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Totalsynthese von Callyspongiolid

Dissertation

Zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

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vorgelegt von

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Die vorliegende Arbeit entstand unter Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Januar 2015 bis Dezember 2018 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits in folgenden Beiträgen veröffentlicht:

”Synthesis and Molecular Editing of Callyspongiolide, Part 1:
The Alkyne Metathesis/*trans*-Reduction Strategy“
G. Mata, B. Wölfl, A. Fürstner, *Chem. Eur. J.* **2019**, *25*, 246-254.

“Total Synthesis of Callyspongiolide, Part 2:
The Ynoate Metathesis/*cis*-Reduction Strategy”
B. Wölfl, G. Mata, A. Fürstner, *Chem. Eur. J.* **2019**, *25*, 255-259.

Die Arbeiten erfolgten zum Teil in enger Zusammenarbeit mit Dr. Guillaume Mata (Kapitel 3). Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesem Mitarbeiter alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

1. Berichterstatter: Prof. Dr. Alois Fürstner

2. Berichterstatter: Prof. Dr. Norbert Krause

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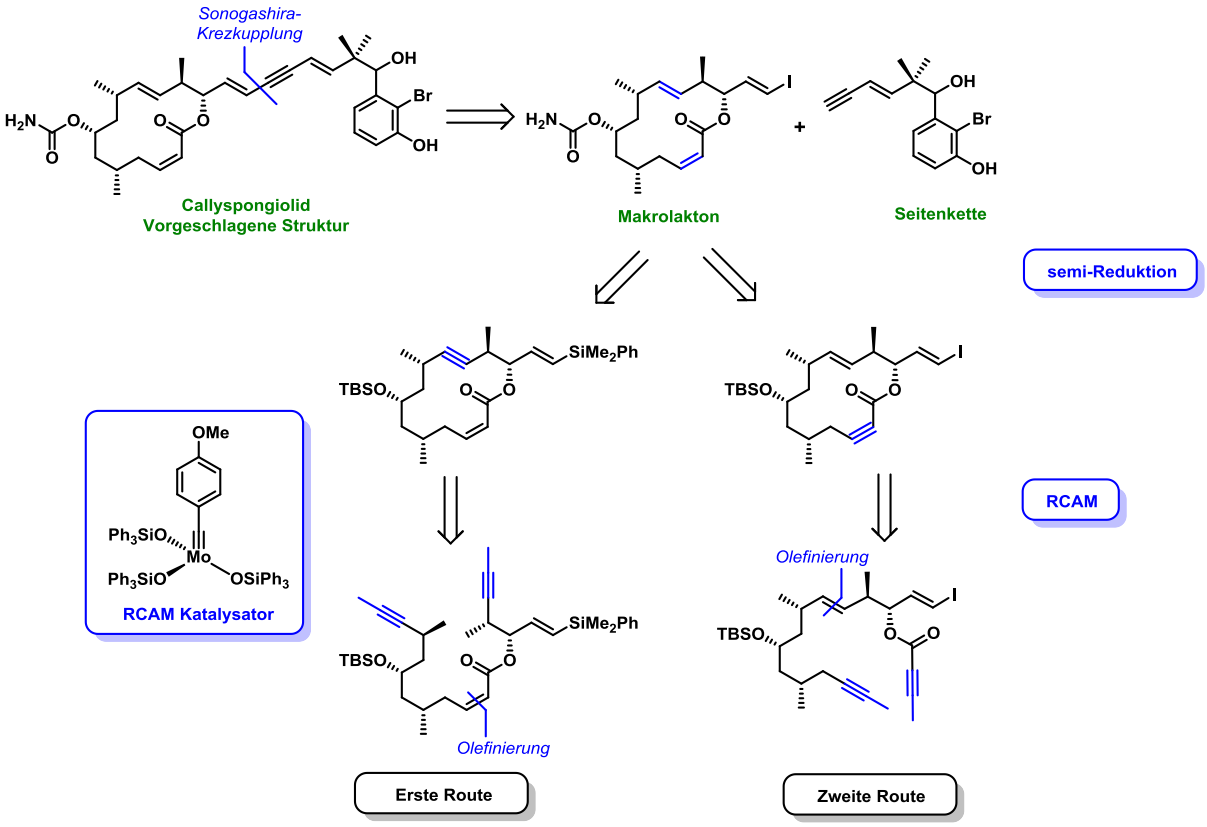
Meiner Familie

“The mind is the limit.
As long as the mind can envision the fact that you can do something,
you can do it, as long as you really believe one hundred percent.”

Arnold Schwarzenegger

Inhalt

Im Rahmen der Totalsynthese des Naturstoffs Callyspongiolid wurde der Anwendungsbereich und die Limitierungen der Ringschluss-Alkinmetathese (RCAM) und relevanter Folgechemie untersucht. Callyspongiolid wurde im Jahr 2014 aus einem marinen Schwamm isoliert, welcher zur Gattung *Callyspongia* gehörte. Dieser Makrozyklus zeigte bemerkenswerte *in vitro* Zytotoxizität an menschlichen Lymphozyten und repräsentiert somit einen potentiellen Ansatzpunkt für die Entwicklung neuer Krebsmedikamente. Der Naturstoff kombiniert diese vielversprechende biologische Aktivität mit einem einzigartigen molekularen Aufbau. Aus diesen Gründen wurde ein Totalsynthese-Projekt begonnen, welches die ursprünglich vorgeschlagene Struktur bestätigen und gleichzeitig genügend Substanz für weitere biologische Untersuchungen liefern sollte.

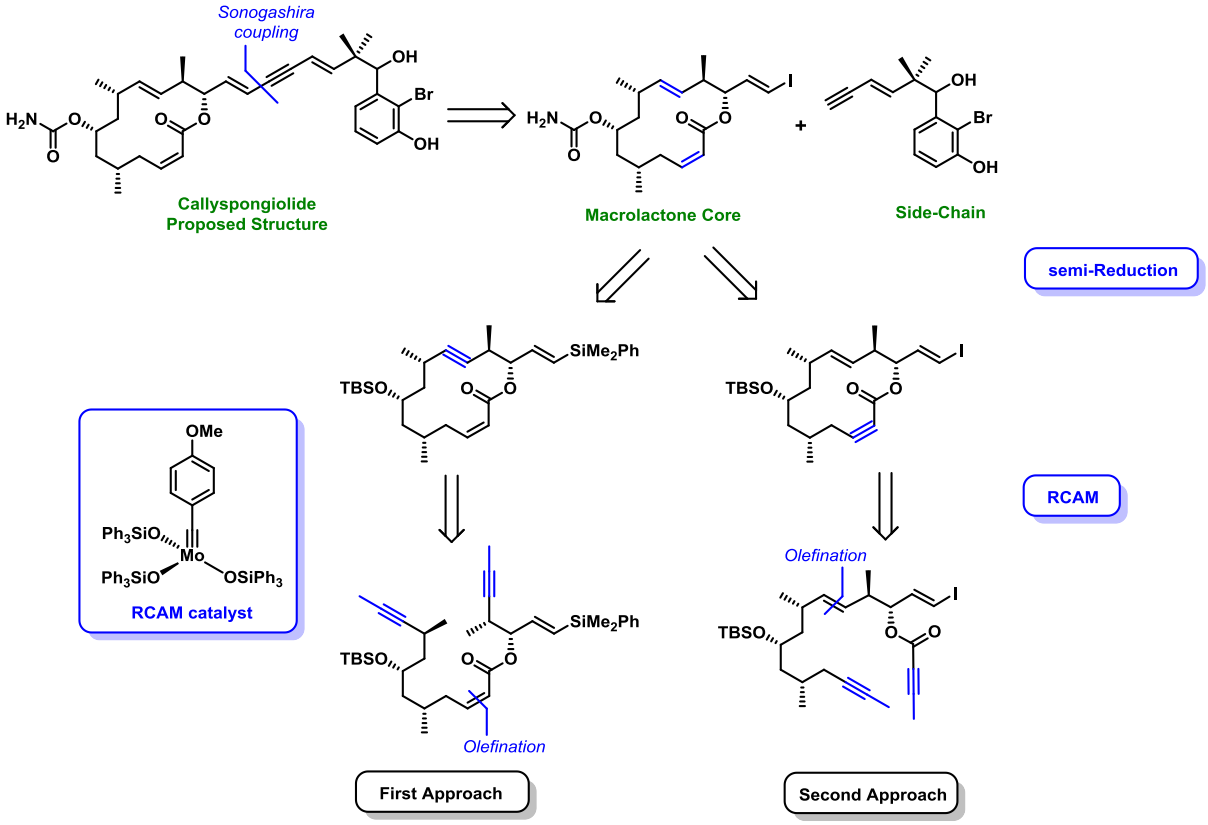


In einem ersten Anlauf zur Herstellung von Callyspongiolid wurde eine Abfolge aus *trans*-Hydrostannierung und Protodestannierung in einer späten Phase der Synthese als postmetathetische Transformation eingesetzt. Die Bestrebungen das anspruchsvolle *E*-Alken im Makrolakton durch diese formale semi-Reduktion zu etablieren, scheiterten jedoch letztendlich.

Anschließend wurde eine zweite Route, basierend auf einer RCAM eines Alkinoat-Derivats, entwickelt. Diese neue Strategie zeichnete sich jedoch durch ein gewisses Riskio aus, da nur wenige Beispiele einer solchen RCAM mit einfachen Alkinoaten in der Literatur bekannt sind. Trotz dieser anfänglichen Bedenken konnte die geplante Alkinoat-Metathese in hoher Ausbeute durchgeführt werden, was die Leistungsfähigkeit moderner Alkinmetathese-Katalysatoren besonders hervorhebt. Ein weiterer Schlüsselschritt dieser Syntheseroute war die nachfolgende *Z*-selektive semi-Reduktion des entstandenen Alkins im Makrozyklus. Dies wurde durch eine optimierte Nickelborid-katalysierte Hydrierung bewerkstelligt, welche eine effiziente Reduktion erlaubte, während Alkene und Alkenyliodide toleriert wurden. Abschließend wurde die einzigartige Enin-Seitenkette mithilfe einer Sonogashira-Kreuzkupplung installiert, wodurch die Totalsynthese von Callyspongiolid in 4 % Gesamtausbeute über 20 Schritte in der längsten linearen Sequenz vollendet wurde. Die ursprünglich vorgeschlagene Struktur von Callyspongiolid wurde während des Projekts revidiert, sodass es sich beim synthetisierten Produkt um das Enantiomer des Naturstoffs handelte. Die beschriebene Synthese stellt das erste Beispiel einer RCAM eines hochkomplexen Alkinoats dar.

Abstract

The scope and limitations of contemporary molybdenum-based ring-closing alkyne metathesis (RCAM) and relevant downstream chemistry were investigated in the context of a challenging total synthesis campaign of Callyspongiolide. This compound was isolated in 2014 from a marine sponge belonging to the genus *Callyspongia* and was found to exhibit remarkable *in vitro* cytotoxicity against human lymphocytes, thus representing a potential lead compound for the development of new anticancer agents. The natural product combines this promising biological activity with a unique molecular framework. In order to verify the originally proposed structure and provide material for further biological testing, a novel synthesis was envisioned.



In a first approach towards callyspongiolide, a sequence of late-stage *trans*-hydrostannation and protodestannation was utilized as a postmetathetic transformation to obtain the desired macrolactone core. The efforts to establish the highly challenging *E*-alkene motif in the macrocycle via this formal semi-reduction ultimately failed due to steric hindrance.

A second approach based on RCAM of an ynoate derivative was therefore developed. However, this strategy bore considerable risk as only few recorded examples of RCAM on simple ynoates exist. Despite our initial concerns, the planned ynoate metathesis could be carried out in high yield, highlighting the performance of the latest generation of molybdenum-based catalysts. Another key-step of the devised synthesis was the subsequent *Z*-selective semi-reduction of the resulting ring-internal alkyne. An optimized nickel boride-catalyzed hydrogenation ensured efficient reduction, while tolerating alkene and alkenyl iodide functionalities. Finally, the unique enyne side-chain was installed via Sonogashira reaction, concluding the efficient total synthesis of callyspongiolide in 20 steps in the longest linear sequence and 4 % overall yield. During the course of this project the structure was revised to be the enantiomer of the originally proposed motif. This total synthesis illustrates the first example of a RCAM on a highly complex ynoate.

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Total Synthesis of Callyspongiolide

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1 Introduction

The very first synthesis of a natural product was performed by Wöhler in 1828 and had a profound impact on science.[1] This event marked the beginning of the discipline of "organic synthesis" as it was the first instance in which an inorganic substance, in this case ammonium cyanate, was transformed into the organic molecule urea. It marked a significant paradigm change, as it demonstrated that the synthesis of naturally occurring products was possible by chemical means in the laboratory and not, as previously believed, only by living organisms through the so-called "vital force".[2] While urea only contains one carbon atom, Kolbe's synthesis of acetic acid in 1845[3] showcased the formation of a carbon-carbon bond.[4] The field continued to rapidly evolve and by the end of the 19th century E. Fischer's synthesis of (+)-glucose,[5] which comprises six carbons and five stereogenic centers, provided an impressive level of complexity that could be reached by chemical methods at that time.

In the following decades a myriad of complex and diverse natural products was discovered through increasingly powerful instrumentation and physical methods such as X-ray crystallography, NMR spectroscopy, mass spectrometry, and various chromatographic techniques.[4] These advances in methodology enabled synthetic chemists to engage in numerous endeavors to successfully synthesize many of the newly discovered biologically active and structurally challenging molecules.

Total synthesis campaigns attracted some of the most creative minds of the twentieth century who massively contributed to drive organic synthesis forward in terms of synthetic technologies and strategies, while also formulating new fundamental theories and concepts. Among the most outstanding accomplishments of this era are the introduction of the principles of retrosynthetic analysis by Corey[6] and the synthesis of vitamin B_{12} by the groups of Woodward and Eschenmoser.[7] This landmark collaborative synthesis of the largest and most structurally complex vitamin involved a remarkable team of 103 co-workers who participated in this project over the course of 12 years.[8]

Thanks to the efforts of synthetic chemists past and present any natural product can supposedly be replicated by chemical means given sufficient funding and time.[4] However, this does not imply total synthesis is not needed anymore today. On the contrary, this branch of organic synthesis fulfills several important roles: the discovery and development of new synthetic methods to fill in gaps in methodology; the confirmation of the molecular structure of natural products; and the synthesis of molecules for biology and medicine.[4]

Natural products are often scarce and the insufficient amounts of material isolated prevents their full and proper investigation. Therefore total synthesis campaigns are often initiated to render these rare naturally occurring molecules, and their analogues, readily available for biological investigations, especially when their properties appear promising with regard to their potential in biology and medicine.[4] Even if the natural product is readily available, the development of analogues that may not be easily accessible by conventional manipulation of the natural product itself can be highly rewarding in terms of drug development. Furthermore, total synthesis is often the final proof of structure as the isolation teams are frequently lacking material for sufficient structure elucidation.[4] These considerations also played an important part in the decision to initiate the total synthesis project described in this thesis.

As the art and science of total synthesis evolves under the influence of new methods, such as automated synthesis[9] and machine learning,[10] it will continue to help us explore and exploit the endless number of fascinating molecules still hidden in nature for the benefits of humanity.

1.1 Isolation, Structural Properties and Biological Activity

In 2014, Proksch *et al.*[11] reported the discovery of a new macrolide named callyspongiolide. It was isolated from a yellowish to reddish marine sponge belonging to the genus *Callyspongia* collected in 1996 at the coast of Ambon Island, Indonesia. The specimen was preserved in a mixture of ethanol and water (70:30) and stored at –20 °C. After a crude extract of this sponge had shown cytotoxic activity, the Proksch group used 500 g of this material for extraction and subsequent chromatographic purification furnishing 4.6 mg of the purified natural product (0.00092 % wet weight), which appeared as a light yellow amorphous solid.[11]

Comprehensive analysis by HRMS and 2D-NMR spectroscopy allowed for structure elucidation and determination of the relative configuration of the stereocenters in the macrocyclic ring (Figure 1). Thus, callyspongiolide comprises a carbamate-substituted 14-membered macrocyclic lactone containing an *E*-configured disubstitued double bond flanked by two tertiary carbons and a *Z*-alkene in α-position to the carboxylate moiety of the lactone. Notably, a unique feature of this molecule is the side-chain that incorporates a conjugated diene-yne and terminates at a brominated benzene ring, which is unprecedented among all marine macrolides reported so far.[11] The molecule contains six stereogenic centers, five embedded in the macrocyclic ring and one in the side-chain. The isolation team attempted to determine the absolute configuration of the stereocenter at C.21 by using a modified Mosher method.[12] Unfortunately, due to the steric hindrance in this position no Mosher ester could be formed.[11] Hence, the absolute stereochemistry of the natural product remained unassigned.

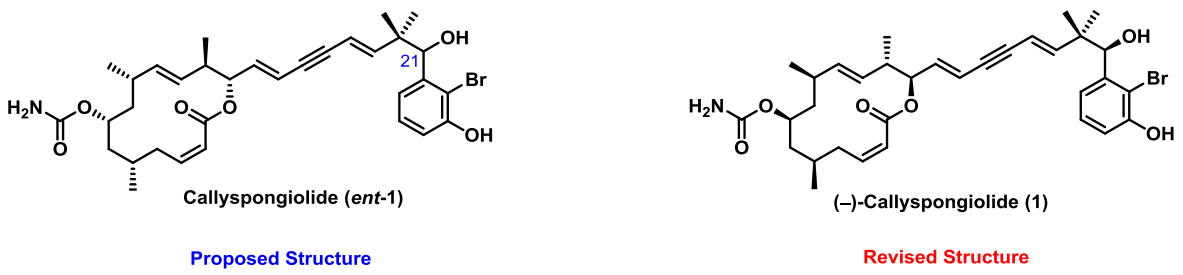


Figure 1: Originally proposed structure of callyspongiolide (left) in comparison to the revised version (right) posing as the enantiomer of the former molecule.

During the course of this thesis, total synthesis efforts by other groups revised the absolute configuration of callyspongiolide to represent structure **1**.[13] As this study had been initiated before the absolute stereochemistry of callyspongiolide was corrected, the enantiomer *ent*-**1** originally proposed by the isolation team dictated the stereochemical format of the project described herein.

Callyspongiolide was found to exhibit remarkable *in vitro* cytotoxicity against human Jurkat J16T and Ramos B lymphocytes with IC_{50} values of 70 and 60 nM respectively. Interestingly, cell death seems to be triggered by a caspase-independent pathway.[11] This implies a non-apoptotic mechanism for cell death, which makes this compound a potential lead for the development of new therapeutic strategies since apoptotic signaling is often suppressed in many cancers and one of the causes for drug resistance.[14] In conclusion, these exceptional structural and biological features render callyspongiolide a valuable target for total synthesis.

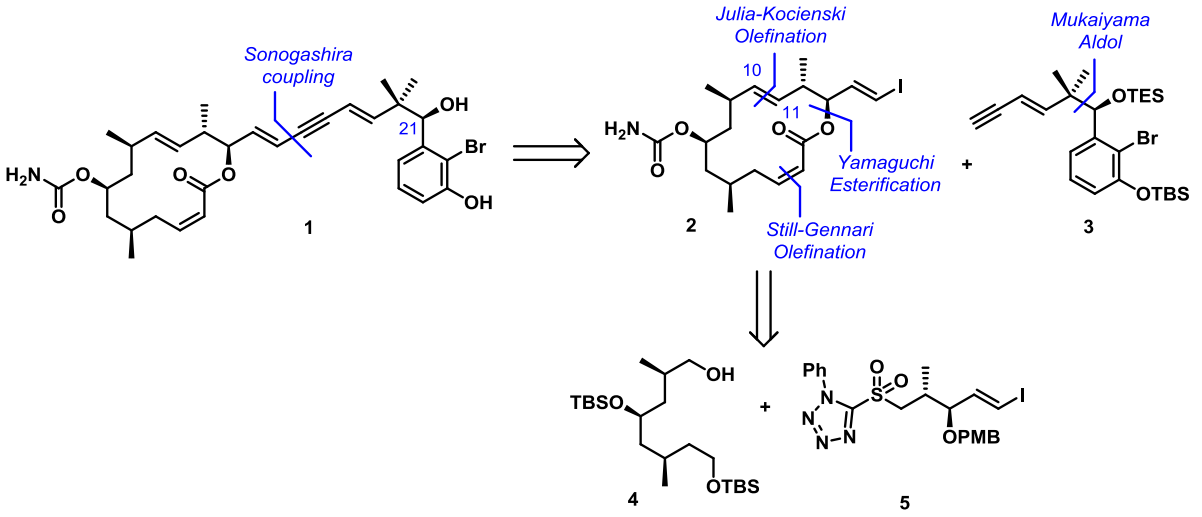
1.2 Previous Synthetic Approaches

Callyspongiolide attracted the interest of several research groups due to its interesting structural and biological features. These studies culminated in two partial[15] and four total syntheses,[13] which were published while this work was in progress. The strategies outlined in these total syntheses as well as their insights are discussed below.

The initial publication from Ye *et al.*[13a] features not only a synthetic pathway towards the structure originally assigned by the isolation team,[11] but also corrects the absolute configuration of the macrolide core and firmly established the previously unknown configuration of the C.21 chiral center in the side-chain. A biological evaluation of the synthesized compound confirmed its potent cytotoxicity in a submicromolar concentration towards some of the tested cancer cell lines, with especially pronounced inhibitory activity against Jurkat T lymphocyte cells. Notably, a synthesized epimer of the natural product, containing an inverted stereocenter at the C.21 position, even outperformed the natural isomer in terms of cytotoxicity when tested on certain cell lines.[13a]

In their strategy the final step consisted of a Sonogashira coupling[16] of macrolactone fragment **2** and side-chain fragment **3** (Scheme 1). This late stage attachment of the side-chain seems to be a common feature in all reported callyspongiolide syntheses so far. In this case, the chiral center C.21, was introduced via a variation of the Mukaiyama aldol reaction developed by Kiyooka *et al*.[17] The key-step of the synthesis was the assembly of fragments **4** and **5** via the Kocienski variant of the Julia olefination.[18] After the highly challenging *E*-alkene between C.10 and C.11 was successfully accessed, the alkenyl ester moiety was installed via Still-Gennari olefination.[19] Finally, the macrolide core **2** was prepared by Yamaguchi macrolactonization.[20]

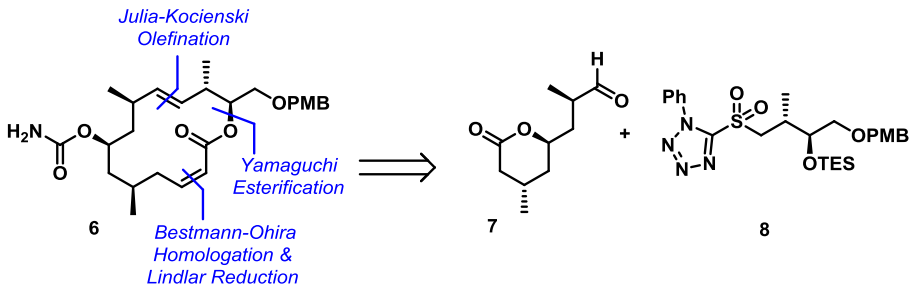
In conclusion Ye's synthesis of callyspongiolide, was completed with an overall yield of 8 % and 25 steps in the longest linear sequence from the commercial (*S*)-(–)-citronellol.[13a]



Scheme 1: Ye's strategy for the synthesis of callyspongiolide.[13a]

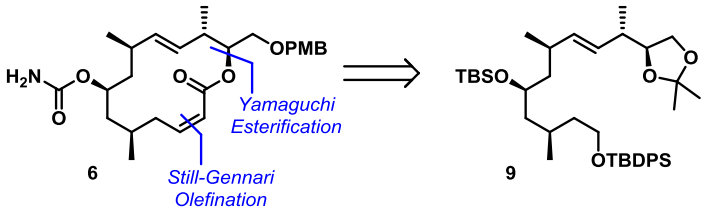
A strikingly similar strategy based on Julia-Kocienski olefination and Yamaguchi macrolactonization was independently pursued by A. K. Ghosh *et al*. (Scheme 2).[13b, 13c] However, in contrast to Ye's approach, the olefination could be optimized to improve the *E* to *Z* ratio of the resulting alkene from 6:1 to 27:1 by emloying DMF as the solvent. Furthermore the alkenyl ester functionality was not prepared via an olefination as shown in the previous example, but originated from a homologation reaction using the Bestmann-Ohira reagent.[21] The resulting terminal alkyne was subsequently acylated to give an alkynyl ester in readiness for macrolactonization. Subsequent Lindlar reduction[22] delivered the *cis*-macrolactone core fragment **6**.

Upon completion of the synthesis, callyspongiolide was furnished in 4 % overall yield and 22 steps along the longest linear sequence from literature known starting-material.[13b, 13c, 23]



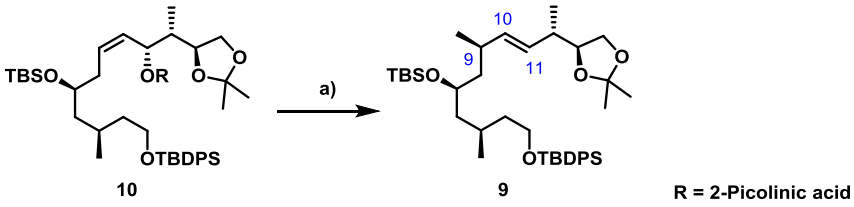
Scheme 2: A. K. Ghosh's strategy for the synthesis of callyspongiolide.[13b, 13c]

Another total synthesis of callyspongiolide was later on reported by the group of S. Ghosh *et al*. (Scheme 3).[13e] As featured in previously discussed strategies, this approach also capitalizes on the Still-Gennari olefination and Yamaguchi esterification in order to forge the macrolactone fragment **6**.



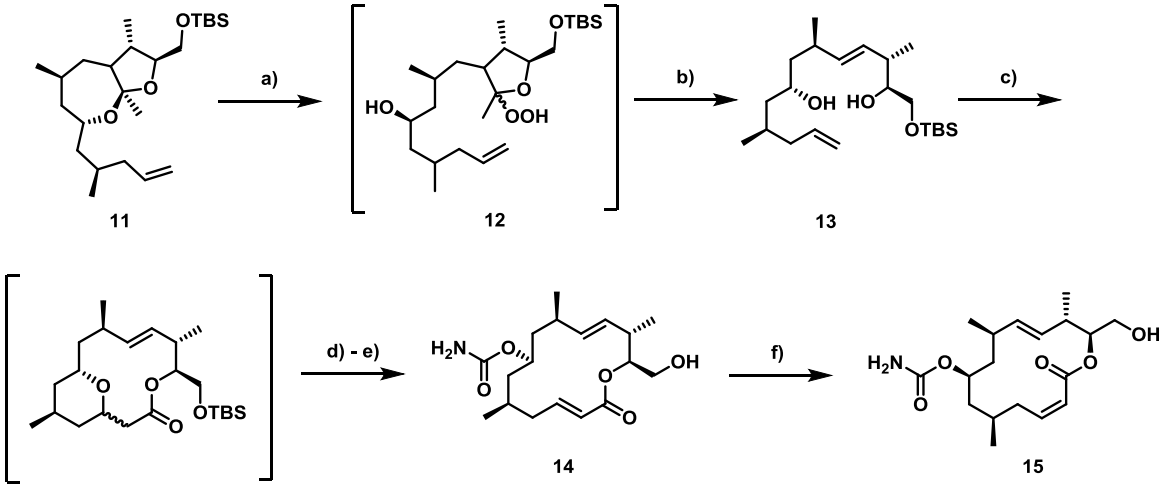
Scheme 3: S. Ghosh's strategy for the synthesis of callyspongiolide.[13e]

However, in contrast to other approaches, which relied on olefination reactions to establish the highly challenging *E*-alkene between C.10 and C.11 of the target structure, the key-step of this strategy consisted of a copper-catalyzed addition of methylmagnesium bromide on the C.9 carbon of **10** in an S_N2' fashion to form the olefin concerned (Scheme 4). This regio- and stereoselective allylic substitution produced fragment **9** in high yield. Despite these excellent results for the key-step in comparison to other olefination strategies, a major drawback of S. Ghosh's callyspongiolide synthesis is the lack of convergence of the route leading to 30 steps in the longest linear sequence and an overall yield of 1 %. It is presently the least efficient of all reported total syntheses of this natural product.



Scheme 4: Key-step of S. Ghosh's callyspongiolide synthesis. Conditions: a) $Me_2S{\cdot}CuBr$, MeMgBr, THF, –40 °C, THF, 95 %.[13e]

An unconventional approach, which targeted the macrolide core of callyspongiolide via an unusual fragment, was investigated by Harran *et al*.[13d] This strategy relied on a sequence of key-transformations of intermediate **11** to generate the desired macrolactone fragment **15**, without passing through a *seco*-acid intermediate (Scheme 5). In the initial steps of this sequence perhemiketal **12**, generated from **13** with hydrogen peroxide and catalytic PPTS, was treated with iron sulfate and copper acetate. This caused a fragmentation[24] resulting in a homoallylic acetate, which was saponified *in situ* to afford diol **13**. By using Dai's cascade variant of the Semmelhack cyclization[25] a macrolactone was furnished, which was further processed to form compound **14** as an *E,E* geometric isomer exclusively. After photoisomerization was utilized to produce fragment **15**, the side-chain was installed to complete the synthesis with an overall yield of 0.8 % and 18 steps in the longest linear sequence, which represents the lowest step-count amongst all the reported callyspongiolide syntheses to date.



