, 107.9, 80.0, 78.6, 68.9, 62.9, 41.5, 33.9, 27.6, 25.3, 19.9, 6.9, 6.7, 5.3, 4.4 ppm. IR (film): $\tilde{\nu}$ = 2954, 2877, 1458, 1378, 1241, 1093, 1005, 910, 740 cm^{-1}. MS (EI) *m/z* (%): 939.6 (25), 545.3 (4), 481.3 (100), 383.3 (10), 327.2 (10). HRMS (ESIpos): *m/z* calcd for $C_{24}H_{50}O_4Si_2Na$: 481.3140, found: 481.3141.

Alkyne 279a. Oxalyl chloride (1.9 mL, 22 mmol) was added dropwise to a solution of DMSO (3.0 mL, 42 mmol) in CH_2Cl_2 (20 mL) at −78 °C ensuring that the internal temperature did not exceed −65 °C. After 15 min of stirring at −78 °C, a solution of **S26a** (2.02 g, 4.39 mmol) in CH_2Cl_2 (12 mL with rinses) was added dropwise, again ensuring the internal temperature did not exceed −65 °C. Stirring was continued at −78 °C for 20 min and then the temperature was raised to −35 °C over 30 min. Stirring was continued at this temperature for 20 min before re-cooling the mixture to −78 °C. Hünig's base (11.5 mL, 66.0 mmol) was added dropwise, again ensuring the internal temperature did not exceed −65 °C. After stirring for 10 min at −78 °C, the mixture was allowed to reach 0 °C over 30 min and the reaction was quenched with sat. NH_4Cl (50 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the aldehyde **308a** as a yellow oil, which was used without further purifcation (1.21 g, 81%, dr = 12.5:1).

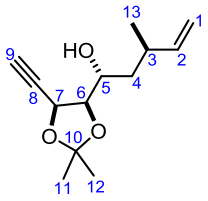


Methanol (95 µL, 2.35 mmol) was added dropwise to a solution of KHMDS (467 mg, 2.33 mmol) in THF (2.5 mL) at 0 °C. The milky suspension was stirred for 20 min at the same temperature and then cooled to −78 °C, at which point a solution of dimethyl-(1-diazo-2-oxopropyl)-phosphonate (486 mg, 2.53 mmol) in THF (1.0 mL) was added dropwise. The yellow solution was stirred for 30 min at −78 °C before a solution of crude aldehyde **308a** (247 mg, 0.72 mmol) in THF (2.0 mL with rinses) was added dropwise. The mixture was allowed to reach −50 °C over 10 min and then stirred for 1 h at −50 °C before quenching the reaction with sat. NH_4Cl (20 mL). The resulting mixture was diluted with methyl *t*-butylether (20 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 x 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude alkyne **310a** as a yellow oil, which was used without further purification.

A solution of TBAF trihydrate (341 mg, 1.08 mmol) in THF (1.1 mL) was added to a solution of crude alkyne **310a** in THF (5 mL) at 0 °C. After removing the ice bath, the mixture was stirred for 10 min at ambient temperature. The reaction was quenched with sat. NH_4Cl (20 mL) and the resulting mixture was diluted with methyl *t*-butylether (20 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 x 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to a yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to afford the title compound as a colourless oil (131 mg, 81% over 2 steps). $[\alpha]_D^{20}$ = +54.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (ddd, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.02 (dt, *J* = 17.3, 1.5 Hz, 1H), 4.93 (ddd, *J* = 10.3, 1.7, 1.0 Hz, 1H), 4.73 (dd, *J* = 5.8, 2.2 Hz, 1H), 4.05 (ddd, *J* = 9.9, 7.4, 2.6 Hz, 1H), 3.95 (dd, *J* = 7.4, 5.7 Hz, 1H), 2.55 (d, *J* = 2.2 Hz, 1H), 2.54–2.47 (m, 1H), 2.21 (s, 1H), 1.61–1.53 (m, 4H), 1.39–1.33 (m, 4H), 1.05 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101

MHz, $CDCl_3$): δ = 144.8, 112.4, 110.6, 81.1, 79.5, 76.1, 69.5, 66.9, 39.3, 33.6, 27.5, 25.9, 18.8 ppm. IR (film): $\tilde{\nu}$ = 3492, 3307, 2896, 2934, 1641, 1457, 1373, 1213, 1162, 1056, 913, 874, 664 cm^{-1}. MS (EI) *m/z* (%): 209 (11), 149 (3), 125 (10), 111 (6), 96 (27), 81 (24), 67 (31), 59 (76), 55 (62), 43 (100). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{20}O_3Na$: 247.1305, found: 247.1306.

Alkyne 279c. Oxalyl Chloride (1.75 mL, 20.38 mmol) was added dropwise to a solution of DMSO (2.9 mL, 40.83 mmol) in CH_2Cl_2 (20 mL) at −78 °C, ensuring that the internal temperature did not exceed −65 °C. After 15 min at −78 °C, a solution of **S26b** (1.87 g, 4.07 mmol) in CH_2Cl_2 (12 mL with rinses) was added dropwise, again ensuring that the internal temperature did not exceed −65 °C. Stirring was continued at −78 °C for 20 min before raising the temperature to −35 °C over 30 min. Stirring was continued at this temperature for 20 min before re-cooling the mixture to −78 °C. Hünig's base (10.5 mL, 60.3 mmol) was added dropwise, again ensuring that the internal temperature did not exceed −65 °C. After 10 min at −78 °C, the mixture was allowed to reach 0 °C over 30 min and the reaction was quenched with sat. NH_4Cl (50 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the aldehyde **308b** as a yellow oil, which was essentially pure and was used without further purifcation (1.07 g, 77%, dr = 4:1).



Methanol (400 µL, 9.87 mmol) was added dropwise to a solution of KHMDS (2 g, 9.98 mmol) in THF (10 mL) at 0 °C. The milky suspension was stirred for 20 min at the same temperature and then cooled to −78 °C. A solution of dimethyl-(1-diazo-2-oxopropyl)-phosphonate (2 g, 10.41 mmol) in THF (5 mL) was added dropwise at the same temperature. The yellow solution was stirred for 30 min at −78 °C before a solution of crude aldehyde **308b** (1.06 g, 3.1 mmol) in THF (9 mL with rinses) was added dropwise. The mixture was allowed to reach −50 °C over 10 min and then stirred for 1 h at −50 °C. The reaction was quenched with sat. NH_4Cl (20 mL) and the mixture was diluted with methyl *t*-butylether (20 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude alkyne **310b** as a yellow oil, which was used without further purification.

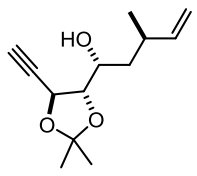
A solution of TBAF trihydrate (1.47 g, 4.65 mmol) in THF (4.7 mL) was added to a solution of the crude alkyne **310b** in THF (30 mL) at 0 °C. After removing the ice bath, the mixture was stirred for 10 min at ambient temperature. The reaction was quenched with sat. NH_4Cl (20 mL) and the mixture was diluted with methyl *t*-butylether (30 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 x 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to a yellow residue. The residue was purified by flash

chromatography (hexane/EtOAc 9:1) to afford the title compound as a colourless oil (264 mg, 38% over 2 steps, contaminated with 10% of the 1,3-*syn* diastereoisomer from **296c**). $[\alpha]_D^{20}$ = −23.4 (c = 1.04, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table* ***S-20***. ^{13}C NMR (150 MHz, $CDCl_3$): *see Table* ***S-20***. IR (film): $\tilde{\nu}$ = 3479, 3298, 2986, 2937, 1640, 1457, 1373, 1227, 1162, 1068, 914, 866, 662 cm^{-1}. MS (EI) *m/z* (%):471.3 (4), 356.2 (5), 247.1 (100), 215.1 (3). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{20}O_3Na$: 247.1305, found: 247.1305.

Table S-20. NMR data of terminal alkyne **279c**; arbitrary numbering scheme as shown in the insert

atom n°	**^{1}H NMR** (600 MHz, $CDCl_3$)					**^{13}C NMR** (150 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1a	5.07	ddd	7.3, 1.8, 1.3	1b, 2	1b,13,3	112.7	3
1b	4.95	ddd	10.3, 1.8, 1.0	1a, 2	1a		
2	5.85	ddd	17.3, 10.3, 7.6	1ab, 3	4b, 13	145.3	1a, 3, 4ab, 13
3	2.52-2.44	m	-	2, 4ab, 13	1a, 5, 5-OH, 4ab, 13	34.7	1ab, 2, 4a, 13
4a	1.75	ddd	14.2, 8.0, 2.6	3, 4b	3, 5, 6, 13	40.8	3, 5-OH, 6, 13
4b	1.58	ddd	14.2, 9.9, 6.4	3, 4a, 5	2, 3, 5, 6, 13		
5	4.03	dddd	9.9, 8.4, 4.5, 2.6	4b, 5-OH, 6	3, 4ab, 5-OH, 13	70.1	6, 4b
6	3.91	dd	8.4, 5.8	7, 5	4ab, 5-OH, 7, 12	80.7	-
7	4.88	dd	5.8, 2.2	6, 9	5-OH, 6, 12	68.1	9
8	-	-	-	-	-	80.3	7, 6
9	2.62	d	2.2	7	-	76.1	7
10	-	-	-	-	-	110.7	7, 11, 12
11	1.52	q	0.5	12	10,12	27.5	12
12	1.35	q	0.5	11	6, 7, 11	25.9	11
13	1.03	d	6.7	3	1a, 2, 3, 4ab, 5	19.8	2, 3, 4

Alkyne 279b. IBX (2.43 g, 8.68 mmol) was added to a solution of diol **278a** (1.00 g, 4.34 mmol) in

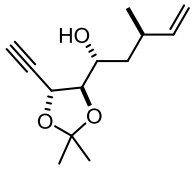


DMSO (8.7 mL). After stirring for 3.5 h, the reaction was quenched with water (40 mL). After sirring for 10 min, the resulting mixture was filtered through a small pad of Celite®, which was rinsed with methyl *t*-butylether (50 mL) and water (10 mL). From the filtrate, the aq. phase was separated and extracted with methyl *t*-butylether (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the lactol **311a** as a colourless oil which was essentially pure and was used without further purification.

K_2CO_3 (1.8 g, 13 mmol) was added to a solution of crude lactol **311a** in methanol (20 mL). The resulting suspension was heated to reflux and dimethyl-(1-diazo-2-oxopropyl)-phosphonate (2.5 g, 13 mmol) in methanol (8 mL) was added dropwise over 6 h. The red homogenous mixture was cooled in an ice bath and neutralized by cautious addition of HCl (1 M, 13 mL). The methanol was evaporated

and the aq. solution was extracted with methyl *t*-butylether (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to afford the title compound as a colourless oil (247 mg, 25% over 2 steps). $[\alpha]_D^{20}$ = −14.4 (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.78 (ddd, *J* = 17.5, 10.2, 7.4 Hz, 1H), 5.02 (dt, *J* = 17.2, 1.4 Hz, 1H), 4.95 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.55 (dd, *J* = 7.5, 2.1 Hz, 1H), 4.00 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.70 (ddt, *J* = 9.4, 7.8, 4.0 Hz, 1H), 2.53 (d, *J* = 2.2 Hz, 1H), 2.49–2.37 (m, 1H), 1.95 (d, *J* = 8.0 Hz, 1H), 1.68 (ddd, *J* = 13.9, 9.3, 6.3 Hz, 1H), 1.49 (s, 3H), 1.46–1.39 (m, 4H), 1.05 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.3, 112.9, 110.7, 84.2, 80.9, 74.8, 68.1, 66.9, 40.8, 34.2, 26.7, 26.0, 19.4 ppm. IR (film): $\tilde{\nu}$ = 3474, 3301, 2988, 2934, 1641, 1457, 1375, 1213, 1162, 1056, 914, 875, 665 cm^{-1}. MS (EI) *m/z* (%): 209 (49), 149 (4), 125 (49), 111 (11), 96 (80), 81 (33), 67 (64), 59 (40), 55 (63), 43 (100). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{20}O_3Na$: 247.1305, found: 247.1307.

Alkyne 279d. IBX (4.52 g, 16.15 mmol) was added to a solution of **278b** (1.86 g, 8.08 mmol) in DMSO



(16 mL). After stirring for 3.5 h, the reaction was quenched with water (80 mL). After stirring for 10 min, the resulting mixture was filtered through a small pad of Celite®, which was rinsed with methyl *t*-butylether (100 mL) and water (20 mL). From the filtrate, the aq. phase was separated and extracted with methyl *t*-butylether (3 x 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the lactol **311b** as a colourless oil, which was essentially pure and was used without further purification.

K_2CO_3 (4.46 g, 32.3 mmol) was added to a solution of crude lactol **297b** in methanol (100 mL). The resulting suspension was stirred under reflux, while a solution of dimethyl-(1-diazo-2-oxopropyl)-phosphonate (4.63 g, 24.1 mmol) in methanol (20 mL) was added dropwise over 6 h. The red homogenous mixture was cooled in an ice bath and neutralized by cautious addition of HCl (1 M, 32.3 mL). The methanol was evaporated and the aq. solution was extracted with methyl *t*-butylether (3 x 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to afford the title compound a colourless oil (511 mg, 28% over 2 steps, contaminated with 10% of the 1,3-*syn* diastereoisomer from **296c**). $[\alpha]_D^{20}$ = −24.3 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.79 (ddd, *J* = 17.3, 10.3, 7.7 Hz, 1H), 5.04 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 1H), 4.96 (ddd, *J* = 10.3, 1.7, 0.9 Hz, 1H), 4.66 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.10 (dd, *J* = 7.2, 3.4 Hz, 1H), 3.96 (ddd, *J* = 8.5, 4.8, 3.4 Hz, 1H), 2.54 (d, *J* = 2.1 Hz, 1H), 2.42 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.15 (br s, 1H), 1.60–1.47 (m, 5H), 1.43 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.4, 113.1, 110.3, 84.0, 81.9, 74.5, 68.2, 65.0, 38.9, 34.7, 26.7, 25.8, 19.8 ppm. IR (film): $\tilde{\nu}$ = 3489, 3301, 2988, 2935, 1718, 1457, 1375, 1212, 1163, 1057, 914, 872, 669 cm^{-1}. MS (EI) *m/z* (%): 209 (87), 149

(4), 125 (17), 116 (7), 105 (17), 96 (27), 81 (49), 67 (100), 59 (13), 43 (43). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{20}O_3Na$: 247.1305, found: 247.1308.

Lactone 312. Bis-(acetoxy)iodobenzene (482 mg, 1.50 mmol) and TEMPO (16 mg, 0.10 mmol) were added to a solution of diol **278a** (115 mg, 0.499 mmol) in CH_2Cl_2 (2.5 mL). After stirring for 24 h, the reaction was quenched with sat. $Na_2S_2O_3$ (2 mL). The aq. phase was separated and extracted with methyl *t*-butyl ether (2 × 5 mL). The combined organic phases were washed with sat. $NaHCO_3$ (2 mL). The combined aq. phases were back-extracted with methyl *t*-butyl ether (2 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 7:3) to afford the title compound (107 mg, 95%) as a colourless amorphous solid. $[\alpha]_D^{20}$ = +47.9 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.05 (dt, *J* = 17.2, 1.4 Hz, 1H), 4.99 (ddd, *J* = 10.2, 1.6, 0.8 Hz, 1H), 4.78 (d, *J* = 5.3 Hz, 1H), 4.71 (dd, *J* = 5.4, 3.5 Hz, 1H), 4.48 (td, *J* = 7.2, 3.4 Hz, 1H), 2.40 (dh, *J* = 14.3, 7.0 Hz, 1H), 1.96–1.77 (m, 2H), 1.47 (s, 3H), 1.40 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 143.2, 113.9, 113.8, 77.9, 76.8, 76.3, 35.2, 34.2, 26.8, 26.0, 20.4 ppm. IR (film): $\tilde{\nu}$ = 2986, 1767, 1378, 1210, 1083, 913, 872, 810 cm^{-1}. MS (EI) *m/z* (%):211 (9), 111 (18), 97 (23), 85 (21), 69 (32), 59 (53), 55 (83), 43 (100) 41 (49). HRMS (ESIpos) *m/z* calcd for $C_{12}H_{18}O_4Na$: 249.1097, found: 249.1099.

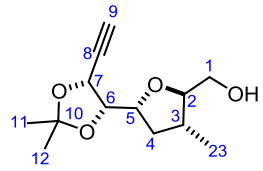
Olefin 313. Tetrachloromethane (0.97 mL, 10 mmol) was added over a period of 2 h to a mixture of lactone **312** (95 mg, 0.42 mmol) and PPh_3 (440 mg, 1.70 mmol) in THF (8 mL) under reflux. After stirring for 1 h, the mixture became yellow cloudy and was stirred for additional 5 h under reflux. After cooling to ambient temperature, the reaction was quenched with half sat. $NaHCO_3$ (10 mL). The aq. phase was separated and extracted with methyl *t*-butyl ether (3 × 10 mL). The combined etheral organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The colourless solid residue was suspended in methyl *t*-butyl ether (20 mL) and filtered through a short plug of Celite®, which was rinsed with methyl *t*-butyl ether (20 mL). The residue was purified by flash chromatography (hexane/CH_2Cl_2 3:2) to afford the title compound (123 mg, 87%) as a pale yellow oil. $[\alpha]_D^{20}$ = +194.8 (c = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.72 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.27 (d, *J* = 5.9 Hz, 1H), 5.03 (ddd, *J* = 17.2, 1.7, 1.0 Hz, 1H), 4.96 (ddd, *J* = 10.2, 1.7, 0.8 Hz, 1H), 4.70 (dd, *J* = 5.9, 3.6 Hz, 1H), 4.15 (td, *J* = 7.2, 3.6 Hz, 1H), 2.36 (dqd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 1.90–1.84 (m, 2H), 1.46 (d, *J* = 0.7 Hz, 3H), 1.41 (d, *J* = 0.8 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.0, 143.5, 113.5, 113.3, 101.0, 83.0, 79.9, 79.6, 35.1, 34.7, 26.6, 26.1, 20.7 ppm. IR (film): $\tilde{\nu}$ = 2961, 1374, 1212, 1081, 1017, 959, 916, 892 cm^{-1}. MS (EI) *m/z* (%): 292 (3), 181 (9), 111 (11), 93 (15), 83 (21), 69 (22), 55 (100), 43 (63). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{18}O_3Cl_2Na$: 293.0706, found: 293.0704.

5.7.1.5 Completion Synthesis of the Southern Fragments

General Procedure for Oxidative Mukaiyama Cyclization of Alcohols 279a-d to THF 280a-d

$Co(nmp)_2$ (10 mol%) was added to a solution of alcohol **279a-d** (0.1 M, 100 mol%) in *i*-PrOH. The homogenous solution was degassed by 3 cycles of freeze-pump-thaw and back-filled with an atmosphere of oxygen. After adding *t*-BuOOH (5 M in decane, 10 mol%), a balloon of oxygen was fitted to the reaction, which was placed in a pre-heated oil bath at 55 °C. The solution turned green within 5 min of heating and stirring was continued for 16 h. After cooling to ambient temperature, the mixture was concentrated to a green oil, which was purified by flash chromatography (hexane/EtOAc 1:1) to give the title compounds.

THF 280a. According to General Procedure using alkyne **279a** (854 mg, 3.81 mmol). Colourless oil



(589 mg, 64%). $[\alpha]_D^{20}$ = +37.6 (c = 1.03, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-21*. ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-21*. IR (film): $\tilde{\nu}$ = 3435, 3276, 2933, 2874, 1457, 1372, 1229, 1160, 1107, 1058, 864, 681 cm^{-1}. MS (EI) *m/z* (%): 225 (11), 165 (12), 151 (7), 121 (10), 115 (74), 95 (28), 95 (28), 79 (16), 71 (100), 67 (30), 55 (21), 43 (94). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{20}O_4Na$: 263.1254, found: 263.1254.

Table S-21. NMR data of THF **280a**; arbitrary numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (150 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1a	3.84	ddd	12.1, 2.8, 0.5	1-OH, 1b, 2	1-OH, 1b, 2, 11	62.1	2, 3
1b	3.55	ddd	12.1, 3.8, 2.9	1-OH, 1a, 2	1-OH, 1a, 3, 23		
1-OH	1.99	br s	-	1ab	1ab	-	-
2	3.60	ddd	9.2, 3.8, 2.8	1ab, 3	1a, 3, 4b, 6, 23	86.3	1a, 3, 4ab, 5, 23
3	2.28	ddp	11.1, 9.2, 6.6, 6.6	2, 4ab, 23	1b, 2, 5, 23	34.4	1a, 2, 4ab, 5, 23
4a	2.39	ddd	12.4, 6.6, 5.7	3, 4b, 5	4b, 5, 7, 23	37.6	3, 5, 6, 23
4b	1.26	ddd	12.4, 11.1, 9.9	3, 4a, 5	2, 4a, 6, 7, 23		
5	4.30	ddd	9.9, 8.2, 5.7	4ab, 6	3, 4a, 7, 11	78.8	4b, 6, 7
6	4.02	dd	8.2, 5.6	5, 7	2, 4b, 7, 11	81.4	4ab, 5, 7
7	4.70	dd	5.6, 2.2	6, 9	4ab, 5, 6, 12	66.7	9
8	-	-	-	-	-	79.8	6, 7, 9
9	2.51	d	2.2	7	-	75.6	6, 7
10	-	-	-	-	-	111.6	7, 11, 12
11	1.59	s	-	12	1a, 5, 12	27.7	12
12	1.40	s	-	11	6, 7, 11	26.3	11
23	1.06	d	6.6	3	1b, 2, 3, 4ab	16.2	2, 3, 4

THF 280b. According to General Procedure using alkyne **279b** (235 mg, 1.05 mmol). Colourless oil (165 mg, 65%). $[\alpha]_D^{20}$ = −35.7 (c = 1.03, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-22*. ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-22*. IR (film): $\tilde{\nu}$ = 3450, 3263, 2933, 2875, 1457, 1381, 1241, 1214, 1160, 1056, 870, 666 cm^{-1}. MS (EI) *m/z* (%): 225 (7), 165 (8), 151 (4), 121 (8), 115 (38), 96 (29), 95 (22), 79 (14), 71 (77), 67 (34), 55 (24), 43 (100). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{20}O_4Na$: 263.1254, found: 263.1255.

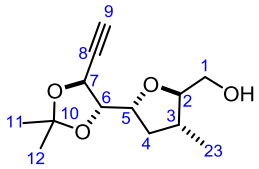
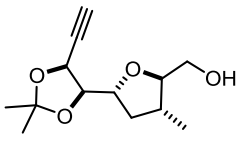


Table S-22. NMR data of THF **280b**; arbitrary numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (150 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1a	3.82	dd	12.0, 2.7	1b, 2	1b, 2, 23	62.3	3
1b	3.53	dd	12.0, 4.1	1a, 2	1b, 2		
1-OH	1.77	br s	-	-	-	-	-
2	3.60	ddd	9.3, 4.1, 2.7	1ab, 3	4b, 6, 11, 23	86.4	1a, 3, 4a, 23
3	2.22	ddp	11.2, 9.3, 6.7, 6.4	2, 4ab, 23	1b, 6, 23	34.6	1a, 4ab, 23
4a	2.17	m	-	3, 4b, 5, 6	4b, 6, 7, 23	37.1	3, 23
4b	1.61	m	-	3, 4a, 5, 6, 7	2, 4a, 6, 23		
5	4.04	m	-	4ab	11	78.4	4b, 7
6	4.05	m	-	4ab, 7	2, 3, 4ab, 12	84.3	4b, 5, 7
7	4.41	dd	7.4, 2.1	4b, 6, 9	4a, 11	66.9	9
8	-	-	-	-	-	80.8	6, 7, 9
9	2.55	d	2.1	7	-	74.9	7
10	-	-	-	-	-	111.0	11, 12
11	1.44	s	-	12	2, 5, 7	26.7	12
12	1.50	s	-	11	6	26.0	11
23	1.07	d	6.4	3	1ab, 2, 3, 4ab	15.9	4b

THF 280c According to General Procedure using alkyne C **279c** (252 mg, 1.05 mmol). Colourless oil (169 mg, 63%). $[\alpha]_D^{20}$ = −54.2 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (dd, *J* = 5.8, 2.2 Hz, 1H), 4.24 (ddd, *J* = 9.3, 7.5, 5.8 Hz, 1H), 4.01 (dd, *J* = 7.5, 5.8 Hz, 1H), 3.72 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.63–3.54 (m, 1H), 3.56–3.46 (m, 1H), 2.55 (d, *J* = 2.2 Hz, 1H), 2.38 (ddd, *J* = 12.6, 7.2, 5.8 Hz, 1H), 2.16 (ddt, *J* = 10.8, 8.6, 6.8 Hz, 1H), 1.99 (br s, 1H), 1.59 (ddd, *J* = 12.3, 10.8, 9.3 Hz, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 110.5, 86.1, 80.3, 80.2, 77.6, 75.9, 68.4, 62.9, 38.8, 34.9, 27.4, 25.9, 16.6 ppm. IR (film): $\tilde{\nu}$ = 3450, 3281, 2934, 2875, 1457, 1372, 1229, 1163, 1075, 1043, 865, 663 cm^{-1}. MS (EI) *m/z* (%): 503.3 (55), 471.2 (5), 355.2 (3), 263.1 (100), 202.1 (3). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{20}O_4Na$: 263.1254, found: 263.1253.



THF 280d According to General Procedure using alkyne **279d** (500 mg, 2.23 mmol). Colourless oil (312 mg, 58%). $[\alpha]_D^{20}$ = +12.4 (c = 1.04, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-23*. ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-23*. IR (film): $\tilde{\nu}$ = 3438, 3282, 2933, 2875, 1457, 1382, 1240, 1213, 1164, 1055, 869, 669 cm^{-1}. MS (EI) *m/z* (%): 225 (19), 165 (9), 151 (61), 121 (2), 115 (54), 109 (42), 97 (47), 91 (17), 81 (33), 69 (91), 57 (9), 43 (100). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{20}O_4Na$: 263.1254, found: 263.1255.

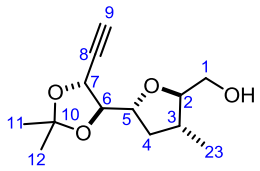


Table S-23. NMR data of THF **280d**; arbitrary numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (150 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1a	3.77	dd	11.8, 2.7	1b 2	3, 23	62.8	3
1b	3.53	dd	11.8, 4.9	1a, 2	3, 23		
1-OH	1.77	br s	-	-	-	-	-
2	3.60	ddd	9.1, 4.9, 2.7	1b, 3	3, 4b, 6, 7, 23	86.4	4a, 23
3	2.18	dddq	10.6, 9.1, 7.2, 6.4	2, 4b, 23	1ab, 2, 5, 23	34.8	1a, 4ab, 23
4a	2.23	ddd	11.8, 7.2, 5.9	4b, 5	4b, 5, 6, 7	37.2	6, 23
4b	1.61	ddd	11.8, 10.6, 9.5	3, 4a, 5	2, 4a, 6, 7, 23		
5	4.11	ddd	9.5, 5.9, 4.9	4ab, 6	3, 4a, 7, 11	78.1	4b, 7
6	4.18	dd	6.6, 4.9	5, 7	2, 4ab, 12	83.7	4b, 7
7	4.53	dd	6.6, 2.1	6, 9	2, 4ab, 5, 11	67.4	9
8	-	-	-	-	-	81.8	6, 7, 9
9	2.55	d	2.1	7	22	74.6	7
10	-	-	-	-	-	110.9	7, 11, 12
11	1.43	s	-	12	5, 7, 12	26.9	12
12	1.51	s	-	11	6, 9, 11	26.0	11
23	1.07	d	6.4	3	1ab, 2, 3, 4b	16.3	4b

General Procedure for Hydroindation and Iodolysis of Alkynes 280a-d to give (*Z*)-Alkenyl Iodides 281a-d

A solution of Dibal-H (1 M in THF, 140 mol%) was added dropwise to a suspension of indium trichloride (0.3 M, 150 mol%) in THF at −78 °C. The reaction was stirred for 30 min at which point the solution was homogenous. A solution of alkyne **280a-d** (0.5 M, 100 mol%) in THF was added dropwise at −78 °C, followed by a solution of triethylborane (1 M, 20 mol%) in THF. The reaction was initiated by slowly injecting 1 mL of air through the bottom of the solution. The mixture was stirred at the indicated temperature until the alkyne was fully consumed. Solid iodine (600 mol%) was added and the reaction was stirred at −78 °C until the alkenylindium species had been fully consumed. The reaction was quenched with $NaHCO_3$ (10 mL) and the resulting mixture was diluted with methyl

t-butylether (30 mL). The aq. phase was separated and extracted with methyl *t*-butylether (3 x 30 mL). The combined organic phases were washed with sat. $Na_2S_2O_3$, brine, dried over Na_2SO_4, filtered and concentrated to a yellow residue. The residue was purified by flash chromatography (hexane/EtOAc 7:3) to afford the title compounds.

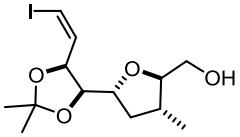
(*Z*)-Alkenyl Iodide 281a. According to General Procedure at −78 °C for 2.5 h using alkyne **280a** (569 mg, 2.37 mmol). Colourless oil (582 mg, 67%). $[\alpha]_D^{20}$ = −61.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.35 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.83 (ddd, *J* = 8.7, 6.3, 0.9 Hz, 1H), 4.16 (t, *J* = 6.6 Hz, 1H), 3.95 (ddd, *J* = 9.7, 6.9, 5.7 Hz, 1H), 3.81 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.58 (ddd, *J* = 8.9, 3.9, 2.7 Hz, 1H), 3.51 (dd, *J* = 11.9, 4.0 Hz, 1H), 2.23–2.07 (m, 2H), 1.85 (br s, 1H), 1.51 (s, 3H), 1.44–1.33 (m, 4H), 1.05 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 110.0, 86.2, 85.7, 81.0, 79.5, 77.1, 62.2, 37.8, 34.6, 27.8, 25.6, 16.1 ppm. IR (film): $\tilde{\nu}$ = 3495, 2931, 2873, 1456, 1379, 1250, 1215, 1161, 1088, 1055, 867, 590, 508 cm^{-1}. MS (EI) *m/z* (%): 759.1 (49), 580.0 (5), 483.0 (3), 391.0 (100), 338.0 (9). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{21}IO_4Na$: 391.0377, found: 391.0377. Analytical and spectral data are matching with **198**.

(*Z*)-Alkenyl Iodide 281b. According to General Procedure at −40 °C for 36 h using alkyne **280b** (153 mg, 0.64 mmol). Colourless oil (216 mg, 92%). $[\alpha]_D^{20}$ = +22.9 (c = 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.61 (dd, *J* = 7.8, 0.8 Hz, 1H), 6.26 (dd, *J* = 8.5, 7.7 Hz, 1H), 4.59 (td, *J* = 8.3, 0.8 Hz, 1H), 4.10–4.04 (m, 1H), 3.86–3.75 (m, 2H), 3.61–3.56 (m, 1H), 3.53 (dd, *J* = 11.8, 4.0 Hz, 1H), 2.22 (dddd, *J* = 16.8, 12.6, 8.0, 6.2 Hz, 2H), 1.99 (br s, 1H), 1.47 (s, 3H), 1.45 (d, *J* = 0.7 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.8, 110.1, 86.8, 86.2, 82.8, 79.6, 78.4, 62.3, 37.2, 34.7, 26.9, 26.8, 16.1 ppm. IR (film): $\tilde{\nu}$ = 3447, 2931, 2873, 1456, 1380, 1250, 1215, 1164, 1056, 873, 714 cm^{-1}. MS (EI) *m/z* (%): 759.1 (33), 631.2 (3), 572.1 (5), 467.0 (2), 391.0 (100), 338.0 (5). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{21}IO_4Na$: 391.0377, found: 391.0378.

(*Z*)-Alkenyl Iodide 281c. According to General Procedure at −40 °C for 36 h using alkyne **280c** (156 mg, 0.65 mmol). Colourless oil (188 mg, 79%). $[\alpha]_D^{20}$ = +75.1 (c = 1.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.34 (t, *J* = 7.9 Hz, 1H), 4.91 (ddd, *J* = 7.9, 6.5, 1.2 Hz, 1H), 4.26 (t, *J* = 6.5 Hz, 1H), 3.99–3.91 (m, 1H), 3.69 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.58 (ddd, *J* = 8.7, 5.6, 2.8 Hz, 1H), 3.46 (dd, *J* = 11.6, 5.6 Hz, 1H), 2.19 (ddd, *J* = 12.0, 7.2, 5.9 Hz, 1H), 2.12–2.02 (m, 1H), 1.89 (br s, 1H), 1.57 (ddd, *J* = 12.0, 10.8, 9.3 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7, 109.2, 86.0, 84.9, 80.2, 80.1, 76.7, 63.3, 38.4, 35.1, 27.5, 25.2, 16.4 ppm. IR (film): $\tilde{\nu}$ = 3457, 2931, 2873, 1455, 1380, 1245, 1214, 1162, 1049, 870, 513 cm^{-1}. MS (EI) *m/z* (%): 759.1 (23), 659.3

(2), 572.1 (4), 467.0 (2), 391.0 (100). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{21}IO_4Na$: 391.0377, found: 391.0378. Analytical and spectral data are matching with **198c**.

(*Z*)-Alkenyl Iodide 281d. According to General Procedure at −78 °C for 2.5 h using alkyne **280d**

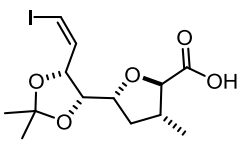


(292 mg, 1.22 mmol). Colourless oil (394 mg, 88%). $[\alpha]_D^{20}$ = −42.6 (c = 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.33–6.24 (m, 1H), 4.53 (td, *J* = 8.2, 0.9 Hz, 1H), 4.12 (ddd, *J* = 9.9, 5.7, 4.2 Hz, 1H), 3.93 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.78–3.69 (m, 1H), 3.71–3.62 (m, 1H), 3.53 (dd, *J* = 11.4, 5.6 Hz, 1H), 2.26 (ddd, *J* = 11.6, 7.1, 5.7 Hz, 1H), 2.17 (ddt, *J* = 11.1, 9.0, 6.6 Hz, 1H), 1.95 (br s, 1H), 1.69–1.60 (m, 1H), 1.46 (s, 2H), 1.44 (s, 3H), 1.08 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 110.0, 86.2, 86.0, 81.6, 80.7, 78.0, 63.1, 36.6, 34.9, 26.9, 26.9, 16.3 ppm. IR (film): $\tilde{\nu}$ = 3440, 2932, 2873, 1456, 1380, 1282, 1239, 1166, 1045, 840, 713 cm^{-1}. MS (EI) *m/z* (%): 759.1 (39), 633.2 (2), 572.1 (4), 489.0 (2), 391.0 (100), 311.0 (2). HRMS (ESIpos) *m/z* calcd for $C_{13}H_{21}IO_4Na$: 391.0377, found: 391.0375.

General Procedure for Oxidation of Alkenyl Iodides 281a-d to Carboxylic Acids 185a-d

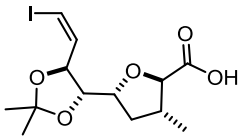
Water (1000 mol%), bis-(acetoxy)iodobenzene (220 mol%) and TEMPO (30 mol%) were added to a solution of alkenyl iodide **281a-d** (0.2 M, 100 mol%) in MeCN. The light orange solution was stirred for 19 h at ambient temperature. The reaction was quenched with aq. NaOH (5% w/w, 100 mL). The separated aq. phase was washed with *t*-butyl methyl ether (2 × 50 mL). The aq. solution was acidified with HCl (2 N) until pH 3 was reached and pH 3.5 phosphate buffer solution (50 mL) was added. The aq. 3-4 pH solution was extracted with EtOAc (2 × 200 mL). The combined organic phases were washed with a 1:1 mixture of pH 5 phosphate buffer and brine (200 mL). After drying over Na_2SO_4 and filtration, the residue was concentrated under reduced pressure to afford title compounds, which were used in the next step without further purification.

Carboxylic Acid 185a. According to general Procedure using alkenyl iodide **281a** (566 mg,



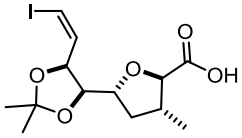
1.54 mmol). Yellow oil (542 mg, 80%). $[\alpha]_D^{20}$ = –65.4 (c = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.45 (t, *J* = 7.9 Hz, 1H), 4.88 (ddd, *J* = 7.8, 6.5, 1.0 Hz, 1H), 4.21 (dd, *J* = 6.6, 5.6 Hz, 1H), 4.12 (dt, *J* = 9.9, 5.7 Hz, 1H), 4.04 (d, *J* = 8.6 Hz, 1H), 2.44–2.31 (m, 1H), 2.17 (ddd, *J* = 12.7, 7.2, 5.8 Hz, 1H), 1.59–1.46 (m, 4H), 1.42 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.1, 137.5, 110.0, 85.6, 82.9, 79.7, 79.6, 78.9, 39.6, 37.3, 27.4, 25.4, 17.5 ppm. IR (film) $\tilde{\nu}$ = 2982, 2933, 1728, 1739, 1285, 1245, 1216, 1055, 866 cm^{-1}. MS (EI) *m/z* (%): 809.0 (5), 787.0 (23), 659.1 (3), 593.0 (2), 405.0 (100), 277.1 (9). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{19}IO_5Na$: 405.0169, found: 405.0170.

Carboxylic Acid 185b. According to general Procedure using alkenyl iodide **281b** (92 mg, 0.25 mmol).



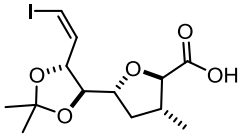
Yellow oil (96 mg, 88%). $[\alpha]_D^{20}$ = +33.2 (c = 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.28 (t, *J* = 8.1 Hz, 1H), 4.71 (td, *J* = 8.3, 0.9 Hz, 1H), 4.27 (ddd, *J* = 10.1, 5.8, 4.3 Hz, 1H), 4.05 (d, *J* = 9.3 Hz, 1H), 3.76 (dd, *J* = 8.3, 4.3 Hz, 1H), 2.40 (ddq, *J* = 10.8, 9.2, 6.6 Hz, 1H), 2.26 (ddd, *J* = 12.5, 7.0, 5.8 Hz, 1H), 1.64 (dt, *J* = 12.3, 10.5 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 137.6, 110.3, 86.6, 82.9, 81.4, 79.5, 79.0, 39.8, 37.0, 27.0, 26.6, 17.0 ppm. IR (film) $\tilde{\nu}$ = 2984, 2933, 1728, 1373, 1285, 1245, 1216, 1056, 872, 715 cm^{-1}. MS (EI) *m/z* (%): 809.0 (5), 787.0 (23), 659.1 (3), 593.0 (2), 405.0 (100), 277.1 (9). HRMS (ESIneg): *m/z* calcd for $C_{13}H_{18}IO_5$: 381.0204 $[M-H]^-$, found: 381.0207.

Carboxylic Acid 185c. According to general Procedure using alkenyl iodide **281c** (174 mg, 0.47 mmol).