Scheme 5: Key-step of Harran's callyspongiolide synthesis. Conditions: a) aq. H_2O_2, PPTS, MeCN, rt; b) $Cu(OAc)_2$, $FeSO_4 \cdot 7H_2O$, MeOH, rt, then K_2CO_3, rt, 21 % over two steps; c) $Pd(OAc)_2$ (10 mol%), $CuCl_2$, CO (1 atm), 4 Å MS, DCE, 40 °C, 65 %;d) LDA, THF, –78 °C, 73 %; e) Chlorosulfonyl isocyanate, CH_2Cl_2 then aq. THF, rt, then HF·pyridine, 90 %; f) $h\nu$ (300 nm), acetone, rt, 55 % (90 % brsm).[13d]

1.3 State of the Art

1.3.1 Ring-closing Alkyne Metathesis (RCAM)

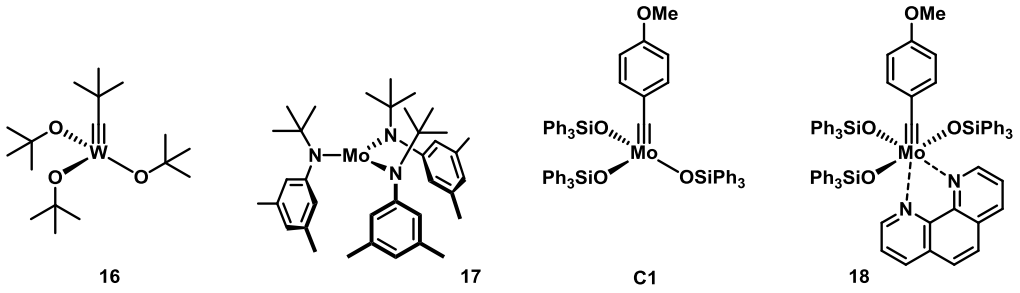
Macrocyclic structures gained increasing importance over the last decades as common strategic targets in drug discovery.[26] Thus modern organic chemistry is tasked with providing robust synthetic methods capable of producing an acceptable chemical diversity of macrocycles. However, one of the challenges associated with the exploration of the macrocyclic framework for drug discovery is the difficulty in synthesizing such structures. In fact, synthetic efforts towards macrocycles are often expensive undertakings and unpractical. The fusing of the two ends of an acyclic precursor, also known as macrocyclization, which often represents the key-step of a synthesis, is regularly plagued by low yields and often requires high dilution conditions to prevent intermolecular processes that can give oligomers and polymers.[26]

To this end, a different approach for macrocyclization, which has gained popularity in recent years, is known as ring-closing metathesis (RCM).[27] This catalytic process provides an efficient route to carbo- and heterocycles of virtually all ring sizes and has allowed access to countless biologically active macrocyclic organic molecules, even for large-scale production.[28]

Despite these merits, RCM proved to be disadvantageous when applied to certain medium-sized or macrocyclic systems.[29] The lack of control over the stereochemistry of the double bond formed in these cases often demands disproportionate effort to optimize the reaction conditions.[30] Herein, ring-closing alkyne metathesis (RCAM) followed by a stereoselective semi-reduction represents a reliable alternative. In comparison to RCM, alkyne metathesis is strictly orthogonal to olefin chemistry and therefore, ideally suited to the preparation and manipulation of polyunsaturated compounds.[31]

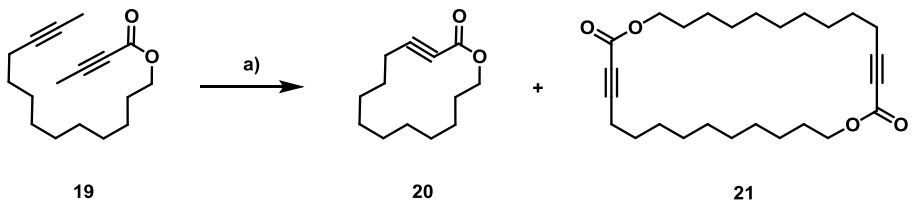
The tungsten alkylidyne complex **16**, developed by Schrock *et al*. in the early 1980s,[32] represents one of the first well-defined catalysts used for RCAM and acted as a benchmark for many years (Scheme 6).[33] However, the inherent Lewis acidity of this complex, bearing a formal 12-electron count, surfaces in many reactions and seriously limits its applicability. Thus, acid sensitive materials and substrates containing donor sites such as amines, thioethers or crown ether segments cannot be metathesized with **16**.[34]

The functional group tolerance was tremendously improved with the advent of molybdenum based RCAM catalysts. In this context, Cummins *et al.* reported the synthesis of the molybdenum complex **17** in the early 2000s.[35] This complex was found to react with dichloromethane in toluene resulting in a mixture that is capable of catalyzing numerous alkyne metathesis reactions at slightly elevated temperature with remarkable tolerance of numerous polar groups, including moderately basic amines and even divalent sulfur substituents.[34b, 36] As a consequence of this excellent profile, this mixture became the RCAM catalyst of choice for almost a decade.[31] Despite these favorable characteristics, precatalyst **17** is prone to oxidation, hydrolysis and can even react with molecular nitrogen.[37] Hence, working under argon with strict Schlenk techniques is mandatory. To overcome this impairment, Fürstner *et al.* developed molybdenum alkylidynes endowed with triarylsilanolate ligands as a more robust alternative.[31] These catalysts, such as **C1**, are highly active, exquisitely selective and can be readily prepared on multigram scale. Moreover, **C1** were rendered bench-stable upon complexation with phenantrolin furnishing complex **18**, which conveniently releases the active species, with its exquisite activity profile, on contact with metal salts.[38]



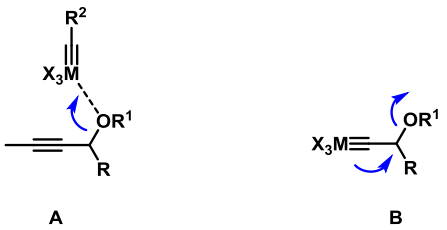
Scheme 6: Portfolio of commonly used alkyne metathesis catalysts.

The excellent functional group tolerance of Fürstner's molybdenum-based catalysts, such as **C1**, allowed for the application of RCAM to substrates containing a plethora of diverse functional groups in late stage synthesis.[31] RCAM reactions utilizing the triple bond of alkynoates would be a valuable addition to this portfolio. This appeared to be a non-trivial task, since all previous attempts to cyclize these electron-deficient systems, using tungsten alkylidine complex **16**, failed.[34a, 39] Challenged by this shortfall, Fürstner *et al.* demonstrated that catalyst **C1** could be successfully applied to ynoate metathesis.[33, 40] The few recorded examples, however, are hardly more than proof-of-concept as they led to entirely unstrained and basically unfunctionalized macrocycles. Moreover, a considerable amount of head-to-tail cyclodimer **21**, was formed as a byproduct of the formation of a 14-membered macrolactone (Scheme 7).[33]



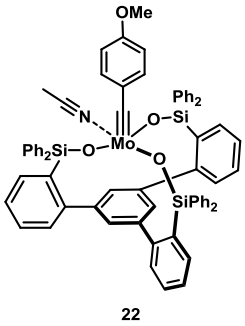
Scheme 7: Example of ynoate ring-closure. Conditions: a) **C1** (10 mol%), 5 Å MS, toluene, 80 °C, 66 % of desired product **20** and 23 % of cyclic dimer **21**.[33]

Another set of challenging substrates for RCAM are compounds comprising propargylic and bispropargylic alcohol derivatives. There are two possible decomposition pathways for metal alkylidyne complexes when encountering these kinds of substrates (Scheme 8). In the first case (see generic structure **A**), the inherent Lewis acidity of alkyne metathesis catalysts can endanger substituents in activated positions. For example: propargylic alcohols may eliminate because of the resonance stabilization of the resulting carbocation. In the latter case a **B** type alkylidyne, which can be formed during the reaction, might decompose by extrusion of the potential leaving group next to the nucleophilic site.[41] Only after the advent of complex **C1** and its congeners became RCAM with in presence of such functional groups possible. However, the number of successful examples with **C1** was still low and certain limitations persisted.[42]



Scheme 8: Possible decomposition pathways on attempted metathesis of propargylic alcohol derivatives.[41]

In order to further expand the substrate scope to encompass a broader variety of challenging substrates, such as the previously discussed propargylic and bispropargylic alcohols, a new alkyne metathesis catalyst was recently developed by Fürstner *et al.* (Figure 2).[43] The bulky tridentate silanolate ligand present in the well-defined molybdenum alkylidyne complex **22**, increased the stability of the catalyst and improved the functional group tolerance. Even substrates comprising unprotected primary alcohols could be converted in excellent yields.[43] Although the new design entails slower catalytic rates than the parent complex **C1**, this approach appears to be a promising gateway for the development of next generation alkyne metathesis catalysts.

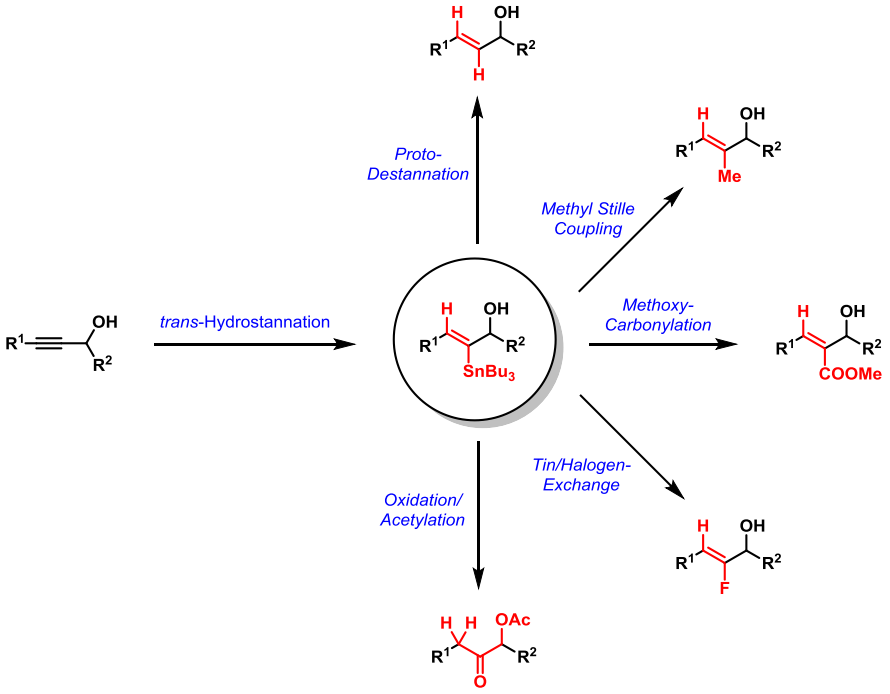


22

Figure 2: Next generation alkyne metathesis catalyst developed by Fürstner *et al*.[43]

1.3.2 Postmetathetic Transformations

As previously discussed, RCAM is a powerful method for the synthesis of macrocyclic structures was heavily featured in numerous total synthesis projects.[31] However, only in rare cases does the cyclic alkyne, formed by RCAM, constitute the actual target.[42e] Therefore it is crucial to combine alkyne metathesis with enabling downstream chemistry to cover substantial chemical space. In this context, semi-reduction of the triple bond, forming the corresponding *Z*-alkene, is among the most commonly used transformations. In contrast to the plethora of canonical *Z*-selective semi-hydrogenation reactions,[44] however, there is a disparity in the number of feasible methods to generate *E*-alkenes. Only after the advent of metal-catalyzed *trans*-addition reactions to alkynes, a number of processes with attractive application profiles have become available.[45] The discovery that pioneered this new field was a ruthenium-catalyzed *trans*-hydrosilylation, reported by Trost *et al.* in 2001.[46] This new methodology became widely used in numerous total synthesis projects,[47] due to its remarkable functional group tolerance and mild reaction conditions. In recent years Fürstner *et al.* further expanded the emerging field of ruthenium-catalyzed *trans*-hydroelementation reactions and developed new methods for *trans*-hydrogenation,[48] *trans*-hydroboration,[49] *trans*-hydrogermylation[50] and *trans*-hydrostannation.[50-51] The latter mentioned *trans*-hydrostannation is, in preparative terms, arguably the most versatile and selective of all these *trans*-addition processes.[47] These transformations are distinguished by excellent chemo- and stereoselectivity and can be controlled in regiochemical terms in many cases. The regioselectivity is particularly pronounced when the neutral complex $[Cp^*RuCl]_4$ was employed for the *trans*-hydrostannation of propargylic alcohols. In this case, the tin-moiety is placed at the site proximal to the –OH group.[50-51] In the context of total synthesis, the resulting highly decorated alkenylstannanes provide ample opportunities for further functionalization, using the rich arsenal of organotin chemistry developed in the past. Protodestannation,[42d] Stille cross-coupling,[52] methoxycarbonylation,[53] tin/halogen exchange[42d, 54] and formal oxidation of the C-Sn bond accompanied with acetylation are just some of the available transformations in the portfolio (Scheme 9).[55] This high versatility of alkenylstannanes appears to be particularly useful when applied to total synthesis, allowing not only the formation of the proper natural product, but also give the opportunity to access a variety of analogues.



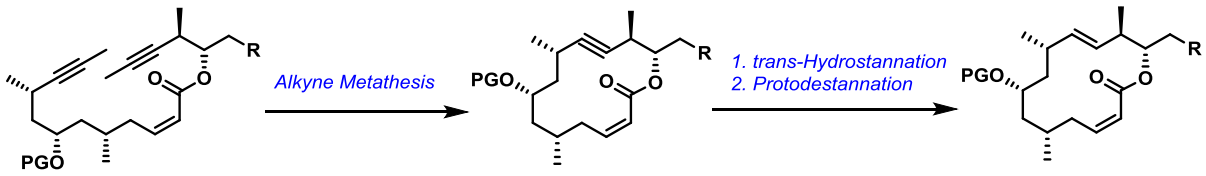
Scheme 9: Explored methods for the downstream functionalization of alkenylstannanes.[45]

For its excellent profile, RCAM in combination with *trans*-hydrostannation seems to be highly adequate for the preparation of elaborate, sensitive, and polyfunctionalized target compounds including bioactive natural products, such as the marine macrolide callyspongiolide, which will be discussed in the following chapters.

2 Objective

Callyspongiolide not only possesses unique structural features, but also displays potent biological activity.[11] In order to verify the originally proposed structure and provide material for further biological testing, a novel synthesis was envisioned.

The combination of well-established alkyne metathesis[31] with a sequence of *trans*-hydrostannation[50-51] and protodestannation enables access to *E*-alkenes in complex ring systems at late stages of total syntheses[45, 47] (Scheme 10).



Scheme 10: Envisioned key-steps of Callyspongiolide synthesis.

The implementation of this formal *trans*-reduction in the synthesis of callyspongiolide would give rise to an efficient and robust synthetic approach. Moreover, this highly convergent strategy could be easily adapted for the synthesis of analogues of the parent natural product.

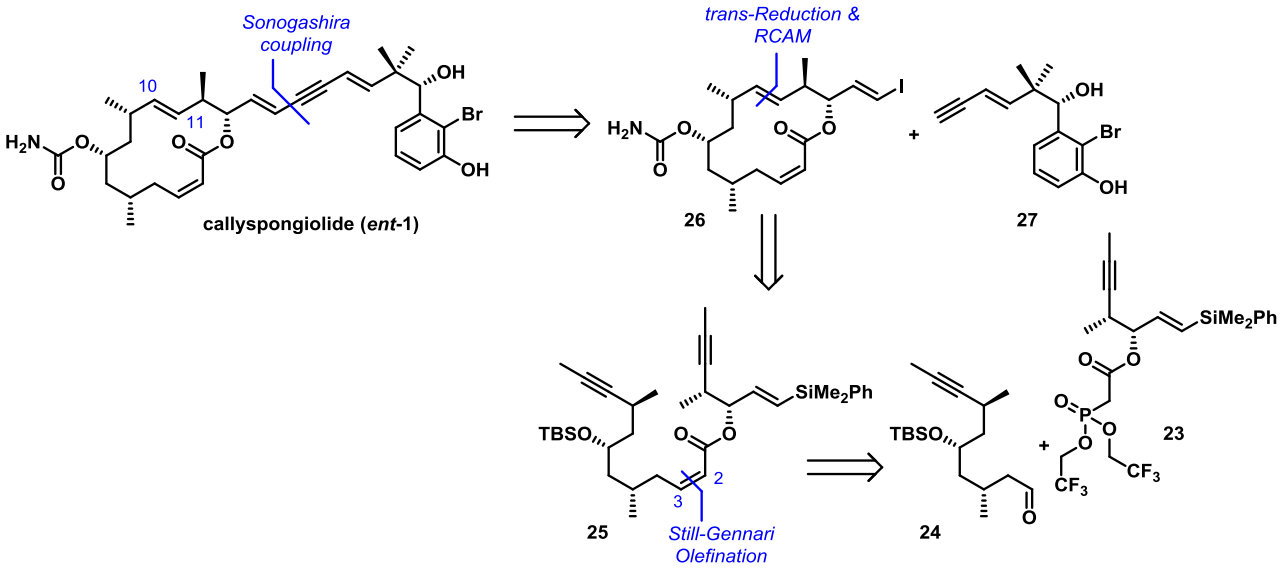
Undoubtedly the sterically demanding nature of the ring-internal *E*-alkene would be the most challenging objective and, if successful, could showcase the scope and relevancy of *trans*-hydroelementation.

3 First Synthetic Approach

3.1 Retrosynthetic Analysis

The first disconnection of the retrosynthetic analysis of callyspongiolide leads to macrolactone **26** and side-chain **27** (Scheme 11). The assembly of these fragments via Sonogashira coupling would allow for the completion of the structure in the final step, rendering the synthesis highly convergent. Focusing on the macrolactone **26**, the key-disconnection relies on a ring-closing alkyne metathesis (RCAM) followed by a formal *trans*-reduction, consisting of a sequence of *trans*-hydrostannation and protodestannation. Through combination of these methods both the otherwise difficult to access *E*-alkene between C.10 and C.11 as well as the macrolactone could be formed at an advanced stage of the synthesis.

The alkenyl iodide in fragment **26** was planned to originate from iododesilylation[56] of a alkenylsilane, which would be introduced at an earlier stage of the synthesis.



Scheme 11: Retrosynthetic analysis of callyspongiolide (*ent*-**1**) – first approach.

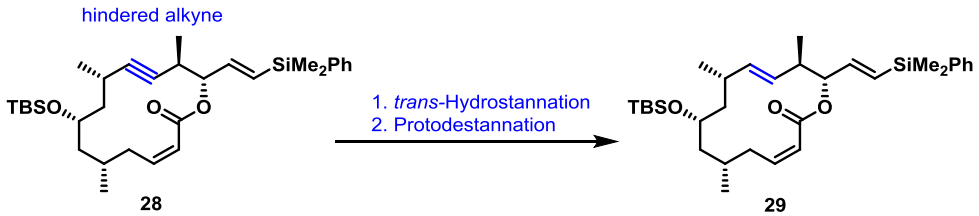
Consequently, through disconnection of fragment **25** between C.2 and C.3 at the α,β-unsaturated ester position the northern fragment **23** and the southern fragment **24** were proposed. These fragments would be coupled by the Still-Gennari modification of the Horner-Wadsworth-Emmons olefination.[19]

3.2 Preliminary Experiments

3.2.1 Model Studies

The main focus of this strategy was to employ *trans*-hydrostannation as the key-step of this synthesis. This implies the success of this route is linked to the feasibility of this methodology. However, unlike the well-established RCAM, *trans*-hydrostannation still has not yet been fully explored. Although proven to be a powerful method for the formation of *trans*-alkenes, it needs further validation as it has mostly been performed an on a small set of simple compounds, with few exceptions.[42d, 47, 50-51]

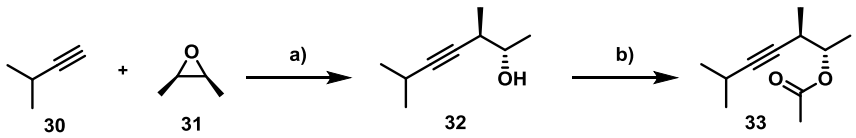
According to the retrosynthetic analysis, macrolactone **29** is supposed to originate from a sequence of *trans*-hydrostannation and protodestannation of alkyne **28** (Scheme 12). The lack of a directing group, as well as the steric demand of the alkyne prompted uncertainty regarding the chosen approach. In order to verify the viability of a late-stage *trans*-hydrostannation three model substrates were synthesized, which would mimic parts of the natural product. Upon subjection of these molecules to the aforementioned method, different aspects of the reaction such as steric hindrance, functional group tolerance and other limitations could be investigated in order to find the optimal conditions for the transformation of the desired substrate.



Scheme 12: Formal *trans*-reduction of envisioned callyspongiolide Synthesis.

3.2.2 Synthesis of a Simplified Model

The first model structure **33** could be synthesized from commercially available starting-materials in two steps and good yield (Scheme 13).[57] Despite of its limited size, both the sterically hindered alkyne as well as the ester bond in close proximity rendered this molecule structurally related to alkyne **28**, making it a relevant model to test *trans*-hydrostannation. Ester **33** was prepared and tested for *trans*-hydrostannation by Dr. Guillaume Mata.[58]



Scheme 13: Synthesis of model substrate **33**. Conditions: a) *n*BuLi, $BF_3 \cdot OEt_2$, THF, –78 °C, 83 %; b) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt, 92 %.

3.2.3 Synthesis of a Macrolactone as Model Structure

For further investigation of the *trans*-hydrostannation, focusing on macrolactones, an additional model substrate **34** was prepared (Figure 3). This model encompasses some different structural features of the target molecule **28** in comparison to the aforementioned model **33**, such as a 14-membered ring as well as an α,β-unsaturated ester bond.

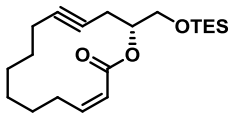
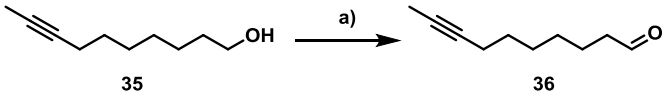


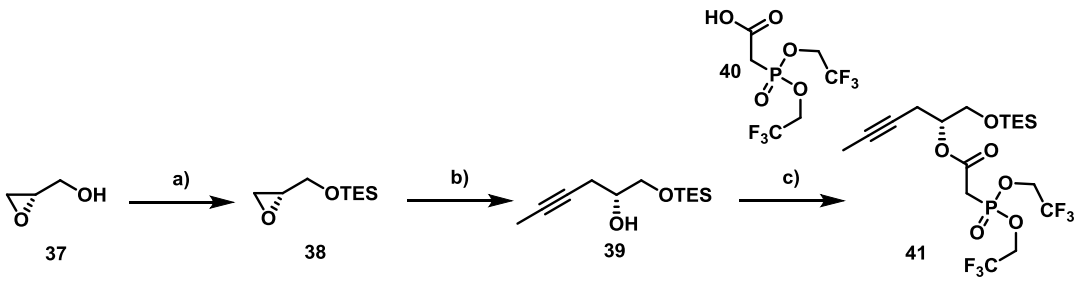
Figure 3: Structure of Macrolactone **34**, serving as an additional model substrate.

The model compound was prepared as follows: The aldehyde **36** was obtained in one step from literature known 8-decyn-1-ol[59] by oxidation with Dess-Martin periodinane (Scheme 14).



Scheme 14: Synthesis of aldehyde **36**. Conditions: a) Dess-Martin periodinane, CH_2Cl_2, rt, 75 %.

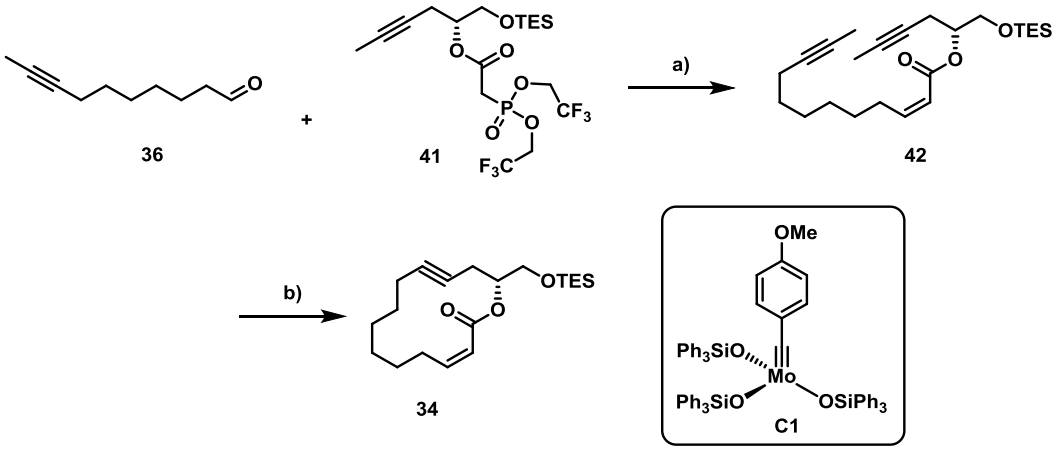
Next, commercial (*S*)-glycidol (**37**) was converted into silyl ether **38**. The subsequent epoxide opening with 1-propinyllithium in the presence of $BF_3{\cdot}Et_2O$ furnished alcohol **39** in 60 % yield on a multigram scale (Scheme 15).[60] Alcohol **39** was then joined by phosphonate **40**[61] to generate the desired precursor for the following fragment assembly.



Scheme 15: Synthesis of ester **41**. Conditions: a) Et_3SiCl, NEt_3, DMAP (cat.), CH_2Cl_2, rt, 98 %; b) 1-propinyllithium, $BF_3{\cdot}OEt_2$, THF, –78 °C, 60 %; c) phosphonate **40**, EDC, HOBt, CH_2Cl_2, rt, 76 %.

Both fragments were combined via Still-Gennari olefination (Scheme 16),[19, 62] which delivered the desired diyne **42** in 62 % yield and excellent *Z* to *E* ratio (12:1). As this reaction would also be applied for the fragment assembly in the following natural product synthesis this step was a valuable indicator for the viability of this reaction.

To complete the synthesis of the desired model substrate **34**, diyne **42** was exposed to the molybdenum alkylidyne complex **C1**,[38b] which proved to be an efficient catalyst for the synthesis of the 14-membered macrolactone **34**. Complete conversion of starting material was observed by applying 15 mol% of catalyst to the reaction, furnishing cycloalkyne **34** in 88 % yield. The addition of 5 Å MS to the reaction mixture prior to the catalyst **C1** aided in the drying of the solvent and removing 2-butyne from chemical equilibrium during the reaction. Through low substrate concentration in the reaction mixture (2 μM) the formation of dimeric or oligomeric species could be avoided, which was reaffirmed upon mass-spectrometric analysis of the product.



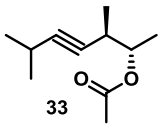
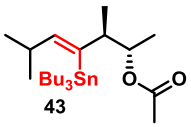
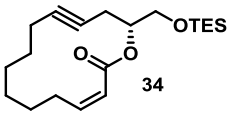
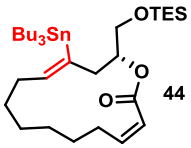
Scheme 16: Synthesis of macrolactone **34**. Conditions: a) 18-crown-6, KHMDS, THF, –78 °C, 62 % (*Z*/*E* = 12:1); b) **C1** (15 mol%), 5 Å MS, toluene, rt, 88 %.

3.2.4 *trans*-Hydrostannation of Model Substrates

With the model substrates **33** and **34** in hand the *trans*-hydrostannation catalysts **C2** and **C3** were tested under standard conditions[50-51] to validate the key-step of the envisioned total synthesis of callyspongiolide. For the sterically challenging ester **33** excellent results could be achieved by using the cationic ruthenium complex **C2** (Table 1, Entry 1). With 5 mol% catalyst loading, full conversion as well as high stereoselectivity for the *trans*-addition (>20:1), were observed.

Similar results were obtained upon subjugating macrolactone **34** to the same conditions (Entry 2), although an increase of the catalyst loading to 10 mol% had to be employed and the yield of *trans*-hydrostannation product **44** slightly decreased to 90 %. The neutral ruthenium complex **C3** was also tested in this transformation (Entry 3). However, the conversion of the substrate significantly dropped resulting in a poor yield of *trans*-hydrostannation product **44**.

Table 1: Results of *trans*-hydrostannation trials on model substrates.

Entry	Substrate	Product	Cat. (mol%)	Conv.[a]	*Z/E* [a]	α/β[a]	Yield[b]
1	 33	 43	**C2** (5)	> 95 %	> 20:1	4:1	95 %
2	 34	 44	**C2** (10)	> 95 %	> 20:1	6:1	90 %
3			**C3** (2.5)	64 %	> 20:1	7:1	52 %

[a] Conversion and ratios determined by ^{1}H NMR analysis of crude mixture.
[b] Isolated yield of mixture of regioisomers.
Only the major regioisomer is displayed.
Conditions: Catalyst **C2** or **C3**, Bu_3SnH, CH_2Cl_2, rt.

The regioselectivity of the *trans*-hydrostannation was of no importance as the tributyltin-group would be next removed via protodestannation in the total synthesis. However, interestingly both tested ruthenium complexes **C2** and **C3** gave preferably the α-alkenylstannanes **43** and **44**, featuring the tin-substituent in close proximity to the ester functionality of the structures. A possible explanation for this behavior would be the homoallylic ester moiety acting as a directing group during the course of the reaction, as it is known that in case of allylic alcohols as substrates the α-addition product can be afforded in high selectivity in combination with catalyst **C3**.[50-51]

The success of these experiments indicated that this methodology should also be applicable for the semi-reduction of the sterically demanding macrolactone **28** as the key-step in the envisioned total synthesis.

3.2.5 Synthesis of an Analogue

3.2.5.1 Diverted Total Synthesis

The previously obtained results (Table 1) however, revealed a notable catalyst dependence, as only ruthenium complex **C2** showed efficient conversion of the model substrates. If the envisioned alkyne motif **28** was not amenable to transformation via the available catalyst system, alternative approaches to the required postmetathetic reduction would be scarce.

Therefore it seemed prudent to synthesize an analogue (**45**) before the synthesis of callyspongiolide commenced. The proposed analogue **45** was lacking the methyl branches at C.9 and C.12, which reduced the steric bulk of the embedded *E*-alkene (Figure 4). Consequently this alkene would originate from a sterically less challenging ring-internal alkyne that was more likely to undergo *trans*-hydrostannation, similar to model **34**, which could be converted to the *E*-alkenylstannane (Table 1, Entry 2).

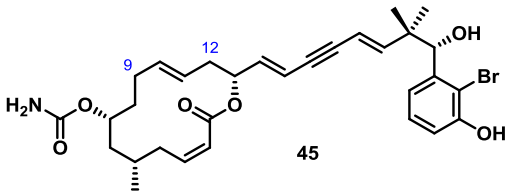
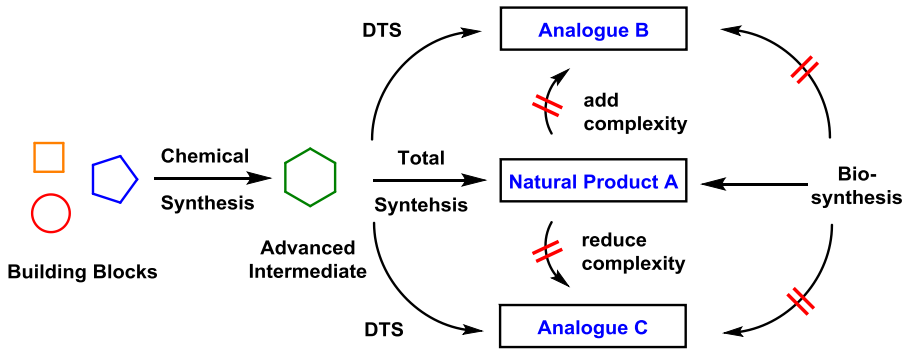


Figure 4: Designed analogue **45** of callyspongiolide (***ent*-1**).

The preparation of the analogue **45** would help to fulfill two objectives: Firstly, the intermediates of the synthesis could function as additional model substrates for the proposed total synthesis, which would allow for further investigation of the *trans*-hydrostannation on highly decorated substrates.

Secondly, the analogue designed by “molecular editing” of the natural product would be a valuable substance in biological testing, investigating if the excision of the two methyl groups compromises the biological activity. Following the logic of “diverted total synthesis” (DTS) as proposed by Danishefsky *et al.*[63] compound **45** cannot be made without excessive effort by modification of the natural product itself.

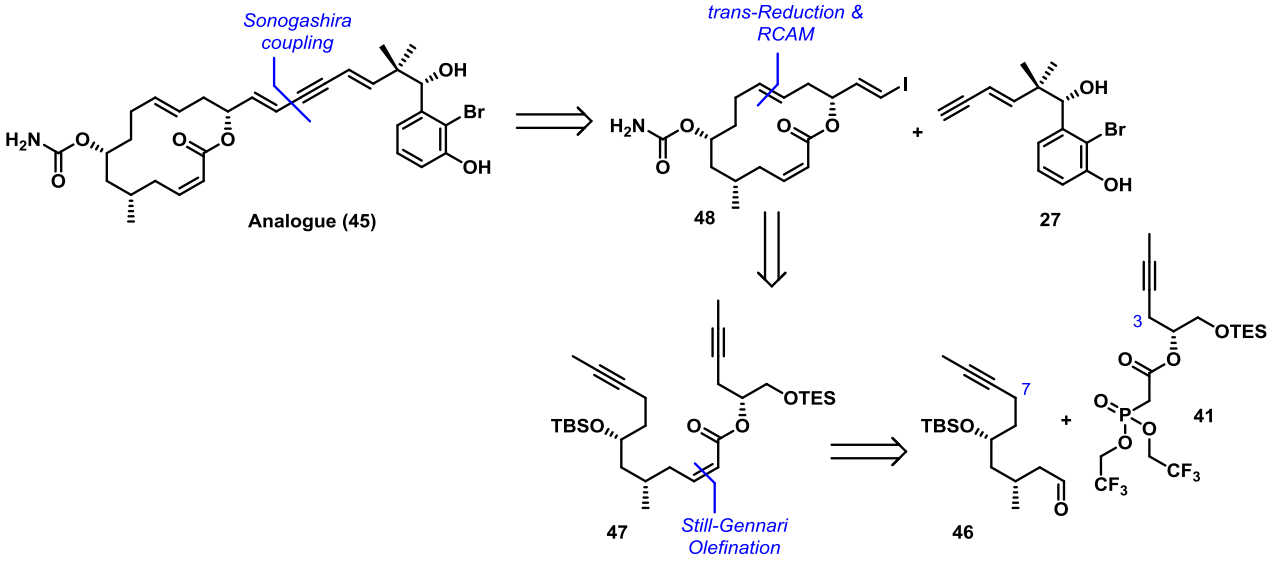
The basic assumption of this concept is that natural products themselves can be improved in terms of properties sought in the eventual drug through utilizing DTS. This means that initial building blocks can be converted to advanced intermediates, which in turn could be either pushed forward to produce natural product **A** or used to generate analogues before reaching the product itself (Scheme 17). Through introduction of a higher order of chemical complexity than found in target molecule **A** analogue **B** could be created, while a transformation of intermediates towards reduced chemical complexity would result in analogue **C**. Neither of those analogues would be possible to reach from the natural product **A** through limitations such as functional group incompatibilities or lack of feasible reactions. It may also not be possible within a reasonable time scale to manipulate the biosynthesis to harvest analogue **B** or **C**. Upon successful application of this approach any unnecessary or even undesirable structural features of natural products could be excluded resulting in analogues, accessible through feasible synthetic routes while maintaining or even improving biological activity.[63]



Scheme 17: Concept of "diverted total synthesis" (DTS) proposed by Danishefsky *et al.*[63]

3.2.5.2 Retrosynthetic Analysis

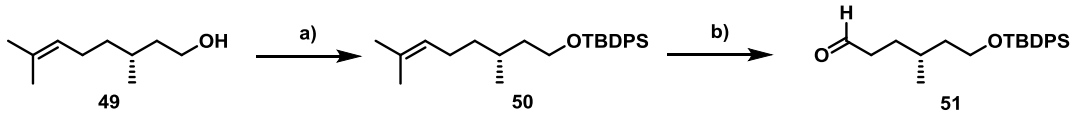
The synthesis of analogue **45** was designed in similar fashion to the previously described strategy of the first synthetic approach to callyspongiolide (see Chapter 3.1). The target molecule **45** was supposed to originate from a Sonogashira coupling of macrolactone **48** and side-chain **27** (Scheme 18), which is also a valuable intermediate in the synthesis of callyspongiolide. The macrolactone **48** would be obtained by a sequence of RCAM and formal *trans*-reduction. Diyne **47**, posing as a precursor for this reaction sequence, was planned to originate from a Still-Gennari olefination[19] of northern fragment **41** with southern fragment **46**. In contrast to the natural product synthesis, these two fragments were lacking a methyl branches next to the alkyne at position C.7 of the aldehyde **46** and C.3 of the phosphonate **41** respectively. While aldehyde **46** could be efficiently produced from an intermediate of the southern fragment **24** in the natural product synthesis, the northern fragment **41** had already been synthesized during the course of the model studies (see Chapter 3.2.3). The alkenyl iodide functionality would be introduced during the course of the endgame by Swern oxidation of the TES protected primary alcohol followed by Takai olefination.[64]



Scheme 18: Retrosynthetic analysis of analogue **45**.

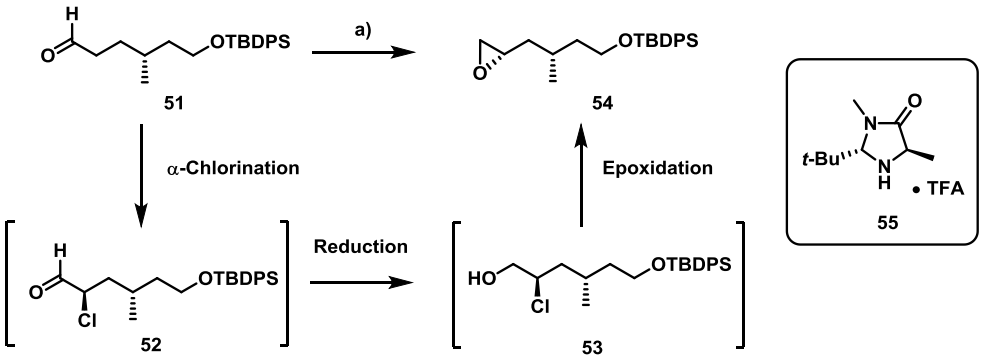
3.2.5.3 Synthesis of the Southern Fragment

In the initial step of the synthesis commercially available (*R*)-(+)-citronellol (**49**) was converted into the silyl ether **50** in quantitative yield, which was subsequently engaged in ozonolysis. The resulting aldehyde **51** was used for the following step without further purification, due to its instability on silica gel (Scheme 19).



Scheme 19: Synthesis of aldehyde **51**. Conditions: a) TBDPSCl, imidazole, CH_2Cl_2, rt, quant. yield; b) O_3, CH_2Cl_2, –78 ° then Me_2S.

The crude aldehyde **51** was subjected to an organocatalytic α-chlorination[65] using MacMillan's imidazolidinone catalyst **55** to afford aldehyde **52**. This aldehyde was *in situ* converted to alcohol **53** via reduction with sodium borohydride followed by a ring-closure under basic conditions to furnish epoxide **54** in a three-stage, one-pot procedure in 72 % yield (Scheme 20).[66] The reaction delivered the crude product in high diastereomeric purity (d.r. = 12:1), which could be improved through flash chromatography (d.r. = 97:3). This method, developed by MacMillan *et al.*, follows the concept of "linchpin catalysis",[65] where enantioenriched reactive intermediates are produced that can be turned rapidly into a broad range of valuable structural motifs. Consequently, a variety of valuable building blocks can be accessed from simple aldehydes by employing this concept. The organocatalyst **55**, used for the preparation of the previously mentioned α-chloroaldehyde **52**, was synthesized by following a procedure from MacMillan *et al*.[67]

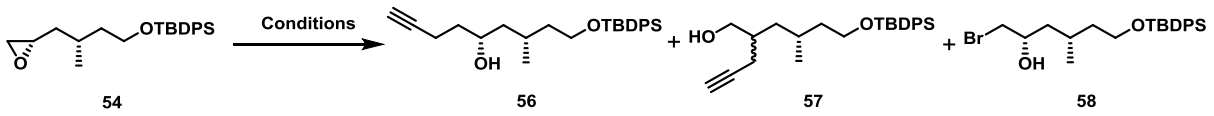


Scheme 20: Synthesis of epoxide **54**. Conditions: a) i) **55** (20 mol%),$Cu(TFA)_2$ (50 mol%), LiCl, $Na_2S_2O_8$, MeCN, H_2O, 10 °C; ii) $NaBH_4$, 0 °C; iii) KOH, rt, d.r. = 12:1, 72 % over four steps.

The introduction of the alkyne moiety into the southern fragment (**46**) was envisioned to originate from an epoxide opening reaction of compound **54** with propargylmagnesium bromide,[68] which needed to be freshly prepared prior to the reaction due to its slow decomposition over time.

The formation of regioisomer **57** and bromoydrin **58** were found to hamper the desired reaction when performed in diethyl ether. While the formation of regiosiomer **57** was caused by reaction of epoxide **54** with propargylmagnesium bromide at the internal position, bromohydrin **58** was the result of a side-reaction of the epoxide **54** with a bromide originating from the Grignard reagent. Regardless of different temperature and extended reaction time, the yield could only be improved from 53 % to 68 %, while significant amounts of the undesired byproducts were formed (Table 2, Entry 1–3).[69] In order to facilitate the epoxide opening in favor of the secondary alcohol **56**, copper iodide was used as an additive (Entry 4).[70] Unexpectedly, almost equal amounts of bromohydrin **58** and the desired product were formed in this reaction, which indicates that the bromide ions in solution display similar nucleophilicity as the transient copper reagent.

Table 2: Attempted epoxide opening of compound **54** under various conditions.

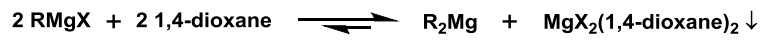


54 56 57 58

Entry	Conditions[a)]	56[b)]	57[b)]	58[b)]
1	0 °C, 1 h	53	18	11
2	–30 °C, 20 h	57	18	14
3	–78 °C to rt, overnight	68	21[c)]	10[c)]
4	–30 °C, 19 h, CuI (20 mol%)	36	9	37

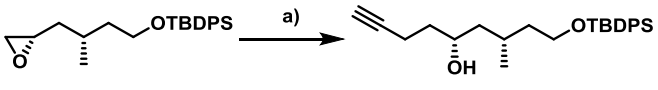
[a)] Reagents and Solvent: propargylmagnesium bromide, Et_2O.
[b)] Isolated yield of reaction product in %.
[c)] Determined by ^1H NMR analysis of crude mixture.

In consideration of the Schlenk equilibrium[71] it was speculated that by performing the epoxide opening reaction in 1,4-dioxane as solvent the bromide present in the reaction mixture would be completely removed as a precipitate. Thus, through a shift of this equilibrium to the right side only the binary organomagnesium compound R_2Mg would remain in solution (Scheme 21).[72]



Scheme 21: Addition of 1,4-dioxane leads to precipitation of $MgX_2(1,4\text{-dioxane})_2$ and shifts the Schlenk equilibrium completely to the right side.[72]

Indeed upon addition of the Grignard reagent to a solution of epoxide **54** in 1,4-dioxane a suspension was formed and the desired product was furnished in 81 % yield on multigram scale with only minor amounts (< 5 %) of the previously mentioned byproducts **57** and **58** formed (Scheme 22).



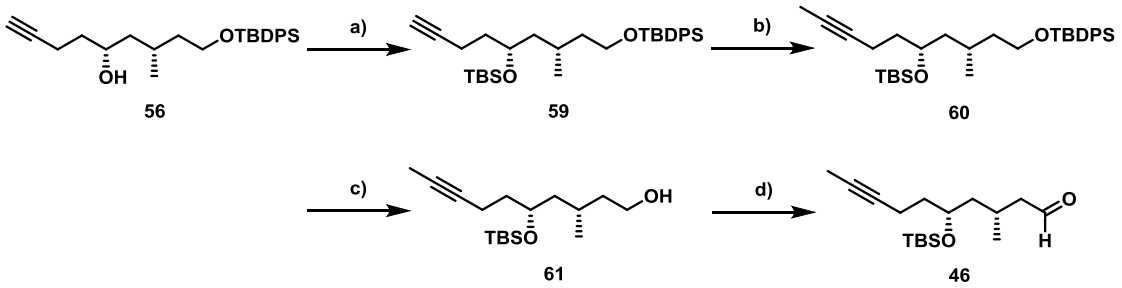
54 56

Scheme 22: Synthesis of alcohol **56**. Conditions: a) propargylmagnesium bromide, 1,4-dioxane, rt, 81 %.

After conversion of the secondary alcohol **56** into silyl ether **59**, the terminal alkyne was methyl-capped to give compound **60** in quantitative yield (Scheme 23). Methyl-capped alkynes pose as commonly used motifs for RCAM and were therefore deemed most suitable for the proposed strategy.[31]

Subsequently, compound **60** was subjected to the conditions developed by Hashimoto *et al.*[73] in order to remove the silyl ether of the primary alcohol moiety, while the secondary alcohol functionality would remain TBS-protected. Fortunately, upon upscaling from milligram to gram scale an increase in yield of **61** from 74 % to 92 % was observed.

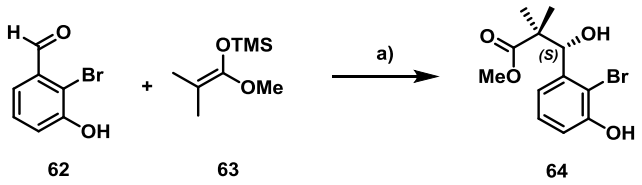
Finally, aldehyde **46**, which acted as the southern fragment of analogue **45**, was prepared by a copper-catalyzed TEMPO/O_2 oxidation of the primary alcohol **61** following the convenient procedure reported by Stahl *et al.*[74] This method proved to be more feasible for this substrate than the commonly used Swern oxidation as the crude aldehyde **46** could be obtained in excellent yield and high purity, which made it possible to continue with the next step without further purification.



Scheme 23: Synthesis of aldehyde **46**. Conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 98 %; b) CH_3I, *n*BuLi, THF, –78 °C to rt, quant. yield; c) TBAF, HOAc, DMF, rt, 92 %; d) O_2 (1 atm), $[Cu(MeCN)_4]BF_4$ (5 mol%), 2,2'-bypyridine (5 mol%), TEMPO (5 mol%), NMI (10 mol%), MeCN, rt, 98 %.

3.2.5.4 Synthesis of the Side-chain

The side-chain **27** was prepared in collaboration with Dr. Guillaume Mata.[58]



Scheme 24: Synthesis of ester **64**. Conditions: a) *N*-Tos-L-valine, BH_3·THF, 0 °C, then aldehyde **62**, –78 °C, 72 %, 89 % *ee*, >99 % *ee* after recrystallization.

The side-chain was prepared by a Mukaiyama aldol reaction.[75] Specifically, commercially available aldehyde **62** was reacted with keteneacetal **63** in the presence of a chiral Lewis acid catalyst formed in situ from *N*-Tos-L-valine and BH_3·THF.[17] The reaction was carried out on a multigram scale and furnished ester **64** in 72 % yield (Scheme 24). The optical purity of **64** reached the limits of detection (*ee* > 99 %) after recrystallization of the crude material (*ee* = 89 %). Both enantiomers were prepared and the constitution and absolute configuration of the products was determined by single crystal X-ray diffraction (Figure 5).

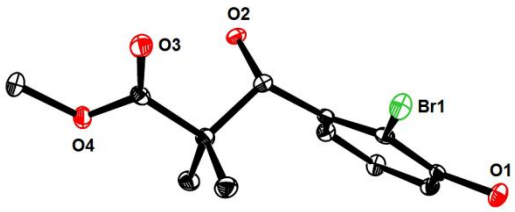
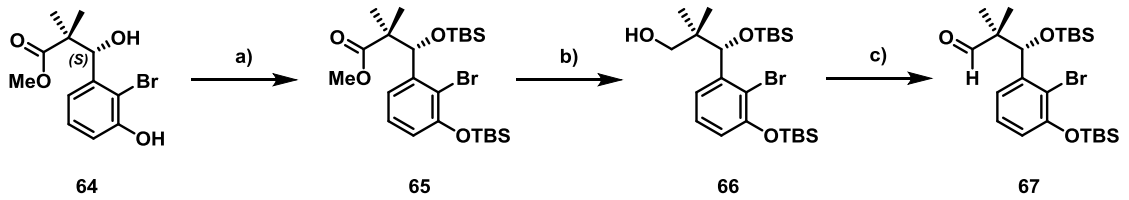


Figure 5: Structure of (*S*)-ester **64** in the solid state.

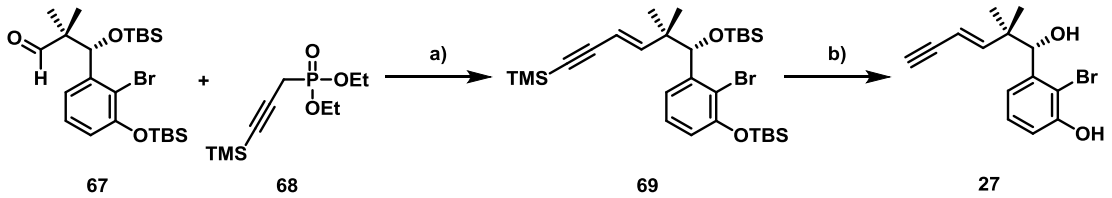
The Ye group published a closely related approach for the aldol formation while this work was in progress, although they chose to protect the phenolic site in the starting aldehyde, which adds an extra step and prevents easy recrystallization of the crude product.[13a] Subsequently, compound **64** was converted into the corresponding protected silyl ether and subjected to reducing conditions in order to acquire aldehyde **67**. However, the utilized reducing agent DIBAL-H failed to directly deliver the desired product **67** and produced alcohol **66** in high yields instead (Scheme 25).



64 65 66 67

Scheme 25: Synthesis of aldehyde **67**. Conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 97 %; b) DIBAL-H, toluene, –78 °C, 96 %; c) Dess-Martin periodinane, CH_2Cl_2, rt, 76 %.

After adjustment of the oxidation state of **66** by treatment with DMP, alkyne **69** was furnished by a Horner-Wadsworth-Emmons olefination[76] with phosphonate **68**[77] in good yield and excellent *E* to *Z* ratio (20:1). Finally, global deprotection with HF/pyridine delivered alkyne **27** in 98 % yield. Notably, only these conditions led to complete deprotection of precursor **69**, whereas other tested deprotection methods such as treatment with TBAF or strong acids[78] failed to deliver the desired product (Scheme 26).



67 68 69 27

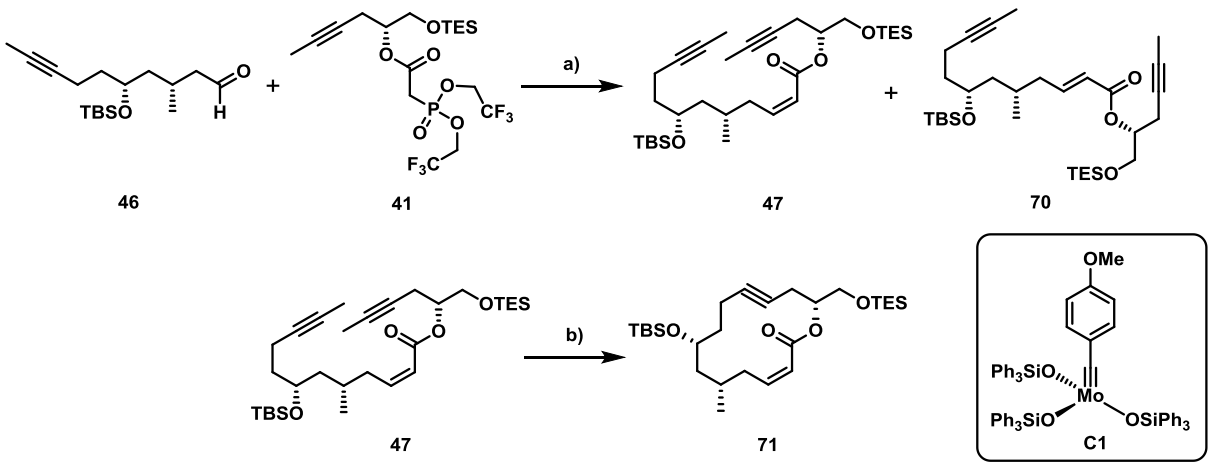
Scheme 26: Synthesis of alkyne **27**. Conditions: a) *n*BuLi, THF, –78 °C, THF, 96 %, (*E*/*Z* = 20:1); b) HF·pyridine, MeCN, 98 %.

The side-chain fragment **27** was obtained in 6 steps with an overall yield of 48 % and could be directly used in the following Sonogashira reaction which was planned to be last step in the synthesis of callyspongiolide and its analogue. As already mentioned, after this work had been initiated, the absolute stereochemistry of callyspongiolide was corrected. The originally proposed structure ***ent*-1** also dictated the stereochemical format of the side-chain.

3.2.5.5 Fragment Assembly and Endgame

With both the northern fragment (**41**) and southern fragment (**46**) in hand, the RCAM precursor diyne **47** was furnished in a Still-Gennari olefination (Scheme 27). Although successfully employed in the formation of model substrate **34** (see Chapter 3.2.3), this reaction was plagued with fluctuating yields (27 % to 42 %). By changing the aldehyde preparation from Swern oxidation to the procedure of Stahl *et al.*[74] the purity of the resulting aldehyde **46** could be increased, which proved beneficial for the following olefination step. Furthermore the reproducibility of the olefination could be increased by changes in the work-up procedure. Through these improvements the desired olefin **47** could be obtained in 57 % yield as single isomer on a 100 milligram scale.

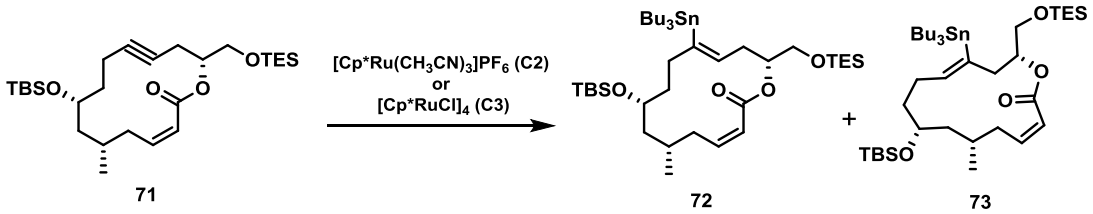
The macrocyclic structure **71** was forged by RCAM of diyne precursor **47** in excellent yield and purity using catalyst **C1**. The applied conditions were similar as the previously described RCAM of diyne **42** (see Chapter 3.2.3), with the exception that the temperature was increased from room temperature to 80 °C, which reduced the reaction time from 2 hours to 10 minutes and prevented the formation of dimeric or oligomeric products.[40]



Scheme 27: Synthesis of macrolactone **71**. Conditions: a) 18-crown-6, KHMDS, THF, –78 °C, 57 % *E*-isomer (**47**), 14 % *Z*-isomer (**70**), (*Z*/*E* = 4:1); b) **C1** (15 mol%), 5 Å MS, toluene, 80 °C, 93 %.

For the *trans*-hydrostannation of macrolactone **71**, cationic ruthenium complex **C2** and tetrameric ruthenium complex **C3** were tested under similar conditions (Table 3). Interestingly, both complexes displayed similar results in terms of *Z* to *E* ratio, and ratio of regioisomers. However, catalyst **C2** gave full conversion of substrate **71** (Entry 1), while the reaction using catalyst **C3** remained incomplete (Entry 2). Remarkably, in contrast to the previously found results (see Chapter 3.2.4) both tested catalysts had no preference to form either one of the two alkenylstannanes **72** and **73**.

Table 3: Comparison of *trans*-hydrostannation catalysts in the synthesis of analogue **45**.

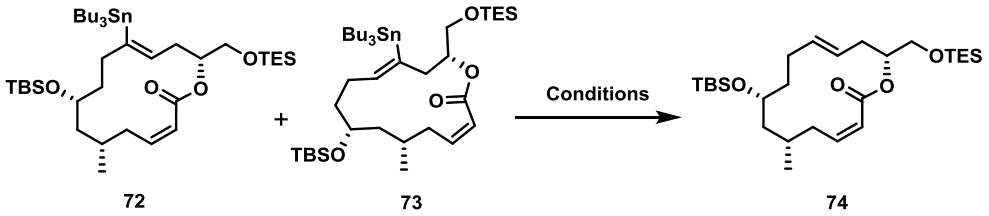


Entry	Cat. (mol%)	Conv.[a]	*Z/E* [a]	α/β [a]	Yield[b]
1	**C2** (10)	> 95 %	> 20:1	1:1	95 %
2	**C3** (2.5)	64 %	> 20:1	1:1	n.d.

[a] Conversion and ratios determined by ^{1}H NMR analysis of crude mixture.
[b] Isolated yield of mixture of regioisomers.
Conditions: Catalyst **C2** or **C3**, Bu_3SnH, CH_2Cl_2, rt.

Next, the mixture of regioisomers **72** and **73** was subjected to protodestannation. Upon exposure to different reagents, a notable difference in the isolated yield of the desired macrolactone **74** was observed (Table 4). It was found that the use of copper(I) diphenylphosphinate (Entry 2)[42d, 79] instead of a combination of CuTC and phosphinate-salt (Entry 1)[80] increased the yield was increased from 54 % to 71 %. Consequently, the method used in Entry 2 seemed to be simpler and more effective for protodestannation and became the method of choice for this transformation.

Table 4: Investigation of protodestannation conditions of alkenylstannanes **72** and **73**.

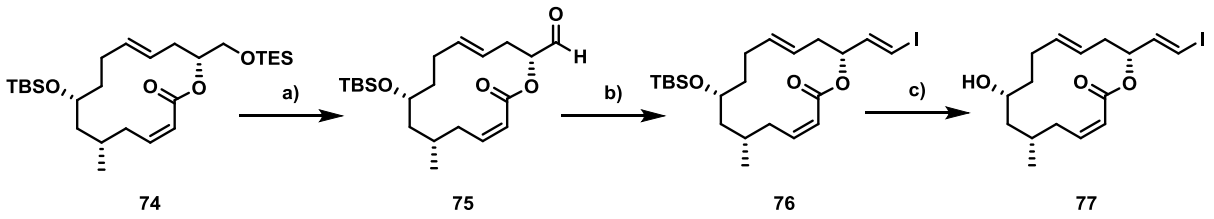


72 73 74

Entry	Reagents[a)]	Yield[b)]
1	CuTC (2.2 eq.), $[Ph_2PO_2][NBu_4]$ (1.1 eq.)	54 %
2	$[(Ph_2PO_2)Cu]$ (1.8 eq.)	71 %

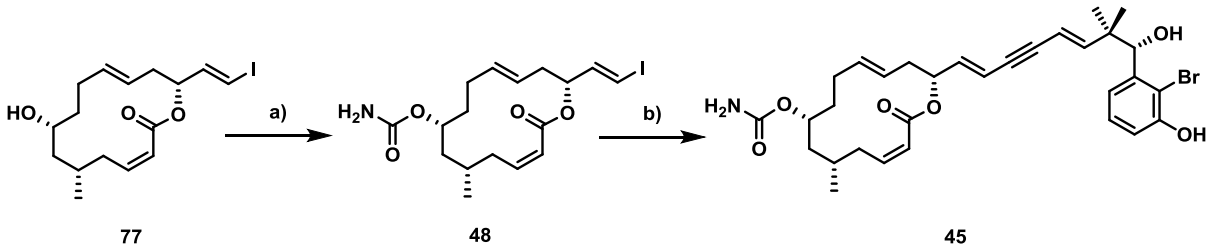
[a)] Conditions: DMF, rt.
[b)] Isolated yield.

In order to furnish alcohol **77** as a precursor for the final reaction, a sequence consisting of oxidation, olefination and deprotection was established (Scheme 28). In the first step of this sequence macrolactone **74** was exposed to Swern conditions, leading to formation of the corresponding aldehyde **75**. Notably, this reaction could be conducted without the need of a deprotection step prior to oxidizing compound **74**. Following the procedure of Spur *et al.,* through a short warming period to –30 °C and re-cooling to –70 °C, primary TES-ethers can be selectively cleaved and simultaneously oxidized.[81] The reaction yielded a highly sensitive aldehyde (**75**) that was prone to epimerization at the hydroxyl substituted α-position of the aldehyde functionality. Hence, this aldehyde was immediately elaborated into alkenyl iodide **76** by Takai olefination,[64] without any further purification. The olefination-step delivered the product in excellent *E* to *Z* ratio (12:1). The furnished product **76** however, contained impurities that could not be properly removed by flash column chromatography. Consequently, the next deprotection-step was performed with the crude product **76** furnishing the polar secondary alcohol **77** in 53 % over three steps after purification.



Scheme 28: Synthesis of alcohol **77**. Conditions: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –70 °C to –30 °C; b) $CrCl_2$·THF, CHI_3, THF, 0 °C, (*E*/*Z* = 12:1); c) CSA, MeOH, rt, 53 % over three steps.

In readiness for the final step of the analogue synthesis a carbamate unit was installed on macrolactone **77** in excellent yield. In the following Sonogashira reaction[16] fragment **48** and the side-chain **27** were joined. In order to prevent isomerization of the α,β-unsaturated ester position, only a small excess of a bulky base was used in the cross-coupling reaction. As expected the reaction was uneventful and delivered the callyspongiolide analogue **45** in 74 % yield.



Scheme 29: Synthesis of analogue **45**. Conditions: a) chlorosulfonyl isocyanate, CH_2Cl_2, rt, 0 °C, then H_2O, THF, rt, 95 %; b) **27**, $Pd(PPh_3)_4$ (10 mol%), CuI, DIPEA, THF, rt, 74 %.

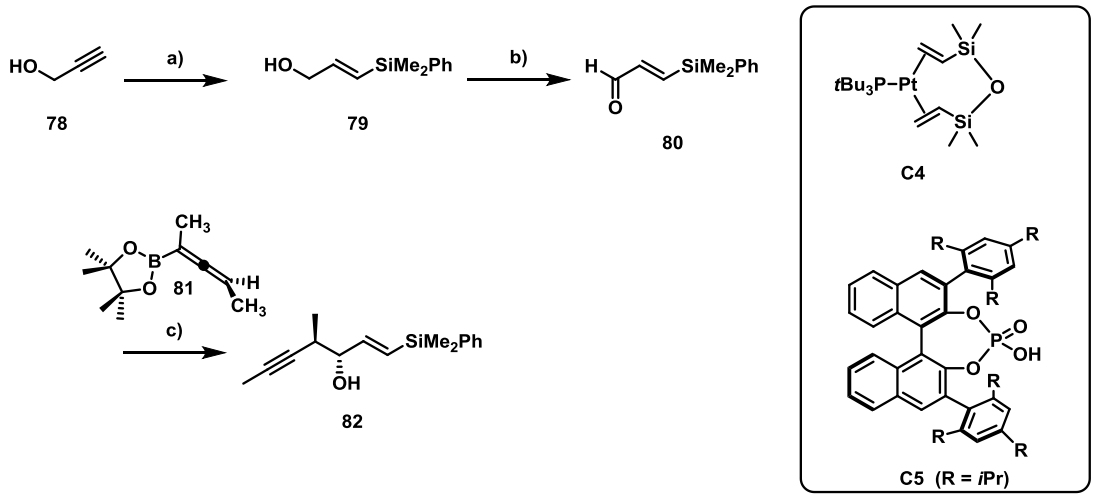
In conclusion the synthesis of an analogoue of callyspongiolide was successfully performed with an overall yield of 7 % and 17 steps in the longest linear sequence. Considering the positive results of the experiments prior to this analogue preparation as well, the feasibility of the proposed strategy of utilizing a *trans*-reduction led to the initiation of the synthesis program of the complete natural product.