Yellow oil (185 mg, 89%). $[\alpha]_D^{20}$ = +116.7 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.39 (t, *J* = 7.9 Hz, 1H), 4.94 (ddd, *J* = 7.9, 6.6, 1.2 Hz, 1H), 4.34 (t, *J* = 6.3 Hz, 1H), 4.14 (dt, *J* = 9.5, 5.8 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 2.38 (ddp, *J* = 10.6, 9.0, 6.6 Hz, 1H), 2.23 (ddd, *J* = 12.6, 7.2, 5.7 Hz, 1H), 1.65 (ddd, *J* = 12.3, 10.6, 9.5 Hz, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.2, 137.5, 109.4, 85.4, 82.6, 79.9, 79.1, 78.8, 39.5, 37.7, 27.3, 25.0, 17.5 ppm. IR (film) $\tilde{\nu}$ = 2983, 2933, 1723, 1380, 1285, 1245, 1214, 1163, 1098, 1054, 867, 715 cm^{-1}. MS (EI) *m/z* (%): 665.3 (3), 637.3 (4), 609.2 (8), 564.3 (2), 539.5 (2), 477.0 (12), 427.0 (4), 397.0 (3), 381.0 (100), 353.2 (3). HRMS (ESIneg): *m/z* calcd for $C_{13}H_{18}IO_5$ $[M-H]^-$: 381.0204, found: 381.0207.

Carboxylic Acid 185d. According to general Procedure using alkenyl iodide **281d** (380 mg, 1.03 mmol).



Yellow oil (421 mg, 93%). $[\alpha]_D^{20}$ = −0.8 (c = 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (d, *J* = 7.8 Hz, 1H), 6.29 (t, *J* = 8.0 Hz, 1H), 4.51 (t, *J* = 8.2 Hz, 1H), 4.32 (ddd, *J* = 9.7, 5.6, 4.0 Hz, 1H), 4.09 (d, *J* = 9.2 Hz, 1H), 3.97 (dd, *J* = 8.3, 4.0 Hz, 1H), 2.52–2.31 (m, 2H), 1.82–1.69 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.32 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4, 137.8, 110.3, 86.3, 82.6, 80.8, 80.7, 79.7, 39.5, 36.2, 26.9, 26.8, 17.2 ppm. IR (film) $\tilde{\nu}$ = 2983, 2930, 1729, 1456, 1380, 1282, 1238, 1218, 1167, 1097, 1061, 873, 716 cm^{-1}. MS (EI) *m/z* (%): 787.0 (23), 659.1 (35), 531.2 (10), 405.0 (100), 277.1 (78). HRMS (ESIneg): *m/z* calcd for $C_{13}H_{18}IO_5$ $[M-H]^-$: 381.0204, found: 381.0207.

General Procedure for the Protection of Carboxylic Acids 185a-d to Southern Fragments 219a-d

DMAP (30 mol%), N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (150 mol%) and 2-(trimethylsilyl)-ethanol (260 mol%) were added to a solution of crude carboxylic acid **185a-d** (0.2 M, 100 mol%) in CH_2Cl_2. After stirring for 4 h at ambient temperature, the mixture was diluted with EtOAc (10 mL) and the reaction was quenched with water (10 mL). The aq. phase was separated and

extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 95:5) to yield the southern fragments **219a-d**.

Southern Fragment 219a. According to general Procedure using carboxylic acid **185a** (528 mg, 1.38 mmol). Colourless oil (523 mg, 78%). $[\alpha]_D^{20}$ = –77 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53–6.43 (m, 2H), 4.89–4.83 (m, 1H), 4.25–4.09 (m, 4H), 4.04–3.98 (m, 1H), 2.35 (dddt, *J* = 14.1, 9.6, 7.5, 6.7 Hz, 1H), 2.11 (ddd, *J* = 11.9, 7.4, 5.8 Hz, 1H), 1.51 (s, 3H), 1.45–1.36 (m, 4H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.04–0.96 (d, *J* = 6.7 Hz, 2H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 137.5, 109.9, 85.5, 83.8, 79.9, 79.8, 78.7, 63.1, 39.4, 37.0, 27.4, 25.5, 18.2, 17.4, −1.5 ppm. IR (film) $\tilde{\nu}$ = 2956, 2897, 1747, 1456, 1379, 1250, 1214, 1175, 1131, 1086, 1058, 860, 837 cm^{-1}. MS (EI) *m/z* (%): 987.2 (28), 875.1 (2), 659.3 (2), 581.1 (1), 505.1 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}IO_5SiNa$: 505.0877, found: 505.0878.

Southern Fragment 219b. According to General Procedure using carboxylic acid **185b** (145 mg, 0.223 mmol). Colourless oil (154 mg, 84%). $[\alpha]_D^{20}$ = +23.8 (c = 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 6.61 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.26 (dd, *J* = 8.4, 7.8 Hz, 1H), 4.62 (td, *J* = 8.2, 0.8 Hz, 1H), 4.31 (dt, *J* = 9.7, 5.9 Hz, 1H), 4.27–4.17 (m, 2H), 4.02 (d, *J* = 8.0 Hz, 1H), 3.82 (dd, *J* = 8.0, 5.9 Hz, 1H), 2.42 (dddt, *J* = 13.4, 9.9, 7.7, 6.6 Hz, 1H), 2.24 (ddd, *J* = 12.2, 7.3, 5.9 Hz, 1H), 1.46 (s, 3H), 1.44–1.34 (m, 4H), 1.20 (d, *J* =6.7 Hz, 3H), 1.05–0.98 (m, 2H), 0.05 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 172.8, 137.8, 110.2, 86.8, 83.7, 82.4, 79.8, 79.6, 63.1, 39.6, 36.7, 26.9, 26.8, 17.8, 17.4, −1.5 ppm. IR (film) $\tilde{\nu}$ = 2957, 2896, 1748, 1456, 1380, 1250, 1215, 1174, 1130, 1059, 860, 838 cm^{-1}. MS (EI) *m/z* (%): 987.2 (23), 859.3 (4), 743.1 (4), 649.2 (1), 505.1 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}IO_5SiNa$: 505.0877, found: 505.0879.

Southern Fragment 219c. According to General Procedure using carboxylic acid **185c** (171 mg, 0.45 mmol). Colourless oil (167 mg, 77%). $[\alpha]_D^{20}$ = +92.2 (c = 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 6.53 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.39 (t, *J* = 7.8 Hz, 1H), 4.92 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 4.39 (dd, *J* = 6.7, 5.2 Hz, 1H), 4.26–4.14 (m, 3H), 4.00 (d, *J* = 7.7 Hz, 1H), 2.43–2.30 (m, 1H), 2.13 (ddd, *J* = 12.2, 7.6, 6.0 Hz, 1H), 1.58 (dt, *J* = 12.2, 9.4, 1H), 1.49 (s, 3H), 1.43–1.38 (m, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.05–0.96 (m, 2H) 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 172.9, 137.2, 109.0, 85.6, 83.3, 79.7, 79.0, 78.6, 63.1, 39.4, 36.5, 27.2, 25.0, 18.2, 17.4, −1.5 ppm. IR (film) $\tilde{\nu}$ = 2955, 2896, 1747, 1456, 1380, 1250, 1215, 1176, 1099, 1058, 861, 838 cm^{-1}. MS (EI) *m/z* (%): 987.2 (31), 903.1 (2), 743.1 (5), 623.2 (2), 505.1 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}IO_5SiNa$: 505.0877, found: 505.0875.

Southern Fragment 219d. According to general Procedure using carboxylic acid **185d** (421 mg, 1.10 mmol). Colourless oil (317 mg, 60%). $[\alpha]_D^{20}$ = −22.4 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.28 (t, *J* = 8.0 Hz, 1H), 4.41 (td, *J* = 8.3, 0.9 Hz, 1H), 4.33 (ddd, *J* = 9.4, 6.0, 2.8 Hz, 1H), 4.27–4.20 (m, 2H), 4.12–4.05 (m, 2H), 2.50–2.36 (m, 1H), 2.27 (ddd, *J* = 11.9, 7.5, 6.0 Hz, 1H), 1.75 (dt, *J* = 11.9, 9.7 Hz, 1H), 1.46 (d, *J* = 0.7 Hz, 3H), 1.43 (s, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.05–0.98 (m, 2H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 137.9, 110.3, 86.0, 83.3, 80.5, 80.4, 79.0, 63.2, 39.4, 34.3, 26.9, 26.8, 17.8, 17.5, −1.5 ppm. IR (film) $\tilde{\nu}$ = 2956, 2896, 1747, 1456, 1380, 1250, 1176, 1097, 1063, 860, 838, 697 cm^{-1}. MS (EI) *m/z* (%): 987.2 (35), 903.1 (2), 743.1 (5), 623.2 (3), 505.1 (100). HRMS (ESIpos): *m/z* calcd for $C_{18}H_{31}IO_5SiNa$: 505.0877, found: 505.0880.

5.7.2 Synthesis of Northern Fragment with inverted THF-ring

5.7.2.1 Auxiliary Based Glycolate *anti*-Aldol Reactions

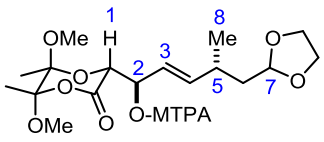
Aldol 319. Titanium tetrachloride (freshly distilled, 0.19 mL, 1.7 mmol) and (−)-sparteine (409 mg, 1.75 mmol) were added to thiooxazolidinone **320** (594 mg, 1.74 mmol) in CH_2Cl_2 (10.5 mL) at −78 °C. After stirring for 1.5 h, the aldehyde **253** (198 mg, 1.16 mmol) was added dropwise at −78 °C to the dark blue mixture. After stirring for 5 h at the same temperature, the cold mixture was poured into a sat. NH_4Cl (10 mL). The aq. phase was separated and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The resulting mixture of diastereoisomers ((2*S,*3*S*)/(2*R,*3*S*)/(2*R,*3*R*)/(2*S,*3*R*) = 1:2.4:3.5:15.5) was purified by flash chromatography (hexane/EtOAc 7:3 to 3:2 to 1:1 to 2:3) to provide the pure title compound *syn* diastereomer (2*S*,3*R*)-**321** (291 mg, 49%) as a yellow oil and the pure *anti* diastereomer (2*R*,3*R*)-**321** (57.4 mg, 10%). Analytical and spectral data for (2*S*,3*R*)-**321:** $[\alpha]_D^{20}$ = +49.7 (c = 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.27 (m, 8H), 7.23–7.18 (m, 2H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.70 (ddd, *J* = 15.6, 7.3, 1.1 Hz, 1H), 5.60 (ddd, *J* = 15.6, 6.0, 0.9 Hz, 1H), 4.85 (ddd, *J* = 10.3, 6.4, 3.3 Hz, 2H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.55–4.48 (m, 1H), 4.34–4.25 (m, 2H), 3.97–3.89 (m, 2H), 3.85 – 3.75 (m, 2H), 3.23 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.71 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.53 (d, *J* = 8.1 Hz, 1H), 2.41 (hept, *J* = 7.0 Hz, 1H), 1.67 (ddd, *J* = 13.8, 7.8, 4.4 Hz, 1H), 1.63–1.55 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.1, 171.5, 138.6, 136.9, 135.1, 129.4, 129.0, 128.5 (2C), 128.2, 127.5, 126.4, 103.2, 79.5, 73.4, 73.3, 70.8, 64.7, 64.7, 60.8, 40.5, 37.5, 32.6, 20.6 ppm. IR (film): $\tilde{\nu}$ = 3441, 2960, 2878, 1704, 1454, 1363, 1323, 1287, 1195, 1155, 1129, 1027, 960, 848, 819, 750, 700, 530, 503 cm^{-1}. MS (ESIpos) *m/z* (%): 534.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{33}O_6NSNa$: 534.1921, found: 534.1923.

Analytical and spectral data for (2*R*,3*R*)-**321:** $[\alpha]_D^{20}$ = +16.7 (c = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.39 (m, 2H), 7.39–7.27 (m, 6H), 7.23–7.17 (m, 2H), 6.46 (d, *J* = 5.7 Hz, 1H), 5.69 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.61 (dd, *J* = 15.7, 6.2 Hz, 1H), 4.85–4.78 (m, 2H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.47 (t, *J* = 5.8 Hz, 1H), 4.31 (dd, *J* = 9.3, 2.3 Hz, 1H), 4.25 (ddd, *J* = 9.3, 7.2, 0.8 Hz, 1H), 3.97–3.87 (m, 2H), 3.84–3.73 (m, 2H), 3.19 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.65 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.47 (s, 1H), 2.45–2.34 (m, 1H), 1.69–1.54 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.7, 172.0, 139.3, 137.1, 135.1, 129.4, 129.0, 128.5, 128.5, 128.2, 127.5, 126.4, 103.2, 79.1, 73.4, 73.1, 70.8, 64.7, 64.7, 60.7, 40.5, 37.5, 32.7, 20.6 ppm.

Lactone 330. Following the literature procedure for the synthesis of Ley auxiliary **330** the title compound was synthesized in 6.49 g (11% over 4 steps). $[\alpha]_D^{20}$ = +187.5 (c = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.32 (d, *J* = 17.6 Hz, 1H), 4.16 (d, *J* = 17.7 Hz, 1H), 3.46 (s, 3H), 3.32 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H) ppm. The analytical and spectral data matches with the literature.[451]

Aldol 331. A solution of LiHMDS (1.0 M in THF, 13 mL, 13 mmol) was added to lactone **330** (2.34 g, 12.3 mmol) in THF (30 mL) at −78 °C. After stirring for 5 min, a solution of aldehyde **253** (2.20 g, 12.9 mmol) in THF (10 mL) was added dropwise at the same temperature. After stirring for 1 h and maintaining the cryogenic conditions, acetic acid (1.3 mL, 23 mmol) was added. After stirring for 5 min at the same temperature, the cold mixture was poured onto sat. NH_4Cl (50 mL). The aq. phase was separated and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The yellow residual oil was purified by flash chromatography (hexane/EtOAc 2:3) to provide the title compound (2.05 g, 46%, pure diastereomer, dr = 9.4:1) as a pale yellow oil. $[\alpha]_D^{20}$ = +68.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74–5.60 (m, 2H), 4.87 (dd, *J* = 6.1, 4.2 Hz, 1H), 4.45 (dt, *J* = 5.8, 2.7 Hz, 1H), 4.17 (d, *J* = 3.4 Hz, 1H), 3.96–3.89 (m, 2H), 3.85–3.77 (m, 2H), 3.41 (s, 3H), 3.31 (s, 3H), 3.25 (d, *J* = 2.9 Hz, 1H), 2.42 (dp, *J* = 7.6, 6.5 Hz, 1H), 1.71 (ddd, *J* = 13.8, 8.1, 4.2 Hz, 1H), 1.58 (dt, *J* = 13.9, 6.2 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 139.3, 125.2, 104.8, 103.2, 98.2, 74.9, 73.6, 64.7, 64.6, 50.2, 49.2, 40.5, 32.8, 20.6, 17.8, 16.8 ppm. IR (film): $\tilde{\nu}$ = 3490, 2955, 2888, 1751, 1456, 1381, 1259, 1218, 1149, 1104, 1034, 973, 899, 862 cm^{-1}. MS (ESIpos) *m/z* (%): 383.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{17}H_{28}O_8Na$: 383.1676, found: 383.1676.

Mosher Ester Analysis of Alcohol 331. Hünig's base (13.5 µL, 77.7 µmol) was added to a solution of



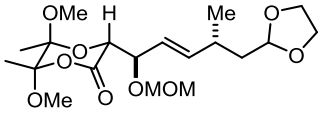
alcohol **331** (10 mg, 28 µmol) in CH_2Cl_2 (0.25 mL) followed by (*R*)-(–)-*α*-methoxy-*α*-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (9.9 µL, 53 µmol). The mixture was stirred at ambient temperature for 17 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 9:1) to give the corresponding (*S*)-Mosher ester **(*S*)-MTPA-331** (11.2 mg, 70%), which analyzed as follows: $[\alpha]_D^{20}$ = +31.2 (c = 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.57–7.50 (m, 2H), 7.41–7.35 (m, 3H), 5.93–5.77 (m, 3H), 4.77 (dd, *J* = 6.3, 4.1 Hz, 1H), 4.39 (d, *J* = 2.6 Hz, 1H), 3.96–3.87 (m, 2H), 3.78–3.70 (m, 2H), 3.54 (q, *J* = 1.2 Hz, 3H), 3.30 (s, 3H), 3.18 (s, 3H), 2.50–2.39 (m, 1H), 1.69 (ddd, *J* = 13.8, 8.3, 4.2 Hz, 1H), 1.64–1.55 (m, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2954, 2887, 2844, 1752, 1453, 1382, 1253, 1165, 1122, 1082, 1035, 979, 899, 864, 721, 703 cm^{-1}. MS (ESIpos) *m/z* (%): 599.2 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{27}H_{35}O_{10}F_3Na$: 599.2074, found: 599.2077.

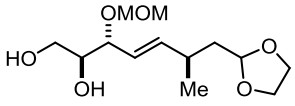
The same procedure using by (*S*)-(–)-*α*-methoxy-*α*-trifluoromethyl-phenylacetyl chloride was followed for the preparation of **(*R*)-MTPA-331** (8.7 mg, 64%), which analyzed as follows: $[\alpha]_D^{20}$ = +90.9 (c = 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.60–7.55 (m, 2H), 7.42–7.36 (m, 3H), 5.86–5.71 (m, 3H), 4.75 (dd, *J* = 6.2, 4.2 Hz, 1H), 4.51 (d, *J* = 2.9 Hz, 1H), 3.95–3.88 (m, 2H), 3.80–3.73 (m, 2H), 3.57 (q, *J* = 1.1 Hz, 3H), 3.32 (s, 3H), 3.26 (s, 3H), 2.49–2.36 (m, 1H), 1.67 (ddd, *J* = 13.8, 8.2, 4.2 Hz, 1H), 1.62–1.55 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H) ppm.

Both products were analyzed according to Hoye and co-workers:[497]

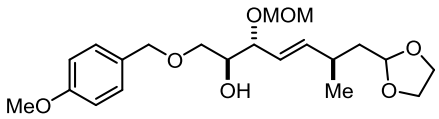
Table S-24. Mosher ester analysis for the assignment of the C(2) stereocenter; arbitrary numbering as shown in the insert.

Assignment	331 [ppm]	(*S*)-MTPA-331 [ppm]	(*R*)-MTPA-331 [ppm]	Δ (*δ*(*S*–*R*)) [ppm]
1	4.17	4.40	4.50	−0.10
2	4.44	5.86	5.79	+0.07
3	5.66	5.84	5.76	+0.08
4	5.66	5.85	5.81	+0.04
5	2.43	2.44	2.43	+0.01
6a	1.69	1.68	1.68	+0.00
6b	1.58	1.59	1.57	+0.02
7	4.87	4.77	4.75	+0.02
8	1.03	1.03	1.02	+0.01

MOM-Ether 332. Tetrabutylammonium iodide (102 mg, 0.276 mmol), MOMCl (1.3 mL, 17 mmol),  Hünig's base (4.6 mL, 26 mmol) were added to a solution of allyl alcohol **331** (2.11 g, 5.85 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was allowed to reach ambient temperature and the reaction was quenched with sat. NH_4Cl (30 mL). After stirring for 2.5 h, the aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 50 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 1:1 to 2:3 to 1:3) to afford the title compound as a yellow oil$[\alpha]_D^{20}$ = +21.0 (c = 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74–5.58 (m, 2H), 4.83 (dd, *J* = 5.9, 4.5 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.53–4.46 (m, 1H), 4.39 (d, *J* = 2.6 Hz, 1H), 3.99–3.86 (m, 2H), 3.88–3.75 (m, 2H), 3.37 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 2.44 (hept, *J* = 6.7 Hz, 1H), 1.70 (ddd, *J* = 13.8, 8.0, 4.5 Hz, 1H), 1.60 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 142.5, 122.9, 105.0, 103.3, 98.2, 93.6, 77.1, 73.9, 64.7, 64.7, 55.4, 49.8, 49.2, 40.6, 33.1, 20.7, 18.0, 16.9 ppm. IR (film): $\tilde{\nu}$ = 2952, 2887, 2840, 1747, 1456, 1379, 1260, 1213, 1143, 1102, 1027, 970, 915, 899, 863 cm^{-1}. MS (ESIpos) *m/z* (%): 427.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{32}O_9Na$: 427.1939, found: 427.1937.

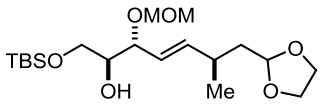
Diol 333. A solution of ketal **332** (2.11 g, 5.01 mmol) in THF (10 mL) was added dropwise to a  suspension of lithium aluminium hydride (1.6 g, 42 mmol) in THF (90 mL) at 0 °C. After stirring for 10 min at the same temperature, the ice bath was removed and the mixture stirred for 2 h under reflux. After cooling to 0 °C, the reaction was quenched with dropwise addition of EtOAc (120 mL) until no hydrogen evolution was observed. After dilution with additional EtOAc (200 mL) and Rochelle salt (500 mL), the resulting mixture was stirred for 18 h until a clear emulsion was obtained. The aq. phase was separated and extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with brine (500 mL), dried over Na_2SO_4 and concentrated. The residual yellow oil was purified by flash chromatography (EtOAc) to afford the title compound (1.15 g, 83%) as a light yellow oil. $[\alpha]_D^{20}$ = −123.4 (c = 1.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddd, *J* = 15.6, 7.5, 0.9 Hz, 1H), 5.37 (ddd, *J* = 15.6, 7.9, 1.1 Hz, 1H), 4.82 (t, *J* = 5.0 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 4.07 (dd, *J* = 7.9, 4.4 Hz, 1H), 3.97–3.89 (m, 2H), 3.84–3.77 (m, 2H), 3.73–3.64 (m, 3H), 3.37 (s, 3H), 2.82 (br s, 1H), 2.53–2.40 (m, 1H), 2.35 (br s, 1H), 1.73–1.66 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.1, 124.3, 103.3, 93.9, 78.3, 73.3, 64.7, 64.7, 63.3, 55.6, 40.5, 32.7, 20.5 ppm. IR (film): $\tilde{\nu}$ = 3424, 2955, 2887, 1412, 1213, 1151, 1099, 1028, 976, 945 cm^{-1}. MS (ESIpos) *m/z* (%): 299.1 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{13}H_{24}O_6Na$: 299.1465, found: 299.1465.

PMB-Ether 335a. *p*-Anisaldehyde dimethyl acetal (0.05 mL, 0.3 mmol) and PPTS (1.3 mg, 5.1 µmol) were added to diol **333** (28 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 16 h, the reaction was quenched with sat. $NaHCO_3$ (1 mL). The aq. phase was separated and extracted with EtOAc (3 × 2 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:7) to afford the PMP-acetal **334** (29 mg, 73%) as a mixture of diastereomers.



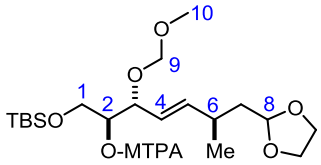
A solution of Dibal-H (1.0 M in heptane, 0.15 mL, 0.15 mmol) was added to a solution of PMP-acetal **334** (29 mg, 74 µmol) in toluene (1.5 mL) at −78 °C. After stirring for 4.5 h at the same temperature, the reaction was quenched with methanol (2 mL). The mixture was diluted with Rochelle salt (10 mL) and EtOAc (10 mL) and stirred for 16 h. The aq. phase was separated from the clear emulsion and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:2 to 1:1) to afford the title compound (18.4 mg, 46%, **335a**/**335b** = 6:1) as a mixture of regioisomers. Spectral and analytical data for **335a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 2H), 6.90–6.84 (m, 2H), 5.68 (ddd, *J* = 15.6, 7.7, 0.8 Hz, 1H), 5.39 (ddd, *J* = 15.6, 8.0, 1.1 Hz, 1H), 4.85–4.79 (m, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.53 (d, *J* = 6.6 Hz, 1H), 4.51–4.42 (m, 2H), 4.06 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 3.96–3.90 (m, 2H), 3.90–3.85 (m, 1H), 3.83–3.76 (m, 5H), 3.52 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.47 (dd, *J* = 9.7, 6.7 Hz, 1H), 3.33 (s, 3H), 2.56 (s, 1H), 2.51–2.39 (m, 1H), 1.74–1.59 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 142.0, 129.4, 124.0, 113.8, 113.8, 103.4, 93.6, 77.2, 73.1, 72.5, 70.6, 64.7, 64.7, 55.5, 55.3, 40.6, 33.0, 20.8 ppm. IR (film): $\tilde{\nu}$ = 3467, 2953, 2884, 1612, 1514, 1463, 1302, 1248, 1212, 1173, 1151, 1097, 1031, 977, 946, 918, 821 cm^{-1}. MS (ESIpos) *m/z* (%): 419.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{21}H_{32}O_7Na$: 419.2040, found: 419.2038.

Alcohol 336. TBSCl (522 mg, 3.46 mmol) and imidazole (282 mg, 4.14 mmol) were added to a solution of diol **333** (839 mg, 3.04 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring for 3 h at the same temperature, the reaction was quenched with sat. NH_4Cl (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 20 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 3:2) to afford the title compound (1.00 g, 85%) as a colourless oil. $[\alpha]_D^{20}$ = −89.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (ddd, *J* = 15.6, 7.7, 0.8 Hz, 1H), 5.43 (ddd, *J* = 15.6, 8.0, 1.0 Hz, 1H), 4.84 (dd, *J* = 5.5, 4.7 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 4.06 (ddd, *J* = 8.0, 4.8, 0.7 Hz, 1H), 3.97–3.89 (m, 2H), 3.86–3.78 (m, 2H), 3.72 (dt, *J* = 6.5, 4.7 Hz, 1H), 3.66 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.36 (s, 3H), 2.53–2.40 (m, 1H),



1.76–1.60 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): *δ* = 141.7, 124.3, 103.5, 93.6, 76.9, 73.8, 64.7, 64.7, 63.7, 55.4, 40.7, 33.1, 25.9, 20.9, 18.3, −5.4 (2C) ppm. IR (film): $\tilde{\nu}$ = 3484, 2953, 2929, 2884, 1472, 1407, 1361, 1253, 1212, 1098, 1062, 1029, 976, 940, 919, 836, 777, 667 cm^{-1}. MS (ESIpos) *m/z* (%): 413.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{19}H_{38}O_6SiNa$: 413.2330, found: 413.2332.

Mosher Ester Analysis of Alcohol 336. Hünig's base (15.6 µL, 90.0 µmol) was added to a solution of alcohol **336** (13 mg, 33 µmol) in CH_2Cl_2 (0.40 mL) followed by (*R*)-(–)-*α*-methoxy-*α*-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (11.8 µL, 63.2 µmol).). The mixture was stirred at ambient temperature for 17 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 4:1) to give the corresponding (*S*)-Mosher ester **(*S*)-MTPA-336** (12 mg, 59%), which analyzed as follows: $[\alpha]_D^{20}$ = −65.1 (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.63–7.57 (m, 2H), 7.42–7.34 (m, 3H), 5.68 (ddd, *J* = 15.6, 7.7, 0.7 Hz, 1H), 5.40–5.28 (m, 2H), 4.81 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.29 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.98–3.88 (m, 2H), 3.85–3.77 (m, 2H), 3.70 (dd, *J* = 10.8, 6.3 Hz, 1H), 3.64 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.55 (q, *J* = 1.1 Hz, 3H), 3.34 (s, 3H), 2.49–2.37 (m, 1H), 1.68 (ddd, *J* = 13.9, 7.8, 4.7 Hz, 1H), 1.60 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2932, 2885, 2858, 1752, 1472, 1255, 1169, 1124, 1022, 978, 837, 779, 719 cm^{-1}. MS (ESIpos) *m/z* (%): 629.3 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{29}H_{45}O_8F_3SiNa$: 629.2728, found: 629.2726.



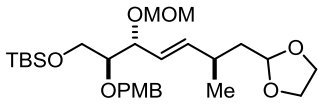
Using (*S*)-(–)-*α*-methoxy-*α*-trifluoromethyl-phenylacetyl chloride the same procedure was followed for the preparation of **(*R*)-MTPA-336** (8.0 mg, 43%), which analyzed as follows: $[\alpha]_D^{20}$ = −26.5 (c = 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.62–7.56 (m, 2H), 7.41–7.36 (m, 3H), 5.62 (ddd, *J* = 15.5, 7.8, 0.9 Hz, 1H), 5.33–5.19 (m, 2H), 4.80 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.44 (d, *J* = 6.6 Hz, 1H), 4.17 (ddd, *J* = 8.1, 4.4, 0.9 Hz, 1H), 3.98–3.90 (m, 2H), 3.84–3.76 (m, 4H), 3.58 (q, *J* = 1.2 Hz, 3H), 3.24 (s, 3H), 2.44–2.30 (m, 1H), 1.70–1.52 (m, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2932, 2884, 2858, 1752, 1473, 1256, 1169, 1124, 1025, 979, 837, 779, 719 cm^{-1}. MS (ESIpos) *m/z* (%): 629.3 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{29}H_{45}O_8F_3SiNa$: 629.2728, found: 629.2727.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-25. Mosher ester analysis for the assignment of the C(2) stereocenter; arbitrary numbering as shown in the insert.

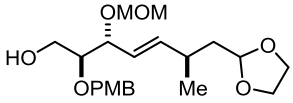
Assignment	336 [ppm]	(*S*)-MTPA-336 [ppm]	(*R*)-MTPA-336 [ppm]	Δ (δ(*S*–*R*)) [ppm]
1a	3.67	3.70	3.80	−0.10
1b	3.62	3.64	3.80	−0.06
2	3.72	5.32	5.30	+0.02
3	4.06	4.29	4.17	+0.12
4	5.43	5.34	5.26	+0.08
5	5.67	5.68	5.62	+0.06
6	2.46	2.43	2.37	+0.06
7a	1.71	1.68	1.64	+0.04
7b	1.65	1.60	1.57	+0.05
8	4.84	4.81	4.80	+0.01
9a	4.71	4.69	4.59	+0.10
9b	4.55	4.54	4.44	+0.10
10	3.36	3.34	3.24	+0.10
*t*BuSi	0.90	0.86	0.88	−0.02

PMB-Ether 337. NaH (134 mg, 5.58 mmol) was added protionwise to alcohol **336** (1.10 g, 2.82 mmol)



in DMF (13 mL) at 0 °C. After stirring for 30 min at the same temperature, PMBBr (1.22 g, 6.07 mmol) was added dropwise to the mixture. After stirring for 18 h and slowly warming to ambient temperature, the reaction was quenched with sat. NH_4Cl (10 mL) and the mixture was diluted with *t*-butyl methyl ether (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 4:1) to afford the title compound (1.27 g, 88%, 6.7:1 r.r.) as a mixture of regioisomers. ^{1}H NMR (major regioisomer, 400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2H), 6.89–6.83 (m, 2H), 5.61 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.45 (ddd, *J* = 15.6, 8.3, 0.9 Hz, 1H), 4.84 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.70–4.58 (m, 3H), 4.54 (d, *J* = 6.5 Hz, 1H), 4.16 (dd, *J* = 8.2, 3.9 Hz, 1H), 3.97–3.90 (m, 2H), 3.83–3.76 (m, 5H), 3.65 (d, *J* = 6.0 Hz, 2H), 3.59–3.54 (m, 1H), 3.34 (s, 3H), 2.51–2.40 (m, 1H), 1.71 (ddd, *J* = 13.8, 8.1, 4.5 Hz, 1H), 1.66–1.58 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H) ppm. ^{13}C NMR (major regioisomer, 101 MHz, $CDCl_3$): δ = 159.0, 141.2, 131.1, 129.3, 124.8, 113.7, 113.6, 103.4, 93.4, 81.8, 72.8, 64.7, 64.7, 63.0, 55.3, 55.2, 40.7, 33.1, 25.9, 20.9, 18.2, −5.4, −5.4 ppm. IR (film): $\tilde{\nu}$ = 2953, 2929, 2883, 2857, 1613, 1513, 1463, 1301, 1247, 1093, 1029, 975, 940, 919, 835, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 533.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{27}H_{46}O_7SiNa$: 533.2905, found: 533.2903.

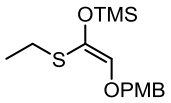
Alcohol 335b. Pyridine (20 mL, 0.25 mol), and HF·pyridine complex (4.4 mL, 49 mmol) were added to



a solution of silyl ether **337** (1.17 g, 2.29 mmol) in THF (50 mL). After stirring for 18 h at ambient temperature, the mixture was diluted with EtOAc (50 mL) and the reaction was quenched with sat. $NaHCO_3$ (50 mL). The aq. phase was separated and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with a 1:1 mixture of sat. NH_4Cl and brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc/hexane/Et_3N = 60:40:1) to afford the title compound (751 mg, 83%, pure regioisomer) as a yellow oil. $[\alpha]_D^{20}$ = −98.2 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 2H), 6.92–6.83 (m, 2H), 5.67 (ddd, *J* = 15.5, 7.8, 0.8 Hz, 1H), 5.39 (ddd, *J* = 15.5, 8.0, 1.1 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 2H), 4.58–4.48 (m, 2H), 4.18 (ddd, *J* = 7.9, 5.3, 0.9 Hz, 1H), 3.97–3.90 (m, 2H), 3.86–3.78 (m, 5H), 3.72 (dd, *J* = 12.0, 4.7 Hz, 1H), 3.69 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.50 (td, *J* = 5.3, 4.6 Hz, 1H), 3.37 (s, 3H), 2.53–2.40 (m, 1H), 1.86 (br s, 1H), 1.71 (ddd, *J* = 13.8, 8.0, 4.6 Hz, 1H), 1.64 (ddd, *J* = 13.8, 6.3, 5.7 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 141.2, 130.3, 129.5, 125.2, 113.9, 103.4, 93.5, 81.0, 76.6, 72.3, 64.7 (2C), 61.8, 55.6, 55.3, 40.7, 33.0, 20.8 ppm. IR (film): $\tilde{\nu}$ = 3500, 2954, 2885, 1613, 1514, 1464, 1403, 1302, 1248, 1099, 1032, 976, 823 cm^{-1}. MS (ESIpos) *m/z* (%): 419.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{21}H_{32}O_7Na$: 419.2040, found: 419.2039.

5.7.2.2 Mukaiyama Glycolate Aldol Reaction

Silylenol-Ether 341b. A solution of *n*-BuLi (1.6 M in THF, 4.2 mL, 6.7 mmol) was added dropwise to a



solution of 2,2,6,6-tetramethylpiperidine (1.14 mL, 6.73 mmol) in THF (40 mL) at 0 °C. After removing the ice bath, the solution was stirred for 10 min at ambient temperature. After cooling the LiTMP solution to −105 °C, *S*-ethyl 2-((4-methoxybenzyl)oxy)ethanethioate (1.44 g, 5.99 mmol) was added dropwise. After stirring for 5 min, TMSCl (0.85 mL, 6.7 mmol) was added dropwise at the same temperature. After stirring for 30 min, the cold bath was removed and the mixture was concentrated under reduced pressure. The residue was diluted with hexane (20 mL) and filtered through a pad of dry Celite® under argon. After rinsing with hexane (2 × 10 mL), the combined filtrates were concentrated under reduced pressure. The residual yellow oil was used without further purification (1.71 g, 91%, *Z*/*E* = 89:11). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H), 6.90–6.86 (m, 2H), 6.24 (s, 1H), 4.71 (s, 2H), 3.80 (s, 3H), 2.67 (q, *J* = 7.4 Hz, 2H), 1.23 (t, *J* = 7.4 Hz, 3H), 0.16 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4, 136.9, 132.7, 129.4, 128.1, 113.8, 73.9, 55.3, 25.2, 15.0, 0.0 ppm. IR (film): $\tilde{\nu}$ = 2959, 2929, 1613, 1514, 1456, 1250, 1154, 1036, 870, 845 cm^{-1}. MS (ESIpos) *m/z* (%): 313 (100 (M+H)). HRMS (ESIpos): *m/z* calcd for $C_{15}H_{24}O_3SSiNa$: 313.1288, found: 313.1288.

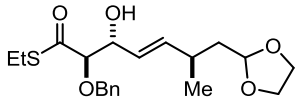
General Procedure for Mukaiyama Aldol Reaction:

(*S*)-1-Methyl-2-(piperidinomethyl)-pyrrolidin (175 mol%) was added to a suspension of tin(II) triflate (150 mol%) in CH_2Cl_2 (0.09-0.20 M). After addition of dibutyltin diacetate (164 mol%) to the orange solution, the reaction was stirred for 30 min at ambient temperature. After cooling the light yellow solution to −65 °C, a solution of silylenol ether (150 mol%) in CH_2Cl_2 was added followed by a solution of aldehyde **253** (617 mg, 3.63 mmol) in CH_2Cl_2 (0.20 M). After stirring for 18 h at −65 °C, sat. $NaHCO_3$ (7.5 mL) was added to the cold mixture and the cold bath was removed. After reaching ambient temperature, the mixture was diluted with EtOAc (50 mL) and water (50 mL). The aq. phase was separated and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The yellow residual oil was purified by flash chromatography (hexane/*t*-butyl methyl ether 2:3 to 1:1 to 3:7) to provide the title compounds.

For recovery of (*S*)-1-Methyl-2-(piperidinomethyl)-pyrrolidin (**342**):

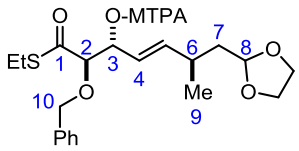
The aq. phase was treated with aq. solution of NaOH (10 w-%) until the solution reached pH = 14. After extracting the aq. phase with *t*-butyl methyl ether (3 × 50 mL) the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by Kugelrohr distillation, collecting the fraction that distilled between 115–125 °C at 12 mbar to give the diamine **342** as a colourless.

Aldol 343a. According to General Procedure using literature-known[8i] silylenol ether **341a** (*Z*/*E* 78:22,



405 mg, 1.44 mmol) and aldehyde **253** in CH_2Cl_2 (0.09 M). Yellow oil (79 mg, 33%, >20:1 dr). $[\alpha]_D^{20}$ = +47.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5H), 5.63 (ddd, *J* = 15.4, 7.5, 0.8 Hz, 1H), 5.52 (ddd, *J* = 15.5, 6.9, 0.8 Hz, 1H), 4.87–4.82 (m, 2H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.33 (dd, *J* = 6.4, 5.0 Hz, 1H), 4.02 (d, *J* = 4.8 Hz, 1H), 3.95–3.89 (m, 2H), 3.83–3.76 (m, 2H), 2.87 (q, *J* = 7.3 Hz, 2H), 2.47–2.25 (m, 2H), 1.68 (ddd, *J* = 13.8, 8.1, 4.3 Hz, 1H), 1.59 (dt, *J* = 7.7, 6.1 Hz, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.7, 139.5, 136.9, 128.5, 128.2, 128.1, 125.5, 103.3, 87.4, 74.3, 73.7, 64.7, 64.7, 40.5, 32.8, 22.5, 20.6, 14.5 ppm. IR (film): $\tilde{\nu}$ = 3446, 2960, 2876, 1677, 1455, 1131, 1029, 973, 739, 701 cm^{-1}. MS (ESIpos) *m/z* (%): 403.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{20}H_{28}O_5SNa$: 403.1550, found: 403.1554.

Mosher Ester Analysis of Alcohol 343a. Hünig's base (9.6 µL, 55 µmol) was added to a solution of



alcohol **343a** (7.5 mg, 20 µmol) in CH_2Cl_2 (0.3 mL) followed by (*S*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*S*)-MTPA-Cl) (7.0 µL, 37 µmol). The mixture was stirred at ambient temperature for 17 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated.

The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether = 9:1) to give the corresponding (*R*)-Mosher ester **(*R*)-MTPA-343a** (8.8 mg, 75%), which analyzed as follows: $[\alpha]_D^{20}$ = +50.0 (c = 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 2H), 7.39–7.29 (m, 8H), 5.77–5.69 (m, 2H), 5.48 (ddd, *J* = 15.6, 8.3, 1.0 Hz, 1H), 4.76 (dd, *J* = 6.3, 4.1 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.16 (d, *J* = 3.5 Hz, 1H), 3.94–3.89 (m, 2H), 3.78–3.73 (m, 2H), 3.50 (d, *J* = 0.9 Hz, 3H), 2.86 (dq, *J* = 13.4, 7.5 Hz, 1H), 2.79 (dq, *J* = 13.4, 7.4 Hz, 1H), 2.41 (dddd, *J* = 15.2, 8.0, 4.7, 1.2 Hz, 1H), 1.65 (ddd, *J* = 13.8, 8.5, 4.1 Hz, 1H), 1.56 (dt, *J* = 13.9, 6.3 Hz, 1H), 1.20 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2958, 2876, 1751, 1678, 1453, 1270, 1247, 1169, 1124, 1082, 1017, 976, 765, 737, 720, 699 cm^{-1}. MS (ESIpos) *m/z* (%): 619.2 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{30}H_{35}O_7F_3SNa$: 619.1948, found: 619.1955.

The corresponding Mosher ester **(*S*)-MTPA-343a** (10.8 mg, 85%) was prepared analogously: $[\alpha]_D^{20}$ = −20.7 (c = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.50 (m, 2H), 7.42–7.34 (m, 3H), 7.33–7.22 (m, 5H), 5.85 – 5.74 (m, 2H), 5.60 (ddd, *J* = 15.5, 8.6, 0.9 Hz, 1H), 4.74 (dd, *J* = 6.3, 4.1 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.11 (d, *J* = 3.3 Hz, 1H), 3.93–3.85 (m, 2H), 3.75–3.67 (m, 2H), 3.54 (d, *J* = 1.3 Hz, 3H), 2.83 (dq, *J* = 13.4, 7.5 Hz, 1H), 2.76 (dq, *J* = 13.4, 7.4 Hz, 1H), 2.42 (hept, *J* = 7.2, 6.7, 6.4 Hz, 1H), 1.66 (ddd, *J* = 13.9, 8.5, 4.2 Hz, 1H), 1.57 (dt, *J* = 13.6, 6.5, 6.0 Hz, 1H), 1.20 (t, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2957, 2877, 1750, 1677, 1453, 1269, 1246, 1168, 1123, 1081, 1017, 976, 739, 718, 699 cm^{-1}. MS (ESIpos) *m/z* (%): 619.2 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{30}H_{35}O_7F_3SNa$: 619.1948, found: 619.1954.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-26. Mosher ester analysis for the assignment of the C(3) stereocenter; arbitrary numbering as shown in the insert.

Assignment	343a [ppm]	(*S*)-MTPA-343a [ppm]	(*R*)-MTPA-343a [ppm]	Δ (δ(*S*–*R*)) [ppm]
2	4.02	4.11	4.16	−0.05
3	4.33	5.78	5.73	+0.05
4	5.53	5.60	5.48	+0.12
5	5.63	5.79	5.73	+0.06
6	2.41	2.42	2.41	+0.01
7a	1.67	1.66	1.65	+0.01
7b	1.59	1.57	1.56	+0.01
8	4.84	4.74	4.76	–0.02
9	1.02	0.99	0.98	+0.01
10a	4.84	4.58	4.70	−0.12
10b	4.53	4.42	4.54	−0.12

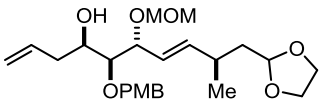
Aldol 343b. According to General Procedure for Mukaiyama aldol using silylenol ether **341b** (*Z*/*E*= 89:11, 1.70 g, 5.44 mmol) and aldehyde **253** in CH_2Cl_2 (0.20 M). Pale yellow oil (975 mg, 66%, >20:1 dr). Additionally, the diamine **342** was recovered as a colourless oil (551 g, 48%). $[\alpha]_D^{20}$ = +42.6 (c = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 2H), 6.92–6.88 (m, 2H), 5.62 (ddd, *J* = 15.5, 7.5, 0.8 Hz, 1H), 5.50 (ddd, *J* = 15.5, 7.0, 0.8 Hz, 1H), 4.83 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.30 (ddd, *J* = 7.0, 4.9, 0.9 Hz, 1H), 3.99 (d, *J* = 4.8 Hz, 1H), 3.96– 3.89 (m, 2H), 3.83–3.77 (m, 5H), 2.88 (d, *J* = 7.4 Hz, 1H), 2.85 (d, *J* = 7.4 Hz, 1H), 2.40 (hept, *J* = 6.9 Hz, 1H), 2.10 (br s, 1H), 1.67 (ddd, *J* = 13.8, 8.1, 4.3 Hz, 1H), 1.57 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.8, 159.6, 139.4, 129.9, 129.0, 125.6, 113.9, 103.3, 87.0, 73.9, 73.7, 64.7, 64.7, 55.3, 40.5, 32.8, 22.5, 20.6, 14.5 ppm. IR (film): $\tilde{\nu}$ = 3474, 2960, 2933, 2876, 1676, 1613, 1514, 1456, 1303, 1248, 1129, 1032, 973, 822 cm^{-1}. MS (ESIpos) *m/z* (%): 433.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{21}H_{30}O_6SNa$: 433.1655, found: 433.1656.

MOM-Ether S27. Tetrabutylammonium idodide (17 mg, 46 µmol), MOMCl (1.4 mL, 18 mmol) and Hünig's base (5.5 mL, 32 mmol) were added to a solution of alcohol **343b** (1.90 g, 4.63 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring for 15 min at 0 °C, the ice bath was removed and the mixture was stirred for 17 h at ambient temperature. The reaction was quenched with sat. NH_4Cl (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 25 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 4:1 to 7:3) to afford the title compound as a pale yellow oil (1.70 g, 81%). $[\alpha]_D^{20}$ = −35.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 2H), 6.91–6.85 (m, 2H), 5.60 (ddd, *J* = 15.6, 7.8, 0.6 Hz, 1H), 5.43 (ddd, *J* = 15.5, 8.4, 1.0 Hz, 1H), 4.81 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.30 (dd, *J* = 8.3, 4.4 Hz, 1H), 4.05 (d, *J* = 4.4 Hz, 1H), 3.96–3.90 (m, 2H), 3.82–3.76 (m, 5H), 3.31 (s, 3H), 2.90–2.80 (m, 2H), 2.49–2.37 (m, 1H), 1.67 (ddd, *J* = 13.8, 8.1, 4.5 Hz, 1H), 1.62–1.55 (m, 1H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.3, 159.3, 142.0, 129.6, 129.4, 123.5, 113.7, 103.3, 93.4, 86.2, 77.8, 73.4, 64.7, 64.7, 55.4, 55.3, 40.6, 33.0, 22.5, 20.7, 14.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2932, 2883, 1678, 1613, 1514, 1456, 1302, 1248, 1140, 1092, 1030, 974, 823 cm^{-1}. MS (ESIpos) *m/z* (%): 477.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{23}H_{34}O_7SNa$: 477.1917, found: 477.1919.

Aldehyde 316. Pd/C (10 wt.-%, 366 mg, 0.344 mmol, 10 mol%) and triethylsilane (1.8 mL, 11 mmol) were added to a solution of thioester **S27** (1.70 g, 3.59 mmol) in CH_2Cl_2 (7.0 mL). After stirring for 2 h at ambient temperature the reaction was

filtered through a pad of Celite®, which was rinsed with CH_2Cl_2 (15 mL), and the combined filtrates were concentrated. Due to approximatly 72% conversion of thioester **S27**, the residual yellow oil was dissolved in acetone (10 mL) and treated with Pd/C (10 wt.-%, 100 mg, 94.0 µmol, 2.6 mol%) and triethylsilane (0.60 mL, 3.8 mmol). After stirring for 2 h at ambient temperature, the reaction was filtered through a pad of Celite®, which was rinsed with CH_2Cl_2 (20 mL), and the combined filtrates were concentrated. An analytical sample was purified by flash chromatography (hexane/*t*-butyl methyl ether 7:3) for characterization. The crude aldehyde was used without further purification in the next step. $[\alpha]_D^{20}$ = −27.1 (c = 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 2.3 Hz, 1H), 7.30–7.24 (m, 2H), 6.90–6.84 (m, 2H), 5.67 (ddd, *J* = 15.5, 7.8, 0.8 Hz, 1H), 5.42 (ddd, *J* = 15.6, 8.2, 1.0 Hz, 1H), 4.82 (dd, *J* = 5.7, 4.5 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 1H), 4.34 (ddd, *J* = 8.0, 4.7, 0.7 Hz, 1H), 3.97–3.91 (m, 2H), 3.83–3.78 (m, 6H), 3.33 (s, 3H), 2.51–2.39 (m, 1H), 1.73–1.57 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.8, 159.5, 142.1, 129.7, 129.2, 123.6, 113.8, 103.3, 93.4, 84.8, 76.4, 72.5, 64.7 (2C), 55.5, 55.3, 40.6, 32.9, 20.7 ppm. IR (film): $\tilde{\nu}$ = 2954, 2886, 1734, 1613, 1514, 1464, 1303, 1249, 1149, 1097, 1031, 976, 822 cm^{-1}. MS (ESIpos) *m/z* (%): 417.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{21}H_{30}O_7Na$: 417.1884, found: 417.1885.

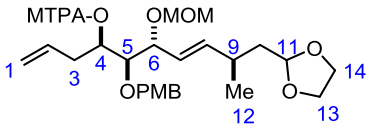
Alcohol 339. Magnesium bromide diethyl etherate (2.30 g, 8.91 mmol) was added to crude aldehyde



316 (1.42 g, 3.59 mmol) in CH_2Cl_2 (18 mL) at −30 °C. After stirring for 20 min, the yellow suspension was cooled to −78 °C and allyltributylstannane (1.3 mL, 4.2 mmol) was added dropwise. After stirring for 3.5 h and allowing the mixture to reach −35 °C, additional magnesium bromide diethyl etherate (500 mg, 1.93 mmol) was added due to unconsumed starting material. After stirring for 1.5 h at the same temperature, the reaction was quenched with sat. NH_4Cl (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 25 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:2) to afford the title compound as a yellow oil (753 mg, 49% over 2 steps, >20:1 dr, single diastereomer). $[\alpha]_D^{20}$ = −89.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2H), 6.90–6.85 (m, 2H), 5.88–5.76 (m, 1H), 5.68 (ddd, *J* = 15.5, 7.8, 0.8 Hz, 1H), 5.44 (ddd, *J* = 15.5, 8.0, 1.0 Hz, 1H), 5.10–5.02 (m, 2H), 4.83 (dd, *J* = 5.7, 4.5 Hz, 1H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.55 (d, *J* = 6.5 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.28 (ddd, *J* = 8.0, 5.1, 0.8 Hz, 1H), 3.97–3.91 (m, 2H), 3.84–3.77 (m, 6H), 3.38 (s, 3H), 3.34 (dd, *J* = 5.1, 3.5 Hz, 1H), 2.77 (br s, 1H), 2.53–2.41 (m, 1H), 2.36–2.24 (m, 2H), 1.75–1.60 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 141.4, 135.0, 130.2, 129.7, 125.0, 117.1, 113.8, 103.3, 93.4, 81.6, 76.6, 73.4, 70.2, 64.7, 64.7, 55.7, 55.3, 40.7, 38.1, 33.1, 20.8 ppm. IR (film): $\tilde{\nu}$ = 3514, 2953,

2886, 1613, 1514, 1464, 1401, 1302, 1248, 1151, 1097, 1031, 977, 917, 823 cm^{-1}. MS (ESIpos) *m/z* (%): 459.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{24}H_{36}O_7Na$: 459.2353, found: 459.2352.

Mosher Ester Analysis of Alcohol 339. Hünig's base (6.5 µL, 37 µmol) was added to a solution of



alcohol **339** (6.0 mg, 14 µmol) in CH_2Cl_2 (0.2 mL) followed by (*S*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*S*)-MTPA-Cl) (4.9 µL, 26 µmol). The mixture was stirred at ambient temperature for 17 h, diluted with CH_2Cl_2 (2 mL) and sat. NH_4Cl (2 mL). The aq. phase was separated and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 7:3) to give the corresponding (*R*)-Mosher ester **(*R*)-MTPA-339** (8.9 mg, 99%), which analyzed as follows: $[\alpha]_D^{20}$ = −32.1 (c = 0.89, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2H), 7.39–7.33 (m, 1H), 7.30–7.25 (m, 2H), 7.23–7.17 (m, 2H), 6.86–6.81 (m, 2H), 5.72–5.60 (m, 2H), 5.50 (ddd, *J* = 15.6, 8.3, 0.9 Hz, 1H), 5.28 (dt, *J* = 6.5, 5.1 Hz, 1H), 5.10–4.99 (m, 2H), 4.83 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 4.51–4.44 (m, 2H), 4.13 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.96–3.92 (m, 2H), 3.82–3.77 (m, 5H), 3.65 (dd, *J* = 5.7, 4.8 Hz, 1H), 3.51 (d, *J* = 1.1 Hz, 3H), 3.31 (s, 3H), 2.55–2.32 (m, 3H), 1.75–1.60 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2887, 1746, 1613, 1514, 1453, 1247, 1169, 1103, 1022, 920, 819, 721, 514 cm^{-1}. MS (ESIpos) *m/z* (%): 675.3 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{34}H_{43}O_9F_3Na$: 675.2751, found: 675.2750.

The corresponding Mosher ester **(*S*)-MTPA-339** (6.7 mg, 75%) was prepared analogously: $[\alpha]_D^{20}$ = −41.6 (c = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2H), 7.32–7.25 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.79–6.74 (m, 2H), 5.74–5.62 (m, 1H), 5.50 (dd, *J* = 15.6, 7.7 Hz, 1H), 5.37 (ddd, *J* = 15.6, 8.2, 0.8 Hz, 1H), 5.24 (dt, *J* = 6.9, 5.2 Hz, 1H), 5.07–4.99 (m, 2H), 4.75 (dd, *J* = 5.7, 4.5 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.37–4.29 (m, 2H), 3.97 (dd, *J* = 8.2, 5.2 Hz, 1H), 3.90–3.83 (m, 2H), 3.76–3.69 (m, 5H), 3.52 (t, *J* = 5.1 Hz, 1H), 3.44 (d, *J* = 1.2 Hz, 3H), 3.22 (s, 3H), 2.47 (dddd, *J* = 9.4, 8.0, 4.1, 2.7 Hz, 1H), 2.43–2.33 (m, 2H), 1.66–1.52 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 2954, 2888, 1746, 1613, 1514, 1452, 1248, 1168, 1122, 1082, 1025, 920, 820, 765, 720 cm^{-1}. MS (ESIpos) *m/z* (%): 675.3 (100 (M+Na)). HRMS (ESI): *m/z* calcd for $C_{34}H_{43}O_9F_3Na$: 675.2751, found: 675.2747.

Both products were analyzed according to Hoye and co-workers:[497]

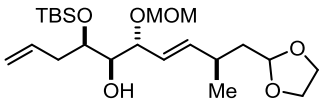
Table S-27. Mosher ester analysis for the assignment of the C(4) stereocenter; arbitrary numbering as shown in the insert.

Assignment	339 [ppm]	(*S*)-MTPA-339 [ppm]	(*R*)-MTPA-339 [ppm]	Δ (*δ*(*S*–*R*)) [ppm]
1a	5.07	5.04	5.03	+0.01
1b	5.06	5.02	5.02	0
2	5.82	5.68	5.65	+0.03
3a	2.31	2.47	2.48	−0.01
3b	2.29	2.38	2.38	0
4	3.80	5.24	5.28	−0.04
5	3.34	3.52	3.65	−0.13
6	4.28	3.97	4.13	−0.16
7	5.44	5.37	5.50	−0.13
8	5.68	5.50	5.65	−0.15
9	2.47	2.38	2.48	–0.10
10a	1.70	1.61	1.71	−0.10
10b	1.63	1.54	1.63	−0.09
11	4.83	4.75	4.83	−0.08
12	1.05	0.94	1.04	−0.10

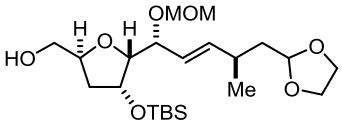
5.7.2.3 Completion of the Synthesis of the Northern Fragment 275

Compound S28. 2,6-Lutidine (0.27 mL, 2.3 mmol) and TBSOTf (0.39 mL, 1.7 mmol) were added to a solution of homoallylic alcohol **339** (500 mg, 1.15 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After stirring for 1 h at the same temperature, the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 7:3) to afford the title compound as a colourless oil (527 mg, 84%). $[\alpha]_D^{20}$ = –75.0 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 2H), 6.89–6.83 (m, 2H), 5.80 (dddd, *J* = 15.8, 11.2, 7.9, 6.4 Hz, 1H), 5.66–5.54 (m, 2H), 5.06–4.98 (m, 2H), 4.84 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.27–4.22 (m, 1H), 3.97–3.91 (m, 2H), 3.83–3.77 (m, 5H), 3.69 (ddd, *J* = 7.0, 6.1, 4.0 Hz, 1H), 3.54 (dd, *J* = 6.1, 2.6 Hz, 1H), 3.33 (s, 3H), 2.52–2.41 (m, 1H), 2.39–2.31 (m, 1H), 2.14 (dddt, *J* = 14.3, 7.7, 6.9, 0.9 Hz, 1H), 1.72 (ddd, *J* = 13.8, 8.1, 4.5 Hz, 1H), 1.63 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), −0.01 (s, 3H), −0.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.9, 141.4, 135.7, 131.4, 129.1, 125.0, 116.7, 113.5, 103.4, 92.7, 83.2, 76.2, 73.4, 72.5, 64.7, 64.7, 55.3, 55.3, 40.7, 38.1, 33.2, 25.9, 20.7, 18.1, −4.3, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2953, 2929, 2884, 2857, 1613, 1514, 1463, 1248, 1148, 1094, 1031, 916, 831, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 573.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{30}H_{50}O_7SiNa$: 573.3218, found: 573.3219.

Alcohol 315. DDQ (680 mg, 3.00 mmol) was added to an emulsion of PMB-ether **S28** (550 mg, 0.999 mmol) in a 4:1 mixture of CH_2Cl_2 (8 mL) and pH 7.4 phosphate buffer (2 mL) at 0 °C. After stirring for 30 min at the same temperature, the reaction was quenched with a 3:1 mixture of sat. $NaHCO_3$ and sat. NaS_2O_3 (10 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (2 times, hexane/*t*-butyl methyl ether 4:1 to 7:3) to afford the title compound as a colourless oil (357 mg, 83%). $[\alpha]_D^{20}$ = –72.4 (c = 1.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.61 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.44 (ddd, *J* = 15.6, 8.3, 1.0 Hz, 1H), 5.14–5.04 (m, 2H), 4.85 (dd, *J* = 5.6, 4.6 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.51 (d, *J* = 6.5 Hz, 1H), 3.99–3.91 (m, 3H), 3.88–3.78 (m, 3H), 3.50 (td, *J* = 6.3, 3.8 Hz, 1H), 3.34 (s, 3H), 2.53–2.36 (m, 3H), 2.23 (dddt, *J* = 12.8, 6.9, 4.7, 0.7 Hz, 1H), 1.71 (ddd, *J* = 13.9, 8.1, 4.6 Hz, 1H), 1.64 (dt, *J* = 13.8, 5.9 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.12–0.09 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.5, 134.0, 125.2, 117.6, 103.4, 93.5, 77.2, 73.8, 71.1, 64.7 (2C), 55.6, 40.7, 39.0, 33.0, 25.9, 20.8, 18.1, −4.1, −4.6 ppm. IR (film): $\tilde{\nu}$ = 3507, 2953, 2929, 2885, 2857, 1472, 1407, 1361, 1252, 1150, 1094, 1067, 1030, 917, 835, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 453.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{42}O_6SiNa$: 453.2643, found: 453.2640.

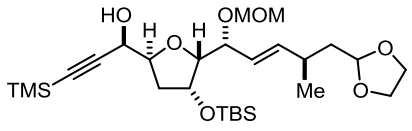


Alcohol 344. $Co(nmp)_2$ (46 mg, 81 µmol) was added to a solution of alcohol **315** (350 mg, 0.813 mmol) in *i*-PrOH (7.5 mL). The solution was degassed by 3 freeze-pump-thaw cycles and back-filled with oxygen. After adding *t*-BuOOH (5.5 M in decane, 14.8 µL, 0.81 µmol), a balloon of oxygen was fitted to the flask which was placed in a pre-heated oil bath at 55 °C. The mixture turned green within 5 min of heating and stirring was continued for 16 h. After reaching ambient temperature, the mixture was concentrated to a green oil, which was purified by flash chromatography (hexane/EtOAc 3:7) to give the title product as a colourless oil (249 mg, 69%, >20:1 dr, >20:1 r.r.). $[\alpha]_D^{20}$ = –21.3 (c = 1.43, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.68 (ddt, *J* = 15.6, 7.6, 0.8 Hz, 1H), 5.51 (ddt, *J* = 15.6, 7.6, 0.8 Hz, 1H), 4.88 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.66 (dt, *J* = 6.3, 0.5 Hz, 1H), 4.60 (dd, *J* = 6.3, 0.6 Hz, 1H), 4.49 (ddd, *J* = 5.3, 4.5, 3.8 Hz, 1H), 4.27 (dddd, *J* = 7.9, 7.2, 5.5, 3.1 Hz, 1H), 4.17 (dd, *J* = 7.7, 5.7 Hz, 1H), 3.97–3.93 (m, 2H), 3.92 (dd, *J* = 5.7, 4.3 Hz, 1H), 3.83–3.79 (m, 2H), 3.66 (dd, *J* = 11.7, 3.1 Hz, 1H), 3.42 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.33 (dd, *J* = 0.5 Hz, 3H), 2.45 (hept, *J* = 6.9 Hz, 1H), 2.03 (br s, 1H), 1.91 (ddd, *J* = 12.8, 7.0, 3.7 Hz, 1H), 1.87 (ddd, *J* = 12.8, 7.9, 5.3 Hz, 1H), 1.72 (ddd, *J* = 13.7, 8.1, 4.3 Hz, 1H), 1.62 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.7, 126.2, 103.4, 94.4, 84.6, 78.1, 76.0, 72.5, 65.1, 64.7, 64.7, 55.6, 40.7, 36.7, 32.9, 25.8, 20.7, 18.0, −4.5, −4.9 ppm. ^{29}Si NMR (99 MHz, $CDCl_3$): δ = 19.3 ppm. IR (film): $\tilde{\nu}$ = 3456, 2952, 2929, 2885, 2857, 1472, 1407, 1361, 1254, 1140, 1099, 1034, 941, 835, 776,



667 cm^{-1}. MS (ESIpos) *m/z* (%): 469.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{22}H_{42}O_7SiNa$: 469.2592, found: 469.2596.

Propargyl Alcohol 345. Hünig's base (2.8 mL, 16 mmol) was added at to a solution of alcohol **344**

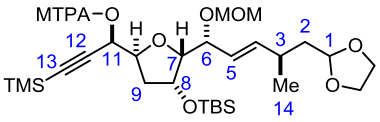


(208 mg, 0.466 mmol) in CH_2Cl_2 (3.0 mL) –25 °C and the resulting mixture was stirred for 5 min at this temperature. In a second flask a suspension of sulfur trioxide pyridine complex (1.26 g, 7.92 mmol) in CH_2Cl_2 (1.0 mL) was treated with DMSO (0.33 mL, 4.6 mmol) and the resulting mixture was stirred for 15 min at ambient temperature. This suspension was added to the alcohol solution at –25 °C, rinsing the flask with CH_2Cl_2 (1.0 mL). The mixture was allowed to slowly reach −10 °C over 1.5 h. The mixture was diluted with *t*-butyl methyl ether (5 mL) and the reaction was quenched with pH 7 phosphate buffer (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude aldehyde **314** as a yellow oil, which was used in the next step without further purification.

A Schlenk tube was charged with $Zn(OTf)_2$ (dried at 120 °C under high vacuum for 24 h, 924 mg, 2.54 mmol) and (–)-*N*-methylephedrine (dried aceotriopically by distilling toluene off the compound (3 x), 510 mg, 2.85 mmol). After the addition of toluene (1.8 mL), Hünig's base (0.50 mL, 2.9 mmol) was added and the resulting suspension was stirred for 3 h at ambient temperature before ethynyltrimethylsilane (0.39 mL, 2.7 mmol) was added. After stirring for another 0.5 h at ambient temperature, a solution of crude aldehyde **314** (207 mg, 0.465 mmol) in toluene (4.0 mL with rinses) was added in one portion to the milky suspension. After stirring for 15 h at ambient temperature, the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 7:3 to 3:2) to provide the title compound as a pale yellow oil (224 mg, 89% over 2 steps, dr = 19:1). $[\alpha]_D^{20}$ = –24.0 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (ddd, *J* = 15.7, 7.7, 0.8 Hz, 1H), 5.51 (ddd, *J* = 15.7, 7.5, 1.0 Hz, 1H), 4.88 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 4.59 (d, *J* = 6.3 Hz, 1H), 4.57 (dt, *J* = 5.7, 4.4 Hz, 1H), 4.38 (d, *J* = 2.9 Hz, 1H), 4.32–4.26 (m, 1H), 4.17 (ddd, *J* = 7.5, 5.6, 0.8 Hz, 1H), 4.03 (dd, *J* = 5.6, 4.6 Hz, 1H), 3.97–3.91 (m, 2H), 3.85–3.80 (m, 2H), 3.33 (s, 3H), 2.57 (br s, 1H), 2.45 (hept, *J* = 6.9 Hz, 1H), 2.13 (ddd, *J* = 13.1, 7.4, 5.7 Hz, 1H), 1.96 (ddd, *J* = 12.9, 7.3, 4.0 Hz, 1H), 1.71 (ddd, *J* = 13.8, 8.2, 4.4 Hz, 1H), 1.63 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.7, 126.1, 103.4, 103.2, 94.4, 90.8, 85.6, 80.3, 75.8, 72.2, 65.1, 64.7 (2C), 55.5, 40.7, 35.8, 33.0, 25.8, 20.7, 18.0, −0.2, −4.5, −4.9 ppm. ^{29}Si NMR (99 MHz, $CDCl_3$): δ = 19.3 ppm. IR (film): $\tilde{\nu}$ = 3436, 2955, 2929, 2887, 2858, 1472,

1408, 1361, 1251, 1140, 1099, 1036, 942, 839, 776, 761 cm^{-1}. MS (ESIpos) *m/z* (%): 565.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{27}H_{50}O_7Si_2Na$: 565.2987, found: 565.2992.

Mosher Ester Analysis of Propargyl Alcohol 345. Hünig's base (12 µL, 69 µmol) was added to a solution of alcohol **345** (11.9 mg, 22 µmol) in CH_2Cl_2 (0.20 mL) followed by (*R*)-(−)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride ((*R*)-MTPA-Cl) (7.8 µL, 42 µmol). After stirring for 17 h at ambient temperature, the mixture was diluted with CH_2Cl_2 (3 mL) and sat. $NaHCO_3$ (3 mL). The aq. phase was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/*t*-butyl methyl ether 4:1) to give the corresponding (*S*)-Mosher ester (*S*)-**MTBA-345** (12.8 mg, 76%) as a colourless oil. $[\alpha]_D^{20}$ = –42.6 (c = 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.50 (m, 2H), 7.42–7.36 (m, 3H), 5.66–5.57 (m, 2H), 5.37 (ddd, *J* = 15.7, 7.8, 1.1 Hz, 1H), 4.84 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.51 (d, *J* = 6.4 Hz, 1H), 4.35 (ddd, *J* = 8.4, 5.7, 3.0 Hz, 1H), 4.26 (q, *J* = 6.0 Hz, 1H), 4.03 (ddd, *J* = 7.8, 4.6, 0.8 Hz, 1H), 3.98–3.90 (m, 2H), 3.85–3.78 (m, 2H), 3.61 (d, *J* = 1.3 Hz, 3H), 3.54 (dd, *J* = 5.6, 4.6 Hz, 1H), 3.30 (s, 3H), 2.48–2.36 (m, 1H), 2.12 (ddd, *J* = 12.4, 6.5, 5.6 Hz, 1H), 1.97 (ddd, *J* = 12.8, 8.0, 5.8 Hz, 1H), 1.70 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.59 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.17 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H) ppm. IR (film) $\tilde{\nu}$ = 2954, 2930, 2887, 2858, 1759, 1452, 1251, 1170, 1123, 1072, 1036, 956, 844, 776, 764, 719, 699, 666 cm^{-1}. MS (ESIpos) *m/z* (%): 781.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{57}O_9Si_2F_3Na$: 781.3385, found: 781.3386.



The corresponding Mosher ester (*R*)-**MTBA-345** (8.6 mg, 52%) was prepared analogously: $[\alpha]_D^{20}$ = −17.2 (c = 0.86, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.48 (m, 2H), 7.42–7.37 (m, 3H), 5.66 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.56 (d, *J* = 2.8 Hz, 1H), 5.43 (ddd, *J* = 15.6, 7.9, 1.0 Hz, 1H), 4.85 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.56 (d, *J* = 6.3 Hz, 1H), 4.44–4.34 (m, 2H), 4.14 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.98–3.91 (m, 3H), 3.84–3.77 (m, 2H), 3.52 (d, *J* = 1.2 Hz, 3H), 3.32 (s, 3H), 2.45 (hept, *J* = 7.1 Hz, 1H), 2.08 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.99 (ddd, *J* = 13.0, 7.9, 5.4 Hz, 1H), 1.71 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.60 (dt, *J* = 13.7, 6.1 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.15 (s, 9H), 0.00-–0.03 (m, 6H) ppm. IR (film) $\tilde{\nu}$ = 2955, 2931, 2887, 2858, 1759, 1453, 1252, 1171, 1147, 1124, 1071, 1037, 958, 922, 845, 777, 764, 722, 699 cm^{-1}. MS (ESIpos) *m/z* (%): 781.3 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{37}H_{57}O_9Si_2F_3Na$: 781.3385, found: 781.3386.

Both products were analyzed according to Hoye and co-workers:[497]

Table S-28. Mosher ester analysis for the assignment of the C(11) stereocenter; arbitrary numbering as shown in the insert.

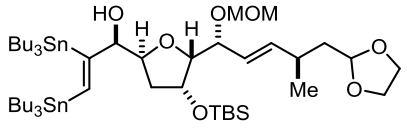
Assignment	345 [ppm]	(*S*)-MTBA-345 [ppm]	(*R*)-MTBA-345 [ppm]	Δ (*δ*(*S*–*R*)) [ppm]
1	4.88	4.84	4.85	−0.01
2a	1.71	1.70	1.71	−0.01
2b	1.63	1.59	1.60	−0.01
3	2.45	2.42	2.45	−0.03
4	5.67	5.61	5.66	–0.05
5	5.51	5.37	5.43	–0.06
6	4.17	4.03	4.14	–0.11
7	4.03	3.54	3.94	–0.40
8	4.57	4.26	4.39	–0.23
9a	2.13	2.12	2.08	+0.04
9b	1.96	1.97	1.99	−0.02
10	4.29	4.35	4.39	–0.04
11	4.38	5.61	5.56	+0.05
14	1.05	1.04	1.04	0
TMS-Me	0.16	0.17	0.15	+0.02

Terminal Alkyne S29. K_2CO_3 (80 mg, 0.58 mmol) was added to a solution of TMS-alkyne **345** (211 mg, 0.389 mmol) in methanol (4.5 mL) at 0 °C and stirred for 1 h at the same temperature. The mixture was warmed to ambient temperature and stirred for 3 h. After diluting the mixture with *t*-butyl methyl ether (5 mL), the reaction was quenched with sat. NH_4Cl (5 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:2) to provide the title compound as a yellow oil (154 mg, 84%). $[\alpha]_D^{20}$ = –27.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *see Table S-29;* ^{13}C NMR (126 MHz, $CDCl_3$): *see Table S-29*. ^{29}Si NMR (99 MHz, $CDCl_3$) *δ* = 19.5 ppm. IR (film): $\tilde{\nu}$ = 3436, 3263, 2953, 2929, 2886, 2858, 1472, 1408, 1361, 1255, 1140, 1100, 1037, 950, 836, 777, 711, 668 cm^{-1}. MS (ESIpos) *m/z* (%): 493.3 (100 (M+Na)). HRMS (ESIpos) *m/z* calcd for $C_{24}H_{42}O_7SiNa$: 493.2592, found: 493.2593.

Table S-29. NMR data of terminal alkyne **S29**S30; arbitrary numbering scheme as shown in the insert

atom n°	^{1}H NMR (500 MHz, $CDCl_3$)					^{13}C NMR (126 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	4.03	dd	5.8, 4.5	2, 5	2, 3a, 6, 14	85.6	3ab, 5
2	4.56	ddd	5.7, 4.5, 3.8	1, 3ab	1, 3ab, 19, 20, 21	72.2	4
3a	2.15	ddd	13.0, 7.5, 5.7	2, 4, 3b	1, 2, 3b, 15	35.7	1
3b	1.97	ddd	13.0, 7.5, 3.8	2, 3a, 4, 20, 21	(1), 15		
4	4.30	tdt	7.5, 3.1, 0.7	3ab, 15	3b, 6, 15	80.0	1, 2, 3a
5	4.17	ddd	5.8, 7.6, 0.6	1, 6	6, 7, 13ab, 14, 19, 20, 21	75.9	1, 6, 7, 13ab
6	5.51	ddt	15.6, 7.6. 0.8	5, 7	1, 4, 5, 8, 22	126.1	1, 7, 8
7	5.68	ddt	15.6, 7.6, 0.8	6, 8	5, 8, 9a, 22	139.8	5, 6, 8, 9b, 22
8	2.45	ddqd	8.3, 7.6, 6.9, 6.0	6, 7, 9ab, 10, 22	6, 7, 9b, 10, 22	33.0	6, 7, 9ab, 10, 22
9a	1.71	dddd	13.7, 8.3, 4.3, 0.6	8, 9b, 10	7, 22	40.7	7, 8, 10, 22
9b	1.62	dtd	13.7, 6.0, 0.6	8, 9a, 10	8, 22		
10	4.89	dd	6.0, 4.3	9ab	8, 11b, 12b, 22	103.4	8, 9
11a	3.98–3.90	m	-	11b	-	64.7	12ab
11b	3.86–3.78	m	-	11a	10		
12a	3.98–3.90	m	-	12b	-	64.7	11ab
12b	3.86–3.78	m	-	12a	10		
13a	4.66	d	6.3	13b	4, 14, 20, 21	94.4	5, 14
13b	4.59	d	6.3	13a	4, 14, 20, 21		
14	3.33	s	-	-	1, 5, 13ab	55.6	13ab
15	4.41	ddd	6.2, 3.1, 2.2	4, 15-OH, 17	3a, 4, 15-OH	64.5	3a, 17
16	-	-	-	-	-	81.5	4, 15
17	2.40	d	2.2	15	-	74.0	3a, 15-OH
18	-	-	-	-	-	18.0	19, 20 , 21
19	0.91	s	-	-	2, 5, 20, 21	25.8	-
20	0.08	s	-	-	2, 3b, 5, 19, 13ab	–5.0	21
21	0.09	s	-	-	2, 3b, 5, 19, 13ab	–4.5	20
22	1.05	d	6.9	8	6, 7, 8, 9ab, 10	20.7	7, 8, 9ab
15-OH	2.62	d	6.2	15	15	-	-

Bis(alkenyl)stannane 275. [(*t*BuNC)$_2$PdCl$_2$] (6.8 mg, 20 µmol) was added to a solution of alkyne **S29** (94.6 mg, 0.201 mmol) in THF (0.65 mL) at ambient temperature. After dropwise addition of hexabutyldistannane (0.15 mL, 0.30 mmol) to the orange suspension, the mixture turned into a dark red solution, which colour intensity increased over time. After stirring for 20 h at ambient temperature, the mixture was concentrated. The residual oil was purified by flash chromatography ((hexane/NEt_3 99:1)/*t*-butyl methyl ether 9:1 to 8:1) to afford the title compound as a yellow-orange



oil (166 mg, 78%). $[\alpha]_D^{20}$ = –13.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (ddd, *J* = 2.1, J_{SnH} = 176.1, 66.2 Hz, 1H), 5.66 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.52 (ddd, *J* = 15.6, 7.5, 0.9 Hz, 1H), 4.87 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 4.59 (d, *J* = 6.3 Hz, 1H), 4.52 (q, *J* = 2.3 Hz, 1H), 4.47– 4.42 (m, 1H), 4.27 (ddd, *J* = 8.3, 6.6, 3.0 Hz, 1H), 4.16 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.99–3.90 (m, 3H), 3.84–3.78 (m, 2H), 3.33 (s, 3H), 2.45 (hept, *J* = 6.7 Hz, 1H), 2.25 (d, *J* = 2.2 Hz, 1H), 1.98 (ddd, *J* = 12.8, 8.4, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.67–1.57 (m, 2H), 1.52–1.41 (m, 12H), 1.38–1.24 (m, 12H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.94–0.85 (m, 39H), 0.07 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 140.8, 139.7, 126.2, 103.5, 94.3, 85.3, 81.1, 78.8, 76.2, 72.5, 64.7, 64.6, 55.5, 40.7, 33.7, 33.0, 29.2, 29.2, 27.5, 27.4, 25.9, 20.7, 18.0, 13.7, 13.7, 11.1, 10.9,–4.5, –5.0 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –60.2, –64.1 ppm. IR (film) $\tilde{\nu}$ = 3437, 2955, 2926, 2872, 2855, 1463, 1376, 1254, 1144, 1101, 1038, 958, 836, 776, 666 cm^{-1}. MS (ESIpos) *m/z* (%): 1073.5 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{48}H_{96}O_7SiSn_2Na$: 1075.4862, found: 1075.4877.

5.8 Establishment of the Compound Library

General Procedure for Stille Reaction of Southern Fragments 219a-d with Northern Fragments 256 or 275 to give Dienylstannanes 264b-d and 346a-d.

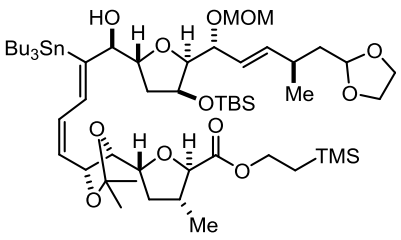
A suspension comprising the northern fragment **256** or **275** (0.08 M, 100 mol%), (t-$Bu_3P)_2Pd$ (20 mol%), tetrabutylammonium diphenylphosphinate (130 mol%), lithium chloride (300 mol%) and the southern fragment **219a-d** (150 mol%) in degassed *N*-methyl-2-pyrrolidone was placed in a preheated oil bath at 50 °C. After stirring for 14 h at 50 °C, the brown mixture was cooled to ambient temperature and the reaction was quenched with pH 7 phosphate buffer (20 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (3 × 30 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography ((hexane/NEt_3=99:1)/*t*-butyl methyl ether = 9:1 to 4:1 to 3:1 to 3:2 to 1:1 to 1:2) to afford the dienylstannanes.