3.3 Forward Synthesis

The starting point of the proposed retrosynthetic strategy outlined in Scheme 11 was the preparation of fragments **23** and **24**. These syntheses, the fragment assembly as well as the following *trans*-hydroelementation studies (Chapters 3.3.1 to 3.3.4) were performed by Dr. Guillaume Mata.[58]

3.3.1 Synthesis of the Northern Fragment

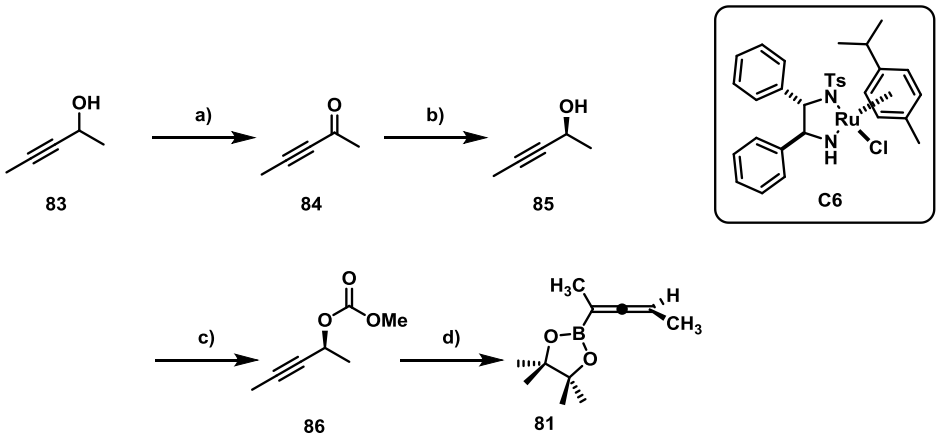
The preparation of the required northern fragment **23** started from propargyl alcohol **78**, which underwent platinum-catalyzed hydrosylilation with dimethylphenylsilane to give product **79** on gram scale using a procedure from Panek *et al*.[82] Literature known catalyst **C4**[83] delivered the desired *E*-alkenylsilane **79** in excellent yield and purity (Scheme 30).
After adjustment of the oxidation state of **79** by treatment with PCC, the *anti*-configured homopropargyl acohol **82** was furnished by reaction with allenylboronate **81** in the presence of (*R*)-TRIP (5 mol%) (**C5**). This chiral Brønsted acid catalyzed allenylboronation protocol, developed by Roush *et al.*,[84] afforded the product in high yield and diastereoselectivity. The absolute configuration of the product (**82**) was determined by Mosher ester analysis.[12a, 58, 85]



Scheme 30: Synthesis of homopropargyl alcohol **82**. Conditions: a) $PhMe_2SiH$, **C4** (0.1 mol%), Na, THF 70 °C, 76 %; b) PCC, CH_2Cl_2, rt, 90 %; c) **81**, (*R*)-TRIP (5 mol%) (**C5**), toluene, 0 °, d.r. = 20:1, 81 %.

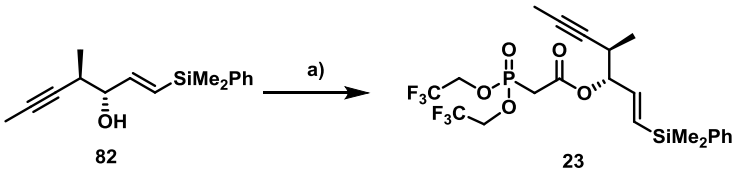
The allenylboronate **81** itself (Scheme 30) was prepared in four steps from commercially available racemic 3-pentyn-2-ol (**83**). In the initial sequence consisting of oxidation and ruthenium-catalyzed asymmetric transfer reduction, the *S*-configured propargyl alcohol **85** was furnished in 93 % *ee* (Scheme 31). This outstanding optical purity was achieved by applying the method based on a chiral ruthenium(II) catalyst **C6**, developed by Noyori *et al*.[86]

To complete the synthesis of allenylboronate **81** the enantioenriched propargyl alcohol **85** was converted to carbonate **86,** followed by a copper-catalyzed regio- and stereoselective substitution reaction with bis(pinacolato)diboron.[84, 87] The high volatility of reagent **81**, combined with its instability on silica gel resulted in low yields.



Scheme 31: Synthesis of allenylboronate **81**. Conditions: a) MnO_2, CH_2Cl_2, rt; b) RuCl[(S,S)-Ts-DPEN](η^6-cymene) (**C6**) (1 mol%), HCOOH/Et_3N (5:2), CH_2Cl_2, rt, 45 % over two steps, 93 % *ee*; c) methyl chloroformate, pyridine, CH_2Cl_2, rt, 91 %; d) CuCl (20 mol%), XantPhos (15 mol%), *tert*-BuONa (25 mol**%**), Bis(pinacolato)diboron, 50 °C, 35 %.

In analogy to the synthesis of fragment **41** of the previously described analogue **45** (see Chapter 3.2.3), the alcohol **82** was joined by phosphonate **40** to generate the desired precursor for the following Still-Gennari olefination in good yield.



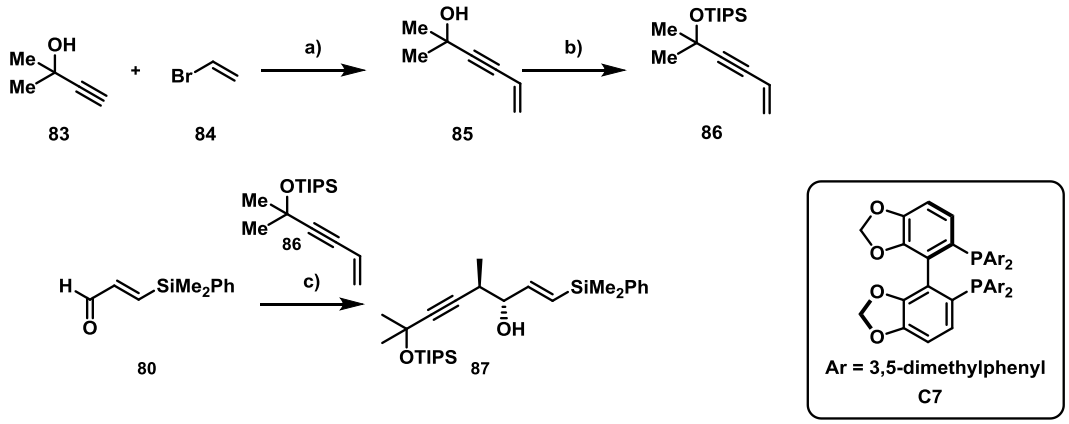
Scheme 32: Synthesis of ester **23**. Conditions: a) phosphonate **40**, EDC, HOBt, CH_2Cl_2, rt, 70 %.

In conclusion, the synthesis of the northern fragment **23** was completed with an overall yield of 39 % yield over 4 steps. The implemented strategy allowed for an efficient and highly selective access to the desired fragment. However, a major drawback of this strategy was the tedious and low-yielding preparation of allenylboronate **81**, limiting its application on large scale.

In pursuit of a more convenient catalytic alternative it was speculated that the approach developed by Krische *et al.* would be more applicable to access the desired homopropargyl alcohol-motif.[88] This reaction would lead to the formation of a terminal alkyne instead of an internal alkyne in comparison to the previous synthesis (see Chapter 3.2.5.5). However, as RCAM reactions with compounds comprising one terminal and one internal alkyne have been successfully performed in other total synthesis projects, this change of strategy represented a tolerable risk.[42c, 89]

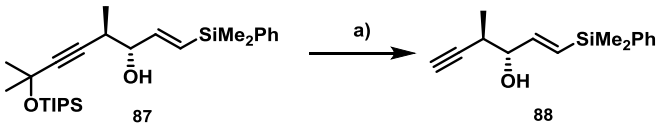
Indeed, application of the reported conditions for Krische propargylation allowed for the efficient synthesis of compound **87** in excellent diastereoselectivity and good enantioselectivity.[88] Although alcohol **79** could be directly submitted to this reaction, a much better yield was obtained by using the derived aldehyde **80**. Further modifications, such as decreasing of the amount of formic acid to 1.05 equivalents in order to suppress concomitant protodesilylation, led to an increase in yield to 55 % on multigram scale, while maintaining high selectivity (Scheme 33).

The enyne reagent **86**, used in the Krische propargylation, was prepared in a two-step procedure on multigram scale by reaction of alkenyl bromide **84** with alkyne **83**, followed by a TIPS-protection of the free alcohol **85**.[88]



Scheme 33: Synthesis of alkyne **87**. Conditions: a) $Pd(PPh_3)_4$ (0.2 mol%), CuI (1.4 mol%), Et_2NH, THF, rt, 78 %; b) TIPSCl, NaH, THF, rt, 83 %; c) enyne **86**, $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-DM-Segphos (**C7**) (5 mol%), THF, HCO_2H, Na_2SO_4, 70 °C, d.r. = 20:1, 82 % *ee*, 65 % (55 % of pure diasterioisomer).

Conversion of internal alkyne **87** to the corresponding terminal alkyne **88** was performed upon exposure to TBAF and NaOH in a two-step protocol and furnished product **88** in 74 % yield (Scheme 34).



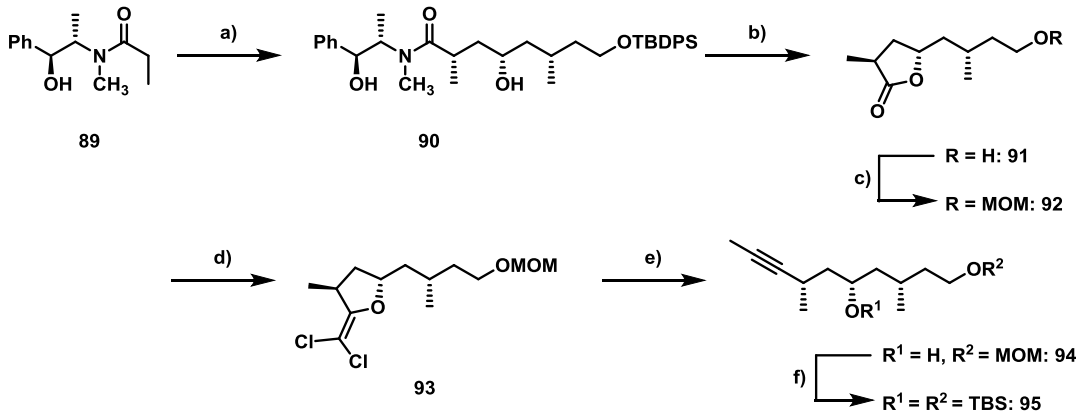
Scheme 34: Synthesis of terminal alkyne **88**. Conditions: a) (i) TBAF, THF, rt; (ii) NaOH, toluene, 110 °C, 74 %.

The terminal alkyne **88** was also used in Chapter 3.3.4 for the preparation of a substrate feasible to carry out *trans*-hydroelementation experiments that would allow accessing other callyspongiolide precursors.

3.3.2 Synthesis of the Southern Fragment

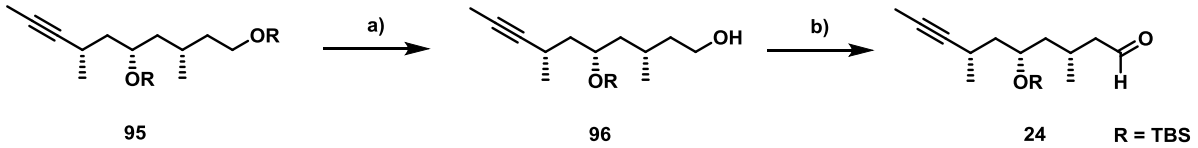
In the initial step of the preparation of the southern fragment **24**, epoxide **54** was used for the alkylation of the propionate enolate, derived from amide **89** in good yield and excellent diastereoselcitivity (Scheme 35).[90] Compound **54** also served as starting material for the preparation of analogue **45** (see Chapter 3.2.5.3) and could be conveniently used to access a pathway to the desired natural product, emphasizing the high convergence of the strategies outlined in this project. The resulting product **90** was treated with acid to induce cyclization with formation of the lactone **91**, which was converted to the MOM-protected primary alcohol **92**.

The transformation of lactone **92** into the internal alkyne **94** was performed according to a procedure previously developed by Fürstner *et al*.[91] To this end, the lactone carbonyl group of compound **92** was converted into dichloro-olefin **93**,[92] which was then treated with methyllithium under iron catalysis[93] to give the desired alkyne **94** on a multigram scale in 50 % yield over two steps. The following TBS-protection of the resulting alcohol **94** was uneventful and delivered the completely protected diol **95** in 89 % yield.



Scheme 35: Synthesis of alkyne **95**. Conditions: a) LDA, LiCl, THF, –78 °C, then epoxide **54**, rt, d.r. = 20:1, 70**%**; b) H_2SO_4, H_2O, 1,4-dioxane, 100 °C, 90 %; c) MOMCl, DIPEA, CH_2Cl_2, rt, 98 %; d) CCl_4, PPh_3, THF, 80 °C, 68 %; e) MeLi, $Fe(acac)_3$, (12 mol%), Et_2O, 1,2-diaminobenzene (25 mol%), 0 °C to rt, 73 %; f) (i) HCl, MeOH, 60 °C; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89 %.

Finally, selective deprotection of **95** delivered the unprotected primary alcohol **96** in good yield, which was then oxidized to give aldehyde **24** in readiness for the follwing fragment coupling (Scheme 36).



95 **96** **24** **R = TBS**

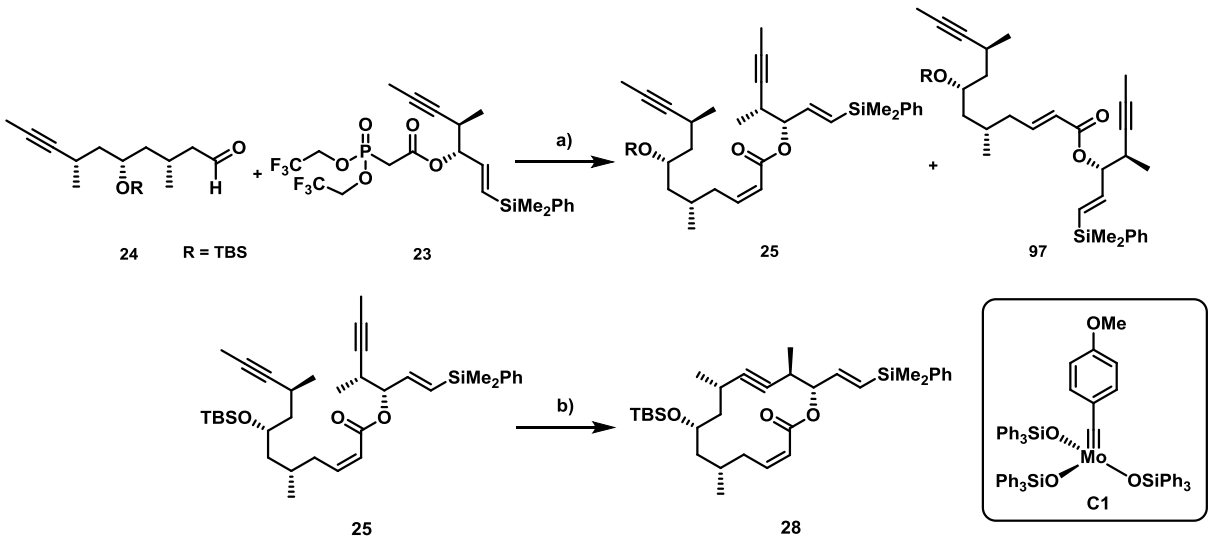
Scheme 36: Synthesis of aldehyde **24**. Conditions: a) PPTS, EtOH, 0°C, 60 % (+ 31 % of fully deprotected material); b) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 79 %.

In conclusion, the synthesis of the southern fragment **24** was achieved with an overall yield of 9 % over 12 steps.

3.3.3 Fragment Assembly

With both the northern fragment **23** and southern fragment **24** in hand, the RCAM precursor diyne **25** was again furnished by Still-Gennari olefination in 67 % yield and acceptable *Z* to *E* ratio of 6:1 (Scheme 37).

The macrocyclic structure **28** was forged through RCAM of diyne **25** in excellent yield and purity using catalyst **C1**. The applied conditions were similar as the previously described RCAM of diyne **47** in the synthesis of analogue **45** (see Chapter 3.2.5.5). Despite the considerable increase in steric bulk due to the flanking methyl groups, the alkyne metathesis was not affected to any noticeable extent, again proving the versatility of Mo-based alkyne metathesis catalysts.



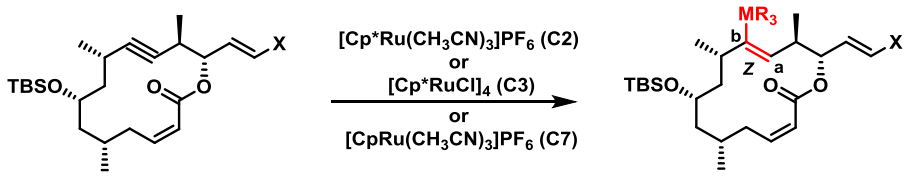
Scheme 37: Synthesis of macrolactone **28**. Conditions: a) 18-crown-6, KHMDS, THF, –78 °C, 67 % of *Z*-Isomer (**25**), 5 % of *E*-Isomer (**97**), (*Z*/*E* = 6:1); b) **C1** (15 mol%), 5 Å MS, toluene, 70 °C, 80 %.

The resulting macrolactone **28** served as substrate for the proposed key-step of the outlined strategy to access the desired natural product.

3.3.4 *trans*-Hydroelementation Studies

The results of the *trans*-hydroelementation studies of macrolactone **28** are depicted in Table 5. A variety of conditions, reagents and catalysts were tested for their potential to react with the internal alkyne **28** in the desired stereoselective fashion to enable a formal *trans*-reduction.

Table 5: Results of *trans*-hydroelementation attempts.



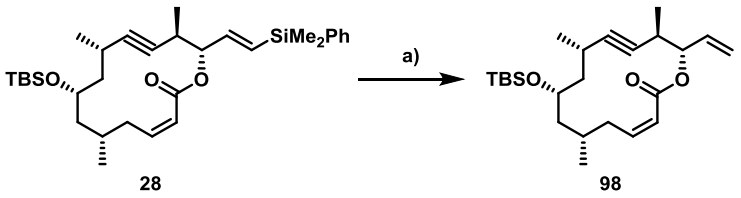
Entry	X	Reagent	Catalyst[a)]	Conditions	Conversions[b)]
1	$SiMe_2Ph$	Bu_3SnH	**C2**	rt, CH_2Cl_2	0 %
2	$SiMe_2Ph$	Bu_3SnH	**C3**	rt, CH_2Cl_2	0 %
3	$SiMe_2Ph$	Bu_3SnH	**C7**	rt, CH_2Cl_2	0 %
4	$SiMe_2Ph$	Bu_3SnH	**C3**	–50 °C, CH_2Cl_2	0 %
5	H	Bu_3SnH	**C2**	rt, CH_2Cl_2	0 %
6	H	Bu_3SnH	**C3**	rt, CH_2Cl_2	0 %
7	$SiMe_2Ph$	$BnMe_2SiH$	**C2**	rt, CH_2Cl_2	0 %
8	$SiMe_2Ph$	$(EtO)_3SiH$	**C2**	rt, neat	0 %
9	$SiMe_2Ph$	$(EtO)_3SiH$	**C7**	rt, neat	80 %[c)]

[a)] Catalyst loading: 10 mol%
[b)] Conversions determined by ^1H NMR analysis of crude mixture.
[c)] Further analysis of isolated material showed only olefin with undesired *E*-geometry was formed.

In the first series of experiments (Entry 1–3) three different ruthenium-catalysts were explored in order to induce the desired reaction. The catalysts used in the first two trials (Entry 1 and 2) were the previously applied cationic complex **C2** and the tetrameric complex **C3**. While good to excellent conversion to the product during the *trans*-hydrostannation reactions of model substrates and analogue **45** (see Chapter 3.2.4 and Chapter 3.2.5.5) was achieved, no product could be detected upon reaction with the macrocycle **28**.

As an additional catalyst the cationic ruthenium complex **C7**, containing the sterically less hindered Cp-ligand instead of a Cp*-ligand, was used (Entry 3). Despite the diminished steric properties of the ligand in this complex, alkyne **28** remained intact throughout the experiment. It was speculated that adding Bu_3SnH over an extended period, while cooling to lower temperatures could promote substrate binding of the catalyst **C3**.[94] However, the product also remained inaccessible upon cooling to –50 °C and adding the reagent over 2 h (Entry 4).

An important issue that needed to be addressed by this point was the possibility of the dimethylphenylsilyl-moiety, located in the side-chain of the substrate might be interfering with the catalyst systems as [Cp*Ru]-fragments are able to coordinate to electron rich aromatic rings in a η^6-fashion.[95] Consequently, treatment of the alkenylsilane **28** with AgF as fluoride source delivered macrolactone **98** in excellent yields (Scheme 38).[96]



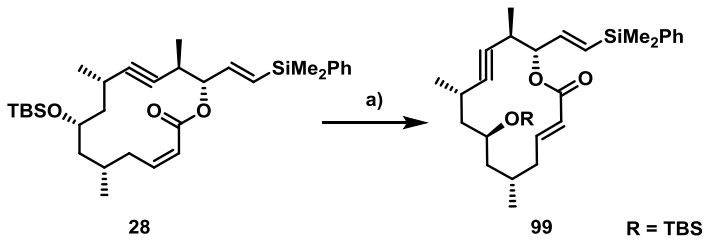
Scheme 38: Synthesis of macrolactone **98**. Conditions: a) AgF, MeOH, THF, H_2O, rt, 92 %.

Yet, the desilylated substrate **98** was just as resilient as the parent compound from which it derived, no matter whether ruthenium complex **C2** or **C3** were used as catalysts for attempted *trans*-hydrostannation. Detrimental catalyst poisoning by irreversible formation of arene sandwich complexes could therefore be safely excluded as the culprit (Entry 5 and 6).

Next, the focus of the investigation was shifted to *trans*-hydrosilylation[46] as a possible alternative to obtain the desired functionalized *Z*-alkene.

Similarly to previous experiments, the two hydrosilylation reagents tested for this purpose $BnMe_2SiH$ (Entry 7) and $(EtO)_3SiH$ (Entry 8) did not lead to any meaningful conversion, despite performing the latter reaction under neat conditions.[96-97] This outcome was remedied by switching to the less bulky cationic ruthenium complex **C7** (Entry 9), which was the only experiment with observable substrate conversion. However, further analysis revealed that only product with undesired *E*-geometry was produced, confirming that the extended umbrella of the Cp* is necessary for high *trans*-selectivity.

Finally, it was attempted to perform *trans*-hydrostannation under free radical conditions.[98] However, upon exposure of macrolactone **28** to Ph_3SnH with AIBN as radical initiator, only isomerization of the *cis*-olefin to form the corresponding *trans*-isomer **99** was observed, while the alkyne site remained unaffected (Scheme 39).



Scheme 39: Synthesis of macrolactone **99**. Conditions: a) Ph_3SnH, AIBN, toluene, 80 °C, 60 %, (*Z*/*E* = 4:1).

3.3.4.1 *trans*-Hydrostannation via Assisted Substrate Binding

In view of the preceding *trans*-hydrostannation experiments, which failed to show any meaningful conversion of **28** to product, it was speculated that the adverse steric effects caused by the substrate structure could be overridden by assisted substrate binding.

In previous works Fürstner *et al.* had shown that unprotected –OH groups adjacent to a triple bond favor substrate binding because they engage in hydrogen bonding with the [Ru-Cl] unit of the catalyst (Figure 6).[50, 51b] Through design of an intermediate, containing alcohol functionalities in close proximity of the alkyne, this effect could be exploited resulting in an enhanced catalyst binding and possibly improved reactivity.

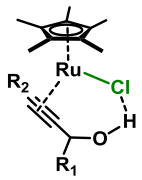
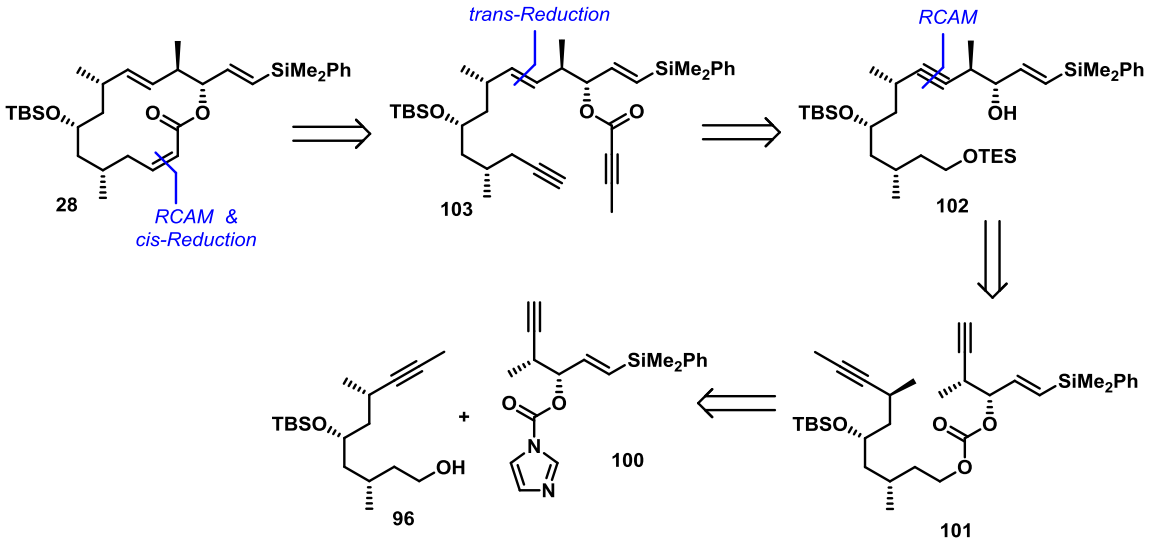


Figure 6: Adduct of alkyne and ruthenium complex featuring an interligand hydrogen bonding.[51b]

Consequently homopropargyl alcohol **102** was chosen as an alternative substrate for the following *trans*-hydrostannation experiments (Scheme 40). Containing the aforementioned features, this compound would not only allow study of the influence of this effect on sterically demanding substrates, but also act as an intermediate in the synthesis of callyspongiolide.

Compound **102** was supposed to originate from a RCAM of one terminal and one internal alkyne. Diyne **101**, posing as a precursor for the RCAM reaction, would be obtained via reaction of carbamate **100** with alcohol **96**. While carbamate **100** would be prepared from a previously synthesized intermediate of the northern fragment synthesis (see Chapter 3.3.1), alcohol **96** had already served as the southern fragment used in the previous synthetic route (see Chapter 3.3.2).

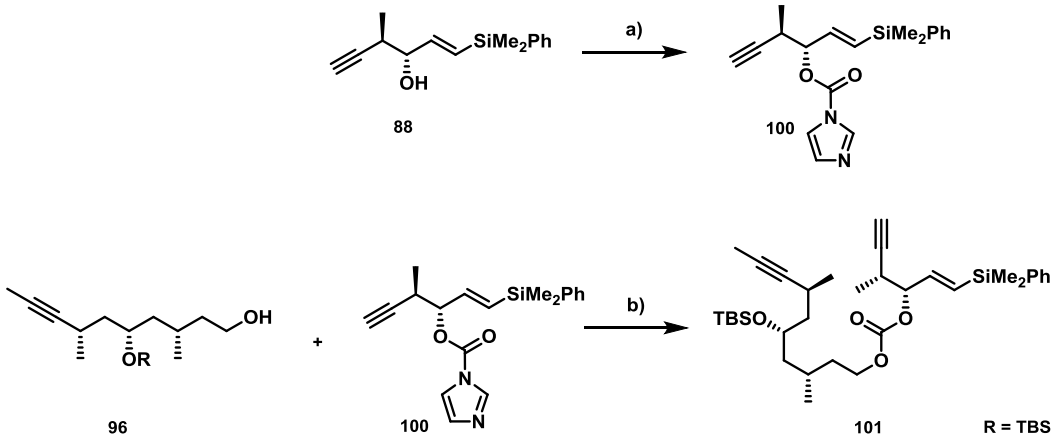


Scheme 40: Retrosynthetic analysis of macrolactone **102**.

Upon successful implementation of the *trans*-hydrostannation of homopropargyl alcohol **102,** the compound would be further processed to deliver diyne **103** as a result of a formal *trans*-reduction, followed by a sequence of esterification and homologation reactions. A second RCAM reaction would harness macrolactone **28**, linking the alternative route, described above, to the originally proposed synthesis of callyspongiolide (see Chapter 3.1). Consequently, this new strategy would allow for the incorporation of already prepared intermediates and paves the way towards completion of the total synthesis of the desired natural product.

In the initial step of the preparation of homopropargyl alcohol **103** (Scheme 40), the previously made allyl alcohol **88** (see Chapter 3.3.1) was transformed into the stable carbamate **100** in good yield (Scheme 41).

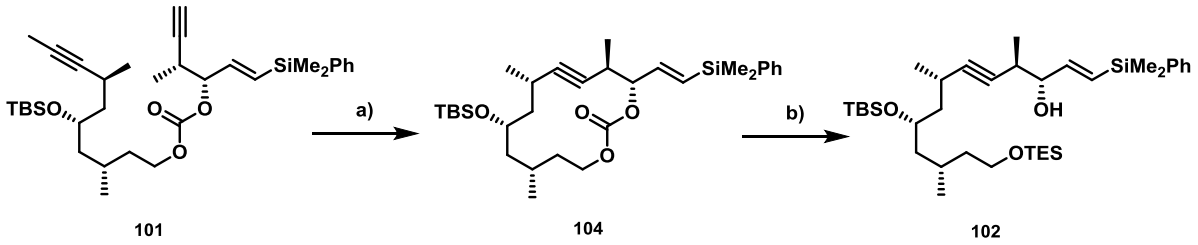
Carbonate **101** was readily accessed from the previously made terminal alkyne derivative **96** (see Chapter 3.3.2) via carbamate **100** in 79 % yield. The introduction of the carbonate tether for assembling the two main fragments of the synthesis created a challenging RCAM precursor, containing one terminal and one internal sterically demanding alkyne, which would give further opportunity to test the limits of alkyne metathesis.



Scheme 41: Synthesis of diyne **101**. Conditions: a) CDI, CH_2Cl_2, rt, 80 %; b) NaH, THF, rt, 79 %.

Whereas alkyne metathesis reactions engaging two terminal acetylene derivatives remain erratic,[99] compound **101**, comprising only one terminal alkyne, reacted readily on treatment with molybdenum alkylidyne complex **C1** (see Chapter 3.2.5.5) in the presence of molecular sieves (5 Å) to trap the released propyne. This example corroborates previous conclusions that RCAM reactions of this type of substrate are robust and reliable when performed with alkylidyne catalysts bearing silanolate ligands (Scheme 42).[42c, 42e, 89, 100]

Cleavage of the carbonate tether in **104** followed by silylation of the primary –OH group gave access to homopropargyl alcohol **102** in excellent yield, which allowed the influence of the protic site onto *trans*-hydrostannation to be tested.

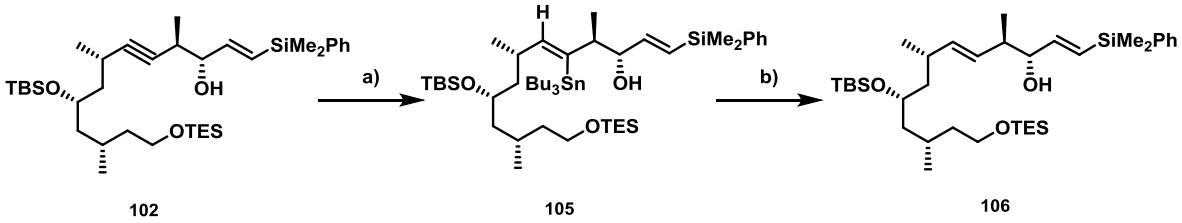


101 104 102

Scheme 42: Synthesis of homopropargyl alcohol **102**. Conditions: a) **C1** (15 mol%), 4 Å and 5 Å MS, toluene, rt, 74 %; b) (i) K_2CO_3, MeOH, rt, 90 %; (ii) TESCl, Et_3N, CH_2Cl_2, rt, 90 %.

Treatment of homopropargyl alcohol **102** with Bu_3SnH in the presence of the chloride-containing ruthenium complex $[Cp^*RuCl]_4$ (**C3**) under standard conditions furnished the desired product **105** as a single regio- and diastereomer, but the reaction ceased prior to reaching full conversion. Upon lowering the temperature to –50 °C[51b] and increasing the loading of the ruthenium complex to one equivalent, however, could stannane **105** be isolated in 71 % yield. Slow addition of Bu_3SnH over 2 hours after pre-mixing the neutral ruthenium complex with the substrate further contributed to this result. Addition of $P(CH_2OH)_3$ at room temperature, after the starting-material was consumed, removed excess amounts of ruthenium complex and consequently improved the following work-up. The reaction was initially performed on a 5 milligram scale, however, when the reaction was carried out on a larger scale, the Bu_3SnH had to be added over 8 hours at an increased reaction temperature of –30 °C in order to reach full conversion.

Finally, protodestannation of compound **106** revealed the desired *E*-alkene in 70 % yield as a single diastereoisomer.



102 105 106

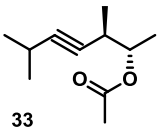
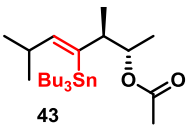
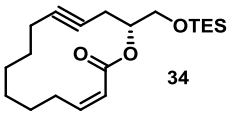
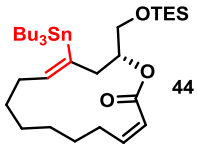
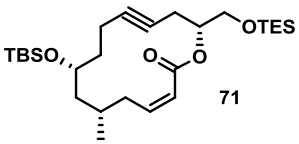
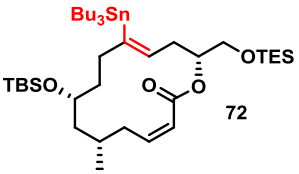
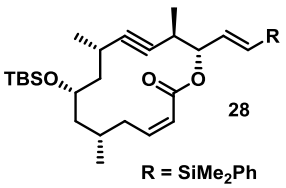
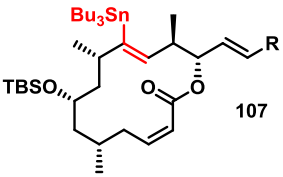
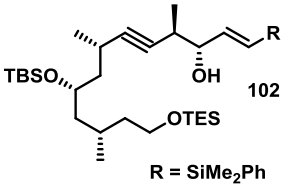
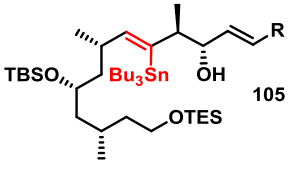
Scheme 43: Synthesis of (*E*)-alkene **106**. Conditions: a) **C3** (100 mol%), Bu_3SnH, CH_2Cl_2, –50 °C, then $P(CH_2OH)_3$, 71 % (α/β = 9:1, *Z*/*E* = 20:1), b) [$(Ph_2PO_2)Cu$], DMF, rt, 70 %.

As mentioned before, the derived (*E*)-alkene **106** is a fully functional building block for the synthesis of callyspongiolide if one relocates macrocyclization to the enoate site. This example confirms the positive influence of an unprotected –OH group on *trans*-hydrostannation, but also shows that the effect does not necessarily suffice to guarantee efficient catalyst turnover.

3.4 Conclusion of *trans*-Hydrostannation Experiments

The results of the *trans*-hydroelementation studies described in this thesis are summarized in Table 6. A variety of different substrates and ruthenium-based catalysts were tested for their potential to react with Bu_3SnH in the desired stereoselective fashion, leading to alkenylstannanes that would act as precursors for *E*-alknes upon protodestannation.

Table 6: Summary of *trans*-hydrostannation experiments.

Entry	Substrate	Product	Cat.	Conv.[a]	*Z/E* [a]	α/β[a]	Yield[b]
1	 33	 43	**C2**	> 95 %	> 20:1	4:1	95 %
2	 34	 44	**C2**	> 95 %	> 20:1	6:1	90 %
3			**C3**	64 %	> 20:1	7:1	52 %
4	 71	 72	**C2**	> 95 %	> 20:1	1:1	91 %
5			**C3**	63 %	> 20:1	1:1	n.d.
6	 28 R = $SiMe_2Ph$	 107	**C2**	0 %	–	–	–
7			**C3**	0 %	–	–	–
8	 102 R = $SiMe_2Ph$	 105	**C3**	90 %	> 20:1	9:1	71 %

[a] Conversion and ratios determined by ^1H NMR analysis of crude mixture.
[b] Isolated yield of mixture of regioisomers.
Only the major regioisomer is displayed.
Conditions for entry 1-5: Catalyst **C2** (Entry 1: 5 mol%; Entry 2, 4, 6: 10 mol%), or **C3** (2.5 mol%), Bu_3SnH, CH_2Cl_2, rt.
Conditions for entry 6: **C3** (100 mol%), Bu_3SnH, CH_2Cl_2, -50 °C.

At the beginning of this endeavor, the key-step of the outlined synthesis was set out to be a sequence consisting of *trans*-hydrostannation and protodestannation of alkyne **28** to establish an *E*-alkene motif in the macrolactone (see Chapter 3.1). The methyl groups on either side of the triple bond turned alkyne **28** into an especially challenging target as the compliance of sterically demanding substrates has not yet been studied in the necessary detail. Therefore it was decided to embark on this project by undertaking extensive studies on model substrates (see Chapter 3.2).

The first two model substrates **33** and **34** (Table 6, Entry 1-3) were designed to explore *trans*-hydrostannation on a sterically hindered acyclic ester (Entry 1) and a 14-membered macrolactone, which was lacking the steric bulk of the natural product precursor **28** (Entry 2 and 3). While structure **71** (Entry 4 and 5) served as yet another test-substrate for the reaction, it also acted as a precursor for the synthesis of analogue **45** (see Chapter 3.2.5). All these models showed excellent yields and *Z* to *E* ratios with cationic ruthenium complex **C2** (Entry 1, 2 and 4), whereas neutral ruthenium complex **C3** led to diminished conversion, while maintaining high *trans*-selectivity.

Interestingly, both tested ruthenium complexes **C2** and **C3** gave preferably the α-alkenylstannanes, with the exception of the analogue precursor **71** (Entry 4 and 5), which led to equal amounts of both regioisomers.

As the model reactions argued well for the projected case, the callyspongiolide precursor **28** was subjected to the conditions that were found suitable for *trans*-hydrostannation of the model substrates (Entry 6 and 7). However, neither of the ruthenium complexes could cause any noticeable conversion of the starting-material. Despite considerable efforts to resolve this problem (see Chapter 3.3.4) the desired alkenylstannane **107** remained elusive. It became apparent that the steric hindrance of the substrate proved to be detrimental for the desired key-step of the outlined synthesis. Since the use of bulky [Cp*Ru]-based complex is mandatory for high *trans*-selectivity,[50-51] future catalyst development must hence try to address the issue that purely steric mismatch between substrate and catalyst designates an important limitation of contemporary *trans*-addition chemistry, which is highly selective and functional group tolerant otherwise.

In the final experiment, depicted in Table 6, a modified callyspongiolide precursor was tested (Entry 8). While previous entries were lacking an -OH group in close proximity to the alkyne, this substrate would allow for hydrogen bonding with the catalytically active [Cp*RuCl] fragment (see Chapter 3.3.4.1). Indeed, through such assisted substrate binding the desired alkenylstannane **105** could be obtained in 71 % yield and exquisite *trans*-selectivity.

Although it was finally possible to produce an intermediate in the callyspongiolide synthesis comprising the desired *E*-olefin, the optimized reaction suffered from several drawbacks, such as the use of a stoichiometric amount of ruthenium-complex and upscaling-problems. Furthermore, the continuation of the synthesis of callyspongiolide from intermediate **105** would afford many additional steps in comparison to the originally outlined strategy (see Chapter 3.1), as additional homologation, esterification and RCAM reactions would be necessary.

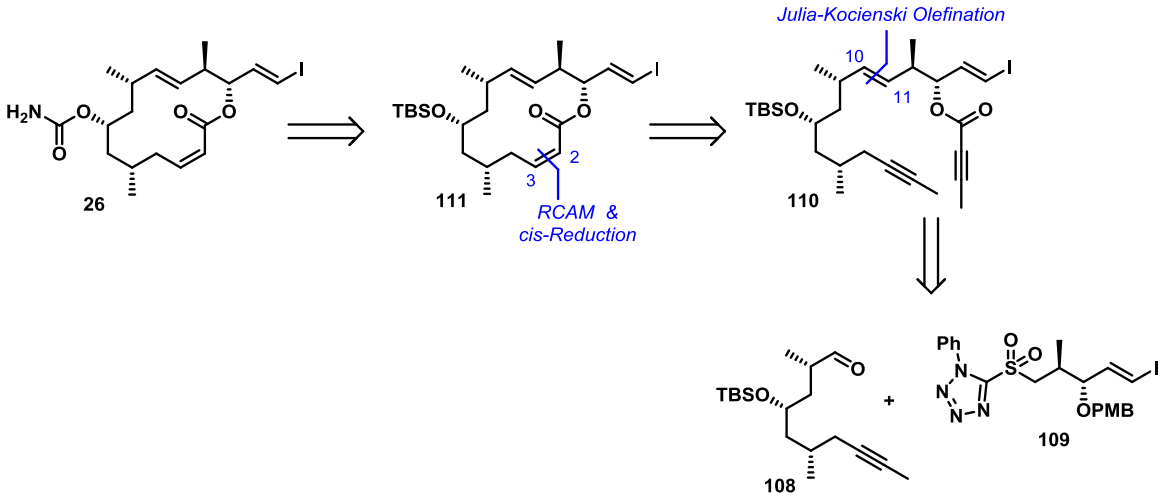
All these factors led to the conclusion that an elegant synthesis of callyspongiolide via *trans*-hydrostannation, as it was originally planned at the beginning of this endeavor, could not be realized with the current catalyst systems. In view of this lesson, an alternative approach was designed that would focus on again closing of the macrocyclic ring at the enoate functionality of callyspongiolide, which would give the opportunity to push the boundaries of alkyne metathesis.

4 Second Synthetic Approach

4.1 Retrosynthetic Analysis

The second approach to develop a synthesis for callyspongiolide was envisioned to derive from macrolactone **26**, which would be converted to the desired natural product by Sonogashira reaction with side-chain **27**, as was outlined in the original synthetic strategy (see Chapter 3.1). Regarding the macrolactone **111**, the key-disconnection, between C.2 and C.3 at the α,β-unsaturated ester position, relied on a RCAM reaction, which was followed by a *cis*-reduction (Scheme 44). The second step of this approach was deemed fairly safe in view of the plethora of canonical *Z*-selective semi-hydrogenation reactions known in the literature.[44] It was actually the projected ring-closure of an ynoate derivative which bore considerable risk as the very few attempted metathesis reactions of substrates of this type, using the classical Schrock catalyst [(*t*BuO)$_3$WC≡CC(Me$_3$)], had invariably failed.[34a, 39] Only after the advent of molybdenum alkylidynes endowed with triarylsilanolate ligands as a new generation of catalysts with a largely improved application profile,[38, 41, 100] did ynoate ring-closure became possible. The few recorded examples, however, are hardly more than proof-of-concept as they led to entirely unstrained and basically unfunctionalized macrocycles.[33, 40] Despite the lack of any serious molecular constraints in these model studies, cyclodimerization was found to infringe with the formation of a 14-membered ring.[33] Yet, the risk associated with the plan to forge the equally 14-membered core of callyspongiolide by ynoate ring closure/semi-reduction was offset by the opportunity to explore a frontier of alkyne metathesis, while trying to establish a productive route to this important lead compound.

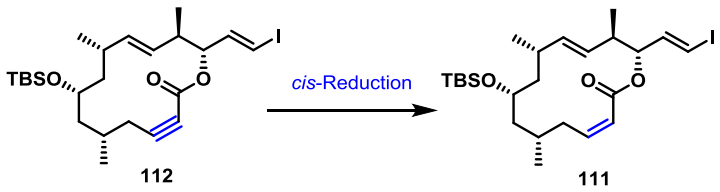
Furthermore, through disconnection of fragment **110** between C.10 and C.11, the northern fragment **109** and the southern fragment **108** were proposed. These fragments would be coupled by the Kocienski variant of the Julia olefination as late-stage maneuver,[18] a step that has precedent in the total syntheses of callyspongiolide reported by Ye *et al.*[13a] and Ghosh *et al*.[13b, 13c]



Scheme 44: Retrosynthetic analysis of callyspongiolide (***ent*-1**) – second approach.

4.2 Preliminary Experiments

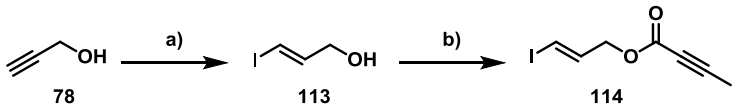
An important part of the outlined synthetic strategy was the incorporation of the alkenyl iodide moiety at an early stage of the synthesis, which was essential for the projected Sonogashira coupling in the final step of the proposed route (Scheme 44). The installment of this functionality at the fragment stage would render this approach convergent in comparison to the synthesis of analogue **45** (see Chapter 3.2.5), avoiding an additional set of steps. As this plan required a late stage *cis*-reduction of an alkyne, following the RCAM that would forge macrolactone **112**, a suitable reduction method had to be found that would establish the α,β-unsaturated ester **111**, while leaving the alkenyl iodide intact (Scheme 45).



Scheme 45: *cis*-Reduction of ynoate **112** in presence of a alkenyl iodide moiety.

Among the hydrogenation methods widely employed in total synthesis,[44d] it is generally believed that alkenyl iodides are incompatible with most conditions used for *Z*-selective semi-hydrogenation of alkynes, resulting in dehalogenation to form the corresponding olefin or leading to saturated carbon-carbon bonds.[101] Only few studies were published in recent years regarding the stability and compatibility of alkenyl iodides under various conditions for hydrogenation.[101-102] The reported methods, based on the utilization of Lindlar catalyst[22] or nickel boride (Brown's P2-Ni catalyst),[103] feature successful *cis*-reductions of propargyl alcohols in presence of an alkenyl iodide moiety. However, it remained unclear if these conditions would also be applicable to the target molecule **112**, as it contained an alkyne in α-position to an electron-withdrawing ester group, making it more electron-deficient than the substrates used in literature.[101-102] Hence, it was deemed necessary to conduct some preliminary experiments on a test-substrate in order to verify the feasibility of this approach, before the actual total synthesis could commence.

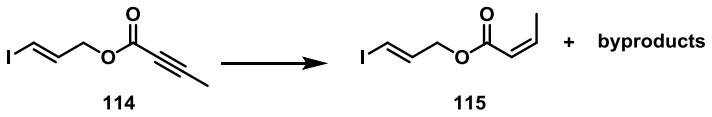
It was decided to use ester **114** as test-substrate, as it contained all structural features that were of main concern for the following hydrogenation reaction, such as an electron-deficient alkyne and a terminal alkenyl iodide. Moreover the small molecule could be simply prepared by reaction of literature known allyl alcohol **113**[104] with 2-butynoic acid (Scheme 46).



Scheme 46: Synthesis of test-substrate **114**. Conditions: a) Cp_2ZrCl_2, DIBAL-H, I_2, Et_2O/THF, -78 °C, 77 %; b) 2-butynoic acid, DIC, DMAP, CH_2Cl_2, rt, 91 %.

The results of the *cis*-reduction studies of test-substrate **114** using a Lindlar catalyst are summarized in Table 7. The reactions were performed at room temperature with 50 mol% catalyst loading at varying hydrogen pressure as reported by Parker *et al.*[102]

Table 7: Investigation of Lindlar hydrogenation of test-substrate **114**.

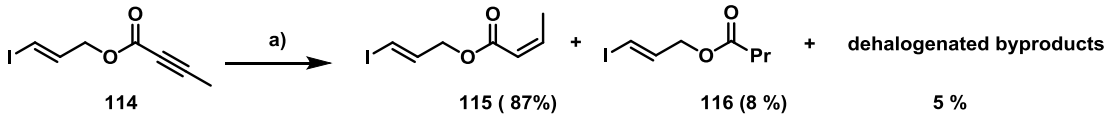


Entry	Hydrogen Pressure	Conversion [%][a)]	Product [%][a)]	Byproducts [%][a), b)]
1	1 bar	9	**9**	0
2	10 bar	31	**23**	8
3	20 bar	46	**29**	17

[a)] Ratio of compounds was determined by GCMS analysis of the crude mixture.
[b)] Possible byproducts originated from dehalogenation, isomerization and overreduction.
Conditions: H_2, Lindlar catalyst ($Pd/CaCO_3$, 50 mol%), hexane, rt, 72 h.

While the initial hydrogenation experiment at atmospheric hydrogen pressure showed only 9 % of product (Table 7, Entry 1), the conversion could be significantly improved by performing the reaction in an autoclave under elevated hydrogen pressure (Entry 2 and 3). However, at these conditions an increasing amount of byproducts from various side-reactions such as isomerization, dehalogenation and overreduction were observed (GCMS). Due to the large number of these side-reactions and the low amounts of product, it did not seem reasonable to further pursue this approach.

Next, the conditions described by Du *et al.*,[101] utilizing nickel boride as a hydrogenation catalyst were tested. Notably, this catalyst was generated *in situ* by fast addition of a sodium borohydride solution to a nickel acetate solution, causing the formation of nickel boride as a heterogeneous catalyst, appearing as fine black particles suspended in ethanol.[103] In comparison to the previous experiments employing Lindlar catalyst, this reaction could be brought to full conversion and produced the desired product **115** in 87 % (GCMS) with only minor amounts of overreduced product **116** and dehalogenated products (Scheme 47). Ethylenediamine is often used as a catalyst poison to prevent overreduction.[44d] Nonetheless, the formation of overreduced product **116** could not be prevented by increasing amounts of this additive in the reaction mixture. In its absence however, dehalogenation, isomerization and other side-reactions occurred. Experiments also revealed that once all starting-material was depleted, the amount of dehalogenated products increased rapidly. Consequently, careful monitoring of the reaction (GCMS) was required to keep the formation of dehalogenated byproducts at a minimum.



Scheme 47: Reaction of test-substrate **114**. Conditions: a) H_2 (1 atm), $Ni(OAc)_2 \cdot 4\ H_2O$ (60 mol%), $NaBH_4$ (60 mol%), ethylenediamine, EtOH, 0 °, ratio of products was determined by GCMS analysis of the crude mixture.

Reportedly, Lindlar-type hydrogenations of complex molecules that faced similar problems, such as overreduction and other chemoselectivity issues could be improved by addition of sacrificial alkenes such as cyclohexene[105] or 1-octene.[106] For this purpose variety of alkynes and alkenes were tested as an additive for the reduction (Figure 7).

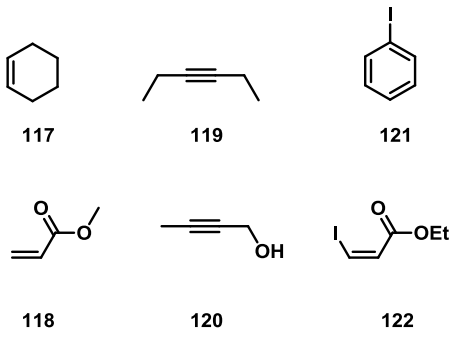
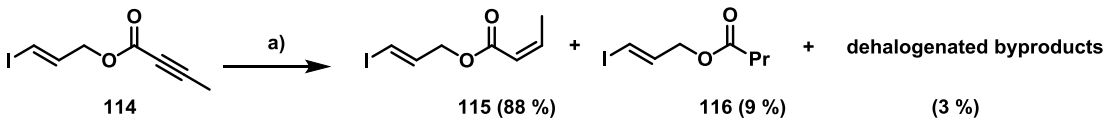


Figure 7: Tested additives to prevent oerreduction/deiodination.

During the first trial reactions excess cyclohexene **117** and acrylate **118** were examined for their use as additive to prevent overreduction and dehalogenation. However, these compounds, as well as the later tested alkynes **119** and **120**, failed to give a cleaner reaction. Finally, it was investigated whether organoiodides could remedy this problem, and while iodobenzene (**121**) could not change the outcome of the reaction, iodoacrylate **122** proved to be effective. In its presence (3 equivalents) no increase in deiodination or overreduction of the desired product was noticed on prolonged stirring (Scheme 48), releasing the requirement for extensive reaction monitoring.



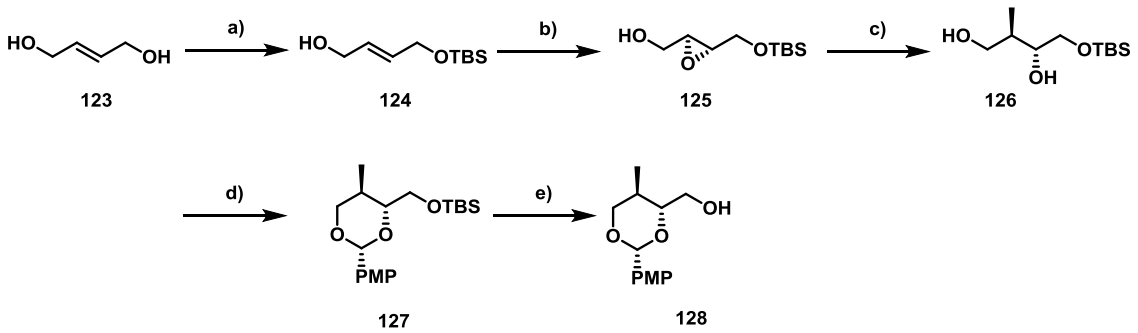
Scheme 48: Reaction of test-substrate **114** in presence of additive **122**. Conditions: a) H_2 (1 atm), $Ni(OAc)_2 \cdot 4\ H_2O$ (60 mol%), $NaBH_4$ (60 mol%), ethylenediamine, **122** (3 equiv.), EtOH, 0 °C to rt, ratio of products was determined by GCMS analysis of the crude mixture.

In summary, while the initial Lindlar hydrogenation of alkyne **114** proved to be ineffective, the *cis*-reduction was successfully accomplished upon employing Brown's P2-Ni catalyst[103] in combination with iodoacrylate **122** as additive, acting as a proper mimic of the actual substrate. This demonstrates the superior functional group tolerance of this catalyst compared to the Linldar catalyst, despite being less frequently used for this type of transformation.[44d] After securing an effective method for the formation of the desired *cis*-alkene **111**, the fragment synthesis could be initiated.

4.3 Synthesis of the Northern Fragment

The preparation of the required northern fragment **109** commenced with the mono-silylation of commercially available but-2-en-1,4-diol (**123**), which gave good results on scale when carried out at low temperature. Sharpless epoxidation[107] of the resulting product furnished compound **125** (93 % *ee*),[108] which underwent a highly selective hydroxy-directed ring-opening with MeMgBr/CuI to give multigram quantities of diol **126** in excellent yield (Scheme 49).[108b]

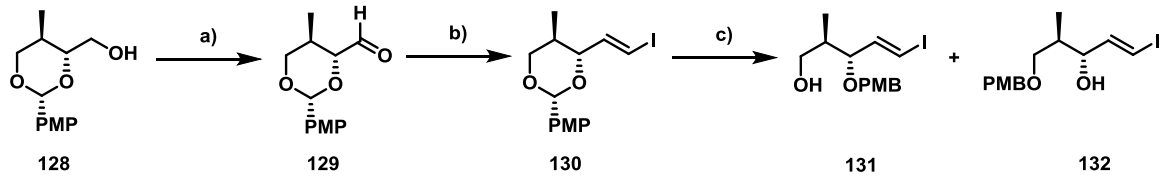
Protection of the diol-functionality of compound **126** delivered *p*-methoxybenzylidene acetal **127**, which was subsequently converted to primary alcohol **128** in good yield.



Scheme 49: Synthesis of primary alcohol **128**. Conditions: a) TBSCl, NaH, THF, rt, 69 %; b) Ti(O*i*Pr)$_4$ (24 mol%), L-(+)-diethyl tartrate (30 mol%), *t*BuOOH, CH_2Cl_2, –20°C, 88 % (93 % *ee*); c) MeMgBr, CuI (30 mol%), Et_2O/THF, –20 °C, 91 %; d) $MeOC_6H_4CH(OMe)_2$, PPTS (10 mol%), CH_2Cl_2, rt, 85 %; e) TBAF, THF, rt, 88 %.

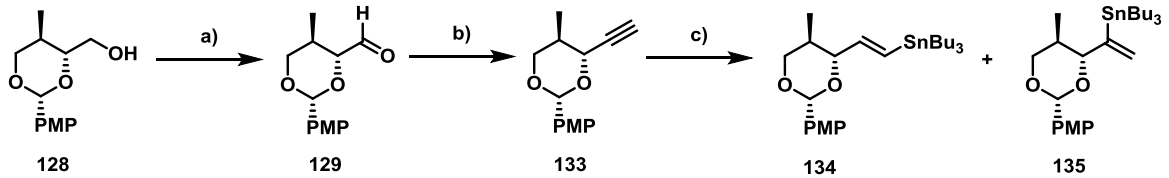
The derived acetal **128** was readily transformed into aldehyde **129**, which proved rather sensitive and prone to epimerization (Scheme 50).[109] The reaction was performed following a procedure developed by Mukaiyama *et al.*,[110] which was a variation of the Corey-Kim oxidation.[111] The aldehyde was then elaborated via Takai olefination[64] into alkenyl iodide **130**, as necessary for the later attachment of the side-chain of callyspongiolide. However, this approach proved to be surprisingly troublesome since this reaction required large excess of $CrCl_2$ (26 equivalents) and delivered the product unsatisfying *E* to *Z* ratio (5:1).

The subsequent reductive acetal opening with DIBAL-H delivered the desired primary alcohol **131** in poor yield with a considerable amount of regioisomer **132**, possibly due to a lack of steric hindrance exerted by the alkenyl iodide moiety.[112] Therefore an alternative route towards targeted compound **109** was pursued.



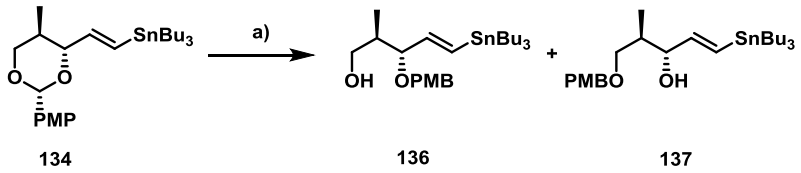
Scheme 50: Synthesis of alkenyl iodide **131**. Conditions: a) NCS, K_2CO_3, PhSNH*t*Bu (10 mol%), 4 Å MS, CH_2Cl_2, rt, 74 %; b) $CrCl_2$·THF (26 eq.), CHI_3, THF, 0 °C, 60 % (*E*/*Z* = 5:1); c) DIBAL-H, CH_2Cl_2, –50 °C, 43 % (63 % brsm, *E*/*Z* = 4:1), regioisomer **132** 15 %.

In this route, aldehyde **129** was furnished by Swern oxidation, which delivered the desired product in higher yields compared to the previous approach (Scheme 50). Moreover, the resulting crude product could be directly used without any further purification in the following transformation into the corresponding terminal alkyne **133** with the Bestmann-Ohira reagent.[21] Preactivation of this reagent with NaOMe prior to the addition of aldehyde at low temperature was crucial for the success of this homologation reaction as other conditions led to considerable epimerization at the chiral center next to the aldehyde moiety (Scheme 51).[42c, 113] The subsequent formation of the alkenylstannane **134** was performed under free radical conditions in excellent yield with only minor amounts of undesired regioisomer **135**,[114] while attempts at palladium-catalyzed hydrostannation[115] were inefficient.



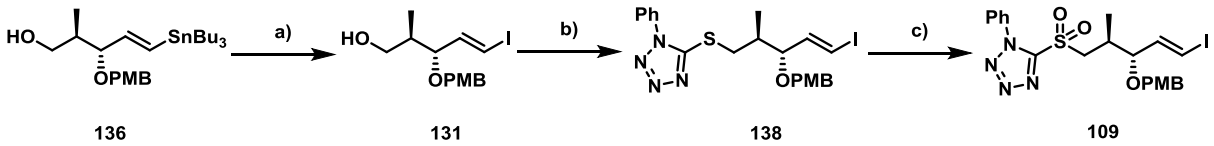
Scheme 51: Synthesis of alkenylstannane **134**. Conditions: a) $(COCl)_2$, DMSO, Et_3N, –78 °C; b) $H_3CC(=O)C(=N_2)P(=O)(OMe)_2$, NaOMe, THF, –78 °C to –50 °C, 74 % over two steps; c) Bu_3SnH, AIBN, benzene, reflux, 84 % (*E*/*Z* = 8:1), regioisomer **135** 11 %.

As the previous route was hampered by the insufficient regioselectivity of the reductive opening of *p*-metoxybenzylidene **130**, it was assumed that by masking the iodide-functionality as the considerably bulkier tributyltin-moiety the selectivity problem could be remedied. Indeed, upon treatment of acetal **134** with DIBAL-H the desired regioisomer **136**, as the major product, was obtained in appreciable yield alongside small amounts of the corresponding regioisomer **137** (Scheme 52).[116]



Scheme 52: Synthesis of primary alcohol **136**. Conditions: a) DIBAL-H, CH_2Cl_2, 0 °C, 68 %, regioisomer **137** 11 %.

The subsequent tin/iodine exchange furnished alcohol **131** in excellent yield and provided further proof of the advantages of employing a tributyltin-group in this approach. The following preparations of thioether **138** and sulfone **109**, described by Ye *et al.*,[13a] sufficed to complete the synthesis of this fragment without any further issues (Scheme 53).

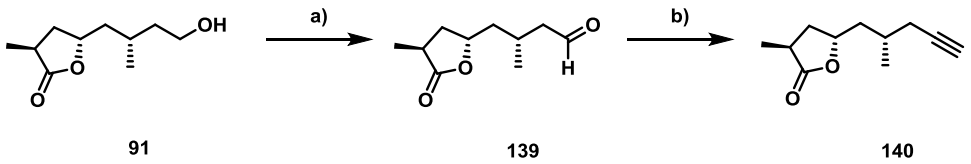


Scheme 53: Synthesis of sulfone **109**. Conditions: a) I_2, CH_2Cl_2, 0 °C to rt, 94 %; b) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, quant. yield; c) aq. H_2O_2, $(NH_4)_6Mo_7O_{24}$ (50 mol%), EtOH, 72 %.

In conclusion, the synthesis of the northern fragment **109** of the second synthetic approach was completed with an overall yield of 12 % over 12 steps. Despite causing additional effort through the more elaborate installation of the alkenyl iodide functionality, the presented detour appears to be the more practical and scalable route.

4.4 Synthesis of the Southern Fragment

The required aldehyde partner **108** for the later olefination with sulfone **109** was attained by adaptation of the previously described southern fragment synthesis of the first synthetic approach (see Chapter 3.3.2). To this end, the readily available butyrolactone derivative **91** was converted to aldehyde **139**, which served as precursor for the transformation into the corresponding alkyne **140**. In order to avoid epimerization of the stereocenter in α-position of the lactone carbonyl-group during the alkyne formation, the same conditions as in the previous northern fragment synthesis were employed (see Chapter4.3) using preactivated Ohira-Bestmann reagent[21] at low temperatures (Scheme 54).[42c, 113] However, due to low yields an alternative route was pursued.

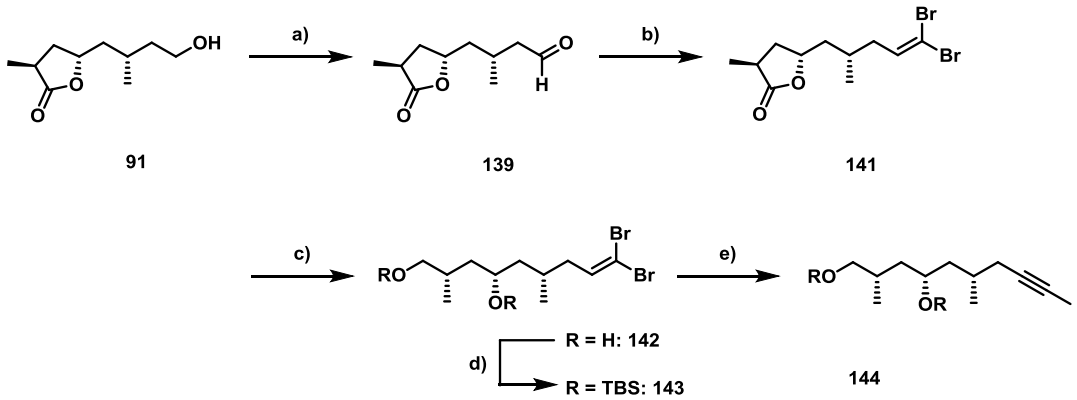


Scheme 54: Synthesis of lactone **140**. Conditions: a) DMP, $NaHCO_3$, CH_2Cl_2, rt, 82 %; b) $H_3CC(=O)C(=N_2)P(=O)(OMe)_2$, NaOMe, THF, –78 °C to –65 °C, 68%.