Dienylstannane 264b. According to General Procedure using northern fragment **256** (58.6 mg, 0.056 mmol) and southern fragment **219b**. Pale yellow oil (25.5 mg, 41%). $[\alpha]_D^{20}$ = –44.3 (c = 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, J = 11.4, J_{SnH} = 112.0 Hz, 1H), 6.20 (td, J = 11.2, 1.0 Hz, 1H), 5.74 (ddd, J = 15.7, 7.5, 1.0 Hz, 1H), 5.49–5.37 (m, 2H), 4.92–4.80 (m, 2H), 4.69 (d, J = 6.5 Hz, 1H), 4.63 (d, J = 6.5 Hz, 1H), 4.32–4.07 (m, 6H), 4.01–3.87 (m, 3H), 3.88–3.76 (m, 2H), 3.76 (dd, J = 8.0, 3.0 Hz, 1H), 3.63 (dd, J = 8.4, 4.9 Hz, 1H), 3.37 (s, 3H), 2.85 (d, J = 2.2 Hz, 1H), 2.41 (h, J = 7.0 Hz, 1H), 2.37–2.24 (m, 1H), 2.10–1.98 (m, 1H), 1.87–1.69 (m, 2H), 1.73–1.65 (m, 1H), 1.66–1.58 (m, 1H), 1.51–1.41 (m, 13H), 1.36–1.24 (m, 6H), 1.16 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.03–0.94 (m, 8H), 0.92–0.84 (m, 18H), 0.07–0.03 (m, 15H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 155.0, 139.5, 134.7, 133.8, 127.7, 125.0, 109.5, 103.3, 94.2, 86.0, 83.6, 83.3, 82.4, 80.5, 78.8, 75.1, 73.3 (2C), 64.7, 64.7, 63.0, 55.3, 40.7, 39.6, 38.3, 36.7, 32.9, 29.0, 27.3, 27.2, 26.8, 25.8, 20.7, 17.9, 17.3, 17.3, 13.6, 11.5, −1.5, −4.0, −4.8 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –51.6 ppm. IR (film) $\tilde{\nu}$ = 3475, 2955, 2928, 1748, 1462, 1378, 1251, 1215, 1174, 1129, 1051, 939, 836, 776, 694 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5678.

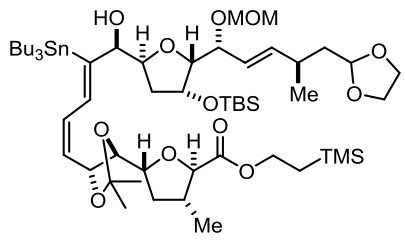
Dienylstannane 264c. According to General Procedure using northern fragment **256** (70 mg, 0.067 mmol) and southern fragment **219c**. Pale yellow oil (34.3 mg, 46%). $[\alpha]_D^{20}$ = +21.6 (c = 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (dd, J = 11.4, J_{SnH} = 111.9 Hz, 1H), 6.16 (td, J = 11.2, 1.3 Hz, 1H), 5.74 (ddd, J = 15.7, 7.6, 1.1 Hz, 1H), 5.56–5.39 (m, 2H),

5.19 (ddd, *J* = 8.5, 7.0, 1.2 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.39 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.31–4.24 (m, 2H), 4.23–4.12 (m, 4H), 4.07–3.91 (m, 4H), 3.88–3.78 (m, 2H), 3.72 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.38 (s, 3H), 2.80 (d, *J* = 2.5 Hz, 1H), 2.50–2.39 (m, 1H), 2.34 (dq, *J* = 9.5, 7.5 Hz, 1H), 2.11 (ddd, *J* = 12.2, 7.5, 6.1 Hz, 1H), 1.82 (ddd, *J* = 13.1, 6.2, 1.6 Hz, 1H), 1.74–1.66 (m, 2H), 1.65–1.59 (m, 2H), 1.50 (s, 3H), 1.50–1.42 (m, 6H), 1.40 (s, 3H), 1.35–1.26 (m, 6H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.04–0.92 (m, 8H), 0.91–0.85 (m, 18H), 0.08 (s, 3H), 0.08 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 154.3, 139.4, 134.9, 132.6, 127.0, 125.0, 108.5, 103.4, 94.3, 86.1, 83.1 (2C), 80.6, 79.5, 79.2, 75.1, 73.2, 72.7, 64.7, 64.7, 63.0, 55.3, 40.7, 39.6, 38.5, 35.8, 33.0, 29.0, 27.3, 27.1, 25.9, 25.0, 20.8, 18.0, 17.9, 17.5, 13.6, 11.4, −1.5, −3.8, −4.8 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = −51.4 ppm. IR (film) $\tilde{\nu}$ = 3475, 2955, 2928, 1749, 1463, 1379, 1251, 1215, 1174, 1100, 1038, 938, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5685.

Dienylstannane 264d. According to General Procedure using northern fragment **256** (61 mg, 0.058 mmol) and southern fragment **219d**. Yellow oil (33.4 mg, 50%). $[\alpha]_D^{20}$ = +1.9 (c = 0.94, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, *J* = 11.1, J_{SnH} = 109.9 Hz, 1H), 6.19 (td, *J* = 11.2, 1.0 Hz, 1H), 5.73 (ddd, *J* = 15.7, 7.6, 1.1 Hz, 1H), 5.51–5.38 (m, 2H), 4.83 (dd, *J* = 5.8, 4.6 Hz, 1H), 4.74–4.67 (m, 2H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.31–4.17 (m, 5H), 4.10 (td, *J* = 8.8, 6.5 Hz, 1H), 4.05–3.88 (m, 5H), 3.84–3.79 (m, 2H), 3.70 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.37 (s, 3H), 2.86 (br s, 1H), 2.46–2.33 (m, 2H), 2.12 (ddd, *J* = 11.9, 7.4, 5.9 Hz, 1H), 1.78 (ddd, *J* = 13.1, 6.2, 1.6 Hz, 1H), 1.73–1.66 (m, 2H), 1.64–1.56 (m, 2H), 1.51–1.41 (m, 12H), 1.33–1.26 (m, 6H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.94 (m, 8H), 0.90–0.84 (m, 18H), 0.08–0.00 (m, 15H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 154.8, 139.5, 135.2, 133.5, 128.4, 125.0, 109.5, 103.4, 94.2, 86.0, 84.5, 83.2, 81.8, 80.6, 79.2, 75.0, 73.9, 73.2, 64.7, 64.7, 63.2, 55.3, 40.6, 39.3, 38.6, 35.1, 32.9, 29.0, 27.3, 27.2, 27.0, 25.8, 20.8, 17.9, 17.8, 17.4, 13.6, 11.6, −1.5, −3.9, −4.8 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = −51.7 ppm. IR (film) $\tilde{\nu}$ = 2956, 2929, 1743, 1462, 1378, 1251, 1215, 1174, 1100, 1042, 943, 861, 836 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5685.

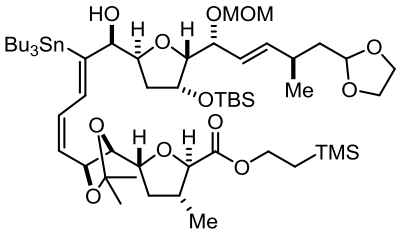


Dienylstannane 346a. According to General Procedure using northern fragment **275** (80 mg, 0.076 mmol) and southern fragment **219a**. Yellow oil (45.3 mg, 53%). $[\alpha]_D^{20}$ = −5.3 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dtd, *J* = 11.5, 1.4, J_{SnH} = 113.0 Hz, 1H), 6.14 (td, *J* = 11.3, 1.0 Hz, 1H), 5.65 (dd, *J* = 16.1, 7.7 Hz, 1H), 5.57 (t, *J* = 10.4 Hz, 1H), 5.50 (ddd, *J* = 15.6, 7.6, 0.9 Hz, 1H), 5.15 (ddd, *J* = 9.8, 6.5, 1.0 Hz, 1H), 4.87 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.61–4.56 (m, 2H), 4.44 (dt, *J* = 5.5,

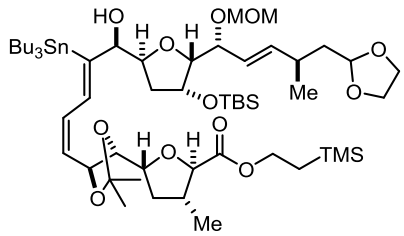


4.2 Hz, 1H), 4.26–4.17 (m, 4H), 4.15 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.09 (t, *J* = 6.8 Hz, 1H), 4.00 (d, *J* = 7.5 Hz, 1H), 3.98–3.91 (m, 3H), 3.84–3.77 (m, 2H), 3.33 (s, 3H), 2.45 (hept, *J* = 6.7 Hz, 1H), 2.38–2.25 (m, 2H), 2.06 (ddd, *J* = 12.2, 7.5, 5.8 Hz, 1H), 1.93 (ddd, *J* = 12.6, 8.4, 5.4 Hz, 1H), 1.71 (ddd, *J* = 13.8, 8.0, 4.5 Hz, 1H), 1.66–1.55 (m, 2H), 1.52 (s, 3H), 1.50–1.41 (m, 6H), 1.39 (s, 3H), 1.35–1.20 (m, 7H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.04–0.93 (m, 8H), 0.90 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 152.8, 140.1, 132.8, 132.1, 127.1, 126.2, 109.6, 103.6, 94.5, 85.5, 83.8, 81.3, 80.9, 79.3, 77.2, 76.3, 72.8, 72.6, 64.9, 64.8, 63.2, 55.7, 40.9, 39.6, 37.3, 34.2, 33.2, 29.2, 27.9, 27.4, 26.0, 25.7, 20.9, 18.4, 18.2, 17.5, 13.8, 11.4, −1.4, −4.3, −4.8 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –53.2 ppm. IR (film) $\tilde{\nu}$ = 3461, 2955, 2929, 1749, 1462, 1378, 1251, 1215, 1130, 1042, 958, 864, 836, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5685.

Dienylstannane 346b. According to General Procedure using northern fragment **275** (97 mg, 0.092 mmol) and southern fragment **219b**. Pale yellow oil (47.4 mg, 46%). $[\alpha]_D^{20}$ = −23.2 (c = 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dtd, *J* = 11.5, 1.4, J_{SnH} = 114.6 Hz, 1H), 6.26–6.14 (m, 1H), 5.70–5.59 (m, 1H), 5.51 (ddd, *J* = 15.6, 7.7, 0.9 Hz, 1H), 5.42 (dd, *J* = 10.9, 9.1 Hz, 1H), 4.96–4.83 (m, 2H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.61 (q, *J* = 1.6 Hz, 1H), 4.58 (d, *J* = 6.3 Hz, 1H), 4.50–4.42 (m, 1H), 4.27–4.12 (m, 5H), 4.03–3.97 (m, 2H), 3.95–3.89 (m, 2H), 3.86–3.78 (m, 2H), 3.65 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.33 (m, 3H), 2.55 (br s, 1H), 2.44 (p, *J* = 7.0 Hz, 1H), 2.40–2.27 (m, 1H), 2.10–1.96 (m, 2H), 1.71 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.65–1.56 (m, 2H), 1.50–1.39 (m, 13H), 1.33–1.26 (m, 6H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.93 (m, 8H), 0.90–0.85 (m, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 152.9, 139.8, 134.4, 131.8, 127.1, 126.1, 109.5, 103.4, 94.2, 85.2, 83.5, 83.2, 80.5, 79.4, 76.7, 76.2, 73.3, 72.5, 64.7, 64.6, 63.2, 55.4, 40.8, 39.6, 36.7, 34.2, 33.0, 29.0, 27.3, 27.2, 26.8, 25.9, 20.7, 18.0, 17.8, 17.4, 13.6, 10.9, −1.5, −4.4, −5.0 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –53.2 ppm. IR (film) $\tilde{\nu}$ = 3517, 2954, 2928, 2856, 1747, 1462, 1378, 1251, 1215, 1173, 1128, 1088, 1039, 958, 836, 776, 666 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5679.

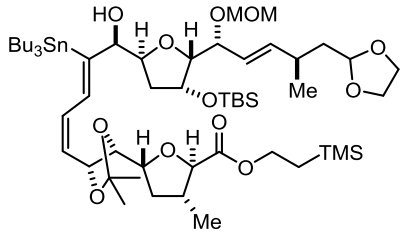


Dienylstannane 346c. According to General Procedure using northern fragment **275** (81 mg, 0.076 mmol) and southern fragment **219c**. Yellow oil (26.9 mg, 32%). $[\alpha]_D^{20}$ = +19.8 (c = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 11.4 Hz, J_{SnH} = 114.7, 1H), 6.13 (td, *J* = 11.3, 1.2 Hz, 1H), 5.66 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.52 (dd, *J* = 13.9, 7.0 Hz, 1H), 5.48 (t, *J* = 10.4 Hz, 1H), 5.23 (td, *J* = 8.3, 6.9, 0.6 Hz, 1H), 4.87 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.68–4.56 (m, 3H), 4.44 (td, *J* = 4.9, 3.2 Hz, 1H), 4.38 (dd, *J* = 7.0, 4.4 Hz,



1H), 4.27–4.09 (m, 5H), 4.01–3.84 (m, 4H), 3.88–3.72 (m, 2H), 3.33 (s, 3H), 2.45 (p, *J* = 7.1 Hz, 1H), 2.38–2.27 (m, 2H), 2.15–2.02 (m, 1H), 1.96 (td, *J* = 8.1, 4.2 Hz, 1H), 1.71 (ddd, *J* = 13.7, 8.0, 4.4 Hz, 1H), 1.66–1.53 (m, 3H), 1.50 (s, 3H), 1.48–1.35 (m, 9H), 1.34–1.24 (m, 6H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.92 (m, 8H), 0.91–0.84 (m, 18H), 0.09–0.00 (m, 15H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 151.9, 139.8, 133.2, 131.9, 126.3, 126.2, 108.4, 103.4, 94.3, 85.4, 83.1, 80.5, 79.6, 79.0, 76.4, 76.1, 72.9, 72.5, 64.7, 64.7, 63.0, 55.5, 40.8, 39.5, 36.0, 34.0, 33.0, 29.0, 27.3, 27.2, 25.9, 25.0, 20.7, 18.0, 18.0, 17.4, 13.6, 11.0, −1.5, −4.4, −5.0 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –53.2 ppm. IR (film) $\tilde{\nu}$ = 3483, 2955, 2930, 1747, 1463, 1379, 1252, 1212, 1100, 1039, 950, 862, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5688.

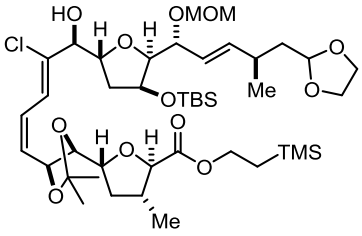
Dienylstannane 346d. According to General Procedure using northern fragment **275** (93 mg, 0.089 mmol) and southern fragment **219d**. Orange oil (69 mg, 70%). $[\alpha]_D^{20}$ = +10.9 (c = 1.32, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (dd, *J* = 11.3, J_{SnH} = 115.3 Hz, 1H), 6.21–6.11 (m, 1H), 5.65 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.51 (ddd, *J* = 15.6, 7.6, 0.9 Hz, 1H), 5.43 (dd, *J* = 10.6, 9.1 Hz, 1H), 4.87 (dd, *J* = 5.8, 4.4 Hz, 1H), 4.69–4.62 (m, 2H), 4.62–4.53 (m, 2H), 4.46–4.41 (m, 1H), 4.26–4.18 (m, 4H), 4.15 (t, *J* = 8.1, 7.0 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.98 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.95–3.88 (m, 3H), 3.86–3.77 (m, 2H), 3.33 (s, 3H), 2.46 (dq, *J* = 14.2, 7.1 Hz, 1H), 2.41–2.30 (m, 2H), 2.14 (ddd, *J* = 11.9, 7.5, 6.1 Hz, 1H), 1.91 (ddd, *J* = 12.8, 8.8, 5.1 Hz, 1H), 1.80–1.68 (m, 2H), 1.66–1.58 (m, 2H), 1.50–1.38 (m, 12H), 1.35–1.26 (m, 6H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.93 (m, 8H), 0.91–0.85 (m, 18H), 0.07 (s, 6H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 153.3, 139.8, 133.7, 132.5, 127.4, 126.3, 109.5, 103.5, 94.5, 85.4, 83.1, 81.7, 80.8, 79.0, 77.5, 76.1, 74.3, 72.5, 64.7, 64.6, 63.1, 55.5, 40.7, 39.4, 34.6, 34.4, 33.0, 29.1, 27.3, 27.2, 26.9, 25.9, 20.8, 18.0, 17.8, 17.4, 13.6, 11.4, −1.5, −4.3, −5.0 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –53.9 ppm. IR (film) $\tilde{\nu}$ = 3482, 2955, 2928, 2856, 1746, 1462, 1378, 1251, 1214, 1174, 1141, 1099, 1059, 1040, 955, 860, 837, 776, 695 cm^{-1}. MS (ESIpos) *m/z* (%): 1139.6 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{54}H_{100}O_{12}Si_2SnNa$: 1139.5668, found: 1139.5676.



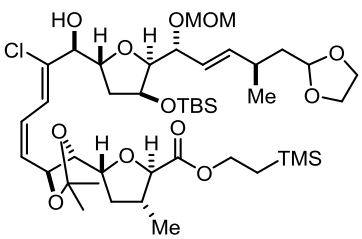
General Procedure for Chloro-Destannylation of Dienylstannanes 264b-d and 346a-d to give Chlorodienes 266b-d and 347a-d.

2,6-Lutidine (630 mol%) and copper(II) chloride (600 mol%) were added to a solution of dienylstannane **264a-d** or **346a-d** (0.05 M, 100 mol%) in THF. The resulting purple suspension was stirred for 20 h at ambient temperature, during which time the colour of the mixture gradually turned brown. After filtration through a short plug of silica, which was rinsed with *t*-butyl methyl ether (25 mL), the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 2:3 to 1:1 to 3:2) to afford the title compound.

Chlorodiene 266b. According to General Procedure using dienylstannane **264b** (31.7 mg, 0.028 mmol). Colourless oil (19.5 mg, 89%). $[\alpha]_D^{20}$ = −24.6 (c = 0.975, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 10.9 Hz, 1H), 6.58 (td, *J* = 11.0, 1.2 Hz, 1H), 5.74 (ddd, *J* = 15.6, 7.5, 1.1 Hz, 1H), 5.60 (ddd, *J* = 11.1, 8.5, 1.1 Hz, 1H), 5.45 (ddd, *J* = 15.6, 6.3, 1.1 Hz, 1H), 4.91 (td, *J* = 8.5, 1.2 Hz, 1H), 4.83 (dd, *J* = 5.8, 4.5 Hz, 1H), 4.71–4.62 (m, 2H), 4.52 (ddd, *J* = 9.3, 6.3, 4.6 Hz, 1H), 4.32 (dd, *J* = 3.4, 1.7 Hz, 1H), 4.28–4.09 (m, 5H), 4.01–3.89 (m, 3H), 3.86–3.77 (m, 3H), 3.62 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.36 (s, 3H), 3.31 (br d, *J* = 5.3 Hz, 1H), 2.43 (dq, *J* = 14.1, 7.0 Hz, 1H), 2.36–2.25 (m, 1H), 2.12–1.93 (m, 3H), 1.70 (ddd, *J* = 13.8, 7.7, 4.6 Hz, 1H), 1.65–1.55 (m, 2H), 1.43 (d, *J* = 3.5 Hz, 6H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (dd, *J* = 9.0, 8.0 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 139.2, 137.2, 130.3, 127.2, 125.1, 120.7, 109.4, 103.4, 94.3, 86.6, 83.5, 82.2, 78.7, 77.7, 77.0, 75.2, 73.8, 73.1, 64.7, 64.7, 63.1, 55.4, 40.7, 39.7, 38.0, 36.6, 32.9, 27.2, 26.6, 25.9, 20.7, 18.0, 17.4, 17.4, -1.5, -4.0, -4.7 ppm. IR (film) $\tilde{\nu}$ = 3471, 2955, 2929, 2859, 1742, 1461, 1380, 1251, 1215, 1172, 1128, 1090, 1034, 939, 834, 806, 774, 696 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4216.

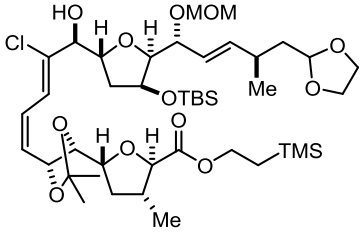


Chlorodiene 266c. According to General Procedure using dienylstannane **264c** (34 mg, 0.031 mmol). Colourless oil (23.4 mg, 89%). $[\alpha]_D^{20}$ = +28.4 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 11.0 Hz, 1H), 6.56 (td, *J* = 11.1, 1.3 Hz, 1H), 5.81–5.64 (m, 2H), 5.44 (ddd, *J* = 15.7, 6.3, 1.1 Hz, 1H), 5.07 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 4.83 (dd, *J* = 5.7, 4.5 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.50 (dt, *J* = 9.5, 5.7 Hz, 1H), 4.34–4.24 (m, 3H), 4.23–4.18 (m, 2H), 4.15 (dt, *J* = 9.1, 5.7 Hz, 1H), 4.05 (d, *J* = 5.0 Hz, 1H), 3.98 (d, *J* = 7.6 Hz, 1H), 3.97–3.90 (m, 2H), 3.87–3.79 (m, 2H), 3.75 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.36 (s, 3H), 3.03 (s, 1H), 2.48–2.30 (m, 2H), 2.17 (ddd, *J* = 12.2, 7.5, 5.9 Hz, 1H), 1.99 (ddd, *J* = 12.9, 6.1, 1.7 Hz, 1H), 1.90 (ddd, *J* = 13.2, 9.6, 4.2 Hz, 1H), 1.70 (ddd, *J* = 13.7, 7.7, 4.6 Hz, 1H), 1.65–1.54 (m, 1H), 1.49 (s, 3H), 1.39 (s,



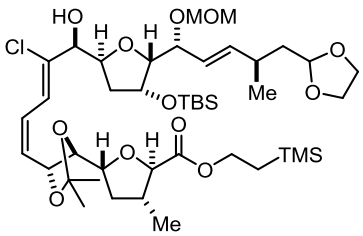
3H), 1.34–1.28 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.98 (m, 2H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 139.4, 136.5, 129.4, 126.4, 124.8, 120.9, 108.8, 103.4, 94.3, 86.8, 83.3, 79.8, 78.9, 78.8, 77.4, 75.1, 73.6, 73.0, 64.7, 64.7, 63.1, 55.4, 40.7, 39.4, 38.4, 36.8, 32.9, 27.3, 25.8, 25.1, 20.8, 18.2, 18.0, 17.4, −1.5, −4.0, −4.8 ppm. IR (film) $\tilde{\nu}$ = 3434, 2955, 2928, 2859, 1732, 1462, 1380, 1251, 1214, 1132, 1099, 1039, 949, 860, 837, 776, 696 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4218.

Chlorodiene 266d. According to General Procedure using dienylstannane **264d** (50 mg, 49 µmol).



Colourless oil (24.4 mg, 63%). $[\alpha]_D^{20}$ = −12.1 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 10.9 Hz, 1H), 6.54 (td, *J* = 11.0, 1.2 Hz, 1H), 5.73 (ddd, *J* = 15.6, 7.6, 1.1 Hz, 1H), 5.63 (ddd, *J* = 11.1, 8.4, 1.0 Hz, 1H), 5.43 (ddd, *J* = 15.7, 6.4, 1.1 Hz, 1H), 4.82 (dd, *J* = 5.8, 4.5 Hz, 1H), 4.72–4.59 (m, 3H), 4.48 (dt, *J* = 9.6, 6.0 Hz, 1H), 4.32–4.12 (m, 5H), 4.06 (d, *J* = 5.9 Hz, 1H), 4.00 (d, *J* = 7.9 Hz, 1H), 3.97–3.91 (m, 2H), 3.86 (dd, *J* = 7.8, 5.4 Hz, 1H), 3.83–3.77 (m, 2H), 3.73 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.36 (s, 3H), 3.14 (s, 1H), 2.47–2.31 (m, 2H), 2.21 (ddd, *J* = 12.7, 7.4, 5.8 Hz, 1H), 1.96 (ddd, *J* = 13.0, 6.1, 1.8 Hz, 1H), 1.81 (ddd, *J* = 13.2, 9.5, 4.3 Hz, 1H), 1.69 (ddd, *J* = 13.6, 7.7, 4.5 Hz, 1H), 1.64–1.54 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.03–0.97 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 139.4, 136.5, 131.2, 126.9, 124.9, 121.8, 109.8, 103.4, 94.2, 86.6, 83.2, 82.4, 80.1, 79.1, 77.9, 75.8, 75.1, 73.0, 64.7, 64.7, 63.2, 55.4, 40.7, 39.2, 38.3, 36.7, 32.9, 27.1, 27.0, 25.8, 20.7, 18.2, 18.0, 17.4, −1.5, −4.0, −4.8 ppm. IR (film) $\tilde{\nu}$ = 3472, 2955, 2930, 2887, 1736, 1461, 1406, 1380, 1251, 1215, 1174, 1132, 1100, 1045, 943, 859, 836, 775 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4224.

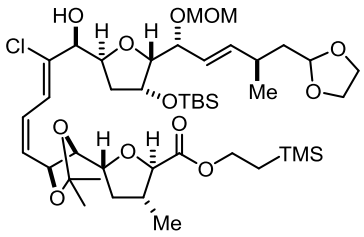
Chlorodiene 347a. According to General Procedure using dienylstannane **346a** (45.3 mg, 41 µmol).



Colourless oil (34.4 mg, 98%). $[\alpha]_D^{20}$ = −0.5 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dt, *J* = 11.1, 1.2 Hz, 1H), 6.54 (td, *J* = 11.1, 1.1 Hz, 1H), 5.77 (t, *J* = 10.4 Hz, 1H), 5.73–5.62 (m, 1H), 5.50 (ddd, *J* = 15.6, 7.5, 0.9 Hz, 1H), 5.02 (ddd, *J* = 9.6, 6.4, 1.1 Hz, 1H), 4.88 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.59 (d, *J* = 6.2 Hz, 1H), 4.57–4.43 (m, 3H), 4.28–4.11 (m, 4H), 4.10 (t, *J* = 6.4 Hz, 1H), 4.01 (d, *J* = 7.4 Hz, 1H), 3.99–3.89 (m, 3H), 3.86–3.77 (m, 2H), 3.33 (s, 3H), 2.67 (d, *J* = 3.6 Hz, 1H), 2.45 (hept, *J* = 6.8 Hz, 1H), 2.41–2.27 (m, 1H), 2.04 (ddd, *J* = 12.0, 7.4, 5.7 Hz, 1H), 1.93 (ddd, *J* = 13.2, 8.3, 5.3 Hz, 1H), 1.72 (dddd, *J* = 12.4, 7.9, 6.7, 3.9 Hz, 2H), 1.62 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.31–1.20 (m, 1H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.05–0.95 (m, 2H), 0.90 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.04 (s,

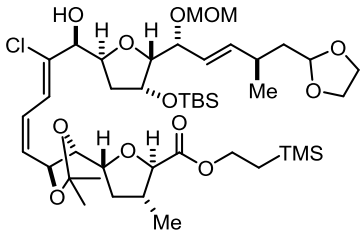
9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 140.0, 135.5, 129.9, 126.3, 126.2, 119.2, 109.9, 103.6, 94.6, 85.7, 83.9, 80.9, 79.1, 78.9, 76.0, 74.8, 73.3, 72.5, 64.9, 64.8, 63.3, 55.7, 40.8, 39.4, 37.1, 34.3, 33.2, 27.8, 26.0, 25.8, 20.9, 18.5, 18.2, 17.5, −1.4, −4.3, −4.7 ppm. IR (film) $\tilde{\nu}$ = 3445, 2955, 2931, 2892, 1746, 1732, 1461, 1379, 1251, 1215, 1129, 1099, 1041, 939, 861, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4220.

Chlorodiene 347b. According to General Procedure using dienylstannane **346b** (34.7 mg, 31 µmol).



Colourless oil (26.2 mg, 98%). $[\alpha]_D^{20}$ = −13.4 (c = 1.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 11.0 Hz, 1H), 6.58 (td, *J* = 11.0, 1.1 Hz, 1H), 5.67 (ddd, *J* = 15.6, 7.7, 0.7 Hz, 1H), 5.61–5.48 (m, 2H), 4.98 (td, *J* = 8.7, 1.1 Hz, 1H), 4.88 (dd, *J* = 6.0, 4.4 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 4.62–4.54 (m, 2H), 4.54–4.48 (m, 2H), 4.26–4.15 (m, 3H), 4.11–4.03 (m, 2H), 4.01 (d, *J* = 8.0 Hz, 1H), 3.97–3.90 (m, 2H), 3.86–3.76 (m, 2H), 3.61 (dd, *J* = 8.6, 3.2 Hz, 1H), 3.33 (s, 3H), 3.30 (d, *J* = 3.6 Hz, 1H), 2.45 (hept, *J* = 6.9 Hz, 1H), 2.39–2.26 (m, 1H), 2.11–1.99 (m, *J* = 13.0, 7.3, 5.7 Hz, 2H), 1.77–1.69 (m, 2H), 1.67–1.56 (m, 2H), 1.46–1.42 (m, 6H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.97 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H), 0.05 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.7, 139.7, 136.8, 129.9, 127.1, 126.1, 119.0, 109.4, 103.4, 94.2, 85.1, 83.4, 81.8, 78.5, 77.4, 76.1, 75.2, 73.8, 72.5, 64.7, 64.6, 63.4, 55.4, 40.7, 39.6, 36.6, 33.9, 33.0, 27.2, 26.6, 25.9, 20.8, 18.0, 17.8, 17.4, −1.5, −4.5, −4.9 ppm. IR (film) $\tilde{\nu}$ = 3493, 2955, 2929, 2859, 1742, 1461, 1379, 1251, 1215, 1174, 1128, 1089, 1041, 943, 860, 837, 776, 696 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4227.

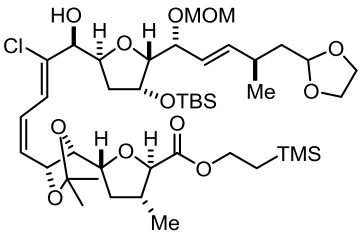
Chlorodiene 347c. According to General Procedure using dienylstannane **346c** (38 mg, 34 µmol).



Yellow oil (31.3 mg, 96%). $[\alpha]_D^{20}$ = +45.3 (c = 1.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (dt, *J* = 11.0, 1.3 Hz, 1H), 6.54 (td, *J* = 11.1, 1.3 Hz, 1H), 5.73–5.61 (m, 2H), 5.52 (ddd, *J* = 15.6, 7.4, 0.9 Hz, 1H), 5.09 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1H), 4.88 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 4.60 (d, *J* = 6.3 Hz, 1H), 4.55 (ddd, *J* = 8.2, 6.8, 3.3 Hz, 1H), 4.51–4.45 (m, 2H), 4.28 (dd, *J* = 6.7, 5.7 Hz, 1H), 4.25–4.09 (m, 4H), 4.01–3.91 (m, 4H), 3.86–3.77 (m, 2H), 3.33 (s, 3H), 2.74 (d, *J* = 3.1 Hz, 1H), 2.51–2.40 (m, 1H), 2.40–2.29 (m, 1H), 2.17 (ddd, *J* = 12.2, 7.5, 5.9 Hz, 1H), 1.97 (ddd, *J* = 13.3, 8.2, 5.4 Hz, 1H), 1.77–1.68 (m, 2H), 1.66–1.54 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.02–0.97 (m, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 139.7, 135.1, 129.2, 126.2 (2C), 119.2, 108.8, 103.5, 94.5, 85.6, 83.3, 80.0, 78.7, 78.6, 75.9, 74.6, 73.8, 72.4, 64.7, 64.7, 63.2, 55.6, 40.7, 39.3, 36.9, 33.9, 33.0, 27.4, 25.9, 25.2, 20.8, 18.1, 18.0, 17.4, −1.5, −4.4, −4.9 ppm. IR (film) $\tilde{\nu}$ = 3493, 2955, 2929, 2859, 1742, 1461, 1379, 1251, 1215, 1174, 1128, 1089, 1041, 943, 860,

837, 776, 696 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4227.

Chlorodiene 347d. According to General Procedure using dienylstannane **346d** (59 mg, 53 µmol).

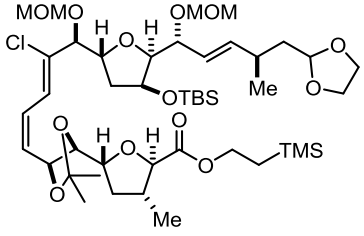


Colourless oil (44.6 mg, 98%). $[\alpha]_D^{20}$ = +13.5 (c = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (dt, *J* = 11.0, 1.1 Hz, 1H), 6.52 (td, *J* = 11.1, 1.2 Hz, 1H), 5.72–5.56 (m, 2H), 5.50 (ddd, *J* = 15.6, 7.6, 1.0 Hz, 1H), 4.87 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.67–4.57 (m, 3H), 4.52–4.44 (m, 2H), 4.42–4.37 (m, 1H), 4.24–4.12 (m, 4H), 3.97 (d, *J* = 8.1 Hz, 1H), 3.95–3.88 (m, 3H), 3.86 (dd, *J* = 8.1, 5.0 Hz, 1H), 3.84–3.76 (m, 2H), 3.32 (s, 3H), 2.77 (d, *J* = 3.6 Hz, 1H), 2.43 (h, *J* = 7.4, 6.9 Hz, 1H), 2.35 (dtt, *J* = 14.0, 9.0, 6.7 Hz, 1H), 2.21 (ddd, *J* = 12.0, 7.5, 5.9 Hz, 1H), 1.96 (ddd, *J* = 13.3, 8.3, 5.2 Hz, 1H), 1.81 (ddd, *J* = 12.9, 6.6, 3.2 Hz, 1H), 1.70 (ddd, *J* = 13.9, 8.2, 4.5 Hz, 1H), 1.66–1.56 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.02–0.96 (m, 2H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 139.7, 135.6, 130.5, 126.7, 126.3, 120.4, 109.7, 103.4, 94.5, 85.2, 83.1, 82.2, 79.9, 78.5, 75.9, 75.7, 75.2, 72.4, 64.7, 64.6, 63.2, 55.5, 40.7, 39.3, 36.3, 34.8, 33.0, 27.1, 26.9, 25.8, 20.8, 18.0, 17.9, 17.4, −1.5, −4.4, −4.9 ppm. IR (film) $\tilde{\nu}$ = 3442, 2954, 2930, 2886, 1733, 1461, 1380, 1251, 1214, 1173, 1098, 1061, 1038, 973, 940, 859, 836, 775, 697 cm^{-1}. MS (ESIpos) *m/z* (%): 883.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{42}H_{73}O_{12}Si_2ClNa$: 883.4221, found: 883.4224.

General Procedure for MOM-Protection of Chlorodienes 266a-d and 347a-d to give MOM-Ethers 269a-d and S30a-d.

Hünig's base (2600 mol%), tetrabutylammonium iodide (25 mol%) and MOMCl (1500 mol%) were added to a solution of chlorodiene **266b-d** or **347a-d** (0.01 M, 100 mol%) in 1,2-dichloroethane. The dark orange mixture was stirred for 16 h at 50 °C. After reaching ambient temperature, the mixture was diluted with *t*-butyl methyl ether (10 mL) and sat. $NaHCO_3$ (15 mL). The aq. phase was separated and extracted with *t*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 7:3 to 3:2 to 1:1 to 1:2) to afford the title compounds.

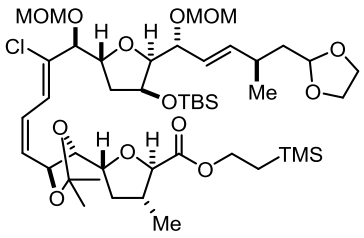
MOM-Ether 269b. According to General Procedure using chlorodiene **266b** (19.5 mg, 23 µmol).



Colourless oil (18.4 mg, 87%). $[\alpha]_D^{20}$ = –67.2 (c = 0.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83–6.75 (m, 1H), 6.58 (td, *J* = 11.0, 1.2 Hz, 1H), 5.74 (ddd, *J* = 15.7, 7.5, 1.1 Hz, 1H), 5.61 (ddd, *J* = 11.2, 8.5, 1.1 Hz, 1H), 5.46 (ddd, *J* = 15.7, 6.3, 1.1 Hz, 1H), 4.88–4.79 (m, 2H), 4.73–4.61 (m, 4H), 4.53 (dt, *J* = 9.7, 6.4 Hz, 1H), 4.28–4.09 (m, 6H), 4.02–3.88 (m, 3H), 3.86–3.76 (m, 3H), 3.65 (dd, *J* = 8.4, 3.8 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.42 (dq, *J* =

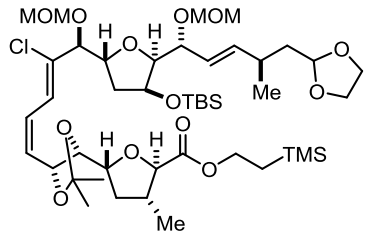
14.1, 7.0 Hz, 1H), 2.37–2.25 (m, 1H), 2.06 (ddd, *J* = 12.1, 7.5, 6.3 Hz, 1H), 1.89 (ddd, *J* = 12.8, 6.1, 1.7 Hz, 1H), 1.80 (ddd, *J* = 13.1, 9.7, 4.1 Hz, 1H), 1.70 (ddd, *J* = 13.8, 7.6, 4.6 Hz, 1H), 1.64–1.55 (m, 2H), 1.44 (s, 6H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.06–0.99 (m, 5H), 0.89 (s, 9H), 0.08–0.04 (m, 15H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 138.9, 134.9, 130.9, 127.0, 125.4, 123.4, 109.7, 103.4, 94.7, 93.9, 86.5, 83.7, 82.7, 81.6, 78.6, 78.0, 75.6, 73.8, 72.8, 64.7, 64.6, 63.1, 55.5, 55.3, 40.7, 39.6, 37.9, 36.6, 32.9, 27.2, 26.7, 25.8, 20.7, 18.0, 17.4, 17.3, −1.5, −4.0, −4.7 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2894, 1743, 1462, 1380, 1251, 1215, 1173, 1129, 1089, 1053, 1047, 919, 837, 775, 694 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4484.

MOM-Ether 269c. According to General Procedure using chlorodiene **266c** (23 mg, 27 µmol).



Colourless oil (20 mg, 80%). $[\alpha]_D^{20}$ = –0.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (dd, *J* = 11.0, 1.0 Hz, 1H), 6.55 (td, *J* = 11.1, 1.3 Hz, 1H), 5.80–5.67 (m, 2H), 5.47 (ddd, *J* = 15.7, 6.1, 1.1 Hz, 1H), 5.05 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 4.83 (dd, *J* = 5.9, 4.5 Hz, 1H), 4.72–4.62 (m, 4H), 4.53 (dt, *J* = 9.8, 6.4 Hz, 1H), 4.30–4.07 (m, 7H), 4.01−3.89 (m, 3H), 3.87–3.77 (m, 2H), 3.72 (dd, *J* = 8.0, 2.9 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.47–2.30 (m, 2H), 2.17 (ddd, *J* = 12.3, 7.5, 5.9 Hz, 1H), 1.93 (ddd, *J* = 13.0, 6.1, 1.6 Hz, 1H), 1.76–1.66 (m, 2H), 1.64–1.55 (m, 2H), 1.49 (s, 3H), 1.40 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.03–0.97 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 138.8, 134.2, 129.8, 126.2, 125.3, 123.4, 108.9, 103.4, 94.8, 93.8, 86.6, 83.4, 81.7, 79.9, 78.9, 78.6, 75.5, 73.6, 72.7, 64.7, 64.7, 63.1, 55.5, 55.4, 40.7, 39.4, 38.0, 36.8, 32.9, 27.3, 25.8, 25.1, 20.8, 18.3, 18.0, 17.4, −1.5, −3.9, −4.8 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2894, 1747, 1462, 1380, 1251, 1215, 1153, 1100, 1037, 919, 836, 775 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4491.