By changing the aldehyde preparation to the procedure of Stahl *et al.*[74] the purity of the resulting aldehyde **139** was sufficient to allow for its direct use in the following olefination without any further purification (Scheme 55). In this route the alkyne was introduced via Corey-Fuchs reaction,[117] which ususally consists of a two-step procedure in which the aldehyde is first converted into a dibromoolefin and subsequently exposed to *n*BuLi resulting in a Fritsch-Buttenberg-Wiechel rearrangement[118] furnishing an alkyne. However, as epimerization was likely to occur under these conditions, it was decided to postpone the second step and retain the dibromoolefin-functionality, until the lacton moiety, containing the concerned chiral center, was reduced and epimerization would no longer be possible. Hence, the derived dibromoolefin **141** was obtained in excellent yield by using standard means.[117]

Next, reduction of the lactone moiety, followed by persilylation delivered dibromoolefin **143**. Treatment of this compound with *n*BuLi and subsequent quenching of the reaction with methyl iodide afforded directly the internal alkyne **144**.[117] Although, a previous example (see Chapter3.3.4.1) had proven that RCAM between a terminal alkyne and an internal alkyne to forge a 14-membered ring is possible, it was decided to proceed with fragments featuring methyl-capped alkynes. Considering the already highly challenging nature of the planned ynoate ring-closing, this approach appeared to be more reasonable.

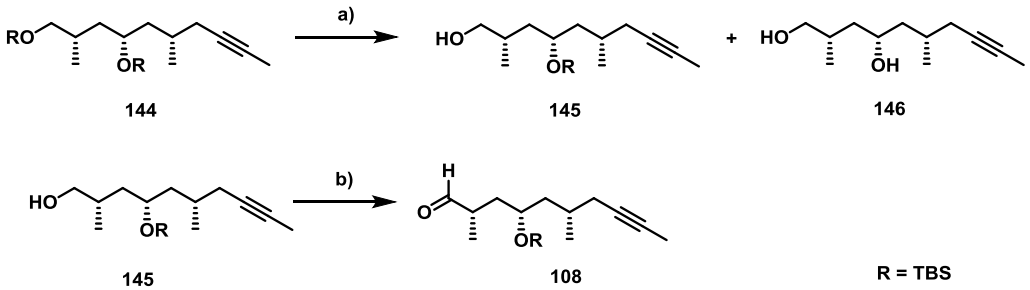
To summarize, the replacement of the alkyne formation with Ohira-Bestmann reagent[21] in favor of a Corey-Fuchs reaction[117] provided compound **144** with improved yield, while the step-count in the overall strategy remained unchanged as the former reaction would only produce a terminal alkyne, which would require an additional alkylation-step to furnish the desired internal alkyne.



Scheme 55: Synthesis of alkyne **144**. Conditions: a) O_2 (1 atm), $[Cu(MeCN)_4]BF_4$ (5 mol%), 2,2'-bypyridine (5 mol%), TEMPO (5 mol%), NMI (10 mol%), MeCN, rt, 97 %; b) CBr_4, PPh_3, CH_2Cl_2, rt, 92 %; c) $LiBH_4$, MeOH, Et_2O, 97 %; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 98 %; e) *n*BuLi, MeI, THF, –78 °C to rt, 96 %.

The selective cleavage of the primary TBS ether in **144** proved delicate as the desired product **145** was furnished alongside considerable amounts of diol **146**.[78b] Further investigations revealed that the reaction was best accomplished with HF pyridine in THF/pyridine by stopping the reaction prior to full conversion in order to minimize overreaction (Scheme 56). The resulting diol was recycled. Other attempts to use a similar substrate containing a TBDPS protection group instead of a TBS-silylether at the primary alcohol position, utilizing a similar procedure as described in the synthesis of analogue **45**, resulted in poor yield (see Chapter 3.2.5.3).[73]

Finally, primary alcohol **145** was oxidized via Swern oxidation to give aldehyde **108** in readiness for the fragment coupling. The resulting aldehyde could be conveniently used in the next step without any further purification. In this case the Stahl oxidation was also attempted, however, it proved to be ineffective, despite being described for complex substrates bearing alkyl substituents in α-position of the formed aldehyde.[74]

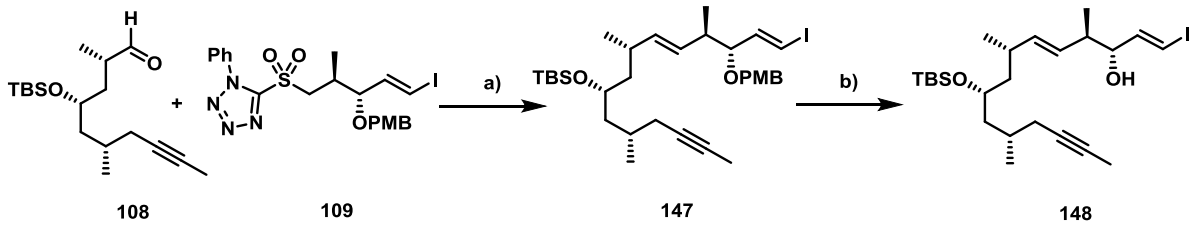


Scheme 56: Synthesis of aldehyde **108**. Conditions: a) HF·pyridine, pyridine, THF, 63 % (77 % brsm), diol **146** 17 %; b) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C.

In conclusion, the synthesis of the southern fragment **108** of the second synthetic approach was achieved with an overall yield of 23 % over 12 steps.

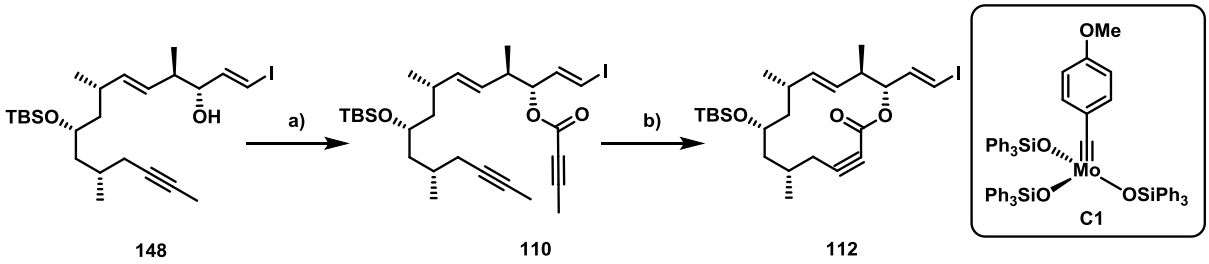
4.5 Fragment Assembly and Endgame

With both the northern fragment **109** and the southern fragment **108** in hand, the assembly of these compounds via the Kocienski variant of the Julia olefination[18] could be examined (Scheme 57). Careful optimization of the reaction conditions showed the use of LiHMDS as the base to be optimal. While Ye *et al.*[13a] and Sasaki *et al.*[119] employed a mixture of THF and HMPA as solvent for an olefination with similar fragments, only low selectivity and poor yield were achieved upon application of these conditions to the concerned reaction. However, significant improvement was accomplished when DMF was used as solvent, as described by Ghosh *et al.*,[13b, 13c] furnishing alkene **147** in high selectivity for the required *E*-isomer (*E/Z* = 15:1). For the sake of robustness and yield, a slight excess of the lithiated sulfone **109** (1.45-1.5 equivalents) was used, which could be largely recovered after work-up, leading to a clean and well reproducible reaction. Further attempts to improve the yield by addition of Lewis acids such as $CeCl_3$ and $LaCl_3 \cdot 2LiCl$ were unsuccessful.[120]
Oxidative cleavage of the PMB group[121] with DDQ under buffered conditions afforded secondary alcohol **148** in fair yield as a single isomer after purification.



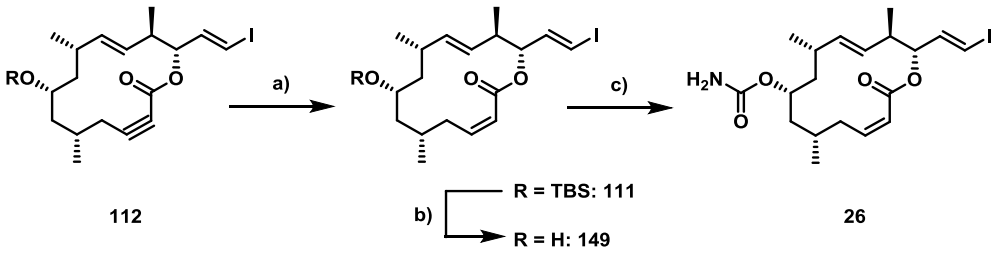
Scheme 57: Synthesis of secondary alcohol **148**. Conditions: a) LiHMDS, DMF, –78 °C, 57 % (*E*/*Z* = 15:1) over two steps; b) DDQ, CH_2Cl_2, phosphate buffer (pH 7.4), 63 %.

The following DIC-mediated esterification[122] of the resulting secondary alcohol with 2-butyonic acid furnished diyne **110** in readiness for macrocyclization (Scheme 58). Despite the largely missing precedent for alkyne metathesis reactions of ynaotes in general,[33, 40] treatment of compound **110** with the molybdenum alkylidyne complex **C1** resulted in fast, clean and essentially quantitative ring closure at ambient temperature.[38a] The desired cycloalkyne **112** was isolated in analytically pure form in 96 % yield. This remarkable outcome further attests to the maturity that alkyne metathesis has reached in recent years as well as to the excellent application profile of this class of alkyne metathesis catalysts previously developed by Fürstner *et al.*[38b, 41, 100]



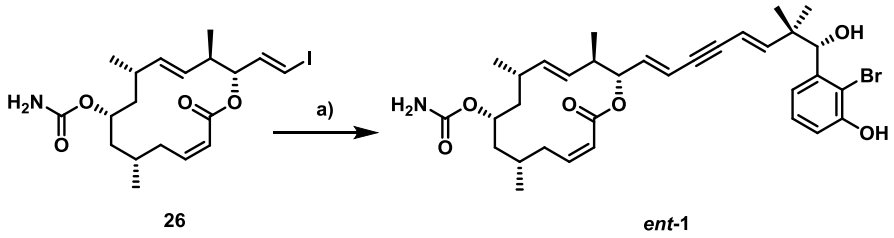
Scheme 58: Synthesis of cycloalkyne **112**. Conditions: a) 2-butynoic acid, DIC, DMAP, CH_2Cl_2, 87 %; b) **C1** (15 mol%), 5 Å MS, toluene, rt, 96 %.

Following the results of the preliminary studies (see Chapter 4.2) nickel boride (Brown's P2-Ni catalyst)[103] was used as hydrogenation catalyst in combination with the optimized conditions developed for model substrate **114**. However, upon application of these conditions only incomplete conversion was observed. An increase in catalyst loading, by adjusting the amounts of added sodium borohydride and nickel acetate from 60 mol% to 3 equivalents respectively, allowed the problem to be remedied (Scheme 59). As previously shown (Scheme 48), iodoacrylate **122** worked excellently as sacrificial alkene. In its presence (3 equivalents) dehalogenation as well as overreduction of the precious cycloalkyne **112** were reliably reduced to as little as ≤ 4 and ≤ 12 % (NMR) in each case. Even, prolonged stirring did not cause an increase in deiodination or overreduction. In absence of this sacrificial compound the reaction would only furnish product mixtures comprising appreciable amounts of the corresponding dehalogenated product (up to 18 % HPLC/MS). Other reduction methods such as activated zinc dust,[123] or reductive decomplexation of a dicobalthexacyrbonyl complex, used by Inoue *et al*.,[124] failed to deliver the desired product. With a robust access to **111** secured, the sequence was completed by cleavage of the remaining TBS-ether and installation of the conspicuous carbamate functionality.[125] Only at this stage could the byproducts formed during the previous reduction step be separated affording the pure precursor for the final step of the synthesis.



Scheme 59: Synthesis of carbamate **26**. Conditions: a) H_2 (1 atm), $Ni(OAc)_2 \cdot 4\ H_2O$ (3 eq.), $NaBH_4$ (3 eq.), ethylenediamine, **122** (3 eq.), EtOH, 0 ° to rt; b) Camphorsulfonic acid, CH_2Cl_2/MeOH, rt; c) Chlorosulfonyl isocyanate, CH_2Cl_2 then aq. THF, rt, 76 % over three steps.

The total synthesis of callyspongiolide was completed by Sonogashira coupling[16] of macrolactone **26** with the side-chain **27** affording the final product in excellent yield and purity (Scheme 60). The conditions used in this reaction were identical to those successfully applied in the final step of the synthesis of the analogue **45** (see Chapter 3.2.5.5). In order to avoid side-reactions such as Hay/Glaser copper-catalyzed homocoupling of the terminal alkyne,[126] it was essential to remove oxygen from the solvent prior to the reaction.[16c]



Scheme 60: Synthesis of (+)-callyspongiolide (***ent*-1**). Conditions: a) **27**, $Pd(PPh_3)_4$ (10 mol%), CuI, DIPEA, THF, rt, 80 %.

In conclusion the synthesis of callyspongiolide (***ent*-1**) was successfully performed with an overall yield of 4 % and 20 steps in the longest linear sequence. The analytical and spectral data of the prepared synthetic samples of callysopongiolide were in excellent accord with those reported in the literature (see Chapter 6.4.3),[11, 13a-d] with exception to the misconception at the outset of this project, owing to the mis-assigned absolute configuration in the original report.[11]

5 Summary and Conclusion

During the course of this thesis, ring-closing alkyne metathesis (RCAM) and *trans*-selective hydrostannation were investigated in the context of a challenging total synthesis campaign. The marine macrolide callyspongiolide was chosen as a target for total synthesis, due to its unique structural features, which made the molecule well suited for the application and investigation of alkyne formation and postmetathetic transformations. Moreover, callyspongiolide immediately attracted attention from the synthetic community for its potentially relevant biological profile as well for its scarcity. These studies culminated in two partial[15] and four total syntheses,[13] which corrected the absolute configuration, originally assigned to the macrolide core by the isolation team,[11] and firmly established the previously unknown configuration of the C.21 chiral center in the side-chain. Based on this work, callyspongiolide is correctly described by structure **1** (Figure 8). As our study had been initiated before the absolute stereochemistry of callyspongiolide was corrected, the enantiomer *ent*-**1** originally proposed by the isolation team dictated the stereochemical format of the project described herein. Despite this unfortunate misconception at the outset of this project, in terms of investigation into scope and limitations of contemporary alkyne metathesis and relevant downstream chemistry, the non-natural callyspongiolide enantiomer proved to be a valuable synthetic target. For further evaluation of the biological activity, however, adaption of the synthesis to the natural series would meet no difficulty.

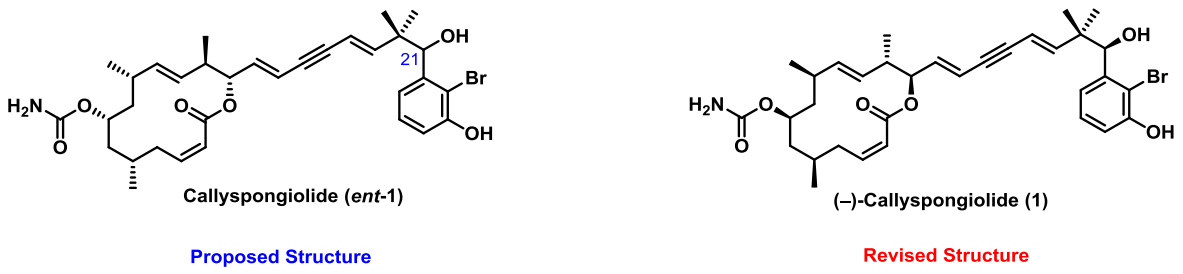
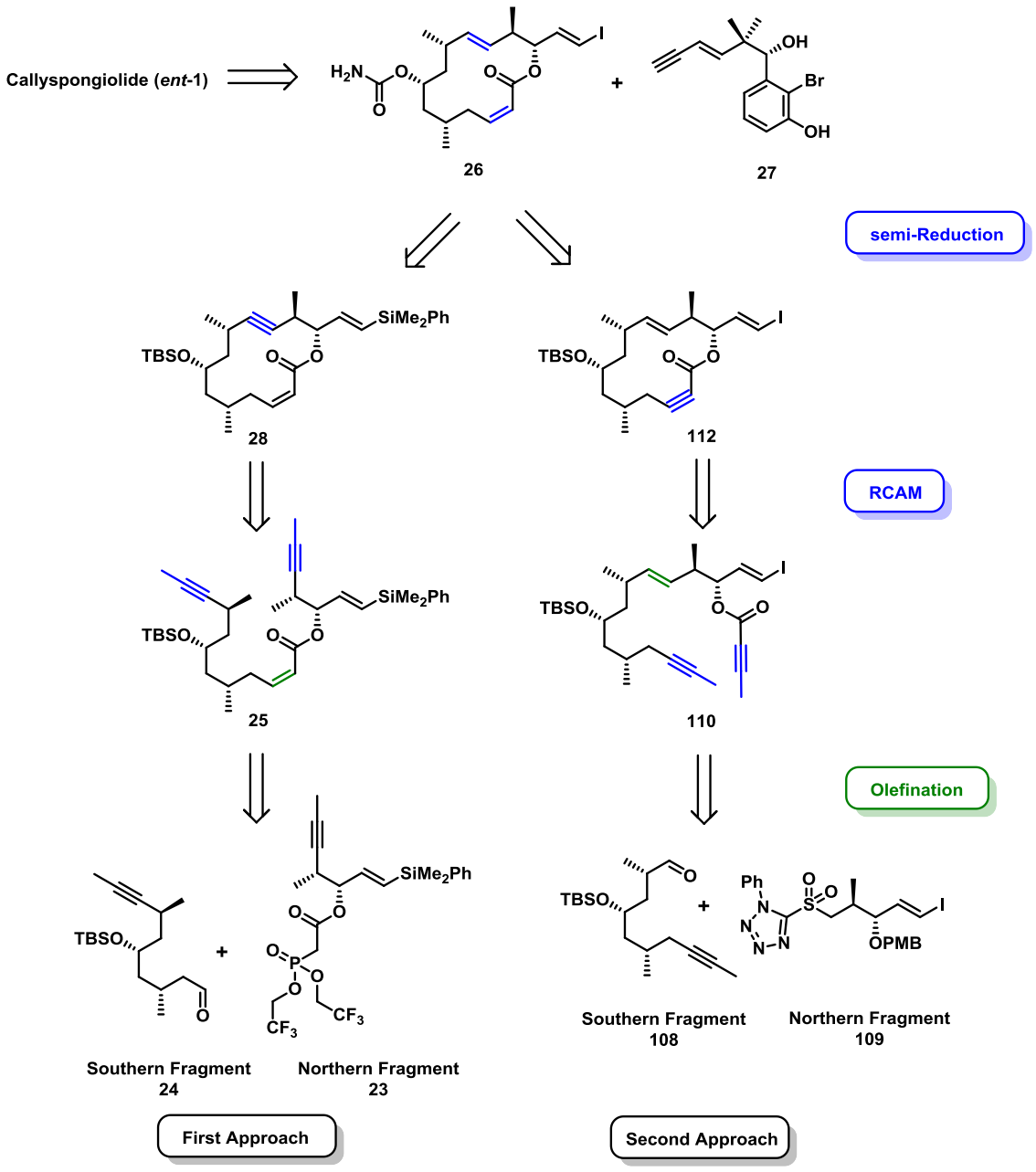


Figure 8: Originally proposed structure of callyspongiolide (left) in comparison to the revised version (right) posing as the enantiomer of the former molecule.

5.1 Strategic Overview

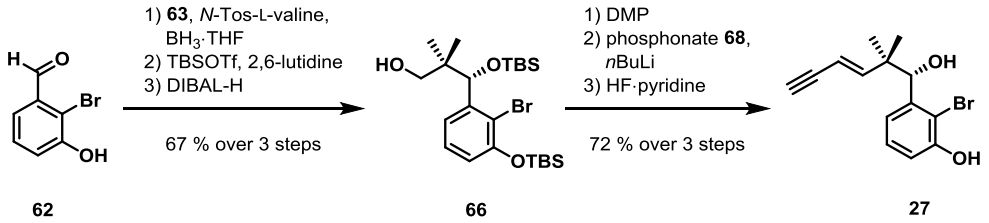
The synthesis of callyspongiolide was pursued via two different routes that were explored during the course of this thesis (Scheme 61). These approaches were envisioned to capitalize on olefination, RCAM and semi-reduction as key-steps for the formation of the macrolactone core of the final product. The retrosynthetic disconnections would result in two distinctive fragments for each strategy, while utilizing similar methodologies to generate the target molecule.



Scheme 61: Two approaches towards callyspongiolide based on RCAM, followed by semi-reduction were envisaged.

While the first approach utilized a sequence of *trans*-hydrostannation and protodestannation as postmetathetic transformation to obtain the desired macrolactone motif, the second approach relied on a RCAM of an alkynoate precursor followed by a Lindlar-type reduction to produce the callyspongiolide precursor **26**.

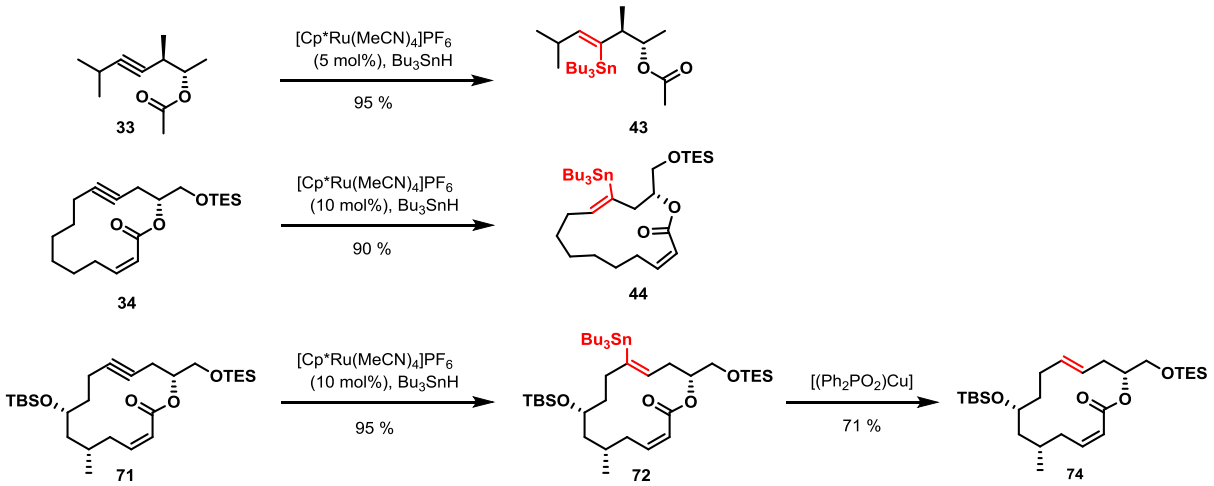
In both approaches the side-chain fragment **27** was introduced via Sonogashira coupling[16] in the final step, while the strategy for the construction of the macrolactone frame notably differed between these routes. The synthesis of the side-chain started with a Mukaiyama aldol reaction[75] of commercially available aldehyde **62**. Excellent optical purity was achieved by recrystallization of the crude product of the first step (ee > 99 %). After TBS-protection and adjustment of the oxidation state, the enyne-functionality was installed via Horner-Wadsworth-Emmons olefination.[76] Global deprotection furnished fragment **27** in 6 steps and 48 % overall yield (Scheme 62).



Scheme 62: Synthesis of side-chain **27**.

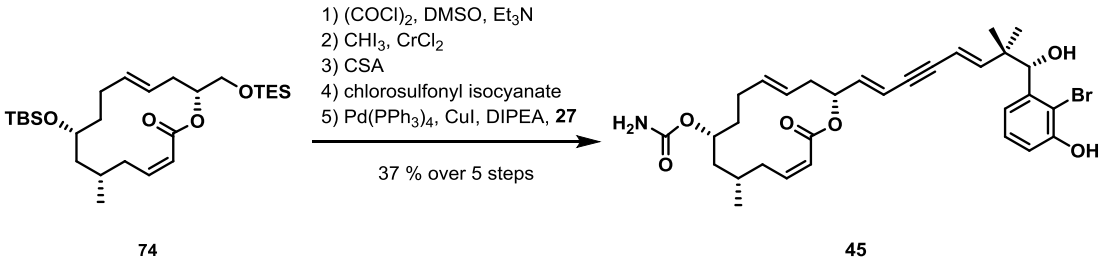
5.2 First Synthetic Approach

For the semi-reduction of the sterically demanding macrolactone **28**, the feasibility of the *trans*-hydrostannation was imperative for this approach. Therefore, extensive model studies were performed (Scheme 63) to ensure its viability. The success of these experiments indicated that this methodology should also be applicable as the key-step in the envisioned total synthesis. The work presented in this chapter was performed in collaboration with Dr. Guillaume Mata.[58]



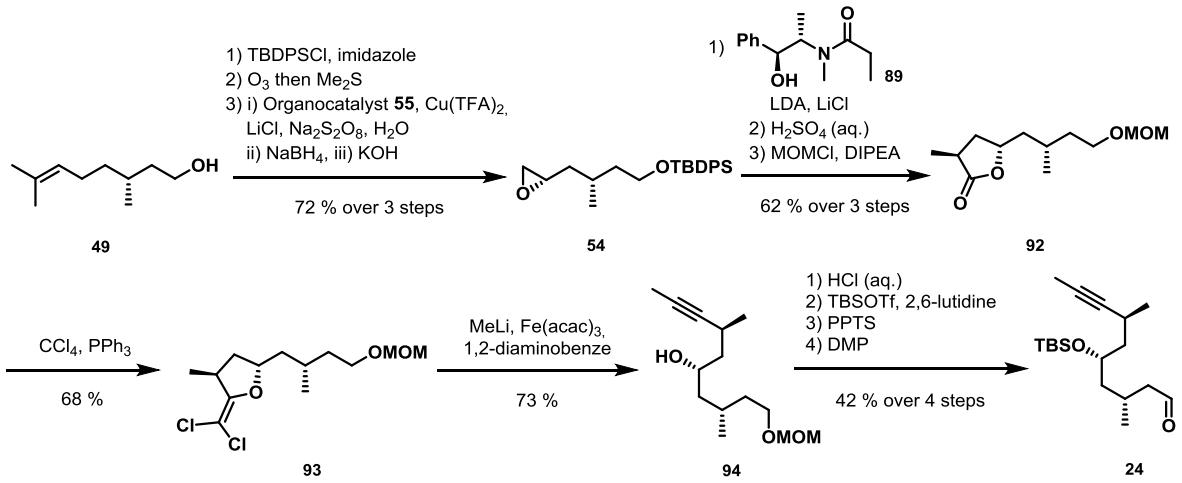
Scheme 63: Results of the *trans*-hydrostannation trials on three model substrates. Only the major regioisomer of the obtained alkenylstannanes is displayed.

In this context, a callyspongiolide analogue was synthesized from model substrate **71** (Scheme 64). Thus macrolactone **74** was subjected to Swern oxidation of the TES-ether, followed by Takai olefination[64] to install an alkenyl iodide moiety. After further functional group manipulation the synthesis was concluded with the attachement of side-chain **27** via Sonogashira coupling,[16] which furnished analogue **45** in 17 steps and 7 % overall yield in longest linear sequence.



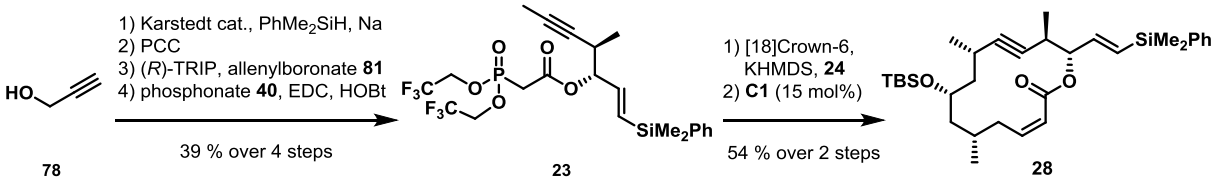
Scheme 64: Preparation of a callyspongiolide analogue **45**.

The southern fragment **24** was synthesized from the literature known epoxide **54**,[66] which was obtained from commercially (*R*)-(+)-citronellol (**49**) using MacMillan's imidazolidinone catalyst **55** for α-chlorination of an aldehyde intermediate (Scheme 65).[65] The following reductive work-up delivered the desired epoxide in high diastereomeric purity (d.r. = 97:3), which subsequently served to alkylate the propionate enolate derived from amide **89**.[90] The following cleavage of the chiral auxiliary and lactone formation were achieved in one step by treatment with acid. After protection of the primary alcohol functionality, the resulting product **92** was subjected to a two-step procedure developed by Fürstner *et al.*[91] in order to install the methyl-capped alkyne functionality in compound **94**. Further protecting group manipulation and oxidation completed the synthesis of the aldehyde fragment **23**, which was achieved with an overall yield of 9 % over 12 steps.



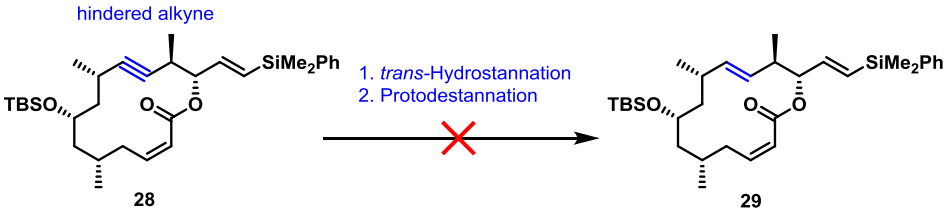
Scheme 65: Synthesis of southern fragment **24**.

The synthesis of the northern fragment **23** was accomplished in four steps with an overall yield of 39 % from propargyl alcohol, which was hydrosilylated and oxidized. The resulting aldehyde was reacted with allenylboronate **81** in presence of catalytic amounts of a chiral Brønsted acid, according to a protocol developed by Roush *et al.*,[84] to afford an *anti*-configured homopropargyl alcohol in high yield and selectivity (d.r. = 20:1). The fragment synthesis was finished by formation of phosphonate ester **23**. The northern and southern fragments were combined through a Still-Gennari olefination,[19] which furnished the desired olefin in good selectivity for the required *Z*-isomer (*Z/E* = 6:1). The subsequent macrocyclization by RCAM proceeded smoothly with the help of molybdenum alkylidyne **C1**, which formed the sterically challenging alkyne **28** in excellent yield (Scheme 66).



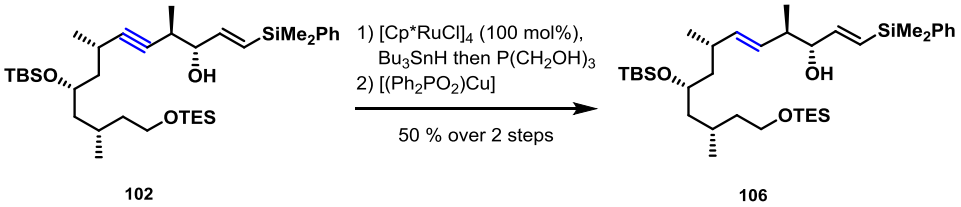
Scheme 66: Synthesis of northern fragment **23** and fragment assembly.

While the presence of the two flanking methyl branches did not affect the alkyne metathesis to any noticeable extent, it was unfortunate to learn that these groups were detrimental for the envisaged *trans*-hydrometalation of cycloalkyne **28** (Scheme 67). Despite considerable experimentation (see Chapter 3.3.4), neither *trans*-hydrostannation nor *trans*-hydrosilylation[46] proved viable. As this reaction represented the key-step of the outlined synthesis, the need arose to develop alternative approaches that would either encompass an advanced intermediate which would be presumably more suitable for this methodology or investigate other routes avoiding *trans*-hydrometalation as a whole.



Scheme 67: Key-steps of the outlined synthesis.

In an attempt to enhance catalyst binding and improve reactivity compound **102** was prepared comprising a homopropargyl alcohol functionality (Scheme 68). Indeed, through assisted substrate binding (see Chapter 3.3.4.1),[50, 51b] it was finally possible to produce an intermediate in the callyspongiolide synthesis containing the desired *E*-olefin. However, the optimized reaction suffered from several drawbacks, such as the use of a stoichiometric amount of ruthenium-complex and upscaling-problems. Furthermore, the continuation of the synthesis of callyspongiolide from intermediate **106** would afford many additional steps in comparison to the originally outlined strategy. Considering these circumstances it became evident that this approach was not a practical solution for the synthesis of the target molecule, which ultimately led to the discontinuation of this route.



102 106

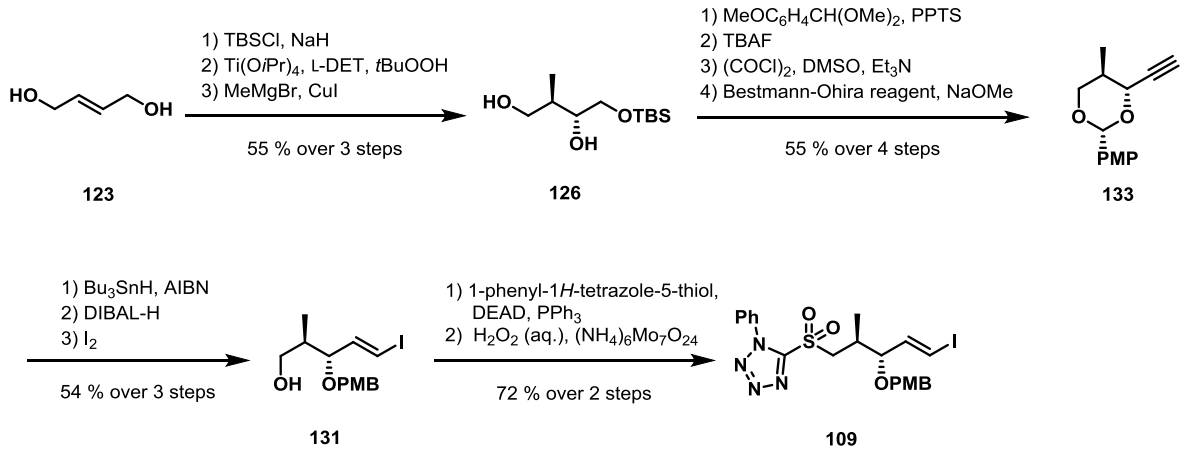
Scheme 68: *trans*-Hydrostannation of an alternative intermediate in the synthesis of callyspongiolide.

All these factors led to the conclusion that synthesis of callyspongiolide via *trans*-hydrostannation, as it was originally planned at the beginning of this endeavor, could not be realized with the current catalyst systems. The collected evidence suggests that the problem of the first approach is steric in nature. In view of this lesson, an alternative approach was designed, which would focus on exploring the boundaries of alkyne metathesis.

5.3 Second Synthetic Approach

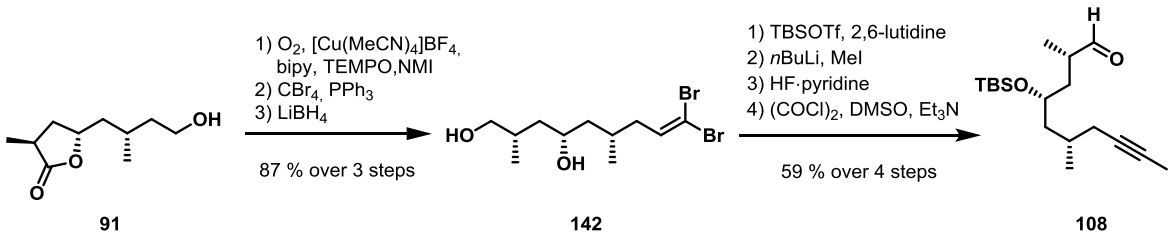
Confronted with the findings of the previous approach, the synthesis blueprint was adjusted such that the *Z*-configured enoate became the new strategic disconnection site (Scheme 61). However, the planned ring-closure of an ynoate bore considerably more risk as only a few examples of ynoate ring-closure can be found in the literature, which lead to entirely unstrained and simple macrocycles.[33, 40] Additionally, these model studies noted substantial cyclodimerization when forming a 14-membered ring (see Chapter 1.3.1).[33] As such, the risk associated with this new plan was offset by the opportunity to explore the frontier in alkyne metathesis while establishing an efficient route to the target compound.

The synthesis of northern fragment **109** started from the commercially available diol **123**, which was protected and consequently subjected to Sharpless epoxidation (Scheme 69).[107] The resulting epoxide, which was furnished in high enantiomeric purity (93 % *ee*), then underwent highly selective hydroxy-directed ring-opening to give diol **126**. After standard functional group manipulation and Swern oxidation the obtained aldehyde was transformed into the corresponding terminal alkyne **133** on treatment with Bestmann-Ohira reagent,[21] which had to be preactivated with NaOMe prior to addition of the aldehyde to avoid epimerization.[42c] The primary alcohol **131** was derived from a hydrostannation of **133** under free radical conditions, followed by reductive opening of the *p*-methoxybenzylidene acetal ring and tin/iodine exchange. Two routine steps then sufficed to complete the synthesis of sulfone **109** as necessary for fragment coupling with an overall yield of 12 % over 12 steps.



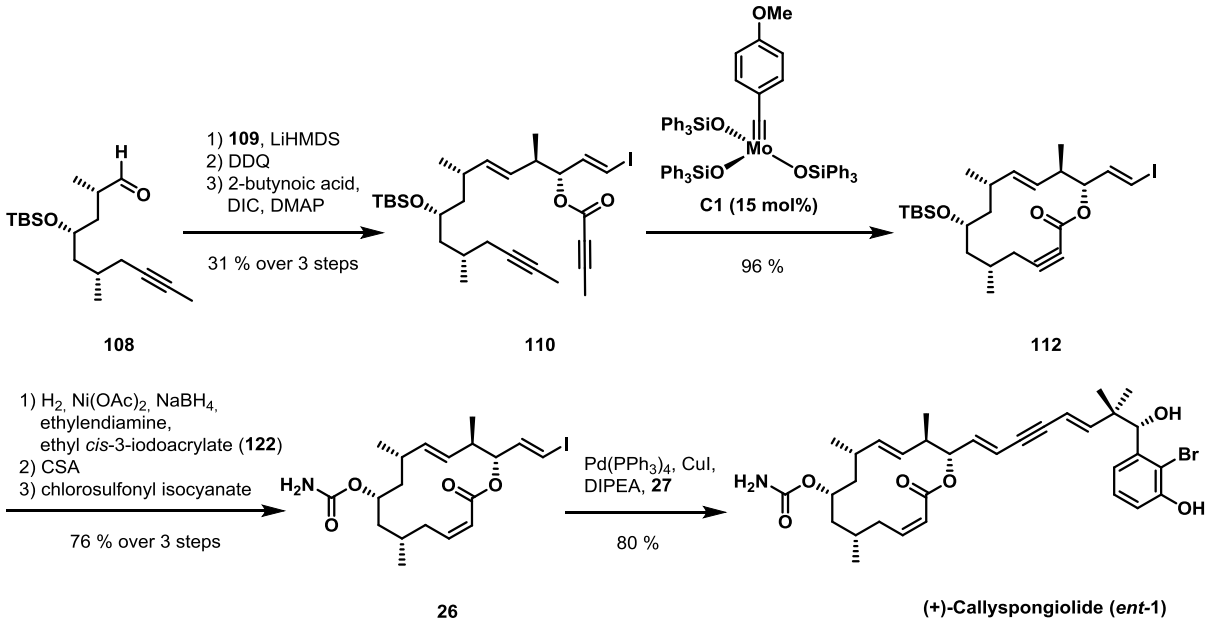
Scheme 69: Synthesis of norther fragment **109**.

The required aldehyde partner was attained by adaption of the previously described synthesis of fragment **108** in the first approach (Scheme 70). To this end, lactone **91** was subjected to Stahl oxidation[74] and the resulting aldehyde transformed into a dibromoolefin by standard means. Reduction of the lactone moiety resulted in diol **142**, which was persilylated. Subsequent treatment with *n*BuLi/MeI, furnished an alkyne. Selective cleavage of the primary TBS-ether followed by Swern oxidation afforded aldehyde **108** in 12 steps and 23 % overall yield.



Scheme 70: Synthesis of southern fragment **108**.

The fragments were combined via the Kocienski variant of the Julia olefination (Scheme 71).[18] Careful optimization of the reaction conditions was required in order to obtain the desired olefin in high selectivity for the required *E*-isomer (*E/Z* = 15:1). Oxidative cleavage of the PMB group under buffered conditions, followed by DIC-mediated esterification of the resulting secondary alcohol furnished diyne **110** in readiness for macrocyclization. Gratifyingly, treatment of compound **110** with alkylidyne complex **C1** resulted in fast, clean and essentially quantitative ring-closure. The ease of formation of **112** shows that metathesis of ynoates and related electron deficient substrates certainly warrants more detailed investigation. The semi-reduction of alkyne **112**, on the other hand, was found to be particularly challenging due to possible overreduction at three different sites and cleavage of the C-I bond at the alkenyl iodide terminus. The formation of dehalogenated substrate considerably reduced the number of feasible *Z*-selective semi-hydrogenation methods. The lack of chemoselectivity, apparent at the hydrogenation, was in stark contrast to the previous ring-closure, which was initially expected as more problematic. Good results were obtained with nickel boride as catalyst[103] in the presence of iodoacrylate **122** as sacrificial additive, which considerably reduced the dehalogenation and overreduction of the cycloalkyne **112**. The total synthesis of callyspongiolide was completed by cleavage of the remaining TBS-ether, followed by the installation of the carbamate functionality and the attachement of the side-chain via Sonogashira coupling.[16]



Scheme 71: Fragment assembly and endgame.

The final product was obtained with an overall yield of 4 % and 20 steps in the longest linear sequence, which makes this synthesis one of the most efficient approaches towards callyspongilide to date (see Chapter 1.2). A noteworthy feature of the outlined strategy was the implementation of a late-stage Lindlar-type semi-reduction of an alkyne in presence of an alkenyl iodide. Although this challenge was ultimately mastered, this total synthesis campaign revealed significant gaps in methodological coverage when polyfunctional substrates need to be addressed.[44d]

The project that had originally intended to merely establish an efficient entry into the cytotoxic marine macrolide callyspongiolide gradually turned into a much broader investigation into scope and limitations of the contemporary alkyne metathesis and relevant downstream chemistry. Overall, it could be shown that this transformation allowed the macrocyclic ring of the target to be closed with similar efficiency at two sites that differed considerably in their steric and electronic character. Notably, this study also provides the first convincing illustration that even complex ynoates can be generated by alkyne metathesis. The maturity of alkyne metathesis, manifest in these examples, stands in certain contrast to the difficulties encountered during the semi-reduction studies presented in this thesis. The emerging field of ruthenium catalyzed *trans*-addition chemistry as a gateway to *E*-alkenes, though successfully used in the context of natural product synthesis on many occasions,[45, 47] finds an important limitation when it comes to the applications to sterically hindered triple bonds. Likewise, seemingly routine Lindlar-type hydrogenations prove challenging when other reducible sites are present in the substrate. Future investigations into improved catalysts that tackle these gaps in methodological coverage could certainly pay off in synthetic dividend.

6 Experimental Section

6.1 General

Unless stated otherwise, all reactions were carried out in flame-dried glassware using anhydrous solvents under argon. The following solvents and organic bases were purified by distillation over drying agents and transferred under argon: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (CaH_2), toluene (Na/K), MeOH (Mg, stored over MS 3 Å); DIPEA, DMF, DMSO, 1,4-dioxane, Et_3N, MeCN and pyridine were dried by an adsorption solvent purification system based on molecular sieves. All commercially available compounds (abcr, Acros, Alfa Aesar, Aldrich, TCI, Strem Chemicals) were used as received unless otherwise noted.

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

Flash chromatography was performed on Merck silica gel 60 (40–63 µm) or Macherey-Nagel fine silica gel 60 (15-40 µm) with pre-distilled or HPLC grade solvents.

NMR Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated. Chemical shifts (δ) are given in ppm relative to TMS; coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.16 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; C_6D_6: δ_C = 128.06 ppm; residual C_6D_5H: δ_H = 7.16 ppm; DMSO-d_6 δ_C= 39.5 ppm; residual CD_3CHD_2SO, δ_H=2.50 ppm). Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: puartet, quint: quintet, hept: heptet, m: multiplet. The abbreviation “br” indicates a broad signal. ^{13}C spectra were recorded in [^1H]-decoupled mode and the values of the chemical shifts are rounded to one decimal point. All spectra from 500 MHz and 600 MHz spectrometers were acquired by the NMR department under the guidance of Dr. Christpophe Farès at the Max-Planck-Institut für Kohlenforschung.

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

Mass spectrometric samples were measured by the department for mass spectrometry at the Max-Planck- Institut für Kohlenforschung using the following devices: MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FTMS (7 T magnet) or Mat 95 (Finnigan).

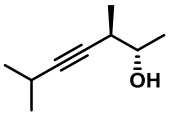
Optical rotations were measured with an A-Krüss Optronic Model P8000-T polarimeter at a wavelength of 589 nm. The values are given as specific optical rotation with exact temperature, concentration (c / (10 mg/mL)) and solvent.

Melting points (m.p.) were measured on a Büchi Melting Point B-540 and are uncorrected.

6.2 Preliminary Experiments and Synthesis of an Analogue

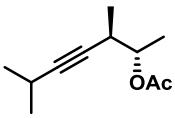
6.2.1 Synthesis and Testing of Model Substrates

(2*S*,3*R*)-3,6-Dimethylhept-4-yn-2-ol (32)[58]



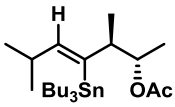
*n*BuLi (1.6 M in hexanes, 20.9 mL, 32.64 mmol) was added over 5 min to a solution of 3-methyl-1-butyne (3.51 mL, 34.36 mmol) at –78°C. The resulting mixture was stirred for 30 min before $BF_3{\cdot}Et_2O$ (3.13 mL, 25.8 mmol) and *cis*-2,3-epoxybutane (1.5 mL, 17.18 mmol) were consecutively added and stirring continued at this temperature for 1 h. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5 then 90:10) to afford the product as a colorless and volatile oil (2.0 g, 83%). (Note: *This compound was used immediately in the next step as it decomposes readily*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.54 (quint, J_1 = 6.1 Hz, 1H), 2.52 (septet doublet, J_1 = 6.9 Hz, J_1 = 2.0 Hz, 1H), 2.42-2.35 (m, 1H), 2.05 (br, s, 1H), 1.18 (d, J_1 = 6.2 Hz, 3H), 1.12 (d, J_1 = 6.8 Hz, 6H), 1.11 (d, J_1 = 5.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 89.4, 79.7, 70.8, 34.9, 23.50, 23.49, 20.8, 20.6, 17.7; **IR** (neat): 3377, 2970, 2934, 2876, 1452, 1375, 1320, 1265, 1098, 100, 914 cm^{-1}.

(2*S*,3*R*)-3,6-Dimethylhept-4-yn-2-yl acetate (33)[58]



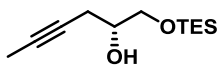
Triethylamine (0.286 mL, 2.05 mmol), Ac_2O (0.194 mL, 2.05 mmol) and DMAP (22 mg, 0.18 mmol) were consecutively added to a solution of alcohol **32** (0.250 g, 1.78 mmol) at room temperature. Stirring was continued for 1 h at this temperature before the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to afford the product as a colorless and volatile oil (0.300 g, 92 %). (Note: *This compound was used immediately in the next step as it decomposes readily*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.88 (quint, J_1 = 6.3 Hz, 1H), 2.63-2.57 (m, 1H), 2.53-2.46 (m, 1H), 2.03 (d, J_1 = 1.1 Hz, 3H), 1.18 (d, J_1 = 6.2 Hz, 3H), 1.22 (dd, J_1 = 6.4 Hz, J_2 = 1.0 Hz, 3H), 1.12-1.08 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 170.7, 87.9, 79.8, 72.6, 31.1, 23.42, 23.40, 21.4, 20.5, 16.7, 16.4; **IR** (neat): 2973, 2937, 2877, 1736, 1371, 1236, 1072, 1018 cm^{-1}.

(2*S*,3*S*,*Z*)-4-(Butyl-stannyl)-3,6-dimethylhept-4-en-2-yl acetate (43)[58]



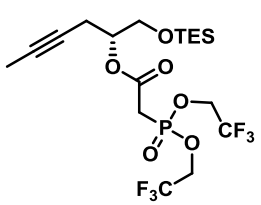
Bu_3SnH (61.5 mg, 0.211 mmol) was added over 10 min to a solution of alkyne **33** (35 mg, 0.192 mmol) and $[Cp^*Ru(CH_3CN)_3]PF_6$ (4.8 mg, 9.6 µmol, 5 mol%) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 15 min before all volatile materials were evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford the product as a colorless oil (86 mg, 95%, *Z*:*E* > 20:1 and α:β = 4:1). Characterization of the α and *Z* isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.80 (d, J_1 = 9.4 Hz, $J_{Sn\text{-}H}$ = 132.8 Hz, 1H), 4.82-4.79 (m, 1H), 2.39-2.32 (m, 1H), 2.12-2.06 (m, 1H), 1.97 (s, 3H), 1.49-1.42 (m, 6H), 1.36-1.27 (m, 6H), 1.14 (d, J_1 = 6.2 Hz, 3H), 0.98-0.87 (m, 24H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 170.5, 148.3, 142.2, 73.9, 48.6, 34.6, 29.4, 27.7, 23.5, 23.4, 21.5, 17.6, 17.2, 13.8, 11.2; **IR** (neat): 2956, 2925, 2871, 1733, 1458, 1371, 1241, 1070, 1044 cm^{-1}; **MS** (EI): *m*/*z* (%) 417 (M^+–57, 31), 416 (12), 415 (23), 413 (13), 297 (17), 295 (15), 294 (11), 293 (100), 292 (33), 291 (76), 290 (27), 289 (44), 179 (42), 178 (13), 177 (43), 176 (14), 175 (28), 123 (17); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{46}O_2SnNa$ $[M + Na]^+$ 497.24146, found 497.24113.

(*R*)-1-((Triethylsilyl)oxy)hex-4-yn-2-ol (39)



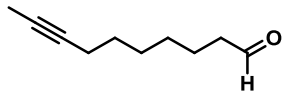
A solution of compound **38**[60] (2.00 g, 10.62 mmol) in THF (4 mL) was added dropwise at −78°C to a solution of 1-propynyllithium (1.14 g, 22.3 mmol) in THF (28 mL). The mixture was stirred for 5 min before $BF_3{\cdot}OEt_2$ (3.17 g, 22.3 mmol) was introduced. After stirring the resulting suspension for 7 h at this temperature, the cooling bath was removed and the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (pentane/Et_2O, 8:1) to afford the product as a colorless oil (1.46 g, 60 %). $[\alpha]_D^{20}$ = –13.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.79 – 3.71 (m, 1H), 3.69 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.57 (dd, *J* = 9.9, 6.1 Hz, 1H), 2.52 (s, 1H), 2.39 – 2.32 (m, 2H), 1.78 (t, *J* = 2.6 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 8.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 77.9, 75.0, 70.6, 65.5, 23.5, 6.8, 4.5, 3.7; **IR** (neat): 3428, 2954, 2914, 2876, 1459, 1415, 1379, 1239, 1110, 1070, 1006, 969, 940, 803, 725, 673 cm^{-1}; **MS** (EI): *m/z* (%) 199 (12), 145 (18), 143 (21), 115 (13), 105 (20), 103 (100), 87 (18), 75 (77); **HRMS** (ESI-pos.) calcd. for $C_{12}H_{24}O_2SiNa$ $[M + Na]^+$ 251.14378, found 251.14402.

(*R*)-1-((Triethylsilyl)oxy)hex-4-yn-2-yl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate (41)



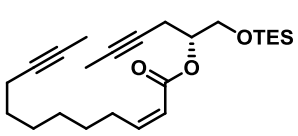
Phosphonoacetic acid **40**[61] (920 mg, 3.03 mmol), HOBt (97.2 mg, 0.604 mmol) and EDC (724 mg, 3.78 mmol) were successively added to a solution of compound **39** (345 mg, 1.51 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred for 4 h at this temperature before the solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 80:20) to afford the product as a colorless oil (594 mg, 76 %). $[\alpha]_D^{20}$ = –1.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.97 (ddt, *J* = 6.5, 5.8, 4.9 Hz, 1H), 4.55 – 4.39 (m, 4H), 3.76 (dd, *J* = 5.0, 1.1 Hz, 2H), 3.18 (dd, *J* = 20.9, 1.4 Hz, 2H), 2.59 – 2.38 (m, 2H), 1.76 (t, *J* = 2.6 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.2 (d, $^2J_{C,P}$ = 4.0 Hz, 1C), 122.6 (qd, $^1J_{C,F}$ = 277.5 Hz, $^3J_{C,P}$ = 8.6 Hz, 2C), 78.3, 75.2, 73.7, 64.1 – 61.9 (m, 3C), 34.2 (d, $^1J_{C,P}$ = 144.9 Hz, 1C), 20.7, 6.8, 4.4, 3.5; **IR** (neat): 2959, 2917, 2879, 1739, 1459, 1418, 1296, 1264, 1167, 1097, 1068, 1005, 961, 897, 843, 801, 729, 656 cm^{-1}; **HRMS** (ESI-pos.) calcd. for $C_{18}H_{29}O_6F_6PSiNa$ $[M + Na]^+$ 537.12675, found 537.12724.

Dec-8-ynal (36)



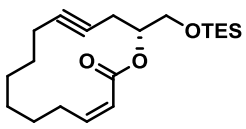
Dess-Martin periodinane (1.03 g, 2.43 mmol) was added to a solution of alcohol **35**[59] (248 mg, 1.61 mmol) at 0 °C. The resulting mixture was stirred for 5h at room temperature before the reaction was quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (pentane/Et_2O, 12:1) to afford the product as a colorless oil (185 mg, 75 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.76 (t, J = 1.8 Hz, 1H), 2.42 (td, J = 7.3, 1.8 Hz, 2H), 2.11 (tt, J = 6.8, 2.5 Hz, 2H), 1.77 (t, J = 2.6 Hz, 3H), 1.64 (p, J = 7.4 Hz, 2H), 1.50 – 1.29 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.8, 79.2, 75.7, 44.0, 28.9, 28.8, 28.7, 22.1, 18.8, 3.6; **IR** (neat): 2932, 2858, 2718, 1723, 1462, 1411, 1390, 1358, 1242, 1091, 1027, 731, 687, 524 cm^{-1}; **MS** (EI): *m/z* (%) 152 (M^+, 0.1), 95 (15), 93 (30), 91 (18), 81 (29), 79 (39), 77 (14), 69 (13), 68 (100), 67 (56), 66 (11), 65 (11), 55 (46), 54 (29), 53 (34), 43 (14), 41 (46), 39 (31), 29 (17), 27 (20); **HRMS** (EI) calcd. for $C_{10}H_{17}O$ $[M + H]^+$ 153.12794, found 153.12779.

(*R*)-1-((Triethylsilyl)oxy)hex-4-yn-2-yl (*Z*)-dodec-2-en-10-ynoate (42)



KHMDS (62.5 mg, 0.313 mmol) was added at −78°C to a solution of phosphonate **41** (160 mg, 0.310 mmol) and [18]-crown-6 (410 mg, 1.55 mmol) in THF (3.8 mL). The mixture was stirred for 1 h before a solution of aldehyde **36** (45 mg, 0.296 mmol) in THF (1.7 mL) was added dropwise. Stirring was continued at this temperature for 4 h before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (fine silica gel, hexane/EtOAc, 98:2) to afford the product (73.8 mg, 62 %) as a colorless oil. $[\alpha]_D^{20}$ = –5.9 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.23 (dt, J = 11.5, 7.5 Hz, 1H), 5.77 (dt, J = 11.5, 1.7 Hz, 1H), 5.26 – 4.67 (m, 1H), 4.12 – 3.57 (m, 2H), 2.65 (qdd, J = 7.4, 2.9, 1.7 Hz, 2H), 2.61 – 2.32 (m, 2H), 2.11 (tq, J = 7.2, 2.5 Hz, 2H), 1.77 (dt, J = 5.4, 2.6 Hz, 6H), 1.53 – 1.30 (m, 8H), 0.95 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.9, 151.1, 119.8, 79.4, 77.6, 75.6, 74.5, 72.5, 62.9, 29.2, 29.1, 29.1, 29.0, 28.9, 20.9, 18.8, 6.8, 4.5, 3.7, 3.6; **IR** (neat): 2931, 2858, 2719, 1723, 1461, 1410, 1391, 1261, 1092, 1026, 804, 733, 521 cm^{-1}; **MS** (EI): *m/z* (%) 376 (M^+–28, 10), 375 (34), 280 (23), 279 (100), 133 (10), 103 (11), 79 (10); **HRMS** (EI) calcd. for $C_{24}H_{40}O_3Si_1$ $[M]^+$ 404.27467, found 404.27480.

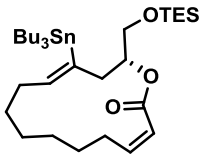
(*R,Z*)-14-(((Triethylsilyl)oxy)methyl)oxacyclotetradec-3-en-11-yn-2-one (34)



A flame-dried flask was charged with freshly activated molecular sieves 5 Å (powder, 2.5 g), compound **42** (63.5 mg, 0.157 mmol) and toluene (80 mL). The suspension was stirred for 1 h at room temperature before a solution of the molybdenum alkylidyne complex **C1** (24.5 mg, 23.5 µmol, 15 mol%) in toluene (1 mL) was added in one portion. Stirring was continued for 1 h at this temperature. For work-up, the mixture was filtered through a pad of silica gel, which was rinsed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the product as a colorless oil (48.6 mg, 88 %). $[\alpha]_D^{20}$ = +24.2 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.12 (ddd, J = 11.6, 10.1, 6.1 Hz, 1H), 5.86 (ddd, J = 11.5, 2.0, 1.1 Hz, 1H), 5.24 – 5.13 (m, 1H), 3.71 (dd, J = 10.5, 5.1 Hz, 1H), 3.64 (dd, J = 10.5, 6.1 Hz, 1H), 3.13 (td, J = 15.5, 15.0, 9.5 Hz, 1H), 2.62 – 2.35 (m, 3H), 2.26 – 2.03 (m, 2H), 1.57 – 1.40 (m, 4H), 1.38 – 1.16 (m, 4H), 0.95 (t, J =

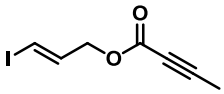
7.9 Hz, 9H), 0.59 (q, J = 7.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.3, 149.5, 121.0, 82.2, 76.2, 71.8, 63.8, 28.1, 26.9, 26.7, 26.6, 25.7, 21.6, 18.4, 6.8, 4.5; **IR** (neat): 2952, 2913, 2875, 1724, 1642, 1457, 1412, 1181, 1158, 1126, 1091, 1014, 809, 727 cm^{-1}; **MS** (EI): *m/z* (%) 322 (M^+–28, 25), 321 (100), 303 (19), 291 (13), 265 (12), 183 (16), 173 (14), 159 (13), 157 (20), 145 (15), 133 (19), 131 (15), 117 (27), 105 (17), 103 (64), 93 (11), 91 (18), 87 (20), 81 (10), 79 (10), 75 (37); **HRMS** (ESI-pos.) calcd. for $C_{20}H_{34}O_3SiNa$ $[M + Na]^+$ 373.26194, found 373.21690.

(*R*,3*Z*,11*Z*)-12-(Tributylstannyl)-14-(((triethylsilyl)oxy)methyl)oxacyclotetradeca-3,11-dien-2-one (44)



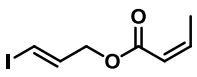
A solution of Bu_3SnH (11.9 mg, 40.9 µmol) in CH_2Cl_2 (100 µL) was slowly added to a solution of alkyne **34** (11.6 mg, 33.1 µmol) and $[Cp^*Ru(CH_3CN)_3]PF_6$ (1.7 mg, 3.3 µmol, 10 mol%) in CH_2Cl_2 (0.6 mL). The mixture was stirred for 1h before all volatile materials were evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford the product as a colorless oil (19.1 mg, 90 %, *E:Z* > 20:1, α:β = 86:14). Characterization of the α and *Z* isomer: $[\alpha]_D^{20}$ = -41.4 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (600 MHz,$CDCl_3$) δ 5.99 (td, *J* = 11.6, 4.3 Hz, 1H), 5.84 (dd, *J* = 11.5, 1.7 Hz, 1H), 5.81 (dd, *J* = 10.6, 3.2 Hz, 1H), 5.04 (dtd, *J* = 11.3, 5.7, 1.5 Hz, 1H), 3.66 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.58 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.25 (dtd, *J* = 16.1, 12.0, 4.5 Hz, 1H), 2.55 (dq, *J* = 13.9, 1.8 Hz, 1H), 2.30 (dd, *J* = 14.1, 11.1 Hz, 1H), 2.26 (ddd, *J* = 13.6, 5.6, 3.0 Hz, 1H), 2.17 (ddd, *J* = 14.6, 4.3, 2.5 Hz, 1H), 1.68 (dddd, *J* = 14.5, 13.2, 10.8, 2.1 Hz, 1H), 1.58 (ddd, *J* = 16.7, 9.0, 4.6 Hz, 1H), 1.54 – 1.48 (m, 6H), 1.46 (ddd, *J* = 8.9, 6.3, 1.0 Hz, 1H), 1.32 (dq, *J* = 14.5, 7.3 Hz, 8H), 1.33 – 1.27 (m, 1H), 1.27 – 1.19 (m, 2H), 1.09 – 1.03 (m, 2H), 0.99 – 0.93 (m, 6H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.90 (t, *J* = 7.3 Hz, 9H), 0.80 (ddd, *J* = 12.5, 6.5, 4.3 Hz, 1H), 0.60 (q, *J* = 7.9 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 165.8, 148.2, 144.4, 139.8, 121.4, 72.4, 65.0, 43.0, 34.5, 29.2, 28.7, 27.5, 27.1, 26.2, 25.7, 25.0, 13.7, 10.3, 6.7, 4.4;**^{119}Sn NMR** (149 MHz, $CDCl_3$) δ: –54.5 (major isomer); –54.0; **IR** (neat): 2955, 2922, 2875, 2855, 1723, 1644, 1458, 1412, 1376, 1239, 1207, 1183, 1161, 1127, 1092, 1011, 858, 813, 745, 667cm^{-1}; **MS** (ESI): *m/z* $[M + H]^+$ 643; **HRMS** (ESI-pos.) calcd. for $C_{32}H_{63}O_3SiSn$ $[M + H]^+$ 643.35623, found 643.35650.