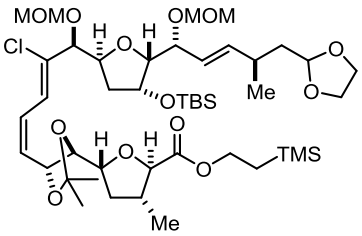
MOM-Ether 269d. According to General Procedure using chlorodiene **266d** (24 mg, 28 µmol). Yellow



oil (20.5 mg, 81%). $[\alpha]_D^{20}$ = –31.7 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (dd, *J* = 10.9, 1.0 Hz, 1H), 6.54 (td, *J* = 11.0, 1.2 Hz, 1H), 5.74 (ddd, *J* = 15.7, 7.6, 1.1 Hz, 1H), 5.66 (ddd, *J* = 11.1, 8.2, 1.0 Hz, 1H), 5.46 (ddd, *J* = 15.6, 6.1, 1.1 Hz, 1H), 4.82 (dd, *J* = 5.9, 4.5 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.65 (d, *J* = 6.5 Hz, 1H), 4.63–4.58 (m, 3H), 4.52 (ddd, *J* = 9.8, 7.4, 5.9 Hz, 1H), 4.20 (m, 5H), 4.08 (d, *J* = 7.4 Hz, 1H), 4.02 (d, *J* = 7.6 Hz, 1H), 3.98–3.89 (m, 3H), 3.83–3.78 (m, 2H), 3.71 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.47–2.34 (m, 2H), 2.18 (ddd, *J* = 12.0, 7.4, 5.9 Hz, 1H), 1.95–1.88 (m, 1H), 1.74–1.55 (m, 4H), 1.43 (s, 6H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.02–0.96 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 138.8, 134.3, 131.7, 126.5,

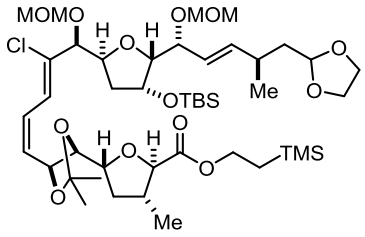
125.3, 124.0, 110.0, 103.4, 94.8, 93.7, 86.6, 83.1, 82.2, 81.9, 79.8, 78.6, 75.5, 75.5, 72.6, 64.7, 64.6, 63.1, 55.4, 55.4, 40.7, 39.3, 38.1, 35.8, 32.9, 27.2, 27.0, 25.8, 20.8, 18.2, 18.0, 17.4, −1.5, −4.0, −4.8 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2886, 1744, 1463, 1371, 1252, 1214, 1153, 1137, 1100, 1050, 1035, 977, 938, 919, 859, 837, 775 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4487.

MOM-Ether S31a. According to General Procedure using chlorodiene **347a** (34 mg, 40 µmol). Yellow



oil (31 mg, 86%). $[\alpha]_D^{20}$ = −43 (c = 1.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 11.0 Hz, 1H), 6.54 (td, *J* = 11.0, 1.1 Hz, 1H), 5.77 (ddd, *J* = 10.7, 9.7, 0.9 Hz, 1H), 5.65 (dd, *J* = 15.6, 7.7 Hz, 1H), 5.43 (ddd, *J* = 15.5, 8.0, 1.0 Hz, 1H), 4.98 (ddd, *J* = 9.6, 6.3, 1.2 Hz, 1H), 4.85 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.66–4.57 (m, 4H), 4.49 (dt, *J* = 5.2, 3.8 Hz, 1H), 4.43 (td, *J* = 7.2, 4.2 Hz, 1H), 4.34 (d, *J* = 4.1 Hz, 1H), 4.25–4.08 (m, 5H), 4.01 (d, *J* = 7.4 Hz, 1H), 3.97–3.91 (m, 2H), 3.86 (dd, *J* = 6.4, 4.2 Hz, 1H), 3.83–3.78 (m, 2H), 3.36 (s, 3H), 3.32 (s, 3H), 2.48–2.29 (m, 2H), 2.12–1.99 (m, 2H), 1.87 (ddd, *J* = 12.8, 7.3, 3.6 Hz, 1H), 1.70 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.59 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.25 (dt, *J* = 12.1, 9.5 Hz, 1H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.05–0.96 (m, 5H), 0.90 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 140.0, 134.9, 130.0, 126.3, 126.2, 121.1, 109.8, 103.4, 94.5, 94.4, 84.6, 83.7, 80.8, 79.9, 79.0, 78.0, 76.2, 73.1, 72.2, 64.7, 64.6, 63.1, 55.8, 55.6, 40.6, 39.3, 36.9, 35.5, 33.0, 27.7, 25.9, 25.6, 20.7, 18.3, 18.1, 17.4, −1.5, −4.4, −4.9 ppm. IR (film): $\tilde{\nu}$ = 2953, 2930, 2889, 2858, 1747, 1731, 1462, 1379, 1252, 1214, 1142, 1036, 937, 863, 837, 777 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4482.

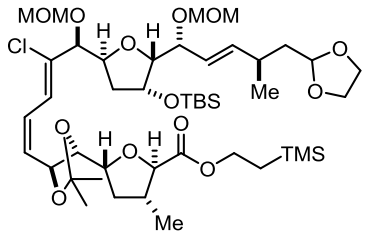
MOM-Ether S30b. According to General Procedure using chlorodiene **347b** (26.2 mg, 0.030 mmol).



Colourless oil (20.9 mg, 74%). $[\alpha]_D^{20}$ = –52.9 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 11.0 Hz, 1H), 6.53 (td, *J* = 11.0, 1.1 Hz, 1H), 5.65–5.49 (m, 2H), 5.37 (ddd, *J* = 15.5, 8.0, 1.0 Hz, 1H), 4.80 (dd, *J* = 6.0, 4.4 Hz, 1H), 4.75 (td, *J* = 8.5, 1.1 Hz, 1H), 4.63–4.57 (m, 3H), 4.53 (d, *J* = 6.3 Hz, 1H), 4.48–4.38 (m, 2H), 4.34 (d, *J* = 4.3 Hz, 1H), 4.25–4.05 (m, 4H), 3.93 (d, *J* = 8.4 Hz, 1H), 3.91–3.86 (m, 2H), 3.83 (dd, *J* = 6.4, 4.3 Hz, 1H), 3.79–3.72 (m, 2H), 3.62 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.33 (s, 3H), 3.27 (s, 3H), 2.42–2.24 (m, 2H), 2.13–1.98 (m, 2H), 1.84 (ddd, *J* = 12.9, 7.3, 3.6 Hz, 1H), 1.66 (ddd, *J* = 13.8, 8.0, 4.4 Hz, 1H), 1.58–1.53 (m, 1H), 1.51–1.42 (m, 1H), 1.39 (s, 6H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.01–0.94 (m, 5H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 139.8, 135.1, 130.2, 127.3, 126.4, 121.4, 109.6, 103.3, 94.4, 94.4, 84.6, 83.7, 83.0, 79.9, 78.4, 77.6, 76.2, 73.8, 72.2, 64.6, 64.6, 62.9, 55.6, 55.4, 40.6, 39.6, 36.6, 35.5, 33.0, 27.1, 26.6, 25.8, 20.7, 18.0, 17.4, 17.3, −1.6, −4.4,

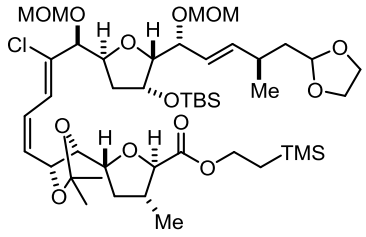
−5.0 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2889, 1746, 1462, 1380, 1251, 1215, 1172, 1129, 1088, 1055, 1036, 939, 860, 836, 775 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4483.

MOM-Ether S30c. According to General Procedure using chlorodiene **347c** (28 mg, 33 µmol).



Colourless oil (24.2 mg, 81%). $[\alpha]_D^{20}$ = +0.6 (c = 1.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (dd, *J* = 11.0, 1.1 Hz, 1H), 6.56 (td, *J* = 11.1, 1.3 Hz, 1H), 5.75–5.62 (m, 2H), 5.45 (ddd, *J* = 15.6, 8.0, 1.0 Hz, 1H), 5.05 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 4.86 (dd, *J* = 6.0, 4.4 Hz, 1H), 4.68–4.57 (m, 4H), 4.52–4.44 (m, 2H), 4.38 (d, *J* = 3.5 Hz, 1H), 4.27–4.10 (m, 5H), 3.99–3.91 (m, 3H), 3.89 (dd, *J* = 6.3, 4.2 Hz, 1H), 3.83–3.77 (m, 2H), 3.36 (s, 3H), 3.33 (s, 3H), 2.48–2.30 (m, 2H), 2.22–2.08 (m, 2H), 1.85 (ddd, *J* = 12.8, 7.3, 3.7 Hz, 1H), 1.71 (ddd, *J* = 13.8, 7.9, 4.4 Hz, 1H), 1.65–1.52 (m, 2H), 1.49 (s, 3H), 1.40 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.02–0.97 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H), 0.04 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 139.8, 134.4, 128.9, 126.5, 126.4, 121.2, 108.8, 103.4, 94.7, 94.4, 84.7, 83.4, 80.0, 79.7, 78.7, 78.1, 76.2, 73.8, 72.3, 64.7, 64.6, 63.1, 55.7, 55.6, 40.6, 39.3, 37.1, 34.9, 33.0, 27.5, 25.9, 25.2, 20.7, 18.3, 18.1, 17.4, −1.5, −4.4, −4.9 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2891, 2858, 1746, 1733, 1463, 1380, 1252, 1215, 1144, 1100, 1066, 1036, 957, 942, 925, 860, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4495.

MOM-Ether S30d. According to General Procedure using chlorodiene **347d** 45 mg, 52 µmol).

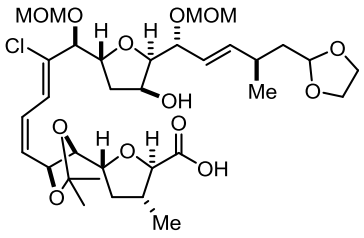


Colourless oil (36 mg, 77%). $[\alpha]_D^{20}$ = −27.6 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (dt, *J* = 11.0, 1.0 Hz, 1H), 6.53 (td, *J* = 11.0, 1.2 Hz, 1H), 5.70–5.58 (m, 2H), 5.42 (ddd, *J* = 15.6, 8.0, 1.1 Hz, 1H), 4.85 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.67–4.51 (m, 5H), 4.48 (dt, *J* = 5.0, 3.6 Hz, 1H), 4.43 (td, *J* = 7.3, 4.3 Hz, 1H), 4.31 (d, *J* = 4.3 Hz, 1H), 4.25–4.12 (m, 3H), 4.16–4.08 (m, 1H), 4.01 (d, *J* = 7.8 Hz, 1H), 3.97–3.89 (m, 3H), 3.84 (dd, *J* = 6.6, 4.1 Hz, 1H), 3.84–3.75 (m, 2H), 3.35 (s, 3H), 3.32 (s, 3H), 2.47–2.32 (m, 2H), 2.21–2.06 (m, 2H), 1.90 (ddd, *J* = 12.9, 7.1, 3.3 Hz, 1H), 1.74–1.63 (m, 2H), 1.58 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.44–1.39 (m, 6H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.05–0.96 (m, 5H), 0.90 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 139.8, 134.5, 130.8, 126.8, 126.5, 122.3, 109.8, 103.4, 94.5, 94.3, 84.6, 83.2, 82.1, 79.9, 79.6, 77.9, 76.2, 75.4, 72.3, 64.7, 64.6, 63.1, 55.7, 55.6, 40.6, 39.3, 35.7, 35.5, 33.0, 27.2, 26.9, 25.9, 20.8, 18.1, 18.0, 17.4, −1.5, −4.4, −4.9 ppm. IR (film): $\tilde{\nu}$ = 2954, 2931, 2891, 1748, 1462, 1371, 1251, 1213, 1144, 1098, 1065, 1035, 937, 861, 837, 776 cm^{-1}. MS (ESIpos) *m/z* (%): 927.4 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{44}H_{77}O_{13}ClSi_2Na$: 927.4483, found: 927.4488.

General Procedure for Liberating the *Seco*-Acids 270b-d and 348a-d from Compounds 269a-d and S30a-d, respectively.

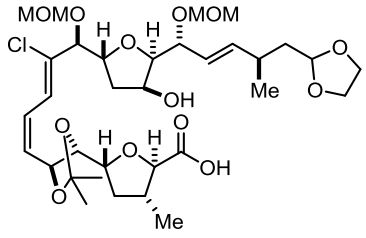
A solution of TBAF (1 M in THF, 500 mol%) was added dropwise to a solution of ester **269b-d** or **S30a-d** (0.15 M, 100 mol%) in THF at 0 °C. After stirring for 2 h at 0 °C, the ice bath was removed and stirring was continued for 2.5 h at ambient temperature. The mixture was diluted with NaOH (0.1 M, 5 mL) and *t*-butyl methyl ether (10 mL). The ethereal phase was extracted with NaOH (0.1 M, 3 mL). The combined aq. phases were washed with *t*-butyl methyl ether (20 mL) and carefully acidified with HCl (1 M, 1 mL) until a visible cloudiness was persistent in the solution (pH = 4). The solution was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with a 3:1 mixture of brine and pH 4 phosphate buffer (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The *seco*-acids were isolated as oils, which were used in the next step without further purification.

***Seco*-Acid 270b**. According to General Procedure using ester **269b** (18.4 mg, 0.11 mmol). Colourless



oil (14.0 mg, 99%). $[\alpha]_D^{20}$ = –111.9 (c = 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (dd, *J* = 11.0, 1.0 Hz, 1H), 6.56 (td, *J* = 11.0, 1.2 Hz, 1H), 5.86 (ddd, *J* = 15.7, 7.1, 0.8 Hz, 1H), 5.63 (ddd, *J* = 11.1, 8.6, 1.1 Hz, 1H), 5.50 (ddd, *J* = 15.7, 8.2, 1.3 Hz, 1H), 4.94 (td, *J* = 8.5, 1.2 Hz, 1H), 4.88 (dd, *J* = 5.3, 4.5 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 4.69–4.61 (m, 3H), 4.55 (dt, *J* = 9.1, 6.6 Hz, 1H), 4.32 (td, *J* = 6.6, 2.1 Hz, 2H), 4.20 (d, *J* = 6.6 Hz, 1H), 4.13–4.05 (m, 1H), 4.03 (d, *J* = 8.6 Hz, 1H), 3.98–3.89 (m, 3H), 3.87–3.78 (m, 2H), 3.62 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 2.46 (dtd, *J* = 8.2, 6.9, 3.5 Hz, 1H), 2.39–2.28 (m, 1H), 2.11 (ddd, *J* = 13.7, 7.1, 4.7 Hz, 1H), 2.00 (ddd, *J* = 13.2, 6.6, 1.6 Hz, 1H), 1.89 (ddd, *J* = 13.5, 9.1, 4.9 Hz, 1H), 1.74–1.63 (m, 3H), 1.47−1.40 (m, 6H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 140.9, 134.7, 131.1, 126.8, 124.5, 123.7, 109.5, 103.3, 94.1, 93.6, 84.0, 83.4, 81.9, 81.1, 78.8, 77.2, 76.6, 73.7, 72.6, 64.7, 64.6, 55.7, 55.5, 40.7, 39.7, 37.4, 36.7, 32.2, 27.2, 26.6, 20.1, 17.2 ppm. IR (film): $\tilde{\nu}$ = 3485, 2957, 2929, 2894, 1742, 1457, 1380, 1258, 1215, 1129, 1091, 1032, 918, 877, 799 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ $[M-H]^-$: 689.2945, found: 689.2948.

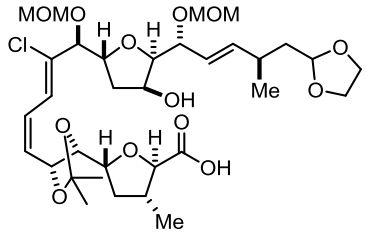
***Seco*-Acid 270c**. According to General Procedure using ester **269c** (20 mg, 0.022 mmol). Colourless oil



(15.3 mg, 99%). $[\alpha]_D^{20}$ = –40.6 (c = 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 11.0 Hz, 1H), 6.56 (td, *J* = 10.9, 1.3 Hz, 1H), 5.85 (dd, *J* = 15.7, 7.0 Hz, 1H), 5.66 (dd, *J* = 10.9, 8.6 Hz, 1H), 5.49 (ddd, *J* = 15.7, 8.4, 1.2 Hz, 1H), 5.08 (ddd, *J* = 8.3, 6.6, 1.3 Hz, 1H), 4.85 (t, *J* = 4.9 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.67–4.61 (m, 3H), 4.54 (dt, *J* =

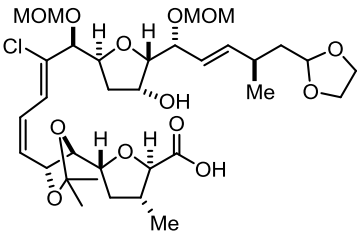
9.2, 6.4 Hz, 1H), 4.34–4.28 (m, 2H), 4.24–4.18 (m, 1H), 4.13 (d, *J* = 6.4 Hz, 1H), 4.06 (dt, *J* = 9.6, 6.1 Hz, 1H), 3.99–3.92 (m, 3H), 3.87 (dd, *J* = 6.4, 3.3 Hz, 1H), 3.84–3.79 (m, 2H), 3.41 (s, 3H), 3.37 (s, 3H), 2.53–2.42 (m, 1H), 2.42–2.32 (m, 1H), 2.27 (dt, *J* = 12.5, 6.3 Hz, 1H), 2.01 (ddd, *J* = 13.3, 6.4, 1.6 Hz, 1H), 1.89–1.81 (m, 1H), 1.79–1.55 (m, 3H), 1.50 (s, 3H), 1.39 (s, 3H), 1.28–1.25 (m, 3H), 1.07 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 141.1, 134.8, 130.7, 125.6, 124.4, 123.3, 109.3, 103.3, 94.0, 93.7, 84.4, 82.7, 81.0, 80.0, 78.9, 78.9, 76.6, 74.2, 72.6, 64.7, 64.7, 55.6, 55.5, 40.8, 39.4, 38.1, 37.5, 32.2, 27.5, 25.1, 20.0, 17.6 ppm. IR (film): $\tilde{\nu}$ = 3472, 2957, 2932, 2894, 1734, 1457, 1381, 1214, 1151, 1100, 1033, 975, 918, 870, 802 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ [M−H]$^-$: 689.2945, found: 689.2934.

***Seco*-Acid 270d**. According to General Procedure using ester **269d** (20 mg, 0.022 mmol). Colourless



oil (14.5 mg, 95%). $[\alpha]_D^{20}$ = –54.3 (c = 1.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (dd, *J* = 11.0, 1.1 Hz, 1H), 6.53 (td, *J* = 11.1, 1.1 Hz, 1H), 5.91 (dd, *J* = 15.8, 6.6 Hz, 1H), 5.64 (ddd, *J* = 11.0, 8.7, 1.1 Hz, 1H), 5.44 (ddd, *J* = 15.7, 8.8, 1.4 Hz, 1H), 4.84 (t, *J* = 4.8 Hz, 1H), 4.73–4.59 (m, 5H), 4.45 (ddt, *J* = 10.2, 7.4, 5.1 Hz, 1H), 4.37–4.27 (m, 2H), 4.16 (dt, *J* = 9.4, 5.9 Hz, 1H), 4.10 (d, *J* = 7.3 Hz, 1H), 3.99–3.92 (m, 3H), 3.89 (dd, *J* = 6.8, 3.0 Hz, 1H), 3.85–3.79 (m, 2H), 3.75 (dd, *J* = 7.9, 6.4 Hz, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 2.52–2.39 (m, 2H), 2.33 (ddd, *J* = 12.5, 7.2, 5.6 Hz, 1H), 1.99 (dd, *J* = 12.9, 5.8 Hz, 1H), 1.89 (ddd, *J* = 13.5, 10.3, 4.6 Hz, 1H), 1.78 (dt, *J* = 14.0, 5.2 Hz, 1H), 1.67 (ddd, *J* = 13.7, 8.4, 4.6 Hz, 1H), 1.57 (dt, *J* = 11.9, 9.7 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.1, 141.6, 133.9, 131.6, 126.2, 124.0, 122.8, 109.9, 103.3, 93.9, 93.6, 84.4, 83.4, 82.3, 81.6, 80.8, 79.8, 76.8, 76.8, 72.8, 64.7, 64.6, 55.6, 55.5, 40.8, 39.2, 37.8, 37.2, 31.9, 27.0, 27.0, 19.6, 17.7 ppm. IR (film): $\tilde{\nu}$ = 3449, 2957, 2933, 2895, 1740, 1381, 1214, 1152, 1100, 1033, 980, 918, 875 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ [M−H]$^-$: 689.2945, found: 689.2951.

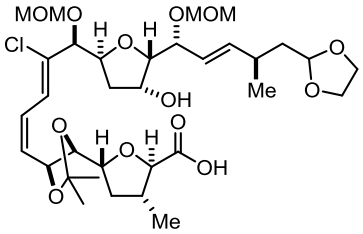
***Seco*-Acid 348a**. According to General Procedure using ester **S30a** (31 mg, 0.034 mmol). Colourless oil



(23.7 mg, 99%). $[\alpha]_D^{20}$ = –68.4 (c = 0.95, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 11.1 Hz, 1H), 6.56 (td, *J* = 11.0, 1.2 Hz, 1H), 5.71 (ddd, *J* = 15.6, 7.6, 1.0 Hz, 1H), 5.70 (ddd, *J* = 11.0, 9.2, 1.0 Hz, 1H), 5.45 (ddd, *J* = 15.5, 7.3, 1.1 Hz, 1H), 5.00 (ddd, *J* = 9.3, 5.7, 1.0 Hz, 1H), 4.84 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.66 (d, *J* = 6.2 Hz, 1H), 4.63 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.57 (ddd, *J* = 9.3, 6.3, 4.5 Hz, 1H), 4.49 (dd, *J* = 4.8, 2.9 Hz, 1H), 4.38 (d, *J* = 4.5 Hz, 1H), 4.23 (td, *J* = 7.1, 1.0 Hz, 1H), 4.16–4.11 (m, 1H), 4.15–4.10 (m, 1H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.98–3.92 (m, 2H), 3.86–3.77 (m, 2H), 3.77 (dd, *J* = 7.0, 2.9 Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.44 (hept, *J* = 7.0 Hz, 1H), 2.39–2.31 (m, 1H), 2.09 (m, 1H), 2.08 (ddd, *J*

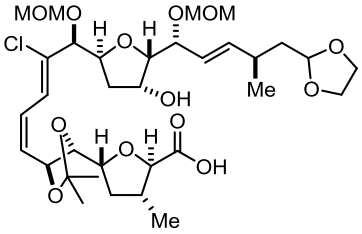
= 13.2, 9.2, 4.3 Hz, 1H), 1.99 (ddd, *J* = 13.2, 6.3, 1.1 Hz, 1H), 1.69 (ddd, *J* = 13.9, 7.9, 4.6 Hz, 1H), 1.62 (dt, *J* = 13.9, 6.1 Hz, 1H), 1.53 (s, 3H), 1.41 (s, 3H), 1.39–1.34 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.4, 140.3, 135.4, 129.7, 126.2, 125.4, 121.2, 109.9, 103.3, 94.9, 94.4, 84.4, 82.8, 80.7, 79.8, 79.3, 78.3, 77.0, 73.3, 72.5, 64.7 (2C), 55.8, 55.8, 40.6, 39.5, 37.3, 35.5, 32.8, 27.7, 25.5, 20.7, 17.4 ppm. IR (film): $\tilde{\nu}$ = 3484, 2929, 1735, 1379, 1215, 1144, 1100, 1051, 1029, 868 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ $[M-H]^-$: 689.2945, found: 689.2949.

***Seco*-Acid 348b**. According to General Procedure using ester **S30b** (20.9 mg, 0.023 mmol). Colourless



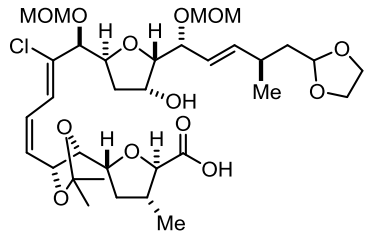
oil (16 mg, 99%). $[\alpha]_D^{20}$ = –116.6 (c = 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 11.0 Hz, 1H), 6.56 (td, *J* = 11.1, 1.0 Hz, 1H), 5.72 (ddd, *J* = 15.5, 7.6, 0.9 Hz, 1H), 5.61 (ddd, *J* = 11.0, 8.7, 1.0 Hz, 1H), 5.44 (ddd, *J* = 15.5, 7.5, 1.1 Hz, 1H), 4.98–4.89 (m, 1H), 4.84 (dd, *J* = 5.7, 4.6 Hz, 1H), 4.69–4.62 (m, 2H), 4.60 (d, *J* = 6.2 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.56–4.46 (m, 2H), 4.39 (d, *J* = 4.6 Hz, 1H), 4.29–4.20 (m, 1H), 4.11–4.00 (m, 2H), 3.98–3.90 (m, 2H), 3.89–3.77 (m, 3H), 3.67–3.58 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.48–2.34 (m, 2H), 2.21–2.03 (m, 3H), 1.73–1.61 (m, 3H), 1.47–1.42 (m, 6H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 140.6, 134.6, 130.8, 127.0, 125.3, 123.1, 109.5, 103.3, 94.8, 94.2, 84.1, 83.4, 81.5, 79.8, 79.2, 77.0, 76.9, 73.7, 72.5, 64.7, 64.7, 55.8, 55.7, 40.6, 39.2, 36.6, 35.8, 32.7, 27.2, 26.6, 20.6, 17.8 ppm. IR (film): $\tilde{\nu}$ = 3320, 2961, 2933, 2878, 1739, 1461, 1380, 1214, 1128, 1089, 1054, 1028, 879 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ $[M-H]^-$: 689.2945, found: 689.2951.

***Seco*-Acid 348c**. According to General Procedure using ester **S30c** (24 mg, 27 µmol). Colourless oil



(17.9 mg, 98%). $[\alpha]_D^{20}$ = –52.7 (c = 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 11.0 Hz, 1H), 6.55 (td, *J* = 11.0, 1.4 Hz, 1H), 5.72 (ddd, *J* = 15.5, 7.6, 0.9 Hz, 1H), 5.63 (dd, *J* = 11.0, 8.8 Hz, 1H), 5.46 (ddd, *J* = 15.5, 7.2, 1.1 Hz, 1H), 5.07 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H), 4.88–4.82 (m, 1H), 4.69–4.61 (m, 3H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.54–4.48 (m, 2H), 4.35 (d, *J* = 4.9 Hz, 1H), 4.30–4.21 (m, 2H), 4.06 (dt, *J* = 9.5, 5.8 Hz, 1H), 3.99–3.92 (m, 3H), 3.85–3.77 (m, 3H), 3.40 (s, 3H), 3.36 (s, 3H), 2.46–2.32 (m, 3H), 2.23 (ddd, *J* = 12.5, 7.3, 5.7 Hz, 1H), 2.15–2.03 (m, 2H), 1.75–1.56 (m, 2H), 1.51 (s, 3H), 1.39 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.7, 140.2, 134.8, 130.5, 125.7, 125.3, 122.6, 109.3, 103.3, 94.8, 94.1, 84.1, 82.8, 80.0, 79.8, 78.7, 77.0, 74.2, 72.8, 64.7, 55.7, 55.7, 40.6, 39.3, 37.7, 36.0, 32.8, 29.7, 27.5, 25.2, 20.7, 17.6 ppm. IR (film): $\tilde{\nu}$ = 3466, 2926, 1731, 1457, 1380, 1214, 1149, 1100, 1028, 976, 922, 870 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ $[M-H]^-$: 689.2945, found: 689.2950.

***Seco*-Acid 348d**. According to General Procedure using ester **S30d** (36 mg, 40 µmol). Colourless oil

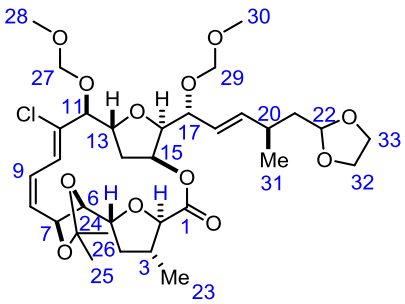


(27.4 mg, 99%). $[\alpha]_D^{20}$ = –70.5 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 11.0 Hz, 1H), 6.54 (td, *J* = 11.0, 1.2 Hz, 1H), 5.70 (ddd, *J* = 15.6, 7.6, 0.9 Hz, 1H), 5.63 (ddd, *J* = 11.1, 8.6, 1.1 Hz, 1H), 5.45 (ddd, *J* = 15.5, 7.3, 1.1 Hz, 1H), 4.84 (dd, *J* = 5.7, 4.5 Hz, 1H), 4.69–4.59 (m, 4H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.54–4.46 (m, 2H), 4.35 (d, *J* = 4.6 Hz, 1H), 4.24 (t, *J* = 6.6 Hz, 1H), 4.15 (dt, *J* = 9.6, 5.6 Hz, 1H), 4.00 (d, *J* = 8.2 Hz, 1H), 3.97–3.92 (m, 2H), 3.86–3.79 (m, 3H), 3.78 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 2.50–2.37 (m, 2H), 2.27 (ddd, *J* = 12.4, 7.2, 5.6 Hz, 1H), 2.16–2.01 (m, 2H), 1.69 (ddd, *J* = 13.8, 7.9, 4.6 Hz, 1H), 1.67–1.55 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 140.2, 134.5, 131.2, 126.5, 125.4, 122.5, 109.9, 103.3, 94.9, 93.9, 84.2, 82.9, 82.1, 80.5, 79.8, 78.7, 76.9, 76.1, 72.6, 64.7, 64.7, 55.8, 55.6, 40.6, 39.2, 37.2, 35.7, 32.7, 27.1, 27.0, 20.7, 17.8 ppm. IR (film): $\tilde{\nu}$ = 3470, 2933, 2890, 1736, 1455, 1372, 1215, 1148, 1098, 1054, 1028, 976, 921, 876, 760 cm^{-1}. MS (ESIneg) *m/z* (%): 689.3 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{33}H_{50}O_{13}Cl$ $[M-H]^-$: 689.2945, found: 689.2949.

General Procedure for Yamaguchi Macrolactonization of *Seco*-Acids 270b-d and 348a-d to give Macrolactones 257b-d and 349a-d.

Hünig's base (650 mol%) and 2,4,6-trichlorobenzoyl chloride (450 mol%) were added to a solution of *seco*-acid **270b-d** or **348a-d** (0.1 M, 100 mol%) in THF at 0 °C. After stirring for 2 h at this temperature, the solvent was removed under reduced pressure and the residue was redissolved in toluene to make a 0.005 M solution. The resulting solution of the mixed Yamaguchi anhydride was added via syringe pump over a period of 20 h to a solution of DMAP (0.01 M, 2500 mol%) in toluene at 110 °C. Once the addition was complete, stirring was continued for additional 2 h at the same temperature. The mixture was cooled to ambient temperature and the reaction was quenched with sat. NH_4Cl (100 mL). The aq. phase was separated and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 3:2 to 4:1 to 9:1) to provide the title compounds.

Macrolactone 257b. According to General Procedure using *seco*-acid **270b** (13.7 mg, 20.3 µmol).



Colourless solid (8.3 mg, 61%). $[\alpha]_D^{20}$ = +0.8 (c = 0.83, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-30*. ^{13}C NMR (150 MHz, $CDCl_3$): *see Table S-30*. IR (film): $\tilde{\nu}$ = 2958, 2929, 2892, 1745, 1456, 1371, 1256, 1214, 1152, 1128, 1096, 1063, 1032, 972, 921 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS

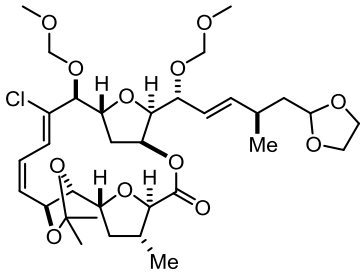
(ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2805.

Table S-30. NMR data of the macrolactone **257b**; numbering scheme as shown in the insert

atom n°	^{1}**H NMR** (600 MHz, $CDCl_3$)					^{13}**C NMR** (151 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	170.8	3, 15
2	3.91	d	9.0	3	3, 4b, 22, 23	85.8	3, 4a, 23
3	2.64	ddp	11.4, 9.0, 6.6	2, 4ab, 23	2, 4a, 5, 23	37.7	2, 4ab, 23
4a	2.18	ddd	12.0, 6.6, 5.6	3, 5, 4b	3, 5, 4b, 6	36.7	5, 23
4b	1.89	td	11.8, 10.4	3, 5, 4a	2, 4a, 6, 23		
5	4.16	ddd	10.4, 5.5, 1.5	4ab	3, 4a, 6, 7, 10, 13	78.0	2, 4b, 6, 7
6	3.68	dd	8.2, 1.4	7	4ab, 5, 7, 8, 21	80.4	4b, 5, 7, 8
7	5.09	ddd	8.3, 7.3, 1.6	8, 6	5, 6, 8, 10, 22	74.7	6, 8, 9
8	5.75	ddd	11.1, 7.4, 0.8	9, 7	6, 7, 9	133.7	6, 10
9	6.46	td	10.7, 1.6	10, 8	8	125.4	7
10	6.37	dt	10.4, 0.8	9	5, 7, 12, 13, 14a	121.4	8, 12
11	-	-	-	-	-	136.1	9, 10, 12
12	4.20	d	8.0	13	10, 14b, 27ab, 28	78.8	10, 13, 14b, 27ab
13	4.43	ddd	11.5, 7.9, 3.3	12, 14ab	5, 13, 14a	80.8	12, 14b, 15
14a	2.14	ddd	12.7, 3.3, 1.3	13, 14b	10, 13, 14b, 15	38.4	12
14b	1.77	ddd	12.7, 11.9, 2.9	13, 14a, 15	12, 14a, 15, 16		
15	5.48	td	3.0, 0.9	14b, 16	14ab, 16, 18	76.2	2, 14a, 16, 17
16	4.13-4.15	m	-	15	14b, 15, 18, 19, 30	82.8	14a, 15, 17, 18
17	4.11–4.15	m	-	18	19, 29ab	75.3	15, 16, 18, 19, 29ab
18	5.25	ddd	15.5, 7.1, 0.9	17, 19	15, 16, 20, 31	123.5	17, 20
19	5.55	dd	15.4, 8.1	18, 20	16, 17, 20, 21a, 31	142.1	17, 20, 21ab, 31
20	2.36-2.45	m	-	19, 21ab, 31	18, 19, 22, 31	33.1	18, 19, 21ab, 22, 31
21a	1.64	ddd	13.9, 8.0, 4.6	20, 21b, 22	19, 31	40.6	19, 20, 22, 31
21b	1.59	dt	13.8, 6.0	20, 21a, 22	31		
22	4.79	dd	5.6, 4.6	21ab	20, 31, 32b, 33b	103.3	20, 21ab, 32ab, 33ab
23	1.17	d	6.6	3	2, 3, 4b	15.8	2, 4b
24	-	-	-	-	-	109.4	25, 26
25	1.43	s	-	-	6	27.1	26
26	1.39	s	-	-	2, 7	26.1	25
27a	5.05	d	6.9	27b	12, 28	97.5	12, 28
27b	4.74	d	6.8	27a	12, 28		
28	3.49	s	-	-	12, 27ab	56.6	27ab
29a	4.69	d	6.7	29b	17, 30	93.2	17, 30
29b	4.60	d	6.7	29a	17, 30		
30	3.37	s	-	-	16, 27b, 29ab	55.1	29ab

31	0.98	d	6.8	20	18, 19, 20, 21ab, 22	21.0	19, 20, 21ab
32a 32b	3.96–3.90 3.84–3.78	AA'm BB'm	-	-	-	64.7	22, 33ab
33a 33b	3.96–3.90 3.84–3.78	AA'm BB'm	-	-	-	64.7	22, 32ab

Macrolactone 257c. According to General Procedure using *seco*-acid **270c** (15.3 mg, 22.1 µmol).



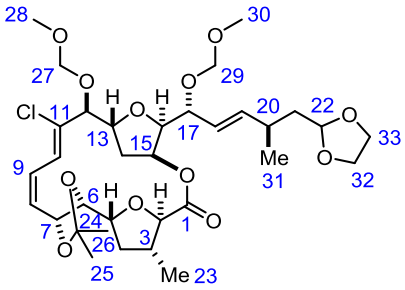
Colorless oil (2.1 mg, 14%). $[\alpha]_D^{20}$ = −24.8 (c = 0.21, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, major rotamer): *see Table S-31*. ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer): *see Table S-31*. IR (film): $\tilde{\nu}$ = 2958, 2929, 2854, 1739, 1651, 1458, 1380, 1221, 1152, 1100, 1032, 973, 920, 875 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2810.

Table S-31. NMR data of the macrolactone **257c**; numbering scheme as shown in the insert

atom n°	**^{1}H NMR** (600 MHz, $CDCl_3$)					**^{13}C NMR** (151 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	170.1	2, 3
2	4.05	d	5.2	3	3, 15, 23	87.1	3, 23
3	2.60–2.51	m	-	2, 23	2, 4b, 23	35.7	4ab, 23
4a 4b	2.60–2.51 1.76–1.70	m td	- 11.8, 10.4	4b, 5 4a, 5	4b, 5, 23 3, 4a, 6, 23	39.1	2, 3, 6, 23
5	4.26	qd	7.7, 2.5	4ab, 6	4a, 8, 10, 25	78.6	2, 3, 4b, 6, 7
6	3.96–3.91	m	-	5, 7	4b, 7, 23, 26	82.5	4ab, 7, 8, 9, 23
7	4.86	ddd	6.4, 5.1, 1.3	6, 8	6, 8, 10, 26	76.7	5, 6, 8, 9
8	5.61	ddd	11.4, 7.1, 1.0	7, 9	5, 7, 9, 25	126.4	-
9	6.53	td	11.4, 1.2	8, 10	8	126.7	7
10	7.22	br s	-	9	5, 7, 12, 13, 25	124.3	8, 9, 12
11	-	-	-	-	-	134.6	9, 12
12	4.23	d	6.8	13	10, 14a, 27ab, 28	80.3	27ab
13	4.11–4.06	m	-	12, 14ab	10, 14b	83.8	12
14a 14b	1.95–1.90 1.89–1.84	m m	- -	13, 14b, 15 13, 14a, 15	12, 15 13	36.9	-
15	5.33–5.31	m	-	14ab	2, 14a, 16, 17	75.3	2, 16
16	4.20	d	4.6	-	15, 18	82.9	17
17	4.19	d	5.7	18	15, 18, 19, 29ab, 30	74.6	16, 18, 19, 29ab
18	5.38–5.27	m	-	17, 19	16, 17, 20, 31	124.0	20
19	5.62	dd	15.6, 8.1	18, 20	17, 20, 21a, 31, 21a, 22	141.7	17, 20, 21ab, 31
20	2.43–2.35	m	-	19, 21ab, 31	18, 19, 22, 21b, 31	33.1	18, 19, 21ab, 22, 31

21a 21b	1.67–1.58 1.67–1.58	m m	- -	20, 21b, 22 20, 21a, 22	19, 22, 31 20, 31	40.5	19, 20, 22, 31
22	4.78	dd	5.7, 4.5	21ab	20, 31, 32b, 33b	103.3	19, 20, 21a, 31, 32b, 33b
23	1.14	d	6.5	3	2, 3, 4ab, 6	18.9	2, 3, 4ab
24	-	-	-	-	-	108.1	6, 7, 25, 26
25	1.53	s	-	-	5, 8, 10, 26	28.2	26
26	1.37	s	-	-	6, 7, 25	25.7	25
27a	4.72	d	6.7	27b	12, 28	95.1	12, 28
27b	4.67	d	6.8	27a	12, 28		
28	3.38	s	-	-	12, 27ab	55.7	27ab
29a	4.71	d	6.6	29b	17, 19, 30	93.2	17, 30
29b	4.60	d	6.6	29a	17, 30		
30	3.40	s	-	-	17, 29ab	55.1	17, 29ab
31	0.98	d	6.8	20	18, 19, 20, 21ab, 22	20.9	19, 20, 21ab
32a 32b	3.96–3.90 3.84–3.78	AA'm BB'm	-	-	-	64.7	22, 33ab
33a 33b	3.96–3.90 3.84–3.78	AA'm BB'm	-	-	-	64.7	22, 32ab

Macrolactone 257d. According to General Procedure using *seco*-acid **270d** (13.5 mg, 19.5 µmol).



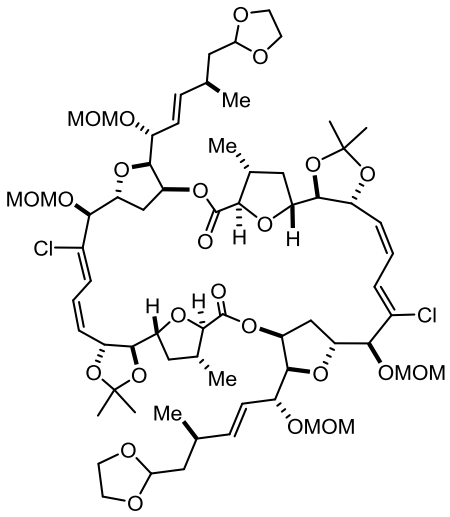
Lactone **257d** (1.5 mg, 11%) as a colourless oil and lactide **S31** (1.2 mg, 9%) as a yellow oil. Analytical and spectral data for lactone **257d**: $[\alpha]_D^{20}$ = +46.7 (c = 0.15, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-31*. ^{13}C NMR (151 MHz, $CDCl_3$): *see Table S-31*. IR (film): $\tilde{\nu}$ = 2918, 2850, 1742, 1252, 1153, 1141, 1098, 1068, 1029 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2801.

Table S-31. NMR data of the macrolactone **257d**; numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	-	-	-	-	-	170.4	3
2	3.99	d	5.3	3	3, 23	85.9	3, 4a, 23
3	2.61	ddqd	7.3, 7.1, 6.9, 5.3	2, 4ab, 23	2, 4a, 23	35.7	4ab, 23
4a 4b	2.43 1.75	ddd ddd	12.5, 7.3, 7.1 12.5, 8.8, 7.1	3, 4b, 5 3, 4a, 5	3, 4b, 5 4a, 5, 23	39.8	2, 3, 6, 23
5	4.04	ddd	8.8, 7.1, 4.5	4ab, 6	4ab, 6, 7, 10	80.1	2, 4b, 6, 7
6	3.81	dd	8.6, 4.5	5, 7	5, 8, 21	81.3	4b, 7
7	4.60	ddd	8.6, 8.5, 1.4	6, 8	5, 10, 22	76.8	5, 6, 9
8	5.67	ddd	11.0 ,8.5, 1,1	7, 9	6, 9	132.	6, 10

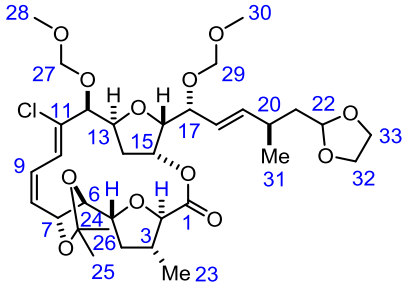
9	6.45	td	11.0, 1.4	8, 10	8	125.8	7, 10
10	6.64	dd	11.0, 1.1	9	5, 7, 13	122.1	8, 9, 12
11	-	-	-	-	-	134.5	9, 10, 12
12	4.14	dt	9.2, 0.9	13	14a, 27ab	81.8	10, 13, 27ab
13	4.08	ddd	12.0, 9.2, 3.1	12, 14a	10, 14b	83.0	12, 15
14a	1.82	ddd	13.0, 12.0, 3.1	13, 14b, 15	12, 14b, 15, 16, 17	38.2	12
14b	1.74-1.57	ddd	13.0, 3.1, 1.2	14a	13, 14a, 15		
15	5.41	ddd	3.3, 3,1, 1.2	14a, 16	14ab, 16, 17, 18	75.2	14b
16	4.18	d	3.30	15	14a, 15, 18, 19, 29ab, 30	84.1	17, 18
17	4.19	d	5.9	18	14a, 15, 18, 19, 29ab, 30	75.6	16, 18, 19, 29a
18	5.25	dddd	15.4, 5.9, 2.3, 1.1	17, 19	15, 16, 17, 20	123.7	20
19	5.60	dd	15.4, 8.0	18, 20	16, 17, 31	141.9	17, 20, 21ab, 31
20	2.38	dqd	8.0, 5.7, 5.9	19, 21ab, 31	18, 21b, 31	33.0	18, 19, 21ab, 22, 31
21a	1.63	dd	13.8, 4.5	20, 21b, 22	31	40.6	19, 20, 22, 31
21b	1.59	dt	13.8, 5.9	20, 21a, 22	20, 31		
22	4.78	dd	5.9, 4.5	21ab	21ab	103.2	20, 21ab, 32ab, 33ab
23	1.14	d	6.9	3	2, 3, 4b	17.8	4b
24	-	-	-	-	-	110.0	25, 26
25	1.44	s	-	-	6	27.0	26
26	1.44	s	-	-	7	26.9	25
27a	4.71	dd	6.7, 0.9	-	12, 28	95.2	12, 28
27b	4.70	dd	6.7, 0.9	-	12, 28		
28	3.37	s	-	-	27ab	55.8	27ab
29a	4.73	d	6.7	29b	16, 17, 30	93.6	17, 30
29b	4.69	d	6.7	29a	16, 17, 30		
30	3.43	s	-	-	16, 17, 29ab	55.3	29ab
31	0.96	d	6.8	20	19, 20, 21ab	20.9	19, 20, 21ab
32a	3.96–3.90	AA‘ m	-	-	-	64.7	33ab
32b	3.84–3.78	BB‘ m					
33a	3.96–3.90	AA‘ m	-	-	-	64.7	32ab
33b	3.84–3.78	BB‘ m					

Analytical and spectral data for lactide **S31**: $[\alpha]_D^{20}$ = +12.5 (c = 0.12, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$):



δ = 6.73 (d, J = 10.8 Hz, 1H), 6.57 (td, J = 11.0, 1.0 Hz, 1H), 5.64–5.57 (m, 2H), 5.27 (ddd, J = 15.5, 8.3, 1.0 Hz, 1H), 5.23 (td, J = 3.3, 2.4, 0.5 Hz, 1H), 4.78 (dd, J = 5.6, 4.5 Hz, 1H), 4.69–4.60 (m, 4H), 4.48 (td, J = 8.8, 1.0 Hz, 1H), 4.40–4.31 (m, 2H), 4.15 (td, J = 8.2, 0.8 Hz, 1H), 4.11 (ddd, J = 9.1, 6.1, 4.5 Hz, 1H), 3.99 (d, J = 8.0 Hz, 1H), 3.96–3.88 (m, 4H), 3.84–3.77 (m, 2H), 3.40 (s, 3H), 3.36 (s, 3H), 2.41–2.28 (m, 2H), 2.16–2.08 (m, 1H), 2.11–2.05 (m, 1H), 2.04–1.97 (m, 1H), 1.72 (dt, J = 12.1, 9.5 Hz, 1H), 1.68–1.55 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.26 (d, J = 7.3 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.1, 141.6, 134.4, 130.4, 127.3, 124.0, 121.4, 109.9, 103.3, 94.9, 93.8, 83.1, 82.6, 81.8, 80.0, 80.0, 79.3, 76.0, 75.2, 74.9, 64.7, 64.7, 55.8, 55.2, 40.5, 39.4, 35.5, 34.7, 33.1, 27.1, 26.9, 20.9, 18.0 ppm. IR (film): $\tilde{\nu}$ = 2957, 2920, 2851, 1738, 1465, 1372, 1252, 1215, 1054, 843, 795 cm^{-1}. MS (ESIpos) *m/z* (%): 1367.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{66}H_{98}O_{24}Cl_2Na$: 1367.5717, found: 1367.5717.

Macrolactone 349a. According to General Procedure using *seco*-acid **348a** (23.7 mg, 34.. µmol). Pale



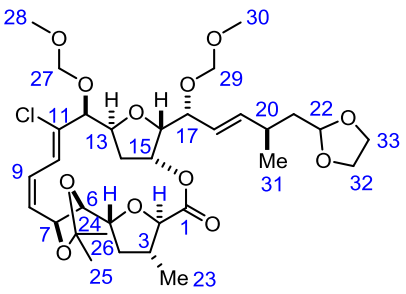
yellow oil (7.8 mg, 34%). $[\alpha]_D^{20}$ = −38.8 (c = 0.17, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-32*. ^{13}C NMR (151 MHz, $CDCl_3$): *see Table S-32*. IR (film): $\tilde{\nu}$ = 2926, 1741, 1726, 1260, 1217, 1163, 1095, 1028, 801 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2802.

Table S-32. NMR data of the macrolactone **349a**; numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	-	-	-	-	-	171.2	2, 3
2	3.98	d	6.4	3	3, 4b, 23, 25	84.2	3, 4a, 23
3	2.64	ddqd	8.4, 7.3, 6.8, 6.4	2, 4ab, 23	2, 4a, 5, 23	36.3	2, 4a, 23
4a	2.00	dt	12.3, 7.3	3, 4b, 5	3, 4b, 5	37.4	2, 6, 23
4b	1.40	ddd	12.3, 8.9, 8.4	3, 4a, 5	2, 4a, 6, 23		
5	3.88	ddd	8.9, 7.3, 4.4	4ab, 6	3, 4a, 6, 8, 10, 13, 25	78.2	2, 4b, 6, 7
6	4.06	dd	6.5, 4.4	5, 7	5, 4b, 7, 8, 26	80.9	4b, 7
7	4.89	ddd	6.5, 4.6, 1.5	6, 8	6, 8, 26	76.8	5, 6, 9
8	5.41	ddd	11.9, 4.6, 1,2	7, 9	5, 6, 7	124.3	7
9	6.46	ddd	11.9, 10.4, 1.5	8, 10	-	126.3	7

10	7.38	dt	10.4, 1.2	9	5, 12, 13, 25	124.4	8
11	-	-	-	-	-	133.7	9, 10
12	4.83	dd	3.2, 1.2	13	10, 13, 27ab, 28	73.4	10, 27ab
13	4.19	ddd	12.2, 3.2, 0.3	12, 14ab	5, 10, 12, 14b, 25	83.9	12
14a	2.03	ddd	13.2, 12.2, 3.1	13, 14b, 15	14b, 15, 16	33.3	12
14b	1.72	ddd	13.2, 2.4, 0.5	13, 14a	13, 14a, 15, 17		
15	5.48	dd	3.5, 3,1	14a, 16	14ab, 16, 17, 30	75.4	13, 14b, 16
16	3.99	dd	3.5, 9.3	15, 17	14a, 15, 18	82.4	17
17	4.19	ddd	9.3, 7.8, 0.5	16, 18	14b, 15, 18, 19, 25, 29ab	74.2	16, 19, 29ab
18	5.36	ddd	15.5, 7.8, 1.1	17, 19	16, 17, 20, 31	126.4	16, 20
19	5.62	ddd	15.5, 7.7, 0.8	18, 20	17, 20, 21a, 31	140.8	17, 20, 21ab, 31
20	2.45	ddqd	8.0, 7.7, 6.8, 6.1	19, 21ab, 31	18, 19, 21b, 31	32.8	18, 19, 21ab, 22, 31
21a	1.71	ddd	13.8, 8.0, 4.5	20, 21b, 22	19, 22, 31	40.7	19, 20, 22, 31
21b	1.62	dt	13.8, 6.1	20, 21a, 22	20, 22, 31		
22	4.85	dd	6.1, 4.5	21ab	21ab, 31, 32ab, 33ab	103.4	20, 21ab, 32ab, 33ab
23	1.14	d	6.9	3	2, 3, 4b	17.8	4b
24	-	-	-	-	-	109.6	6, 25, 26
25	1.66	s	-	-	3, 5, 10, 13, 17, 26	26.5	26
26	1.42	s	-	-	6, 7, 25	25.3	25
27a	4.74	d	6.5	-	12, 28	95.6	12, 28
27b	4.69	d	6.5	-	12, 28		
28	3.40	s	-	-	12, 27ab	55.6	27ab
29a	4.66	d	6.6	29b	17, 30	93.5	17, 30
29b	4.43	d	6.6	29a	17, 30		
30	3.23	s	-	-	15, 17, 23, 32a, 33a, 29ab	55.5	29ab
31	1.06	d	6.8	20	18, 19, 20, 21ab, 22	20.8	19, 20, 21ab
32a	3.97–3.92	AA' m	-	-	-	64.7	33ab
32b	3.85–3.78	BB' m					
33a	3.97–3.92	AA' m	-	-	-	64.7	32ab
33b	3.85–3.78	BB' m					

Macrolactone 349b. According to General Procedure using *seco*-acid **348b** (15.6 mg, 23.1 µmol).



Colourless oil (11.2 mg, 72%). $[\alpha]_D^{20}$ = −136.9 (c = 1.12, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) *see Table S-33*. ^{13}C NMR (151 MHz, $CDCl_3$) *see Table S-33.* IR (film): $\tilde{\nu}$ = 2985, 2960, 2931, 2879, 1737, 1456, 1380, 1214, 1181, 1151, 1125, 1079, 1051, 972, 923, 884 cm^{-1}. MS (ESIpos) *m/z* (%): 1367 (100 (2M+Na)); HRMS

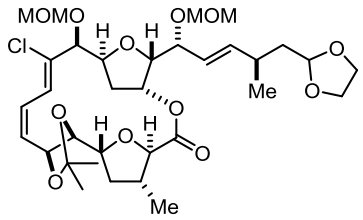
(ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2805.

Table S-33. NMR data of the macrolactone **349b**; numbering scheme as shown in the insert

atom n°	^{1}H NMR (600 MHz, $CDCl_3$)					^{13}C NMR (151 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	170.6	2, 3, 15, 23
2	4.13	d	2.4	3	3, 23, 30	84.6	4ab, 23
3	2.74	dqdd	8.4, 7.1, 4.5, 2.3	4a, 23	2, 4a, 23	33.4	4ab, 23
4a	2.38	dt	12.3, 8.5	3, 4b, 5	3, 4b, 5	35.5	2, 5, 23
4b	1.75	ddd	12.3, 7.5, 4.4	4a, 5	4a, 6, 23		
5	3.75	ddd	8.7, 7.5, 1.6	4ab	4a, 6, 7, 9, 10	75.7	2, 4ab, 6, 7
6	3.62	dd	8.8, 1.6	7	4b, 5, 7, 8, 21	80.4	4ab, 5, 7, 8
7	4.95	td	9.0, 1.0	6, 8	5, 6, 9, 10, 22	73.2	5, 6, 9, 10, 22
8	5.51-5.58	m	-	7, 9	6, 9, 10	130.5	6, 10
9	6.48	td	9.7, 0.9	8, 10	5, 7, 8, 12, 13, 14b	127.6	7
10	6.46	dd	9.7, 1.5	9	5, 7, 8, 12, 13, 14b	121.0	8, 12
11	-	-	-	-	-	136.1	8, 9, 12
12	4.74	d	2.1	13	9, 10, 13	73.5	10, 13, 14a, 27ab
13	4.51	ddd	11.9, 3.7, 2.7	12, 14ab	9, 10, 12, 14b, 15, 17	81.3	12, 14ab, 15
14a	2.13	ddd	13.4, 11.9, 3.1	13, 14b, 15	14b, 15, 16	32.4	12
14b	1.73	ddd	13.8, 8.1, 4.5	13, 14a	9, 10, 13, 14ab, 15		
15	5.39	t	3.0	14a, 16	13, 14ab, 16, 17, 29a, 30	75.3	14b, 16, 17
16	4.00	dd	8.9, 3.2	15, 17	14a, 15, 28	82.6	14b, 17, 18
17	4.26	ddd	8.6, 7.8, 0.7	16, 18	13, 15, 19, 29ab, 30	74.0	16, 18, 19, 29ab
18	5.38	ddd	15.5, 7.9, 1.1	17, 19	20, 22, 29a, 30, 31	126.1	16, 17, 20
19	5.74	ddd	15.6, 7.7, 0.7	18, 20	17, 20, 21a, 22, 29a, 31	141.2	17, 20, 21ab, 31
20	2.47	ddqd	8.6, 7.7, 6.8, 5.9	19, 21ab, 31	18, 19, 22, 31	32.9	18, 19, 21ab, 22, 31
21a	1.73	dd	13.4, 13.7	20, 21b, 22	19, 22, 31	40.6	19, 20, 22, 31
21b	1.64	dt	13.8, 5.9	20, 21a, 22	22, 31		
22	4.86	dd	5.9, 4.4	21ab	18, 19, 20, 21ab, 32b, 33b	103.4	20, 21ab, 32ab, 33ab
23	1.13	d	7.1	3	2, 3, 4b, 25	19.4	2, 3, 4ab
24	-	-	-	-	-	108.9	25, 26
25	1.44	s	-	-	6	27.2	26
26	1.44	s	-	-	7, 23	26.4	25
27a	4.82	d	6.6	27b	28	96.9	12, 28
27b	4.75	d	6.6	27a	28		
28	3.44	s	-	-	16, 27ab	56.0	27ab
29a	4.71	d	6.8	29b	15, 17, 18, 19, 30	93.2	17, 30
29b	4.44	d	6.8	29a	17, 30		

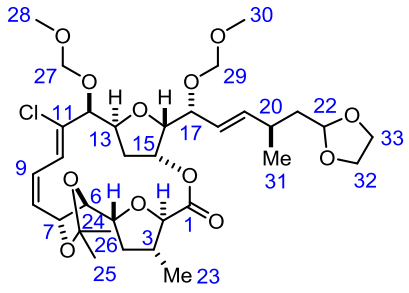
30	3.25	s	-	-	2, 15, 17, 18, 29ab	55.5	29ab
31	1.07	d	6.8	20	18, 19, 20, 21ab, 22	21.0	19, 20, 21ab
32a 32b	3.97–3.92 3.86–3.78	AA‘ m BB‘ m	-	-	- 22	64.7	33ab
33a 33b	3.97–3.92 3.86–3.78	AA‘ m BB‘ m	-	-	- 22	64.7	32ab

Macrolactone 349c. According to General Procedure using *seco*-acid **348c** (19 mg, 27.5 µmol). Pale



yellow oil (9.4 mg, 51%). $[\alpha]_D^{20}$ = −117.3 (c = 0.94, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.43 (td, *J* = 10.8, 1.4 Hz, 1H), 6.37–6.31 (m, 1H), 5.74 (ddd, *J* = 15.6, 7.7, 0.7 Hz, 1H), 5.49 (dd, *J* = 10.9, 9.5 Hz, 1H), 5.41–5.32 (m, 2H), 5.02 (ddd, *J* = 9.5, 5.9, 1.3 Hz, 1H), 4.86 (dd, *J* = 5.8, 4.5 Hz, 1H), 4.81 (d, *J* = 3.5 Hz, 1H), 4.74–4.65 (m, 3H), 4.41 (d, *J* = 6.8 Hz, 1H), 4.24 (dd, *J* = 9.0, 7.9 Hz, 1H), 4.11 (dt, *J* = 11.9, 3.5 Hz, 1H), 4.04 (dd, *J* = 8.1, 5.9 Hz, 1H), 4.01–3.90 (m, 3H), 3.88–3.79 (m, 4H), 3.39 (s, 3H), 3.23 (s, 3H), 2.68 (ddt, *J* = 11.6, 8.8, 6.6 Hz, 1H), 2.46 (p, *J* = 7.0 Hz, 1H), 2.33–2.25 (m, 1H), 2.01 (td, *J* = 12.5, 2.7 Hz, 1H), 1.79–1.69 (m, 2H), 1.67–1.57 (m, 1H), 1.57–1.52 (m, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.08 (d, *J* = 1.9 Hz, 3H), 1.06 (d, *J* = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.2, 141.2, 134.8, 130.6, 126.2, 125.1, 121.3, 109.0, 103.4, 95.5, 93.0, 84.0, 83.5, 82.8, 81.4, 77.6, 75.6, 74.7, 73.7, 72.9, 64.7(2), 55.5, 55.4, 40.6, 39.4, 35.2, 32.9, 32.3, 28.1, 25.7, 20.9, 16.0. IR (film): $\tilde{\nu}$ = 2956, 2927, 2889, 1745, 1456, 1380, 1371, 1213, 1149, 1081, 1031, 919, 866, 808, 755 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2805. The macrolactone **349c** decomposed upon storage under an argon atmosphere in the freezer.

Macrolactone 349d. According to General Procedure using *seco*-acid **348d** (27.6 mg, 40 µmol). Pale



yellow oil (15.1 mg, 56%). $[\alpha]_D^{20}$ = −154.4 (c = 0.39, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): *see Table S-34.* ^{13}C NMR (151 MHz, $CDCl_3$): *see Table S-34*. IR (film): $\tilde{\nu}$ = 2935, 2887, 1744, 1198, 1156, 1091, 1029 cm^{-1}. MS (ESIpos) *m/z* (%): 695.3 (100 (M+Na)); HRMS (ESIpos): *m/z* calcd for $C_{33}H_{49}O_{12}ClNa$: 695.2805, found: 695.2812.

Table S-34. NMR data of the macrolactone **349d**; numbering scheme as shown in the insert

atom n°	**^{1}H NMR** (600 MHz, $CDCl_3$)					**^{13}C NMR** (151 MHz, $CDCl_3$)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	171.1	2, 3, 15
2	4.01	d	6.4	3	23	84.7	2, 4a. 23

3	2.84	ddqd	10.7, 7.1, 6.8, 6.4	2, 4ab, 23	4a, 5, 23	34.0	2, 4ab, 23
4a	2.40	ddd	11.8, 7.1, 4.3	3, 4b, 5	3, 4b, 5	39.6	6, 23
4b	1.41	dt	11.8, 10.7	3, 4a, 5	4a, 23		
5	3.92	dd	10.7, 4.3	4ab	3, 4a, 7, 25	83.0	2, 4b, 7
6	3.81	d	4.1	7	7, 8	83.3	4b, 5
7	4.77	dd	8.9, 4.1	6, 8	5, 6, 10	79.1	5, 9
8	5.74	ddd	10.5, 8.9, 0,9	7, 9, 10	6, 9, 26	134.9	6, 10
9	6.36	td	10.5, 1.3	8, 10	8	124.8	7
10	6.43	d	10.5	8, 9	7, 12, 14b	121.8	8, 12
11	-	-	-	-	-	135.7	9, 10, 12
12	4.58	s			10, 27ab	78.4	10, 13, 27ab
13	4.55	dd	11.6, 3.5	14ab	14b	80.2	12
14a	2.25	ddd	13.3, 11.6, 2.9	13, 14b, 15	14b, 15	34.2	12
14b	1.99	ddd	13.3, 3.5, 1.0	13, 14a	10, 13, 14a		
15	5.63	dd	3.3, 2,9	14a, 16	14a, 16	76.3	14b, 16, 17
16	3.97	dd	3.3, 8.3	15, 17	15, 18	81.1	14b, 17, 18
17	4.18	dd	8.3, 8.0	16, 18	19, 29a	73.8	16, 18, 19, 29ab
18	5.35	ddd	15.6, 8.0, 1.1	17, 19	16, 20	125.8	16, 20
19	5.67	ddd	15.6, 7.7, 0.7	18, 20	17, 31	141.5	17, 20, 21ab, 31
20	2.46	ddqd	8.1, 7.7, 6.8, 6.0	19, 21ab, 31	18, 31	32.9	18, 19, 21ab, 22, 31
21a	1.71	ddd	13.8, 8.1, 4.4	20, 21b, 22	31	40.6	19, 20, 22, 31
21b	1.63	ddd	13.8, 6.0, 5.9	20, 21a, 22			
22	4.84	dd	5.9, 4.4	21ab	32b, 33b	103.4	20, 21ab, 32ab, 33ab
23	1.13	d	6.8	3	2, 3, 4b	17.8	2, 3, 4b
24	-	-	-	-	-	110.9	6, 7, 25, 26
25	1.39	s	-	-	5	28.0	26
26	1.44	s	-	-	8	27.5	25
27a	4.86	d	6.4	27b	12, 28	97.3	12, 28
27b	4.80	d	6.4	27a	12, 28		
28	3.43	s	-	-	27ab	56.1	27ab
29a	4.71	d	6.8	29b	17	93.0	17, 30
29b	4.42	d	6.8	29a	30		
30	3.24	s	-	-	29b	55.6	29ab
31	1.06	d	6.8	20	19, 20, 21b	20.9	19, 20, 21ab
32a	3.97–3.92	AA‘ m	-	-	-	64.7	33ab
32b	3.85–3.78	BB‘ m			22		
33a	3.97–3.92	AA‘ m	-	-	-	64.7	32ab
33b	3.85–3.78	BB‘ m			22		

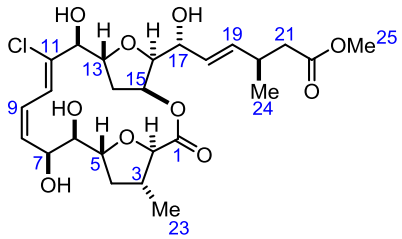
General Procedure for the Endgame: Global Deprotection, Pinnick Oxidation, Esterification

A solution of Me_2BBr (0.5 M in CH_2Cl_2, 2000 mol%) was added dropwise to a solution of macrolactone **257b-d** or **349a-d** (0.01 M, 100 mol%) in CH_2Cl_2 at –78 °C. After stirring for 30 min at –78 °C, the yellow mixture was poured into a solution of pH 7 phosphate buffer (0.15 ml), rinsing the flask with CH_2Cl_2 (1.5 mL). The emulsion was concentrated under reduced pressure to yield the crude aldehyde, which was used in the next step without further purification.

The residue was dissolved into a 1:1 solution of THF and *t*-BuOH (0.01 M) before 2-methyl-2-butene (100000 mol%) was introduced. A solution of sodium chlorite (800 mol%) and sodium dihydrogen phosphate (960 mol%) in water (90000 mol%) was added at 0 °C with a glass pipette. After stirring for 30 min at 0 °C the reaction was quenched with sodium thiosulfate pentahydrate (1300 mol%). After removing the ice bath, the mixture was stirred for 5 min before adding sodium sulfate in small portions until the organic phase was dried. The mixture was diluted with CH_2Cl_2 (2 mL), filtered through a short pad of Na_2SO_4, which was rinsed with CH_2Cl_2 (15 mL in total). The combined filtrates were evaporated under reduced pressure at ambient temperature and the resulting crude carboxylic acid was used in the next step without further purification.

A freshly prepared solution of diazomethane in diethyl ether (ca. 0.1 mL) was added dropwise to a solution of the crude carboxylic acid in CH_2Cl_2 (0.02 M) at ambient temperature until a yellow colour persisted. After stirring for 5 min, the reaction was quenched with drops of formic acid until the yellow colour had dissipated. After concentrating the mixture under reduced pressure at ambient temperature, the residue was purified by preparative HPLC.

Macrocycle 273b. According to General Procedure using macrocycle **257b** (4.7 mg, 7.0 µmol) and



purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 30:70, v = 20 mL/min, λ = 250 nm, 35 °C, 93 bar, t(methyl ester) = 5.58 min). Colourless amorphous solid (2.0 mg, 54% over 3 steps). [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 0.8 mL/min, λ = 250 nm, 35 °C, 77 bar, t(aldehyde) = 5.67 min, t(carboxylic acid) = 2.67 min, t(methyl ester) = 6.94 min]. λ_{max}(MeCN) = 252 nm, λ_{max}(MeOH) = 249 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): δ = 7.20–7.17 (m, 1H, H-10), 6.42 (ddd, *J* = 11.6, 10.5, 1.2 Hz, 1H, H-9), 5.73 (ddd, *J* = 15.5, 7.3, 1.0 Hz, 1H, H-19), 5.71 (dd, *J* = 11.4, 7.6 Hz, 1H, H-8), 5.53 (ddd, *J* = 15.5, 7.1, 1.2 Hz, 1H, H-18), 5.39 (td, *J* = 3.1, 1.2 Hz, 1H, H-15), 4.82–4.75 (m, 1H, H-7), 4.46 (ddd, *J* = 11.6, 6.8, 3.3 Hz, 1H, H-13), 4.42 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1H, H-17), 4.33 (d, *J* = 6.9 Hz, 1H, H-12), 4.10 (dd, *J* = 8.7, 3.4 Hz, 1H, H-16), 4.09–4.05 (m, 1H, H-5), 3.99 (d, *J* = 9.0 Hz, 1H, H-2), 3.51 (s, 3H, H-25), 3.45 (dd, *J* = 7.2, 2.7 Hz, 1H, H-6), 2.58 (tdq, *J* = 7.3, 7.1 6.9 Hz, 1H, H-20), 2.42

(ddp, *J* = 11.2, 9.0, 7.0 Hz, 1H, H-3), 2.24 (ddd, *J* = 15.2, 7.3, 5.8 Hz, 1H, H-21), 2.18 (ddd, *J* = 15.0, 7.2, 5.1 Hz, 1H, H-21), 2.04–1.94 (m, 2H, H-14, H-4), 1.89 (t, *J* = 10.8, 1H, H-4), 1.79 (td, *J* = 12.2, 3.0 Hz, 1H, H-14), 0.96 (d, *J* = 6.6 Hz, 3H, H-23), 0.90 (dd, *J* = 6.8, 1.0 Hz, 3H, H-24) ppm. MS (ESIneg) *m/z* (%): 529.2 (100 (M−H)). HRMS (ESIneg): *m/z* calcd for $C_{25}H_{35}O_{10}Cl$ $[M-H]^-$: 529.1846, found: 529.1852.

Analytical and spectral data for **D_3-methyl ester 350b**: [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 86 bar, t(**273b**) = 8.50 min, t(**350b**) = 7.42 min]. $[\alpha]_D^{20}$ = −8.5 (c = 0.20, $CHCl_3$). λ_{max}(MeCN) = 247 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *δ* = 7.21–7.14 (m, 1H, H-10), 6.50 (td, *J* = 11.1, 1.2 Hz, 1H, H-9), 5.90 (ddd, *J* = 15.6, 7.1, 1.4 Hz, 1H, H-19), 5.83–5.77 (m, 2H, H-18, H-8), 4.80 (ddd, *J* = 7.4, 6.6, 1.3 Hz, 1H, H-7), 4.77 (dt, *J* = 9.4, 5.3 Hz, 1H, H-13), 4.65 (dddd, *J* = 6.6, 5.3, 1.4, 0.7 Hz, 1H, H-17), 4.39 (t, *J* = 3.7 Hz, 1H, H-15), 4.35 (d, *J* = 6.6 Hz, 1H, H-12), 4.23 (ddd, *J* = 9.8, 5.9, 2.7 Hz, 1H, H-5), 4.01 (d, *J* = 8.9 Hz, 1H, H-2), 3.87 (dd, *J* = 7.7, 3.0 Hz, 1H, H-16), 3.50 (s, 3H, H-25), 3.45 (dd, *J* = 7.2, 2.7 Hz, 1H, H-6), 2.60 (hept, *J* = 6.9 Hz, 1H, H-20), 2.25 (dd, *J* = 15.0, 7.2 Hz, 1H, H-21), 2.20–2.11 (m, 3H, H-21, H-14, H-3), 2.05 (ddd, *J* = 13.1, 6.5, 1.0 Hz, 1H, H-14), 1.98 (ddd, *J* = 11.9, 7.2, 5.9 Hz, 1H, H-4), 1.77 (ddd, *J* = 11.9, 10.7, 9.8 Hz, 1H, H-4), 1.03 (d, *J* = 6.5 Hz, 3H, H-23), 0.90 (d, *J* = 6.8 Hz, 3H, H-24). ^{13}C NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *δ* = 174.3 (C1), 173.6 (C22), 137.7 (C11), 136.4 (C8), 136.3 (C19), 129.9 (C18), 125.6 (C9), 123.8 (C10), 87.8 (C16), 84.4 (C2), 81.0 (C5), 80.7 (C13), 79.2 (C12), 76.3 (C6), 73.2 (C15), 72.2 (C17), 70.7 (C7), 51.7 (C25), 42.0 (C21), 40.7 (C3), 39.5 (C14), 37.6 (C4), 34.3 (C20), 20.5 (C24), 17.5 (C23). IR (film): $\tilde{\nu}$ = 3403, 2971, 1739, 1558, 1222, 1088, 813, 769 cm^{-1}. MS (ESIpos) *m/z* (%): 588.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{36}O_{11}ClD_3Na$: 588.2261, found: 588.2256.

Macrocycle 273c. According to General Procedure using macrocycle **257c** (2.1 mg, 3.1 µmol) and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 30:70, v = 20 mL/min, λ = 250 nm, 35 °C, 95 bar, t(methyl ester) = 5.57 min). Colourless amorphous solid (0.3 mg, 18% over 3 steps). [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeOH/H_2O = 50:50, v = 0.8 mL/min, λ = 250 nm, 35 °C, 120 bar, t(aldehyde) = 6.06 min, t(carboxylic acid) = 3.31 min, t(**273c**) = 10.74 min; YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 86 bar, t(**273c**) = 6.77 min (λ_{max}(MeCN) = 249 nm; λ_{max}(MeOH) = 249 nm), t(**350c**) = 6.21 min].

Analytical and spectral data for **methyl ester 350c**: $[\alpha]_D^{20}$ = 10.0 (c = 0.03, $CHCl_3$). ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, decomposition of **273c** by exposure to methanol): δ = 7.19–7.16 (m, 1H, H-10), 6.53 (td, *J* = 11.0, 1.2 Hz, 1H, H-9), 5.97–5.88 (m, 2H, H-19, H-8), 5.79 (ddd, *J* = 15.6, 5.3, 1.1 Hz, 1H, H-18), 4.80 (ddd, *J* = 9.1, 4.7, 1.3 Hz, 1H, H-7), 4.76 (dt, *J* = 9.3, 6.6, 6.5 Hz, 1H, H-13), 4.65–4.62 (m, 1H, H-17), 4.36 (t, *J* = 3.7 Hz, 1H, H-15), 4.33 (d, *J* = 6.5 Hz, 1H, H-12), 4.29 (dt, *J* = 9.4, 5.7 Hz, 1H, H-5), 3.97 (d, *J* = 8.1 Hz, 1H, H-2), 3.95 – 3.93 (m, 1H, H-6), 3.84 (dd, *J* = 7.7, 3.0 Hz, 1H, H-16), 3.59 (s, 3H, H-26), 3.51 (s, 3H, H-25), 2.64–2.56 (m, 1H, H-20), 2.25 (dd, *J* = 15.0, 7.2 Hz, 1H, H-21''), 2.22–2.15 (m, 3H, H-21', H-4'', H-3), 2.10 (td, *J* = 9.1, 4.7 Hz, 1H, H-14'), 2.04 (ddd, *J* = 13.2, 6.5, 1.1 Hz, 1H, H-14''), 1.68 (dt, *J* = 11.8, 9.7 Hz, 1H, H-4'), 1.02 (d, *J* = 6.4 Hz, 3H, H-23), 0.91 (d, *J* = 6.8 Hz, 3H, H-24) ppm. ^{13}C NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, decomposition by exposure to methanol): δ = 173.3 (C1), 172.6 (C22), 136.2 (C11), 135.4 (C8), 135.2 (C19), 128.8 (C18), 124.3 (C9), 122.8 (C10), 86.7 (C16), 83.0 (C2), 80.8 (C5), 79.6 (C13), 78.1 (C12), 76.6 (C6), 72.1 (C15), 71.1 (C17), 69.3 (C7), 51.2 (C26), 50.7 (C25), 40.9 (C21), 39.6 (C3), 38.5 (C14), 36.5 (C4), 33.2 (C20), 19.4 (C24), 16.9 (C23) ppm. IR (film): $\tilde{\nu}$ = 3410, 3375, 2922, 1736, 1571, 1438, 1289, 1219, 979, 807 cm^{-1}. MS (ESIpos) *m/z* (%): 585.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{39}O_{11}ClNa$: 585.2073, found: 585.2074.

Macrocycle 273d. According to General Procedure using macrocycle **257d** (1.5 mg, 3.1 µmol) and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 30:70, v = 20 mL/min, λ = 250 nm, 35 °C, 95 bar, t(methyl ester) = 6.60 min). Colourless amorphous solid (0.3 mg, 26% over 3 steps). [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeOH/H_2O = 50:50, v = 0.8 mL/min, λ = 250 nm, 35 °C, 120 bar, t(aldehyde) = 7.79 min, t(carboxylic acid) = 4.10 min, t(**273d**) = 15.67 min]. λ_{max}(MeCN) = 248 nm, λ_{max}(MeOH) = 246 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, opening of macrolactone over time): δ = 6.76 (d, *J* = 10.9 Hz, 1H, H-10), 6.30 (t, *J* = 11.1 Hz, 1H, H-9), 5.83 (dd, *J* = 15.7, 7.4 Hz, 1H, H-19), 5.60 (ddd, *J* = 11.6, 8.6, 1.0 Hz, 1H, H-8), 5.53 (ddd, *J* = 15.7, 8.7, 7.3 Hz, 1H, H-18), 5.42 (t, *J* = 3.4 Hz, 1H, H-15), 4.47 (t, *J* = 7.6 Hz, 1H, H-17), 4.29 (d, *J* = 8.7 Hz, 1H, H-12), 4.22–4.16 (m, 3H, H-16, H-13, H-7), 3.77 (d, *J* = 7.0 Hz, 1H, H-2), 3.71 (dd, *J* = 9.7, 1.6 Hz, 1H, H-6), 3.52 (s, 3H, H-25), 3.46 (dd, *J* = 8.5, 4.3 Hz, 1H, H-5), 2.58–2.52 (m, 1H, H-20), 2.21–2.16 (m, 4H, H-21, H-14, H-3), 2.01–1.97 (m, 1H, H-4), 1.87–1.83 (m, 1H, H-14), 1.42–1.38 (m, 1H, H-4), 0.92 (d, *J* = 6.6 Hz, 3H, H-23), 0.90 (d, *J* = 6.8 Hz, 3H, H-24).

Analytical and spectral data for **D_3-methyl ester 350d**: [YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 99 bar, t(**273d**) = 8.42 min, t(**350d**) = 5.77 min]. λ_{max}(MeCN) = 247 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): δ = 7.11 (d, *J* = 11.0 Hz, 1H), 6.47 (td, *J* = 11.1, 1.2 Hz, 1H), 5.94–5.86 (m, 2H), 5.78 (ddd, *J* = 15.6, 5.3, 1.2 Hz, 1H), 4.76–4.69 (m, 2H), 4.64–4.58 (m, 1H), 4.32 (d, *J* = 5.0 Hz, 1H), 4.21 (d, *J* = 6.1 Hz, 1H), 4.00 (d, *J* = 8.4 Hz, 1H), 3.77–3.71 (m, 2H), 3.51 (s, 3H), 3.46 (ddd, *J* = 8.5, 4.8, 3.5 Hz, 1H), 2.61 (hept, *J* = 7.5 Hz, 1H), 2.26 (dd, *J* = 15.0, 7.3 Hz, 1H), 2.20–2.15 (m, 2H), 2.13–2.08 (m, 1H), 2.03–1.96 (m, 1H), 1.92 (ddd, *J* = 13.5, 9.6, 4.5 Hz, 1H), 1.70 (dt, *J* = 12.1, 10.2 Hz, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 12.5 Hz, 3H). MS (ESIpos) *m/z* (%): 588.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{36}O_{11}ClD_3Na$: 588.2261, found:588.2260.

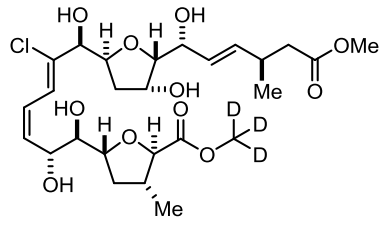
Macrocycle 351a. According to General Procedure using macrocycle **349a** (7.8 mg, 12 µmol) and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 30:70, v = 20 mL/min, λ = 250 nm, 35 °C, 95 bar, t(**352a**) = 5.44 min, t(**351a**) = 7.52 min) affording the title compound **351a** (1.7 mg, 28%) and 18-membered macrolactone **352a** (1.0 mg, 16%) as colourless amorphous solids. [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 0.8 mL/min, λ = 250 nm, 35 °C, 99 bar, t(aldehyde) = 7.69 min, t(carboxylic acid) = 2.27 min, t(**351a**) = 9.72 min; YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 105 bar, t(**353a**) = 6.27 min t(**352a**) = 6.76 min, t(**351a**) = 9.77 min].

Analytical and spectral data for **expanded macrolactone 352a**: $[\alpha]_D^{20}$ = −4.1 (c = 0.17, $CHCl_3$). λ_{max}(MeCN) = 248 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): δ = *see Table S-35;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-35*. IR (film): $\tilde{\nu}$ = 3422, 2961, 2924, 2856, 1728, 1606, 1400, 1260, 1087, 1020, 798 cm^{-1}. MS (ESIpos) *m/z* (%): 553.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found: 553.1812.

Table S-35. NMR data of expanded macrolactone **352a**; numbering scheme as shown in the insert

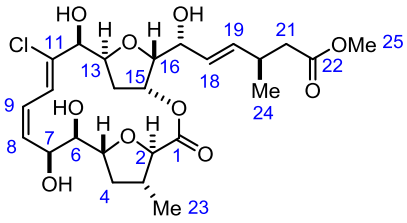
atom n°	**^{1}H NMR** (600 MHz, $CD_3OD/[D_5]$-pyridine 1:1 (v/v), referenced on CD_2HOD)					**^{13}C NMR** (151 MHz, $CD_3OD/[D_5]$-pyridine 1:1)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	172.7	17
2	4.09	d	8.1	3	23	86.5	23
3	2.42-2.37	m	-	2, 4ab, 23	2, 4a, 5, 23	39.5	2, 23
4a	2.00	ddd	12.1, 7.0, 5.7	3, 4b, 5	4b, 5, 6	38.7	23
4b	1.80	dt	11.8, 10.4	3, 4a, 5	4a, 6		
5	4.41	ddd	10.2, 5.6, 1.4	4ab	4a, 6	81.6	2, 4b
6	3.73	dd	2.3, 1.4	7	4ab, 5, 7, 8	73.7	-
7	4.81	ddd	5.5, 2.3, 1.8	6, 8	6, 8, 10	77.6	9
8	5.61	ddd	11.8, 5.5	7, 9	6, 7, 9	134.0	-
9	6.55	ddd	11.7, 11.1, 1.7	8, 10	8	125.2	-
10	7.76	d	11.0	9	7, 12	124.8	12
11	-	-	-	-	-	137.3	9, 10
12	4.18	d	7.6	13	10, 13, 14a, 16	78.2	10, 14ab
13	4.60	td	7.6, 6.0	12, 14ab	12, 14b	78.6	12, 14a
14a	2.37	dt	13.9, 6.1	13, 14b, 15	12, 14b, 15, 16	39.9	-
14b	2.20	ddd	13.9, 8.0, 1.2	13, 14a	13, 14a		
15	4.41	dd	6.1, 1.4	14a, 16	14a, 16, 17	73.6	14b
16	3.71	dd	3.3, 1.4	15	12, 14a, 15, 17	84.5	13, 14b
17	5.80	dt	7.0, 1.4	18	15, 16, 19	74.4	16, 18, 19
18	6.04	ddd	15.8, 6.9, 1.3	17, 19	-	125.5	17, 20
19	5.73	ddd	15.8, 7.1, 1.1	18, 20	17	139.4	17, 20. 21ab, 24
20	2.48	hept d	7.1, 1.2	19, 21ab, 24	21ab, 24	34.2	18, 19, 21ab, 24
21a	2.13	dd	15.1, 7.2	20	24	41.7	19, 20, 24
21b	2.06	dd	15.1, 7.3	20	20, 24		
22	-	-	-	-	-	173.4	21ab, 25
23	1.03	d	6.6	3	2, 3	17.9	2, 3
24	0.79	d	6.8	20	19, 20, 21ab	19.9	19, 20, 21ab
25	3.47	s	-	-	-	51.7	-

Analytical and spectral data for **D_3-methyl ester 353**: λ_{max}(MeCN) = 245 nm. ^{1}H NMR (600 MHz, $CD_3OD/[D_5]$-pyridine 1:1 (v/v), referenced on CD_2HOD): δ = 7.21–7.19 (m, 1H), 6.54–6.49 (m, 1H), 5.97–5.92 (m, 1H), 5.78–5.75 (m, 2H), 4.85–4.81 (m, 1H), 4.81–4.79 (m, 1H), 4.74 (ddd, *J* = 10.9, 9.2, 4.6 Hz, 1H), 4.60–4.52 (m, 2H), 4.51–4.45 (m, 1H), 4.00 (d, *J* = 8.7 Hz, 1H), 3.87 (td, *J* = 6.8, 3.1 Hz, 1H), 3.61–3.57 (m, 1H), 3.50 (s,



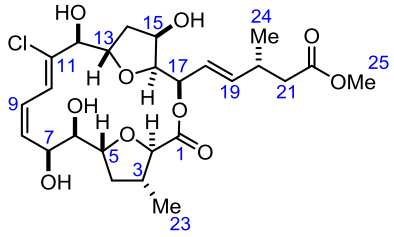
3H), 2.59 (ddd, *J* = 14.7, 11.7, 6.6 Hz, 1H), 2.26–2.20 (m, 3H), 2.16–2.11 (m, 1H), 2.03–1.97 (m, 2H), 1.67 (dt, *J* = 12.1, 10.4 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

Macrocycle 351b. According to General Procedure using macrocycle **349b** (10.0 mg, 14.8 µmol) and



purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 25:75, v = 20 mL/min, λ = 250 nm, 35 °C, 100 bar, t(**352b**) = 8.80 min, t(**351b**) = 11.92 min)) affording the title compound **351b** (2.0 mg, 25%) and 18-membered macrolactone **352b** (2.2 mg, 28%) as colourless amorphous solids. [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 0.8 mL/min, λ = 250 nm, 35 °C, 87 bar, t(aldehyde) = 6.46 min, t(carboxylic acid) = 3.12 min, t(**351b**) = 7.61 min, t(**352b**) = 5.75 min; YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 99 bar, t(**352b**) = 5.86 min, t(**351b**) = 7.67 min, t(**353b**) = 7.69 min]. Analytical and spectral data for **351b**: λ_{max}(MeCN) = 248 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, decomposition of title compound to 18-membered ring **352b** and open D_3-methyl ester **353b** over time): *δ* = 6.61 (dt, *J* = 10.1, 1.4 Hz, 1H, H-10), 6.43–6.38 (m, 1H, H-9), 5.87–5.82 (m, 2H, H-19, H-18), 5.57–5.53 (m, 2H, H-15, H-8), 4.86 (d, *J* = 1.4 Hz, 1H, H-12), 4.74 (dd, *J* = 10.2, 9.0 Hz, 1H, H-7), 4.53–4.48 (m, 2H, H- 17, H-13), 4.07 (dd, *J* = 9.5, 3.4 Hz, 1H, H-16), 4.00 (d, *J* = 7.0 Hz, 1H, H-2), 3.86 (ddd, *J* = 9.4, 6.4, 1.0 Hz, 1H, H-5), 3.51 (s, 3H, H-25), 3.39 (dd, *J* = 9.3, 1.0 Hz, 1H, H-6), 2.70–2.62 (m, 2H, H-20, H-3), 2.28 (dd, *J* = 15.0, 6.8 Hz, 1H, H-21), 2.26–2.22 (m, 1H, H-14), 2.18 (dd, *J* = 15.0, 7.6 Hz, 1H, H-21), 2.00–1.97 (m, 2H, H-4), 1.88–1.82 (m, 1H, H-14), 0.93 (d, *J* = 6.8 Hz, 3H, H-24), 0.90 (d, *J* = 6.7 Hz, 3H, H-23). ^{13}C NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, signals and asignment by 2D-spectra): *δ* = 173.4 (22), 172.7 (1), 138.3 (11), 135.7 (19), 134.3 (8), 131.5 (18), 126.1 (9), 121.5 (10), 85.5 (16), 85.4 (2), 80.5 (5), 76.9 (15), 76.6 (17), 75.2 (6), 70.1 (7), 70.0 (12), 69.5 (13), 51.4 (25), 41.8 (21), 37.3 (4), 35.1 (3), 33.9 (20), 32.4 (14), 20.2 (24), 17.3 (23) ppm. MS (ESIpos) *m/z* (%): 553.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found:553.1809.

Analytical and spectral data for **expanded macrolactone 352b**: $[\alpha]_D^{20}$ = −6.4 (c = 0.22, CH_2Cl_2).

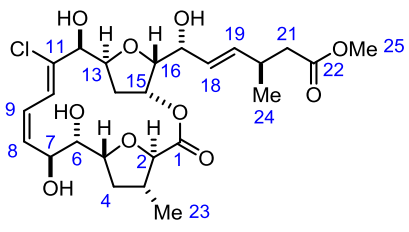


λ_{max}(MeCN) = 246 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *δ = see Table S-36;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-36*. IR (film): $\tilde{\nu}$ = 3413, 2964, 2927, 1726, 1262, 1084, 1059, 797 cm^{-1}. MS (ESIpos) *m/z* (%): 553.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found: 553.1810.

Table S-36. NMR data of expanded macrolactone **352b**; numbering scheme as shown in the insert.

atom n°	^{1}H NMR (600 MHz, $CD_3OD/[D_5]$-pyridine 1:1 (v/v), referenced on CD_2HOD)					^{13}C NMR (151 MHz, $CD_3OD/[D_5]$-pyridine 1:1)	
	δ [ppm]	m	*J* [Hz]	COSY	NOESY	δ [ppm]	HMBC
1	-	-	-	-	-	172.8	-
2	4.13	d	9.6	3	23	86.5	23
3	2.47–2.40	m	-	2, 4, 23	4, 5, 23	40.5	2, 23
4a 4b	1.93-1.99 1.93-1.99	m	-	3, 5	3, 5, 6, 23	37.7	23
5	4.20	dd	9.7, 6.5	4	3, 4, 6	80.8	-
6	3.41	d	9.2	7	4, 5, 7, 8	75.4	5, 7
7	4.89	t	9.7	6, 8	6, 8, 10	70.3	6, 9
8	5.54	ddd	11.0, 10.1, 1.0	7, 9	6, 7	135.2	-
9	6.57	td	11.1, 0.8	8, 10	-	126.8	7
10	6.79	dd	11.0, 1.0	9	7, 12	123.4	8
11	-	-	-	-	-	140.0	-
12	4.09	d	9.5	13	10, 14a, 16	77.4	10, 14ab
13	4.51	ddd	9.5, 8.0, 5.0	12, 14ab	14b	76.9	12, 15
14a 14b	2.37 2.22	ddd dd	14.1, 6.2, 5.1 14.3, 8.1	13, 14b, 15 13, 14a	12, 14b, 15 13, 14a	40.3	-
15	4.43	dd	6.1, 3.1	14a, 16	14a, 16, 17	73.6	14b
16	3.71	dd	3.1, 1.4	15	12, 15, 17	84.3	13, 14a, 15
17	5.88	dt	6.9, 1.2	18	15, 16, 19	74.3	16, 18, 19
18	6.05	ddd	15.7, 6.9, 1.3	17, 19	20, 24	125.5	16, 17, 20
19	5.71	ddd	15.5, 7.0, 1.1	18, 20	17, 20, 24	139.2	17, 20, 21ab, 24
20	2.43	hept	7.0	19, 21ab, 24	18, 19, 24	34.1	18, 19, 21ab, 24
21a 21b	2.10 2.02	dd dd	15.0, 7.1 15.1, 7.4	20, 21b 20, 21a	24 24	41.6	19, 20, 24
22	-	-	-	-	-	173.4	21ab, 25
23	1.05	d	6.5	3	2, 3, 4	16.5	2
24	0.76	d	6.8	20	18, 19, 20, 21ab	19.8	19, 20, 21ab
25	3.46	s	-	-	-	51.8	-
4xOH	5.07	s	-	-	-	-	-

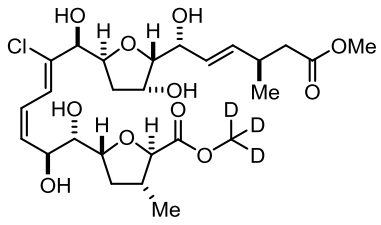
Macrocycle 351c. According to General Procedure using macrocycle **349c** (2.0 mg, 3.0 µmol) and



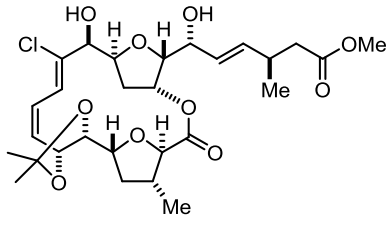
purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 25:75, v = 20 mL/min, λ = 250 nm, 35 °C, 93 bar, t(**341c**) = 8.29 min). Colourless amorphous solid (0.3 mg, 19% over 3 steps). [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 0.8 mL/min, λ = 250 nm, 35 °C, 92 bar, t(aldehyde) = 4.95 min, t(carboxylic acid) = 2.33 min; YMC-ODS-A C18,

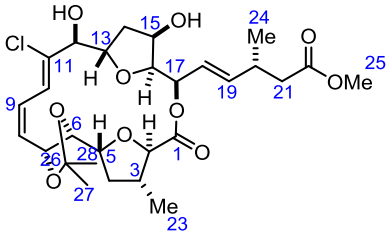
5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 96 bar, t(**352c**) = 3.48 min, t(**351c**) = 5.70 min, t(**353c**) = 6.76 min]. Analytical and spectral data for **351c**: λ_{max}(MeCN) = 247 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, decomposition of title compound **351c** to open D_3-methyl ester **353c** over time, contains **352c**: *δ* = 6.66–6.62 (m, 1H, H-10), 6.47–6.42 (m, 1H, H-9), 6.01–5.96 (m, 1H, H-8), 5.85 (dd, *J* = 15.5, 5.9 Hz, 1H, H-19), 5.82 (dd, *J* = 15.6, 4.8 Hz, 1H, H-18), 5.53 (t, *J* = 3.2 Hz, 1H, H-15), 4.91 (dd, *J* = 10.1, 1.4 Hz, 1H, H-7), 4.86 (d, *J* = 10.7 Hz, 1H, H-12), 4.56 (dt, *J* = 11.9, 3.1 Hz, 1H, H-13), 4.52 (dd, *J* = 9.3, 4.8 Hz, 1H, H-17), 4.07 (dd, *J* = 9.3, 3.4 Hz, 1H, H-16), 4.01 (d, *J* = 4.9 Hz, 1H, H-2), 3.86 (dd, *J* = 9.8, 1.8 Hz, 1H, H-6), 3.66 (dt, *J* = 9.7, 7.3 Hz, 1H, H-5), 3.51 (s, 3H, H-25), 2.65 (hept, *J* = 7.4 Hz, 1H, H-20), 2.64–2.56 (m, 2H, H-14, H-3), 2.47 (dt, *J* = 12.6, 7.2 Hz, 1H, H-4), 2.27 (dd, *J* = 15.0, 6.9 Hz, 1H, H-21), 2.17 (dd, *J* = 15.0, 7.7 Hz, 1H, H-21), 1.82 (dd, *J* = 13.1, 3.5 Hz, 1H, H-14), 1.63 (dt, *J* = 12.6, 7.4 Hz, 1H, H-4), 0.93 (d, *J* = 6.7 Hz, 3H, H-24), 0.87 (d, *J* = 6.9 Hz, 3H, H-23). MS (ESIpos) *m/z* (%): 553.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found:553.1811.

Analytical and spectral data for **D_3-methyl ester 353c**: λ_{max}(MeCN) = 246 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *δ* = 7.25 (dt, *J* = 10.9, 1.1 Hz, 1H), 6.54 (td, *J* = 11.0, 1.2 Hz, 1H), 5.94 (ddd, *J* = 11.1, 8.8, 1.1 Hz, 1H), 5.78–5.75 (m, 2H), 4.80–4.75 (m, 2H), 4.61 (t, *J* = 3.8 Hz, 1H), 4.59 (d, *J* = 4.3 Hz, 1H), 4.58–4.55 (m, 1H), 4.40 (dt, *J* = 9.7, 5.4 Hz, 1H), 4.00–3.97 (m, 2H), 3.90 (dd, *J* = 7.2, 3.1 Hz, 1H), 3.51 (s, 3H), 2.63–2.56 (m, 2H), 2.27–2.21 (m, 1H), 2.22–2.14 (m, 2H), 2.17–2.11 (m, 2H), 1.73 (dt, *J* = 12.0, 10.1 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). MS (ESIpos) *m/z* (%): 588.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{26}H_{36}O_{11}ClD_3Na$: 588.2261, found:588.2260.

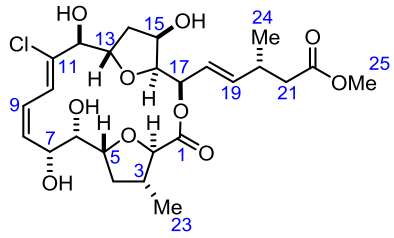


Acetonide 354. According to General Procedure using macrocycle **349d** (3.2 mg, 4.8 µmol) and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 50:50, v = 20 mL/min, λ = 250 nm, 35 °C, 77 bar, t(**355**) = 6.71 min, t(**354**) = 13.41 min) affording the 16-membered ring **354** (1.0 mg, 37%) and 18-membered macrolactone **355** (0.5 mg, 18%) as colourless amorphous solids. [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 50:50, v = 0.8 mL/min, λ = 250 nm, 35 °C, 53 bar, t(aldehyde) = 13.29 min, t(carboxylic acid) = 7.85 min, t(**354**) = 15.86 min, t(**355**) = 10.18 min; YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 50:50, v = 1.0 mL/min, λ = 250 nm, 35 °C, 86 bar, t(**355**) = 8.66 min, t(**354**) = 18.33 min].



Analytical and spectral data for **18-membered acetonide 355**: $[\alpha]_D^{20}$ = +12.0 (c = 0.05, $CHCl_3$). 

λ_{max}(MeCN) = 248 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD, ring extension of 16-membered to 18-membered ring): δ = *see Table S-37;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-37*. IR (film): $\tilde{\nu}$ = 3468, 2960, 2931, 1727, 1608, 1454, 1379, 1259, 1171, 1059, 1015, 873, 798, 760 cm^{-1}. MS (ESIpos) *m/z* (%): 593.2 (100 (M+Na)). HRMS (ESIpos): *m/z* calcd for $C_{28}H_{39}O_{10}ClNa$: 593.2124, found: 593.2125.

Expanded Macrolactone 352d. According to General Procedure using macrocycle **349d** (3.2 mg, 4.8 µmol), dimethylborobromide (0.38 mL, 40 equiv.) and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 25:75, v = 20 mL/min, λ = 250 nm, 35 °C, 90 bar, t(**352d**) = 9.67 min) affording the 18-membered macrolactone (0.6 mg, 24%), the acetonide-protected macrolactone **354** (0.4 mg, 15%) and its 18-membered analogue **355** (0.2 mg, 7%) as colourless amorphous solids. [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 30:70, v = 1.0 mL/min, λ = 250 nm, 35 °C, 97 bar, t(**352d**) = 13.27 min]. Analytical and spectral data for **352d**: $[\alpha]_D^{20}$ = +10.0 (c = 0.06, $CHCl_3$). 

λ_{max}(MeCN) = 248 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): δ = *see Table S-37;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-37*. IR (film): $\tilde{\nu}$ = 3430, 2951, 2922, 2850, 1731, 1261, 1059, 1018, 795 cm^{-1}. MS (ESIpos) m/z (%): 553.2 (100 (M+Na)). HRMS (ESIpos): m/z calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found: 553.1811.

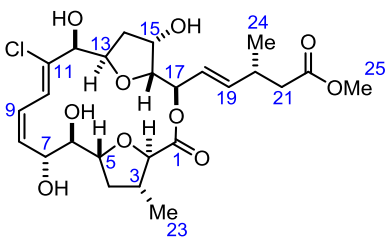
Table S-37. NMR data of 18-membered acetonide **355**; numbering scheme as shown in the insert.

atom n°	**^{1}H NMR** (600 MHz, $CD_3OD/[D_5]$-pyridine 1:1 (v/v), referenced on CD_2HOD)					**^{13}C NMR** (151 MHz, $CD_3OD/[D_5]$-pyridine 1:1)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**NOESY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	-	172.8	3, 17
2	3.99	d	6.7	3	3, 23	86.7	3, 4a, 5, 23
3	2.50	dh	8.7, 6.8	2, 4ab, 23	2, 4a, 5, 23	39.3	2, 4b, 23
4a	2.28	ddd	11.9, 7.3, 5.8	3, 4b, 5	3, 4b, 5	38.6	2, 3, 6, 23
4b	1.41	dt	11.9, 9.2	3, 4a, 5	3, 5, 6, 23		
5	4.09	ddd	9.4, 6.5, 5.7	4ab, 6	3, 4a, 6, 7, 10	81.8	2, 4b, 6, 7
6	3.72	dd	8.1, 6.5	5, 7	4b, 5, 7, 8, 27	83.1	4b, 7
7	4.71	ddd	9.3, 8.0, 1.0	6, 8	5, 6, 8, 10, 28	78.4	5, 9
8	5.64	ddd	11.0, 9.4, 1.2	7, 9	6, 7, 9	132.2	6, 10
9	6.56	td	11.0, 1.0	8, 10	8, 10	127.6	7
10	7.29	d	10.4	9	5, 7, 9, 13	123.4	8
11	-	-	-	-	-	137.6	-
12	4.29	d	3.7	13	13, 14a	79.0	10, 14ab
13	4.79	ddd	9.4, 7.1, 3.7	12, 14ab	10, 12, 14b	82.0	14a
14a	2.31	ddd	13.4, 9.4, 5.3	13, 14b, 15	12, 14b, 15, 16	38.8	14ab
14b	2.16	ddd	13.4, 7.1, 1.7	13, 14a	13, 14a, 15		
15	4.43	ddd	5.2, 3.4, 1.7	14a, 16	14ab, 16, 17	73.0	14b, 17
16	3.87	dd	3.5, 1.9	15, 17	14a, 15, 17	85.6	18
17	5.77	dt	6.8, 1.6	16, 18	15, 16	75.1	16, 18, 19
18	6.09	ddd	15.7, 6.6, 1.3	17, 19	20, 24	125.5	16, 17, 20
19	5.79	ddd	15.6, 7.0, 1.3	18, 20	20, 24	139.0	17, 21ab, 24
20	2.55	heptd	6.5, 1.2	19, 21ab, 24	18, 19, 24	34.2	18, 19, 21ab, 24
21a	2.20	dd	15.1, 7.4	20, 21b	24	41.7	19, 20, 24
21b	2.13	dd	15.2, 7.1	20, 21a	24		
22	-	-	-	-	-	173.4	20, 21ab, 25
23	1.03	d	6.7	3	2, 3, 4b	18.7	2, 3, 4b
24	0.84	d	6.8	20	18, 19, 20, 21ab	20.0	19, 20, 21ab
25	3.49	s	-	-	-	51.8	-
26	-	-	-	-	-	110.3	27, 28
27	1.31	s	-	-	6, 28	27.6	28
28	1.20	s	-	-	7, 27	27.4	27

Table S-38. NMR data of 18-membered macrolactone **352d**; numbering scheme as shown in the insert.

atom n°	**^{1}H NMR** (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD)				**^{13}C NMR** (151 MHz, CD_3OD/[D_5]-pyridine 1:1)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	172.6	17
2	4.09	d	5.9	3	86.1	4a, 23
3	2.51	ddq d	7.9, 7.5, 6.8, 5.9	2, 4ab, 23	38.8	2, 23
4a	2.37	ddd	12.1, 7.5, 6.3	3, 4b, 5	38.0	6, 23
4b	1.65	ddd	12.1, 8.9, 7.9	3, 4a, 5		
5	4.38	dt	8.9, 6.2	4ab, 6	82.7	2, 4b, 6, 7
6	3.87	t	6.2	5, 7	76.9	4b, 7
7	4.66	td	6.6, 1.4	6, 8	74.7	6, 9
8	5.83	ddd	11.7, 6.7, 1.1	7, 9	135.0	6, 7
9	6.57	ddd	11.6, 11.2, 1.4	8, 10	125.4	7
10	7.57	dd	10.9, 1.0	9	124.5	8, 12
11	-	-	-	-	137.2	9, 10, 13
12	4.22	d	6.5	13	78.8	10, 14ab
13	4.63	q	7.0	14ab	79.9	12, 14a
14a	2.34	ddd	13.7, 7.0, 5.4	13, 15	39.9	12
14b	2.22	ddd	13.7, 7.7, 1.6	13		
15	4.44	ddd	5.4, 3.5, 1.5	14a, 16	73.3	14b
16	3.80	dd	3.5, 1.7	15	84.8	13, 14b
17	5.77	dt	7.0, 1.4	18	74.8	18, 19
18	6.01	ddd	15.8, 7.1, 1.3	17, 19	125.4	17, 20
19	5.73	ddd	15.8, 7.1, 1.1	18, 20	139.4	17, 20, 21ab, 24
20	2.45–2.54	m	-	19, 21ab, 24	34.2	18, 21ab, 24
21a	2.15	dd	15.1, 7.3	20	41.7	19, 20, 24
21b	2.07	dd	15.1, 7.2	20		
22	-	-	-	-	173.4	20, 21ab, 25
23	1.06	d	6.8	3	19.2	2, 4b
24	0.79	d	6.8	20	20.0	19, 20, 21ab
25	3.47	s	-	-	51.7	-
4xOH	5.08	s	-	-	-	-

Expanded macrolactone 357. A solution of macrocycle **273** (0.4 mg, 0.8 µmol) in toluene (2.5 mL) was heated under reflux. After stirring for 268 h, the solution was cooled to ambient temperature, concentrated and purification by preparative HPLC (YMC-ODS-A C18, 5 µm, 150 × 20 mm, MeCN/H_2O = 25:75, v = 20 mL/min, λ = 250 nm, 35 °C, 90 bar, t(**273a**) = 8.34 min t(**357**) = 8.92 min) affording the title compound



(0.3 mg, 75%) as a courless amorphous solid. [Conditions for LC-MS: YMC-ODS-A C18, 5 µm, 150 × 4.6 mm, MeCN/H_2O = 25:75, v = 1.0 mL/min, λ = 250 nm, 35 °C, 102 bar, t(**273a**) = 10.66 min, t(**357**) = 11.39 min]. $[\alpha]_D^{20}$ = +230 (c = 0.03, CH_2Cl_2). λ_{max}(MeCN) = 245 nm. ^{1}H NMR (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *δ = see Table S-37;* ^{13}C NMR (151 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD): *see Table S-37*. IR (film): $\tilde{\nu}$ = 3477, 3366, 3318, 2959, 2923, 2856, 1729, 1462, 1286, 1121, 1074, 1034, 796 cm^{-1}. MS (ESIpos) m/z (%): 553.2 (100 (M+Na)). HRMS (ESIpos): m/z calcd for $C_{25}H_{35}O_{10}ClNa$: 553.1811, found: 553.1816.

Table S-39. NMR data of 18-membered macrolactone **357**; numbering scheme as shown in the insert

atom n°	**^{1}H NMR** (600 MHz, CD_3OD/[D_5]-pyridine 1:1 (v/v), referenced on CD_2HOD)				**^{13}C NMR** (151 MHz, CD_3OD/[D_5]-pyridine 1:1)	
	δ [ppm]	**m**	***J*** [Hz]	**COSY**	**δ** [ppm]	**HMBC**
1	-	-	-	-	172.9	17
2	4.00	d	6.4	3	86.7	4a, 23
3	2.46	dqt	8.2, 6.8, 6.5	2, 4ab, 23	39.3	2, 4a, 23
4a	2.16–2.21	m	-	3, 4b, 5	37.9	3, 23
4b	1.75	dt	12.0, 8.8	3, 4a, 5		
5	4.31	ddd	9.1, 6.3, 2.8	4ab, 6	83.0	2, 4b, 6
6	3.99	dd	2.8, 1.3	5, 7	78.5	-
7	4.92	dt	9.2, 1.3	6, 8	72.4	-
8	6.07	t	10.3	7, 9	134.1	7
9	6.49	td	11.2, 0.9	8, 10	124.4	7
10	7.35	d	11.3	9	121.1	-
11	-	-	-	-	137.2	9, 12
12	4.18	d	2.0	13	77.5	13
13	4.69	td	7.7, 1.7	14ab	77.3	-
14a	2.62	ddd	13.2, 7.8, 4.9	13, 14b, 15	38.3	-
14b	2.09	dd	13.2, 7.3	13, 14a		
15	4.44	dd	4.9, 2.8	14a, 16	73.4	14b
16	4.17	dd	9.0, 2.8	15, 17	86.5	13, 14b, 17
17	5.76	dd	9.1, 5.8	16	75.3	16, 18, 19
18	5.73	ddd	15.6, 5.6, 1.1	19	125.5	19, 20
19	5.82	ddd	15.5, 7.1, 0.9	18, 20	138.6	20, 21ab, 24
20	2.58	ddqd	8.0, 7.5, 6.8, 6.7	19, 21ab, 24	34.2	18, 19, 21ab, 24
21a	2.20	dd	15.2, 7.5	20	41.8	20, 24
21b	2.18	dd	15.1, 8.0	20		
22	-	-	-	-	173.4	20, 21ab, 25
23	0.97	d	6.7	3	18.8	2
24	0.87	d	6.7	20	19.9	19, 20, 21ab
25	3.49	s	-	-	51.7	-
4xOH	5.08	s	-	-	-	-

6 Glossary

Ac	acetyl
AI	artificial intelligence
acac	acetylacetonate
AIBN	azobis-*iso*-butyronitrile
aq.	aqueous
Ar	aryl
BAIB	bis-(acetoxy)iodibenzene
BEP	2-bromo-1-ethyl pyridinium tetrafluoroborate
Bn	benzyl
br	broad
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic
CBS	Corey-Bakshi-Shibata
CD	circular dichroism
cod	1,4-cycloocatadiene
conc.	concentrated
CPO	chloroperoxidase
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
dr	diastereomeric ratio
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
$(DHQD)_2PHAL$	hydroquinidine-1,4-phthalazinediyl diether
$(DHQD)_2PYR$	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIAD	diisopropyl azodicarboxylate
Dibal-H	diisobuylaluminium hydride
DMA	dimethylacetamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1-bis(diphenylphosphino)ferrocene
EDCI	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
ent	enantiomeric
epi	epimeric
equiv	equivalent(s)
Et	ethyl
exp.	experimental
g	gram

GC	gas chromatography
h	hour
h	hexett
hep	heptet
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HTS	high-throughput screening
i	*iso* (branched)
INT	intermediate
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium hexamethyldisilazide
L	liter
l.l.s.	longest linear sequence
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar
m	multiplet
Me	methyl
Mes	mesityl
mg	milligram
min	minute
mL	milliliter
MMA	methyl methacrylate
MOM	methoxymethyl
m.p.	melting point
ms	milisecond
Ms	methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
MTBE	*t*-methyl ether
µg	microgram
µL	microliter
n	*normal* (linear)
n.d.	not determined
n.r.	not reported
N	normal (mol/kg)
NCS	*N*-chloro succinimide
NHC	*N*-heterocyclic carbine
NHK	Nozaki-Hiyama-Kishi
NME	*N*-methylephedrine
NMI	*N*-methylimidazole
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
4-NO_2-Bz	4-nitrobenzoyl
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PIDA	phenyliodonium diacetate

pin	pinacol
PG	protecting group
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium-*para*-toluenesulfonate
Pr	propyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
quant	quantitative
R	arbitrary organic substituent
r.r.	regioisomeric ratio
rac	racemic
RCAM	ring-closing alkyne metathesis
RCM	ring-closing alkene metathesis
RRCM	relay ring-closing alkene metathesis
RT	room temperature
s	singlet
SAR	structure-activity-relationship
s.m.	starting material
sat.	saturated
t	triplet
TBAF	tetra-*n*-ammonium fluoride
TBAI	tetra-*n*-ammonium iodide
TBS	dimethyl-*t*-silyl
TC	thiophene-2-carboxylate
TDMPP	tris-(2,6-dimethoxyphenyl)phosphine
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMP	tetramethylpiperidine
Tol	*ortho*-tolyl
TPPO	triphenylphosphine oxide
TS	transition state
Ts	toluenesulfonyl
UV	ultraviolet
(S,S_{FC})-WalPhos	(S)-1-((S_{FC})-2-[2-(diphenylphosphino)-phenyl]-ferrocenyl)-ethylbis-[3,5-bis-(trifluoromethyl)-phenyl]phosphine

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8 Appendix

8.1 Crystallographic Data

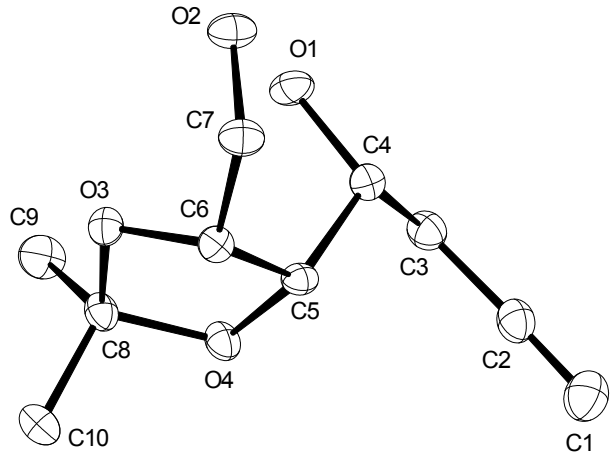


Figure S-9. Structure of *syn*-diol **299** in the solid state; hydrogen atoms have been omitted for clarity

X-ray Crystal Structure Analysis of *syn*-diol 299: C_{10} H_{16} O_4, Mr = 200.23 g · mol^{-1}, colorless, crystal size 0.380 x 0.200 x 0.180 mm^3, orthorhombic, space group $P2_12_12_1$, a = 7.8637(3) Å, b = 8.3178(3) Å, c = 16.4246(7) Å, α = 90°, β = 90°, γ = 90°, V = 1074.31(7) Å ^{3}, T = 100(2) K, Z = 4, D_{calc} = 1.238 g · cm^3, λ = 1.54178 Å, μ(Mo-Kα) = 0.791 mm^{-1}, Gaussian absorption correction (T_{min} = 0.82, T_{max} = 0.90), Bruker AXS Enraf-Nonius KappaCCD diffractometer, 5.386° < Θ < 72.139°, 33485 measured reflections, 2097 independent reflections, 2069 reflections with I > 2σ(I), R_{int} = 0.0299. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.0372 [I > 2σ(I)], wR^2 = 0.0893, 191 parameters. Three crystals were analyzed to determine chirality.

8.2 Detailed NMR Comparisons

8.2.1 *J*-Coupling Constants within the THF Moieties

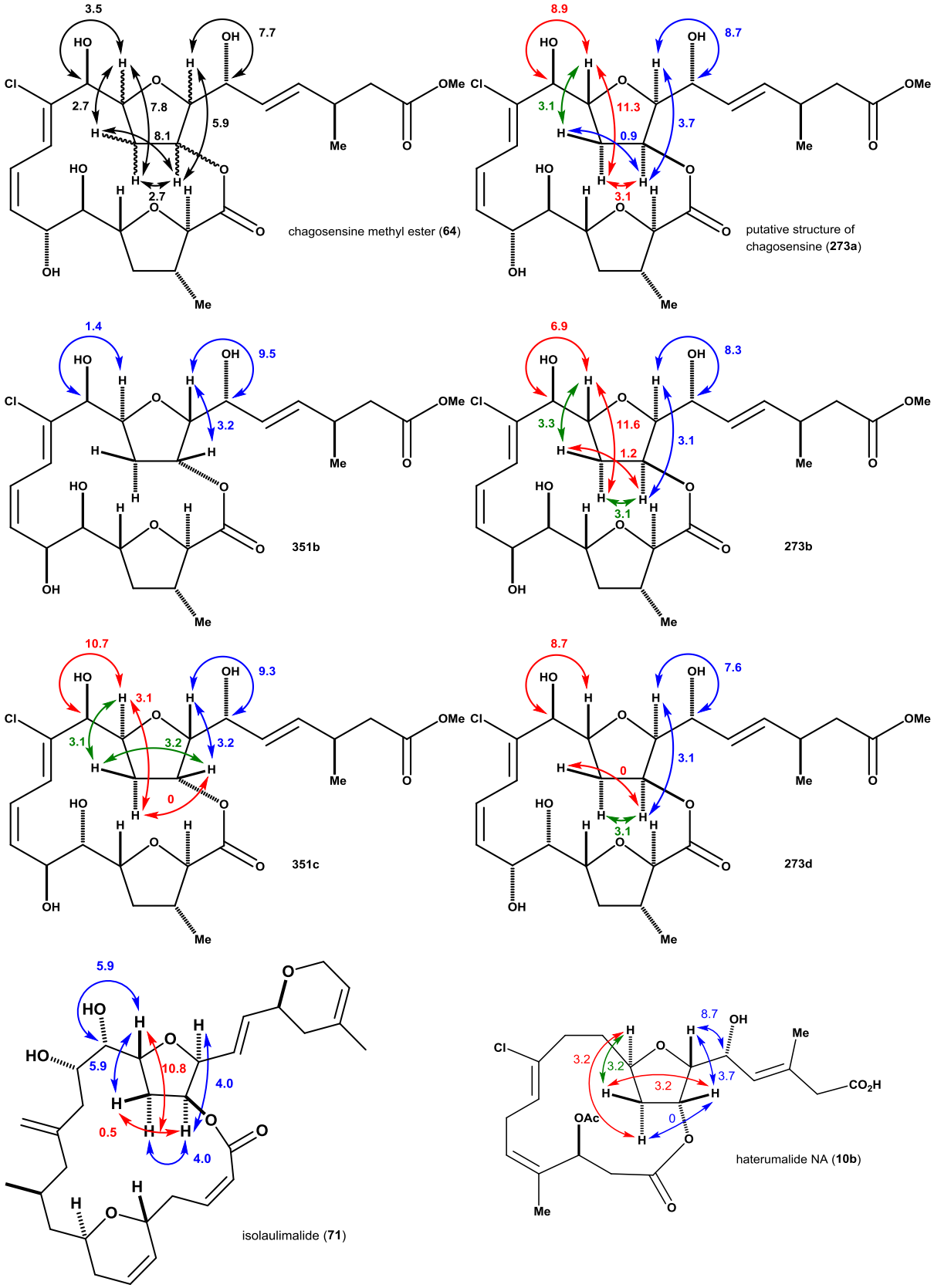


Figure S-10. Comparison of the *J*-Couplings of the northern THF-ring. Color code: ***J*** ≤ **1.0 Hz**; **1.0 < Δ*J*** < **3.0 Hz**; **Δ*J*** ≥ **3.0 Hz**.

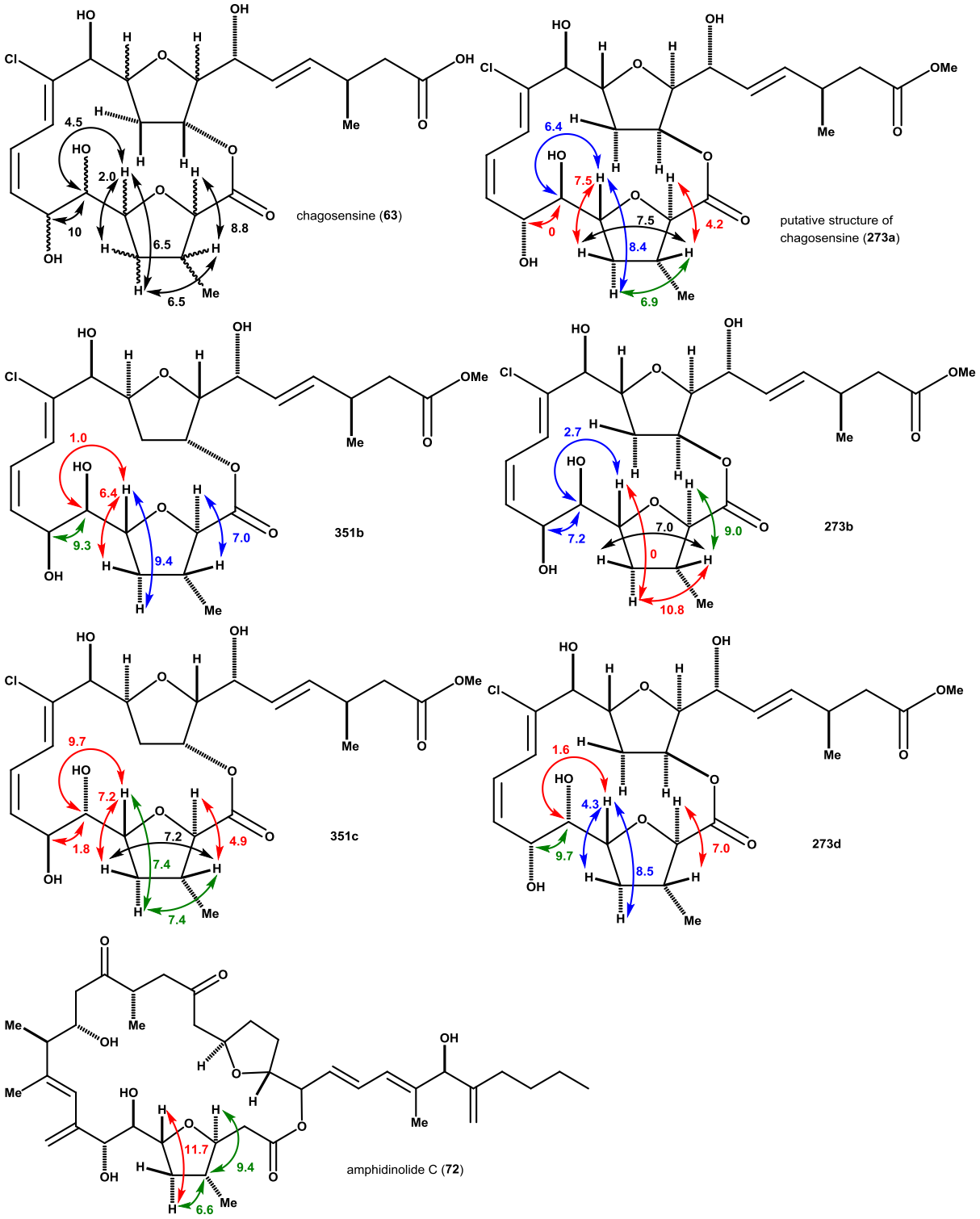


Figure S-11. Comparison of the *J*-Couplings of the southern part. Color code: $J \leq 1.0$ Hz; $1.0 < \Delta J < 3.0$ Hz; $\Delta J \geq 3.0$ Hz.

8.2.2 NOESY Cross Peaks along the Macrocyclic Framework

Comparison of chagosensine (**63**) with methyl ester of putative structure **273a**, **351b** and the protected macrocycles **257b**, **257d** and **349a-b**, **349d**, which were stable overtime.

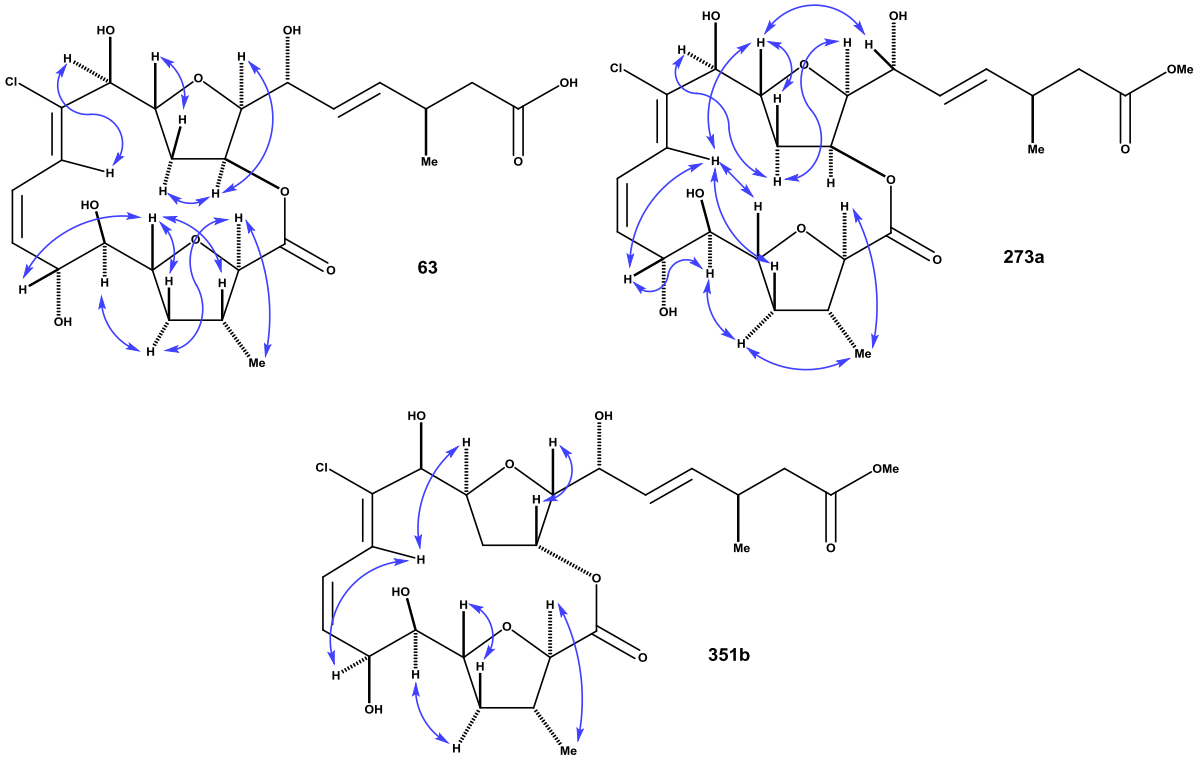


Figure S-12. Comparison of observed correlations in the isolated natural product (**63**) reported by the isolation team with NOESY correlations of putative structure (**273**) of chagosensine and preliminary NOESY data of unstable derivative **351b**.[170]

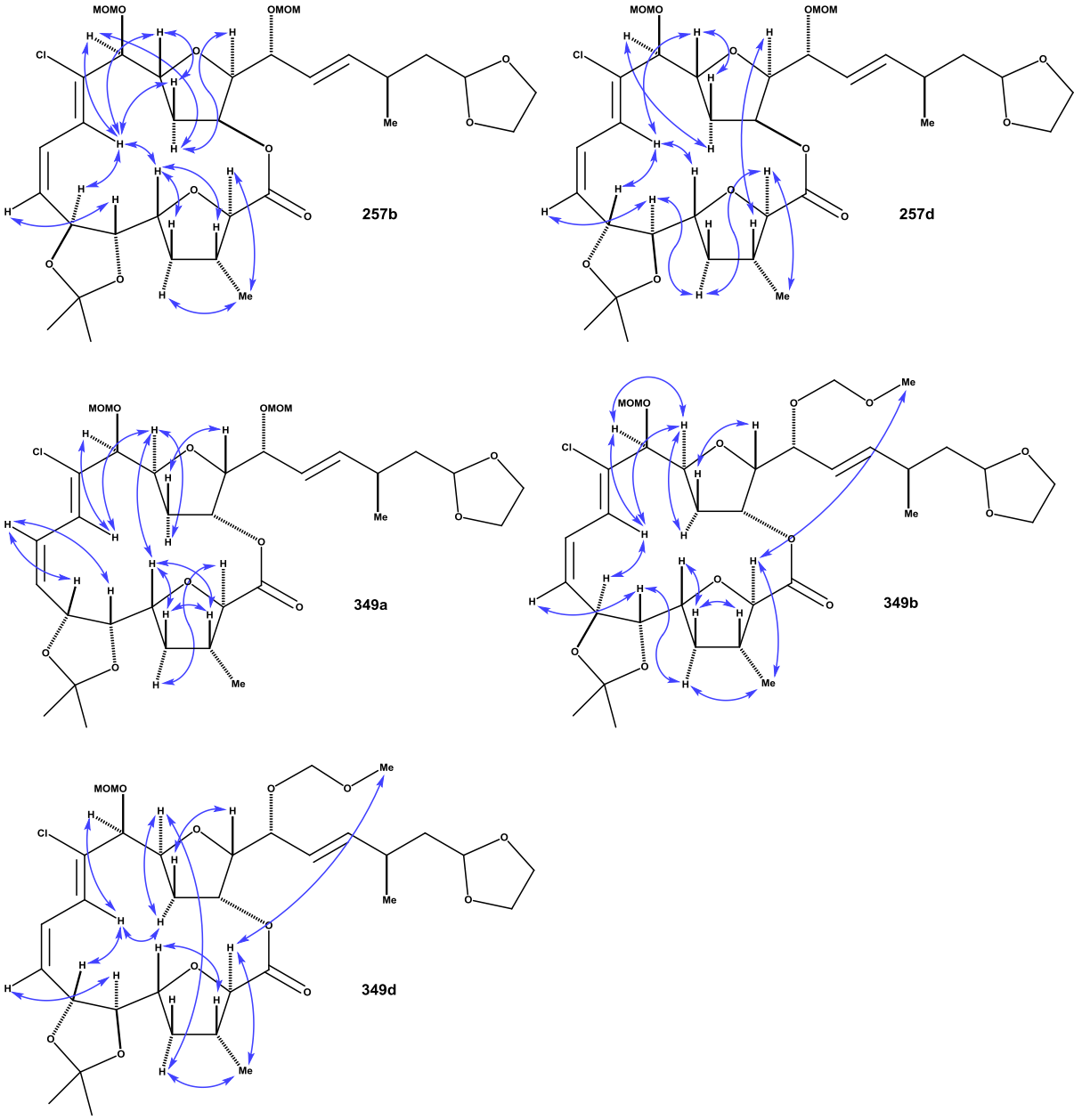
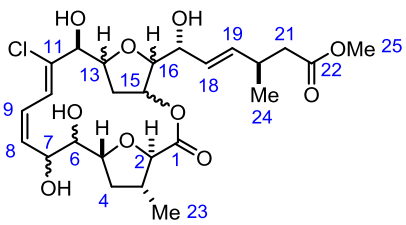


Figure S-13. NOSY correlations of stable macrolactones, which displayed rapid decomposition after global protection.

8.2.3 Detailed Analysis of ^{1}H-NMR data

Comparison of methyl ester from chagosensine (**64**) and synthesized methyl esters **273a-b**, **273d**, **351b-d**.



atom number	**isolated chagosensine methyl ester (64)**	**273a (CD_2HOD as reference)**
2	4.38 (d, $J_{(2-3)}$ = 8.8 Hz, 1H)	4.09 (d, $J_{(2-3)}$ = 4.2 Hz, 1H)
3	2.38 (m, 1 H)	2.58-2.50 (m, 2H)
4a	2.14 (dt, $J_{(4a-4b)}$ = 11.8, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 6.5 Hz, 1H)	2.22 (dt, $J_{(4a-4b)}$ = 12.3, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 7.5 Hz, 1H)
4b	1.96 (m, 1 H)	1.35 (ddd, $J_{(4b-4a)}$ = 12.3, $J_{(4b-5)}$ = 8.4, $J_{(4b-3)}$ = 6.9 Hz, 1H)
5	4.19 (ddd, $J_{(5-4a)}$ = 6.5, $J_{(5-6)}$ = 4.5, $J_{(5-4b)}$ = 2.0 Hz, 1H)	3.77 (dt, $J_{(5-4b)}$ = 8.4, $J_{(5-6)}$ = $J_{(5-4a)}$ = 6.9, 1H)
6	4.03 (dd, $J_{(6-7)}$ = 10.0, $J_{(6-5)}$ = 4.5 Hz, 1H)	4.02 (d, $J_{(6-5)}$ = 6.4 Hz, 1H)
7	4.31 (dd, $J_{(7-6)}$ = 10,0, $J_{(7-8)}$ = 8,1 Hz, 1H)	4.66 (d, $J_{(7-8)}$ = 8.7 Hz, 1H)
8	5.93 (dd, $J_{(8-9)}$ = 10.9, $J_{(8-7)}$ = 8.1 Hz, 1H)	6.07 (ddd, $J_{(8-9)}$ = 11.3, $J_{(8-7)}$ = 8.8, $J_{(8-10)}$ = 1.1 Hz, 1H)
9	6.17 (dd, $J_{(9-8)}$ = 10.9, $J_{(9-10)}$ = 7.7 Hz, 1H)	6.35 (td, $J_{(9-8)}$ = $J_{(9-10)}$ = 11.2, $J_{(9-7)}$ = 1.2 Hz, 1H)
10	6.42 (d, $J_{(10-9)}$ = 7.7 Hz, 1H)	6.93 (dd, $J_{(10-9)}$ = 10.9, $J_{(10-8)}$ = 1.2 Hz, 1H)
12	4.42 (d, $J_{(12-13)}$ = 3.5 Hz, 1H)	4.32 (d, $J_{(12-13)}$ = 8.9 Hz, 1H)
13	4.15 (ddd, $J_{(13-14b)}$ = 7.8, $J_{(13-12)}$ = 3.5, $J_{(13-14a)}$ = 2.7 Hz, 1H)	4.28 (ddd, $J_{(13-14a)}$ = 11.3 , $J_{(13-12)}$ = 9.0, $J_{(13-14b)}$ = 3.1 Hz, 1H)
14a	2.14 (dt, $J_{(14a-14b)}$ = 12.3, $J_{(14a-13)}$ = $J_{(14a-15)}$ = 2.7 Hz, 1H)	1.73 (ddd, $J_{(14a-14b)}$ = 12.7, $J_{(14a-13)}$ = 11.3, $J_{(14a-15)}$ = 3.1 Hz, 1H)
14b	1.58 (m, 1 H)	1.67 (ddd, $J_{(14b-14a)}$ = 12.8, $J_{(14b-13)}$ = 3.1, $J_{(14b-15)}$ = 0.9 Hz, 1H)
15	5.08 (ddd, $J_{(15-14b)}$ = 8.1, $J_{(15-16)}$ = 5.9, $J_{(15-14a)}$ = 2.9 Hz, 1H)	5.40 (m, 1H)
16	4.20 (dd, $J_{(16-17)}$ = 7.7, $J_{(16-15)}$ = 5.9 Hz, 1H)	4.20 (dd, $J_{(16-17)}$ = 8.7, $J_{(16-15)}$ = 3.7 Hz, 1H)
17	4.52 (dd, $J_{(17-16)}$ = 7.7, $J_{(17-18)}$ = 6.1 Hz, 1H)	4.54 (dd, $J_{(17-16)}$ = 8.7, $J_{(17-18)}$ = 6.8 Hz, 1H)
18	5.52 (dd, $J_{(18-19)}$ = 15.0, $J_{(18-17)}$ = 6.1 Hz, 1H)	5.55 (ddd, $J_{(18-19)}$ = 15.5, $J_{(18-17)}$ = 6.8, $J_{(18-20)}$ = 1.2 Hz, 1H)
19	5.71 (dd, $J_{(19-18}$) = 15.0, $J_{(19-20)}$ = 7.8 Hz, 1H)	5.60 (ddd, $J_{(19-18}$) = 15.5, $J_{(19-20)}$ = 7.3, $J_{(19-17)}$ = 1.1 Hz, 1H)
20	2.75 (m, 1H)	2.58-2.50 (m, 2H)
21a	2.33 (dd, $J_{(21a-21b)}$ = 16, $J_{(21a-20)}$ = 5 Hz, 1H)	2.18 (dd, $J_{(21a-21b)}$ = 15.1, $J_{(21a-20)}$ = 7.5 Hz, 1H)
21b	2.45 (dd, $J_{(21b-21a)}$ = 16, $J_{(21b-20)}$ = 10 Hz, 1H)	2.15 (dd, $J_{(21b-21a)}$ = 15.1, $J_{(21b-20)}$ = 6.9 Hz, 1H)
23	0.98 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)	0.83 (d, $J_{(23-3)}$ = 6.9 Hz, 3H)
24	1.08 (d, $J_{(24-20)}$ = 6.5 Hz, 3H)	0.85 (d, $J_{(24-20)}$ = 6.8 Hz, 3H)
25	3.67 (s, 3H)	3.58 (s, 3H)

atom number	**isolated chagosensine methyl ester (64)**	**273b (CD_2HOD as reference)**
2	4.38 (d, $J_{(2-3)}$ = 8.8 Hz, 1H)	3.99 (d, $J_{(2-3)}$ = 9.0 Hz, 1H)
3	2.38 (m, 1 H)	2.42 (ddp, $J_{(3-4b)}$ = 11.2, $J_{(2-3)}$ = 9.0, $J_{(3-4a)}$ = $J_{(3-23)}$ = 7.0 Hz, 1H)
4a	2.14 (dt, $J_{(4a-4b)}$ = 11.8, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 6.5 Hz, 1H)	1.99 (m, 2H)
4b	1.96 (m, 1 H)	1.89 (ddd, $J_{(4b-4a)}$ = $J_{(4b-3)}$ = 10.8, 1H)
5	4.19 (ddd, $J_{(5-4a)}$ = 6.5, $J_{(5-6)}$ = 4.5, $J_{(5-4b)}$ = 2.0 Hz, 1H)	4.09-4.05 (m, 1H)
6	4.03 (dd, $J_{(6-7)}$ = 10.0, $J_{(6-5)}$ = 4.5 Hz, 1H)	4.45 (dd, $J_{(6-7)}$ = 7.2, $J_{(6-5)}$ = 2.7 Hz, 1H)
7	4.31 (dd, $J_{(7-6)}$ = 10,0, $J_{(7-8)}$ = 8,1 Hz, 1H)	4.82-4.75 (m, 1H)
8	5.93 (dd, $J_{(8-9)}$ = 10.9, $J_{(8-7)}$ = 8.1 Hz, 1H)	5.71 (dd, $J_{(8-9)}$ = 11.4, $J_{(8-7)}$ = 7.6 Hz, 1H)
9	6.17 (dd, $J_{(9-8)}$ = 10.9, $J_{(9-10)}$ = 7.7 Hz, 1H)	6.42 (ddd, $J_{(9-8)}$ = 11.5, $J_{(9-10)}$ = 10.5 Hz, $J_{(9-7)}$ = 1.2 Hz, 1H)
10	6.42 (d, $J_{(10-9)}$ = 7.7 Hz, 1H)	7.17-7.20 (m, 1H)
12	4.42 (d, $J_{(12-13)}$ = 3.5 Hz, 1H)	4.33 (d, $J_{(12-13)}$ = 6.9 Hz, 1H)
13	4.15 (ddd, $J_{(13-14b)}$ = 7.8, $J_{(13-12)}$ = 3.5, $J_{(13-14a)}$ = 2.7 Hz, 1H)	4.46 (ddd, $J_{(13-14a)}$ = 11.6 , $J_{(13-12)}$ = 6.8, $J_{(13-14b)}$ = 3.3 Hz, 1H)
14a	2.14 (dt, $J_{(14a-14b)}$ = 12.3, $J_{(14a-13)}$ = $J_{(14a-15)}$ = 2.7 Hz, 1H)	2.04-1.94 (m, 2H)
14b	1.58 (m, 1 H)	1.79 (td, $J_{(14b-14a)}$ = $J_{(14b-13)}$ = 12.2, $J_{(14b-15)}$ = 3.0 Hz, 1H)
15*	5.08 (ddd, $J_{(15-14b)}$ = 8.1, $J_{(15-16)}$ = 5.9, $J_{(15-14a)}$ = 2.9 Hz, 1H)	5.39 (td, $J_{(15-14a)}$ = $J_{(15-16)}$ = 3.1, $J_{(15-14b)}$ = 1.2 Hz, 1H)
16	4.20 (dd, $J_{(16-17)}$ = 7.7, $J_{(16-15)}$ = 5.9 Hz, 1H)	4.10 (dd, $J_{(16-17)}$ = 8.7, $J_{(16-15)}$ = 3.4 Hz, 1H)
17	4.52 (dd, $J_{(17-16)}$ = 7.7, $J_{(17-18)}$ = 6.1 Hz, 1H)	4.42 (ddd, $J_{(17-16)}$ = 8.3, $J_{(17-18)}$ = 7.1, $J_{(17-18)}$ = 1.0 Hz, 1H)
18	5.52 (dd, $J_{(18-19)}$ = 15.0, $J_{(18-17)}$ = 6.1 Hz, 1H)	5.53 (ddd, $J_{(18-19)}$ = 15.5, $J_{(18-17)}$ = 7.1, $J_{(18-20)}$ = 1.2 Hz, 1H)
19	5.71 (dd, $J_{(19-18}$) = 15.0, $J_{(19-20)}$ = 7.8 Hz, 1H)	5.73 (ddd, $J_{(19-18}$) = 15.5, $J_{(19-20)}$ = 7.3, $J_{(19-17)}$ = 1.0 Hz, 1H)
20	2.75 (m, 1H)	2.58 (tdq, $J_{(20-19)}$ = $J_{(20-21a)}$ = 7.3, $J_{(20-21a)}$ = 7.1, $J_{(20-24)}$ = 6.9 Hz, 1H)
21a	2.33 (dd, $J_{(21a-21b)}$ = 16, $J_{(21a-20)}$ = 5 Hz, 1H)	2.24 (dd, $J_{(21a-21b)}$ = 15.2, $J_{(21a-20)}$ = 7.3 Hz, 1H)
21b	2.45 (dd, $J_{(21b-21a)}$ = 16, $J_{(21b-20)}$ = 10 Hz, 1H)	2.18 (dd, $J_{(21b-21a)}$ = 15.2, $J_{(21b-20)}$ = 7.1 Hz, 1H)
23	0.98 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)	0.96 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)
24	1.08 (d, $J_{(24-20)}$ = 6.5 Hz, 3H)	0.90 (d, $J_{(24-20)}$ = 6.8 Hz, 3H)
25	3.67 (s, 3H)	3.51 (s, 3H)

atom number	**isolated chagosensine methyl ester (64)**	**273d (CD_2HOD as reference)**
2	4.38 (d, $J_{(2-3)}$ = 8.8 Hz, 1H)	3.77 (d, $J_{(2-3)}$ = 7.0 Hz, 1H)
3	2.38 (m, 1 H)	2.21-2.16 (m, 4H)
4a	2.14 (dt, $J_{(4a-4b)}$ = 11.8, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 6.5 Hz, 1H)	2.01-1.97 (m, 1H)
4b	1.96 (m, 1 H)	1.42-1.38 (m, 1H)
5	4.19 (ddd, $J_{(5-4a)}$ = 6.5, $J_{(5-6)}$ = 4.5, $J_{(5-4b)}$ = 2.0 Hz, 1H)	3.46 (dd, J = 8.5, J = 4.3, 1H)
6	4.03 (dd, $J_{(6-7)}$ = 10.0, $J_{(6-5)}$ = 4.5 Hz, 1H)	3.71 (dd, J = 9.7, J = 1.6 Hz, 1H)
7	4.31 (dd, $J_{(7-6)}$ = 10,0, $J_{(7-8)}$ = 8,1 Hz, 1H)	4.22-4.16 (m, 3H)
8	5.93 (dd, $J_{(8-9)}$ = 10.9, $J_{(8-7)}$ = 8.1 Hz, 1H)	5.60 (ddd, $J_{(8-9)}$ = 11.6, $J_{(8-7)}$ = 8.6, $J_{(8-10)}$ = 1.0 Hz, 1H)
9	6.17 (dd, $J_{(9-8)}$ = 10.9, $J_{(9-10)}$ = 7.7 Hz, 1H)	6.35 (t, $J_{(9-8)}$ = $J_{(9-10)}$ = 11.1, 1H)
10	6.42 (d, $J_{(10-9)}$ = 7.7 Hz, 1H)	6.76 (d, $J_{(10-9)}$ = 10.9 Hz, 1H)
12	4.42 (d, $J_{(12-13)}$ = 3.5 Hz, 1H)	4.29 (d, $J_{(12-13)}$ = 8.7 Hz, 1H)
13	4.15 (ddd, $J_{(13-14b)}$ = 7.8, $J_{(13-12)}$ = 3.5, $J_{(13-14a)}$ = 2.7 Hz, 1H)	4.22-4.16 (m, 3H)
14a	2.14 (dt, $J_{(14a-14b)}$ = 12.3, $J_{(14a-13)}$ = $J_{(14a-15)}$ = 2.7 Hz, 1H)	2.21-2.16 (m, 4H)
14b	1.58 (m, 1 H)	1.87-1.83 (m, 1H)
15	5.08 (ddd, $J_{(15-14b)}$ = 8.1, $J_{(15-16)}$ = 5.9, $J_{(15-14a)}$ = 2.9 Hz, 1H)	5.42 (t, $J_{(15-14a)}$ = $J_{(15-16)}$ = 3.1, 1H)
16	4.20 (dd, $J_{(16-17)}$ = 7.7, $J_{(16-15)}$ = 5.9 Hz, 1H)	4.22-4.16 (m, 3H)
17	4.52 (dd, $J_{(17-16)}$ = 7.7, $J_{(17-18)}$ = 6.1 Hz, 1H)	4.47 (t, $J_{(17-16)}$ = $J_{(17-18)}$ = 7.6 Hz, 1H)
18	5.52 (dd, $J_{(18-19)}$ = 15.0, $J_{(18-17)}$ = 6.1 Hz, 1H)	5.54 (ddd, $J_{(18-19)}$ = 15.7, $J_{(18-17)}$ = 7.3, $J_{(18-20)}$ = 1.3 Hz, 1H)
19	5.71 (dd, $J_{(19-18}$) = 15.0, $J_{(19-20)}$ = 7.8 Hz, 1H)	5.83 (dd, $J_{(19-18)}$ = 15.7, $J_{(19-20)}$ = 7.4, $J_{(19-17)}$ = 1.0 Hz, 1H)
20	2.75 (m, 1H)	2.58-2.50 (m, 2H)
21a	2.33 (dd, $J_{(21a-21b)}$ = 16, $J_{(21a-20)}$ = 5 Hz, 1H)	2.21-2.16 (m, 4H)
21b	2.45 (dd, $J_{(21b-21a)}$ = 16, $J_{(21b-20)}$ = 10 Hz, 1H)	2.21-2.16 (m, 4H)
23	0.98 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)	0.92 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)
24	1.08 (d, $J_{(24-20)}$ = 6.5 Hz, 3H)	0.90 (d, $J_{(24-20)}$ = 6.8 Hz, 3H)
25	3.67 (s, 3H)	3.52 (s, 3H)

atom number	**isolated chagosensine methyl ester (64)**	**351b (CD_2HOD as reference)**
2	4.38 (d, $J_{(2-3)}$ = 8.8 Hz, 1H)	4.00 (d, $J_{(2-3)}$ = 7.0 Hz, 1H)
3	2.38 (m, 1 H)	2.70-2.62 (m, 2H)
4a	2.14 (dt, $J_{(4a-4b)}$ = 11.8, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 6.5 Hz, 1H)	2.00-1.97 (m, 2H)
4b	1.96 (m, 1 H)	2.00-1.97 (m, 2H)
5	4.19 (ddd, $J_{(5-4a)}$ = 6.5, $J_{(5-6)}$ = 4.5, $J_{(5-4b)}$ = 2.0 Hz, 1H)	3.86 (ddd, $J_{(5-4)}$ = 9.4, $J_{(5-4)}$ = 6.4, $J_{(5-6)}$ = 1.0 Hz, 1H)
6	4.03 (dd, $J_{(6-7)}$ = 10.0, $J_{(6-5)}$ = 4.5 Hz, 1H)	3.39 (dd, $J_{(6-7)}$ = 9.3, $J_{(6-5)}$ = 1.0 Hz, 1H)
7	4.31 (dd, $J_{(7-6)}$ = 10,0, $J_{(7-8)}$ = 8,1 Hz, 1H)	4.74 (dd, $J_{(7-8)}$ = 10.2, $J_{(7-6)}$ = 9.0 Hz, 1H)
8	5.93 (dd, $J_{(8-9)}$ = 10.9, $J_{(8-7)}$ = 8.1 Hz, 1H)	5.57-5.53 (m, 2H)
9	6.17 (dd, $J_{(9-8)}$ = 10.9, $J_{(9-10)}$ = 7.7 Hz, 1H)	6.43-6.38 (m, 1H)
10	6.42 (d, $J_{(10-9)}$ = 7.7 Hz, 1H)	6.61 (dt, $J_{(10-9)}$ = 10.1, $J_{(10-8)}$ = $J_{(10-12)}$ = 1.4 Hz, 1H)
12	4.42 (d, $J_{(12-13)}$ = 3.5 Hz, 1H)	4.86 (d, $J_{(12-10)}$ = 1.4 Hz, 1H)
13	4.15 (ddd, $J_{(13-14b)}$ = 7.8, $J_{(13-12)}$ = 3.5, $J_{(13-14a)}$ = 2.7 Hz, 1H)	4.53-4.48 (m, 2H)
14a	2.14 (dt, $J_{(14a-14b)}$ = 12.3, $J_{(14a-13)}$ = $J_{(14a-15)}$ = 2.7 Hz, 1H)	2.26-2.22 (m, 1H)
14b	1.58 (m, 1 H)	1.88-1.82 (m, 1H)
15	5.08 (ddd, $J_{(15-14b)}$ = 8.1, $J_{(15-16)}$ = 5.9, $J_{(15-14a)}$ = 2.9 Hz, 1H)	5.57-5.53 (m, 2H)
16	4.20 (dd, $J_{(16-17)}$ = 7.7, $J_{(16-15)}$ = 5.9 Hz, 1H)	4.07 (dd, $J_{(16-17)}$ = 9.5, $J_{(16-15)}$ = 3.2 Hz, 1H)
17	4.52 (dd, $J_{(17-16)}$ = 7.7, $J_{(17-18)}$ = 6.1 Hz, 1H)	4.53-4.48 (m, 1H)
18	5.52 (dd, $J_{(18-19)}$ = 15.0, $J_{(18-17)}$ = 6.1 Hz, 1H)	5.87-5.82 (m, 1H)
19	5.71 (dd, $J_{(19-18}$) = 15.0, $J_{(19-20)}$ = 7.8 Hz, 1H)	5.87-5.82 (m, 1H)
20	2.75 (m, 1H)	2.70-2.62 (m, 2H)
21a	2.33 (dd, $J_{(21a-21b)}$ = 16, $J_{(21a-20)}$ = 5 Hz, 1H)	2.28 (dd, $J_{(21a-21b)}$ = 15.0, $J_{(21a-20)}$ = 7.7 Hz, 1H)
21b	2.45 (dd, $J_{(21b-21a)}$ = 16, $J_{(21b-20)}$ = 10 Hz, 1H)	2.18 (dd, $J_{(21b-21a)}$ = 15.0, $J_{(21b-20)}$ = 6.9 Hz, 1H)
23	0.98 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)	0.90 (d, $J_{(23-3)}$ = 6.7 Hz, 3H)
24	1.08 (d, $J_{(24-20)}$ = 6.5 Hz, 3H)	0.93 (d, $J_{(24-20)}$ = 6.7 Hz, 3H)
25	3.67 (s, 3H)	3.51 (s, 3H)

atom number	**isolated chagosensine methyl ester (64)**	**351c (CD_2HOD as reference)**
2	4.38 (d, $J_{(2-3)}$ = 8.8 Hz, 1H)	4.01 (d, $J_{(2-3)}$ = 4.9 Hz, 1H)
3	2.38 (m, 1 H)	2.64-2.56 (m, 2H)
4a	2.14 (dt, $J_{(4a-4b)}$ = 11.8, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 6.5 Hz, 1H)	2.47 (dt, $J_{(4a-4b)}$ = 12.6, $J_{(4a-3)}$ = $J_{(4a-5)}$ = 7.2 Hz, 1H)
4b	1.96 (m, 1 H)	1.63 (dt, $J_{(4b-4a)}$ = 12.6, $J_{(4b-3)}$ = $J_{(4b-5)}$ = 7.4 Hz, 1H)
5	4.19 (ddd, $J_{(5-4a)}$ = 6.5, $J_{(5-6)}$ = 4.5, $J_{(5-4b)}$ = 2.0 Hz, 1H)	3.66 (dt, $J_{(5-6)}$ = 9.7, $J_{(5-4a)}$ = $J_{(5-4b)}$ = 7.3 Hz, 1H)
6	4.03 (dd, $J_{(6-7)}$ = 10.0, $J_{(6-5)}$ = 4.5 Hz, 1H)	3.86 (dd, $J_{(6-5)}$ = 9.8, $J_{(6-7)}$ = 1.8 Hz, 1H)
7	4.31 (dd, $J_{(7-6)}$ = 10,0, $J_{(7-8)}$ = 8,1 Hz, 1H)	4.91 (dd, $J_{(7-8)}$ = 10.1, $J_{(7-6)}$ = 1.4 Hz, 1H)
8	5.93 (dd, $J_{(8-9)}$ = 10.9, $J_{(8-7)}$ = 8.1 Hz, 1H)	6.01-5.96 (m, 1H)
9	6.17 (dd, $J_{(9-8)}$ = 10.9, $J_{(9-10)}$ = 7.7 Hz, 1H)	6.47-6.42 (m, 1H)
10	6.42 (d, $J_{(10-9)}$ = 7.7 Hz, 1H)	6.66-6.62 (m, 1H)
12	4.42 (d, $J_{(12-13)}$ = 3.5 Hz, 1H)	4.86 (d, $J_{(12-13)}$ = 10.7 Hz, 1H)
13	4.15 (ddd, $J_{(13-14b)}$ = 7.8, $J_{(13-12)}$ = 3.5, $J_{(13-14a)}$ = 2.7 Hz, 1H)	4.86 (dt, $J_{(13-12)}$ = 11.9, $J_{(13-14a)}$ = $J_{(13-14b)}$ = 3.1 Hz, 1H)
14a	2.14 (dt, $J_{(14a-14b)}$ = 12.3, $J_{(14a-13)}$ = $J_{(14a-15)}$ = 2.7 Hz, 1H)	2.64-2.56 (m, 2H)
14b	1.58 (m, 1 H)	1.82 (dd, $J_{(14b-14a)}$ = 13.1, $J_{(14-13)}$ = 3.5 Hz, 1H)
15	5.08 (ddd, $J_{(15-14b)}$ = 8.1, $J_{(15-16)}$ = 5.9, $J_{(15-14a)}$ = 2.9 Hz, 1H)	5.53 (t, $J_{(15-14a)}$ = $J_{(15-16)}$ = 3.2 Hz, 1H)
16	4.20 (dd, $J_{(16-17)}$ = 7.7, $J_{(16-15)}$ = 5.9 Hz, 1H)	4.07 (dd, $J_{(16-17)}$ = 9.3, $J_{(16-15)}$ = 3.4 Hz, 1H)
17	4.52 (dd, $J_{(17-16)}$ = 7.7, $J_{(17-18)}$ = 6.1 Hz, 1H)	4.52 (dd, $J_{(17-16)}$ = 9.3, $J_{(17-18)}$ = 4.8 Hz, 1H)
18	5.52 (dd, $J_{(18-19)}$ = 15.0, $J_{(18-17)}$ = 6.1 Hz, 1H)	5.82 (dd, $J_{(18-19)}$ = 15.6, $J_{(18-17)}$ = 4.8 Hz, 1H)
19	5.71 (dd, $J_{(19-18}$) = 15.0, $J_{(19-20)}$ = 7.8 Hz, 1H)	5.85 (dd, $J_{(19-18)}$ = 15.6, $J_{(19-20)}$ = 5.9 Hz, 1H)
20	2.75 (m, 1H)	2.65 (hept, $J_{(20-19)}$ = $J_{(20-21)}$ = $J_{(20-24)}$ = 7.4 Hz, 1H)
21a	2.33 (dd, $J_{(21a-21b)}$ = 16, $J_{(21a-20)}$ = 5 Hz, 1H)	2.27 (dd, $J_{(21a-21b)}$ = 15.0, $J_{(21a-20)}$ = 6.9 Hz, 1H)
21b	2.45 (dd, $J_{(21b-21a)}$ = 16, $J_{(21b-20)}$ = 10 Hz, 1H)	2.17 (dd, $J_{(21b-21a)}$ = 15.0, $J_{(21b-20)}$ = 7.7 Hz, 1H)
23	0.98 (d, $J_{(23-3)}$ = 6.6 Hz, 3H)	0.87 (d, $J_{(23-3)}$ = 6.9 Hz, 3H)
24	1.08 (d, $J_{(24-20)}$ = 6.5 Hz, 3H)	0.93 (d, $J_{(24-20)}$ = 6.7 Hz, 3H)
25	3.67 (s, 3H)	3.51 (s, 3H)