***(E)*-3-iodoallyl but-2-ynoate (114)**



2-Butynoic acid (195 mg, 2.32 mmol), DMAP (42.6 mg, 0.348 mmol), triethylamine (176 mg, 1.74 mmol) and EDCI·HCl (579 mg, 3.02 mmol) were successively added to a solution of alcohol **113**[104] (214 mg, 1.61 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 19 h before the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to afford the product as a colorless oil (209 mg, 72 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.64 (dt, J = 14.6, 5.9 Hz, 1H), 6.56 (dt, J = 14.6, 1.0 Hz, 1H), 4.55 (dd, J = 5.9, 1.0 Hz, 2H), 2.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.1, 138.7, 86.7, 82.3, 72.1, 66.7, 4.0; **IR** (neat): 2239, 1704, 1611, 1440, 1369, 1238, 1191, 1084, 1062, 981, 942, 810, 749, 668, 571 cm^{-1}; **MS** (EI): *m/z* (%) 250 (3), 167 (20), 123 (18), 77 (16), 67 (100), 39 (16); **HRMS** (ESI-pos.) calcd. for $C_7H_7O_2INa$ $[M + Na]^+$ 272.938297, found 272.93801.

(*E*)-3-Iodoallyl (*Z*)-but-2-enoate (115)[58]

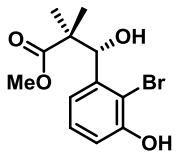


A solution of $NaBH_4$ (11.3 mg, 0.30 mmol) in ethanol (0.5 mL, not dry) was added in one portion to a solution of $Ni(OAc)_2·4H_2O$ (74.6 mg, 0.30 mmol) in ethanol (1.8 mL). The resulting black suspension was vigorously stirred for 30 min at room temperature. Ethylenediamine (8.0 µL, 0.12 mmol) and a solution of alkyne **114** (25 mg, 0.10 mmol) in ethanol (0.5 mL) were added. The flask was sealed with a septum and connected to a balloon of H_2. The mixture was stirred for 20 min before it was flushed with argon. The reaction was carefully quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 97:3) to afford the product as a colorless and volatile oil (8.5 mg, 34%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.67 (dt, *J* = 14.6, 6.1 Hz, 1H), 6.50 (dt, *J* = 14.5, 1.4 Hz, 1H), 6.38 (dq, *J* = 11.4, 7.2 Hz, 1H), 5.81 (dq, *J* = 11.4, 1.8 Hz, 1H), 4.53 (dd, *J* = 6.0, 1.4 Hz, 2H), 2.15 (dd, *J* = 7.3, 1.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.84, 146.45, 139.97, 120.03, 80.81, 65.18, 15.64; **IR** (neat): 3046, 2926, 2853, 1720, 1647, 1611, 1440, 1360, 1246, 1163, 1088, 983, 939, 813 cm^{-1}; **MS** (EI): *m/z* (%) 167 (M^+–85, 21), 125 (8), 69 (100), 41 (27), 39 (38); **HRMS** (ESI-pos.) calcd. for $C_7H_9O_2I_1Na_1$ $[M + Na]^+$ 274.95395, found 274.95373.

6.2.2 Synthesis of the Side-chain

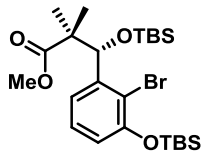
The following reactions listed in this chapter, depicting the preparation of side-chain **27**, were carried out by Dr. Guillaume Mata.[58]

Methyl (*S*)-3-(2-bromo-3-hydroxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (64)



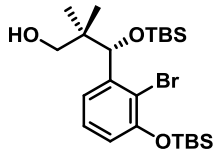
BH_3·THF (1 M in THF, 23.5 mL, 23.51 mmol) was added dropwise to a solution of *N*-Tos-L-Val-OH (6.68 g, 24.62 mmol) in THF (190 mL) at 0 °C. After the gas evolution had ceased, the mixture was stirred at room temperature for 20 min before it was cooled to –78 °C. 2-Bromo-3-hydroxybenzaldehyde **62** (4.50 g, 22.39 mmol) was added in one portion followed by ketene acetal **63** (5.22 mL, 25.74 mmol). Stirring was continued at –78 °C for 3 h before the reaction was quenched with a phosphate buffer solution (pH = 7). The mixture was warmed to room temperature and extracted with EtOAc (3 x). The combined extracts were washed with sat. aq. $NaHCO_3$ (2 x) and brine (1 x) and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5 then 75:25) to afford the product as a white solid (4.89 g, 72 %, 89 % *ee*). The product was recrystallized from CH_2Cl_2 to afford crystals suitable for X-ray diffraction (>99 % *ee*). $[\alpha]_D^{20}$ = –29.2 (*c* 0.64, $CHCl_3$); HPLC (150 mm Chiralpak IC-3, 4.6 mm, *n*-heptane/2-propanol = 95:5, 1.0 mL/min, 298K, 65 bar), t_R (*R*) = 22.45 min (minor), t_R (*S*) = 24.76 min (major); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.22 (t, J = 7.9 Hz, 1H), 7.05 (ddd, J = 7.8, 1.6, 0.4 Hz, 1H), 6.97 (dd, J = 8.0, 1.6 Hz, 1H), 5.76 (s, 1H), 5.41 (d, J = 4.2 Hz, 1H), 3.76 (s, 3H), 3.45 (d, J = 4.8 Hz, 1H), 1.21 (s, 3H), 1.21 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.4, 151.0, 139.4, 127.3, 120.3, 114.5, 112.0, 75.6, 51.5, 47.7, 22.7, 18.1; **IR** (neat): 3436, 2990, 2985, 1710, 1574, 1463, 1439, 1287, 1261, 1193, 1161, 1135, 1059, 1024, 781 cm^{-1}; MS (EI): *m*/*z* (%) 201 (9), 102 (100), 94 (19), 87 (20), 70 (13); **HRMS** (ESI-pos.) calcd. for $C_{12}H_{15}BrO_4Na$ $[M + Na]^+$ 325.00460, found 325.00494.

Methyl (*S*)-3-(2-bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoate (65)



2,6-Lutidine (1.69 mL, 14.51 mmol) and TBSOTf (2.0 mL, 8.71 mmol) were successively added to a solution of compound **64** (> 99% *ee*, 1.10 g, 3.63 mmol) in CH_2Cl_2 (22 mL) at 0 °C. The mixture was stirred for 2 h before the reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were dried over $Na_2S_2O_3$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1 then 98:2) to afford the product as a colorless oil (1.88 g, 97 %). $[\alpha]_D^{20}$ = +11.0 (*c* 0.85, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.17 – 7.11 (m, 1H), 7.10 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.82 (dd, *J* = 7.6, 1.9 Hz, 1H), 5.68 (s, 1H), 3.70 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 1.04 (s, 9H), 0.82 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.00 (s, 3H), -0.39 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 177.2, 152.1, 142.0, 126.7, 123.9, 119.4, 118.1, 76.8, 52.0, 50.1, 26.0, 25.8, 22.9, 18.6, 18.3, 18.0, -4.0, -4.1, -4.6, -5.4; **IR** (neat): 2952, 2930, 2886, 2858, 1739, 1752, 1461, 1428, 1285, 1253, 1132, 1087, 997, 879, 862, 835, 777 cm^{-1}; **MS** (EI): *m*/*z* (%) 477 (11), 476 (30), 475 (100), 473 (91), 285 (12), 283 (12), 209 (10), 89 (46), 73 (46); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{43}O_4BrSi_2Na$ $[M + Na]^+$ 553.17756, found 553.17805.

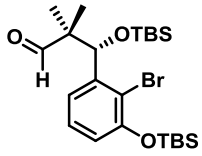
(*S*)-3-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropan-1-ol (66)



DIBAL-H (1.2 M in toluene, 7.52 mL, 9.03 mmol) was added over 5 min to a stirred solution of the methyl ester **65** (1.60 g, 3.00 mmol) in toluene (25 mL) at –78 °C. The mixture was stirred at –78 C for 1 h and the reaction was quenched with H_2O. A sat. aq. solution of potassium sodium tartrate was added and the resulting mixture was stirred vigorously. EtOAc was added and stirring was continued for 1 h while the solution was warmed to ambient temperature. The phases were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 98:3 then 96:4) to afford the product as a colorless oil (1.46 g, 96 %). $[\alpha]_D^{20}$ = –2.2 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.22 – 7.13 (m, 2H), 6.86 – 6.79 (m, 1H), 5.23 (s, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.24 (d, *J* = 11.0 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 9H), 0.86 (s, 9H), 0.76 (s, 3H), 0.22 (s, 3H), 0.22 (s, 3H), 0.08 (s, 3H), -0.33 (s, 3H); **^{13}C NMR** δ: (100 MHz, $CDCl_3$)

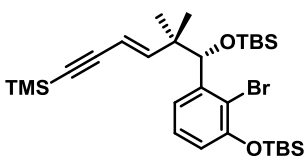
152.2, 142.7, 127.2, 123.0, 119.3, 117.9, 80.8, 70.3, 40.7, 26.0, 25.9, 23.4, 20.7, 18.6, 18.0, -4.0, -4.1, -4.8, -5.2; **IR** (neat): 3449, 2955, 2929, 2885, 2858, 1571, 1461, 1427, 1284, 1253, 1020, 995, 865, 832, 804, 776 cm^{-1}; **MS** (EI): *m*/*z* (%) 448 (14), 447 (47), 446 (13), 445 (43), 432 (17), 431 (37), 430 (18), 429 (60), 355 (41), 353 (40), 348 (27), 315 (14), 313 (11), 274 (15), 217 (11), 147 (20), 119 (11), 105 (12), 75 (41), 73 (100); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{43}O_3BrSi_2Na$ $[M + Na]^+$ 525.18265, found 525.18315.

(*S*)-3-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanal (67)



Dess-Martin periodinane (55.6 mg, 0.13 mmol) was added to a solution of alcohol **66** (22 mg, 0.044 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C. The mixture was stirred at room temperature for 4 h before sat. aq. $NaHCO_3$ was introduced. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99.2:0.8) to afford the product as a colorless oil (16.6 mg, 76 %). Note: The flash chromatography must be performed rapidly as the product decomposes on silica gel. $[\alpha]_D^{20}$ = –7.8 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.44 (s, 1H), 1.06 (s, 3H), 1.04 (s, 12H), 0.84 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.05 (s, 3H), -0.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 205.7, 152.3, 141.8, 127.3, 123.0, 119.5, 117.4, 76.7, 52.8, 26.0, 25.8, 19.6, 18.6, 18.1, 16.7, -4.06, -4.12, -4.6, -5.2. **IR** (neat): 2955, 2930, 2886, 2858, 1728, 1571, 1461, 1428, 1391, 1362, 1285, 1253, 1085, 1023, 994, 884, 858, 831, 775, 719 cm^{-1}; **MS** (EI): *m*/*z* (%) 447 (11), 446 (30), 445 (100), 444 (28), 443 (92), 431 (17), 129 (16), 401 (17), 399 (15), 329 (24), 327 (23), 321 (11), 320 (39), 129 (26), 75 (45), 73 (79); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{41}O_3BrSi_2Na$ $[M + Na]^+$ 523.16700, found 523.16740.

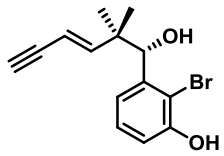
(*S,E*)-((1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethyl-6-(trimethylsilyl)hex-3-en-5-yn-1-yl)oxy)(*tert*-butyl)dimethyl-silane (69)



*n*BuLi (1.6 M in THF, 1.2 mL, 1.93 mmol) was slowly added to a solution of phosphonate **68**[77] (0.48 g, 1.93 mmol) in THF (20 mL) at 0 °C. The colorless solution became red and the reaction was stirred for 20 min at 0 °C and for 10 min at room temperature. After cooling the mixture to

–78 °C, a solution of aldehyde **67** (0.485 g, 0.967 mmol) in THF was added dropwise and stirring was continued for 1 h 30 min before the reaction was quenched with NH_4Cl. A standard extractive work up followed by purification of the residue by flash chromatography (hexane) afforded the product as a colorless oil (0.552 g, 96 %, *E:Z* > 20:1). $[\alpha]_D^{20}$ = –69.7 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.16 – 7.07 (m, 1H), 7.02 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.41 (d, *J* = 16.3 Hz, 1H), 5.34 (d, *J* = 16.4 Hz, 1H), 5.03 (s, 1H), 1.06 (s, 3H), 1.04 (s, 9H), 0.99 (s, 3H), 0.85 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H), 0.18 (s, 9H), 0.04 (s, 3H), -0.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.0, 151.9, 143.1, 126.7, 123.4, 119.2, 117.8, 107.9, 104.8, 93.1, 79.1, 44.2, 26.0, 26.0, 24.1, 22.2, 18.6, 18.2, 0.2, -4.0, -4.1, -4.7, -5.1; **IR** (neat): 2957, 2930, 2896, 2858, 2163, 1571, 1461, 1427, 1285, 1251, 1086, 1069, 999, 909, 838, 777 cm^{-1}; **MS** (EI): *m/z* (%) 433 (10), 432 (30), 431 (100), 430 (28), 429 (92), 73 (58); **HRMS** (ESI-pos.) calcd. for $C_{29}H_{51}O_2BrSi_3Na$ $[M + Na]^+$ 617.22726, found 617.22780.

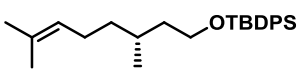
(*S,E*)-((1-(2-Bromo-3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,2-dimethylhex-3-en-5-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (27)



HF-pyridine (1.22 mL, 46.9 mmol) was added to a solution of **69** (40.3 mg, 0.0676 mmol) in MeCN (3.5 mL) and the resulting mixture was stirred for 7 h. The reaction was quenched by dropwise addition of the resulting mixture to an ice-cold sat. aq. $NaHCO_3$ under stirring. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 80:20) to afford the product as a colorless oil (19.5 mg, 98 %). $[\alpha]_D^{20}$ = –102.6 (*c* 1.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.23 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.45 (d, *J* = 16.4 Hz, 1H), 5.69 (s, 1H), 5.42 (dd, *J* = 16.4, 2.2 Hz, 1H), 5.00 (s, 1H), 2.85 (d, *J* = 2.2 Hz, 1H), 1.97 (s, 1H), 1.14 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.9, 151.7, 141.2, 128.2, 121.5, 115.3, 112.8, 108.1, 82.6, 78.5, 77.0, 43.6, 24.3, 22.0; **IR** (neat): 3503, 3291, 2968, 2930, 2873, 1574, 1463, 1440, 1386, 1365, 1285, 1249, 1183, 1504, 1016, 966, 767, 772, 717, 690, 638 cm^{-1}; **MS** (EI): *m/z* (%) 201 (7), 94 (73), 93 (14), 91 (18), 80 (10), 79 (100), 77 (33), 65 (16); **HRMS** (ESI-neg.) calcd. for $C_{14}H_{15}O_2Br$ $[M - H]^-$ 293.01828, found 293.01852.

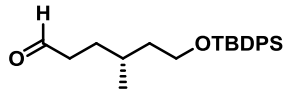
6.2.3 Synthesis of the Analogue 45

(*R*)-*tert*-Butyl((3,7-dimethyloct-6-en-1-yl)oxy)diphenylsilane (50)[127]



Imidazole (18.3 g, 269.4 mmol) and TBDPSCl (36.8 mL, 141.4 mmol) were added over 10 min to a solution of (*R*)-citronellol (**49**) (21 g, 134.7 mmol) in CH_2Cl_2 (200 mL) at 0 °C and the resulting mixture was stirred for 16 h. Water was added and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 98:2 then 97:3) to afford the product as a colorless oil (53.1 g, 99 %). $[\alpha]_D^{20}$ = –3.5 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: : 7.72 – 7.63 (m, 4H), 7.47 – 7.33 (m, 6H), 5.09 (tdt, *J* = 7.1, 2.8, 1.4 Hz, 1H), 3.77 – 3.61 (m, 2H), 2.06 – 1.86 (m, *J* = 7.3 Hz, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.65 – 1.57 (m, 5H), 1.41 – 1.26 (m, 2H), 1.18 – 1.09 (m, 1H), 1.05 (s, 9H), 0.83 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 135.7, 134.3, 131.2, 129.6, 127.7, 125.0, 62.3, 39.7, 37.3, 29.1, 27.0, 25.9, 25.6, 19.7, 19.4, 17.8; **IR** (neat): 3071, 2959, 2929, 2857, 1428, 1111, 701 cm^{-1}; **MS** (EI): *m*/*z* (%) 338 (27), 337 (92), 200 (18), 199 (100), 183 (26), 137 (26), 95 (19), 81 (41), 69 (16); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{38}OSiNa$ [M + Na]$^+$ 417.25808, found 417.25841.

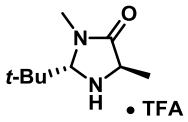
(*R*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhexanal (51)[127]



Ozone was bubbled through a solution of compound **50** (23.5 g, 59.5 mmol) in CH_2Cl_2 (190 mL) at –78 °C for 4 h until a light blue color persisted. The mixture was then purged with Ar before dimethyl sulfide (7.00 mL, 95.3 mmol) was introduced at –78 °C. The mixture was slowly warmed to ambient temperature and stirring continued for 1h. Water was added, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered and evaporated to afford the product as a colorless oil (25.2 g) which was used directly in the next step without further purification. For characterization purposes, an analytical sample was obtained by flash chromatography (hexane/EtOAc, 92:8 to 90:10). $[\alpha]_D^{20}$ = +1.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.74 (t, *J* = 1.9 Hz, 1H), 7.73 – 7.62 (m, 4H), 7.47 – 7.33 (m, 6H), 3.79 – 3.62 (m, 2H), 2.38 (dtd, *J* = 8.8, 6.1, 1.8 Hz, 2H), 1.69 – 1.54 (m, 3H), 1.47 – 1.33 (m, 2H), 1.04 (s, 9H), 0.84 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 203.0, 135.7, 134.1, 129.7, 127.8, 62.0, 41.8, 39.3, 29.2, 29.0, 27.0, 19.5, 19.3; **IR** (neat): 2930,

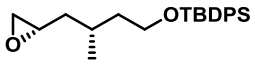
2857, 1725, 1227, 1106, 1087, 701, 504; **MS** (EI): *m/z* (%) 312 (18), 311 (71), 281 (14), 233 (13), 225 (12), 203 (21), 200 (18), 199 (100), 183 (30), 181 (13), 139 (25); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{32}O_2SiNa$ $[M + Na]^+$ 391.20623, found 391.20638.

(2*S*,5*R*)-2-(*tert*-Butyl)-3,5-dimethylimidazolidin-4-one trifluoroacetic (55)



A solution of imidazolidinone hydrochloride salt[67] (4.05 g, 19.6 mmol) in $CHCl_3$ (60 mL) was washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$, the combined organic phases were dried over Na_2SO_4, filtered and evaporated to afford the corresponding salt-free imidazolidinone as a colorless oil. Next, this crude product was added to a solution of TFA (1.53 mL, 19.9 mmol) in Et_2O (10.1 mL) at 0 °C. The resulting mixture was stirred at room temperature for 10 min before the formed precipitate was collected by filtration to afford the product as a white solid (5.18 g, 93 %). $[\alpha]_D^{20}$ = +27.1 (*c* 1.0, MeOH); **^{1}H NMR** (400 MHz, CD_3OD) δ: 4.70 (d, *J* = 0.8 Hz, 1H), 4.22 (qt, *J* = 7.1, 0.8 Hz, 1H), 3.05 (d, *J* = 0.8 Hz, 3H), 1.50 (d, *J* = 7.1 Hz, 3H), 1.13 (s, 9H); **^{13}C NMR** (100 MHz, CD_3OD) δ: 171.7, 163.3, 163.0, 162.7, 162.3, 122.4, 119.5, 116.6, 113.7, 81.9, 54.7, 37.6, 32.3, 25.2, 14.8. **IR** (neat): 2965, 2729, 1721, 1670, 1604, 1459, 1429, 1401, 1374, 1263, 1205, 1256, 1127, 1093, 1031, 837, 797, 722, 664 cm^{-1}; **MS** (EI): *m/z* (%) 113 (M^+–57, 100), 85 (16), 44 (31), 42 (10); **HRMS** (ESI-pos.) calcd. for $C_9H_{19}N_2O$ $[M + H]^+$ 171.14906, found 171.14919.

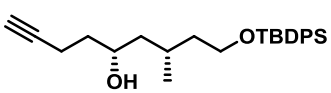
***tert*-Butyl((*S*)-3-methyl-4-((*S*)-oxiran-2-yl)butoxy)diphenylsilane (54)**[66]



A jacketed flask containing imidazolidinone trifluoroacetic salt **55** (3.38 g, 11.9 mmol, 20 mol%), LiCl (3.78 g, 89.3 mmol), $Na_2S_2O_8$ (14.2 g, 59.5 mmol) and $Cu(TFA)_2$ (8.61 g, 29.8 mmol) was cooled to 10 °C and MeCN (580 mL) and H_2O (2.40 mL, 133 mmol) were added. The mixture was stirred at 10 °C for 10 min before a solution of aldehyde **51** (21.9 g, 59.5 mmol) in MeCN (40 mL) was added, causing a color change from brown to green. The reaction mixture was stirred at 10 °C for 18 h. It was then cooled to 0 °C and $NaBH_4$ (6.77 g, 179 mmol) was added slowly. The reaction was stirred at 0 °C for 10 min and at room temperature for 10 min before EtOH (490 mL) was introduced, followed by aqueous KOH (360 mL, freshly prepared by dissolving 180 g of KOH in 360 mL of H_2O). The mixture was stirred vigorously at room temperature for 30 min and the reaction was quenched with H_2O. The organic phase was diluted with

tert-butyl methyl ether and the aqueous phase was extracted with the same solvent. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to afford the crude epoxide (dr = 12:1), which was purified by by flash chromatography (hexane/EtOAc, 98:2 to 95:5) to afford the title compound as a colorless oil (15.8 g, 72 %, dr > 20:1). $[\alpha]_D^{20}$ = –7.1 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.74 – 7.69 (m, 4H), 7.48 – 7.38 (m, 6H), 3.76 (td, J = 6.6, 1.9 Hz, 2H), 2.93 (dddd, J = 6.7, 5.2, 4.0, 2.8 Hz, 1H), 2.75 (ddd, J = 5.2, 4.0, 0.6 Hz, 1H), 2.42 (dd, J = 5.1, 2.7 Hz, 1H), 1.94 (dh, J = 13.4, 6.7 Hz, 1H), 1.76 – 1.66 (m, 1H), 1.57 – 1.45 (m, 2H), 1.41 (td, J = 13.9, 13.4, 6.5 Hz, 1H), 1.10 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 135.7, 134.1, 129.7, 127.7, 61.9, 51.3, 47.0, 39.9, 39.5, 28.3, 27.0, 20.2, 19.3; **IR** (neat): 2957, 2929, 2857, 1472, 1428, 1109, 1089, 701 cm^{-1}; **MS** (EI): *m/z* (%) 312 (13), 311 (50), 281 (22), 225 (11), 213 (10), 203 (43), 200 (18), 199 (100), 197 (14), 183 (35), 181 (17), 173 (17), 161 (10), 139 (18), 135 (13), 95 (13), 91 (10); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{32}O_2SiNa$ $[M + Na]^+$ 391.20666, found 391.20638.

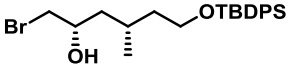
(5*R*,7*S*)-9-((*tert*-Butyldiphenylsilyl)oxy)-7-methylnon-1-yn-5-ol (56)



A solution of freshly prepared propargylmagnesium bromide[68] (0.45 M in Et_2O, 150 mL, 67.5 mmol) was added over 1 h to a solution of epoxide **54** (4.03 g, 10.9 mmol) in 1,4-dioxane (50 mL). The resulting suspension was stirred for 2 d before the reaction was quenched with sat. aq. NH_4Cl and water at 0 °C. The solution was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 90:10) to afford the title compound as a colorless oil (3.61 g, 81 %). $[\alpha]_D^{20}$ = –3.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.71 – 7.65 (m, 4H), 7.46 – 7.41 (m, 2H), 7.41 – 7.37 (m, 4H), 3.86 – 3.81 (m, 1H), 3.75 (ddd, *J* = 10.3, 6.6, 5.7 Hz, 1H), 3.69 (ddd, *J* = 10.3, 7.3, 6.3 Hz, 1H), 2.33 (ddd, *J* = 7.7, 6.6, 2.7 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.72 – 1.64 (m, 2H), 1.57 (ddt, *J* = 13.7, 8.8, 6.6 Hz, 1H), 1.39 – 1.32 (m, 3H), 1.06 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 135.7, 135.7, 134.1, 134.1, 129.7, 127.8, 84.4, 68.8, 68.8, 62.3, 45.0, 39.2, 36.0, 27.0, 27.0, 26.5, 20.7, 19.3, 15.1; **IR** (neat): 3308, 3071, 3050, 2929, 2857, 1472, 1462, 1427, 1389, 1361, 1307, 1261, 1188, 1107, 1083, 1007, 938, 895, 822, 799, 737, 700, 688, 613, 503, 488 cm^{-1}; **MS** (EI): *m/z* (%) 351 (9), 229 (13), 211 (21), 200 (18), 199 (100), 139 (32), 135 (22), 107 (23), 93 (45), 91

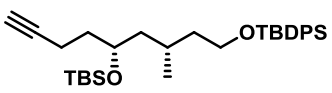
(19), 79 (27), 77 (12), 67 (10); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{36}O_2SiNa$ $[M + Na]^+$ 431.23768, found 431.23818.

(2*S*,4*S*)-1-Bromo-6-((tert-butyldiphenylsilyl)oxy)-4-methylhexan-2-ol (58)



$[\alpha]_D^{20}$ = +10.6 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.71 – 7.65 (m, 4H), 7.47 – 7.40 (m, 2H), 7.42 – 7.36 (m, 4H), 3.87 – 3.80 (m, 1H), 3.78 – 3.66 (m, 2H), 3.50 (dd, *J*=10.3, 3.3, 1H), 3.34 (dd, *J*=10.3, 7.1, 1H), 2.17 (s, 1H), 1.89 – 1.76 (m, 1H), 1.66 (dtd, *J*=13.7, 6.9, 5.0, 1H), 1.51 – 1.39 (m, 2H), 1.37 (ddt, *J*=13.9, 8.0, 6.1, 1H), 1.06 (s, 9H), 0.90 (d, *J*=6.7, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 135.6, 135.6, 133.9, 133.9, 129.6, 127.6, 69.2, 61.9, 42.3, 40.8, 39.0, 26.9, 26.6, 20.3, 19.2; **IR** (neat): 3309, 3071, 3049, 2956, 2929, 2857, 1589, 1472, 1462, 1427, 1389, 1361, 1261, 1188, 1106, 1085, 998, 908, 822, 799, 733, 700, 613, 503, 488 cm^{-1}; **MS** (EI): *m/z* (%) 311 (12), 229 (17), 200 (18), 199 (100), 177 (11), 175 (12), 139 (15), 135 (10), 95 (52); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{33}O_2BrSiNa$ $[M + Na]^+$ 471.13255, found 471.13296.

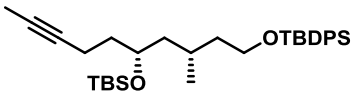
(5*R*,7*S*)-5-(But-3-yn-1-yl)-2,2,3,3,7,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (59)



TBSOTf (2.88 g, 10.9 mmol) was slowly added to a solution of compound **56** (3.75 g, 9.18 mmol) and 2,6-lutidine (2.02 g, 18.9 mmol) in CH_2Cl_2 (85 mL) at 0 °C. The mixture was stirred for 6 h at room temperature, the reaction was quenched with methanol (6.5 mL) and the resulting solution poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 98:2) to afford the title compound as a colorless oil (4.73 g, 98 %). $[\alpha]_D^{20}$ = +17.5 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.76 – 7.63 (m, 4H), 7.48 – 7.34 (m, 6H), 3.84 (dtd, *J* = 7.9, 5.3, 3.9 Hz, 1H), 3.77 – 3.61 (m, 2H), 2.24 (td, *J* = 7.3, 6.7, 2.4 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.80 – 1.47 (m, 4H), 1.48 – 1.32 (m, 2H), 1.27 (ddd, *J* = 13.9, 8.8, 5.3 Hz, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 135.7, 134.2, 129.7, 127.8, 84.9, 69.3, 68.3, 62.1, 45.0, 40.5, 35.6, 27.0, 26.5, 26.1, 20.1, 19.3, 18.2, 14.6, -4.1, -4.4; **IR** (neat): 3312, 3071, 2955, 2929, 2893, 2857, 1472, 1462, 1428, 1389, 1361, 1254, 1189, 1110, 1083, 991, 938, 899, 834, 824,

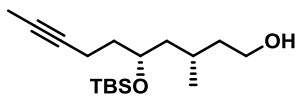
773, 736, 700, 688, 614, 503 cm^{-1}; **MS** (ESI): *m/z* $[M + Na]^+$ 522; **HRMS** (ESI-pos.) calcd. for $C_{32}H_{50}O_2Si_2Na$ $[M + Na]^+$ 545.32454, found 545.32416.

(5*R*,7*S*)-2,2,3,3,7,12,12-Heptamethyl-5-(pent-3-yn-1-yl)-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (60)



*n*BuLi (1.6 M in hexane, 8.5 mL, 13.6 mmol) was slowly added at −78°C to a solution of alkyne **59** (4.61 g, 8.82 mmol) in THF (90 mL). The mixture was stirred for 20 min at this temperature before methyl iodide (5.02 g, 35.3 mmol) was added dropwise. The resulting solution was allowed to reach room temperature overnight before the reaction was quenched with water. The aqueous layer was extracted with Et_2O, the combined extracts were dried over $MgSO_4$, filtered and evaporated, and the residue used in the next step without further purification (4.75 g, quant.). $[\alpha]_D^{20}$ = +14.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.75 – 7.61 (m, 4H), 7.47 – 7.34 (m, 6H), 3.86 – 3.75 (m, 1H), 3.76 – 3.61 (m, 2H), 2.17 (qt, *J* = 5.9, 2.6 Hz, 2H), 1.77 (t, *J* = 2.5 Hz, 3H), 1.73 – 1.31 (m, 6H), 1.32 – 1.18 (m, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 135.7, 134.2, 129.7, 127.7, 79.4, 75.6, 69.5, 62.2, 45.1, 40.5, 36.2, 27.0, 26.5, 26.1, 20.1, 19.3, 18.2, 15.0, 3.6, -4.1, -4.4; **IR** (neat): 3071, 3051, 2954, 2929, 2857, 1472, 1462, 1428, 1389, 1361, 1254, 1188, 1110, 1085, 1005, 774, 737, 701, 614, 505 cm^{-1}; MS (ESI): *m/z* $[M + Na]^+$ 559; **HRMS** (ESI-pos.) calcd. for $C_{33}H_{52}O_2Si_2Na$ $[M + Na]^+$ 545.32416, found 545.32454.

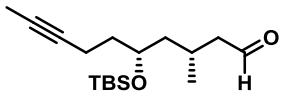
(3*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-methyldec-8-yn-1-ol (61)



Acetic acid (629 mg, 10.5 mmol) and TBAF (1 M in THF, 10.5 mL, 10.5 mmol) were added at 0 °C to a solution of compound **60** (4.69 g, 8.74 mmol) in DMF (165 mL). The mixture was stirred overnight, the reaction was quenched with water, the aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 80:20) to afford the product as a colorless oil (2.40 g, 92 %). $[\alpha]_D^{20}$ = +25.2 (*c* 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.84 (tdd, *J* = 7.3, 5.6, 4.2 Hz, 1H), 3.76 – 3.60 (m, 2H), 2.22 – 2.12 (m, 2H), 1.77 (t, *J* = 2.5 Hz, 3H), 1.73 – 1.24 (m, 8H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 79.3, 75.7, 69.4, 61.1, 44.9, 40.5, 36.2, 26.4, 26.1, 20.2, 18.2, 14.9, 3.6, -

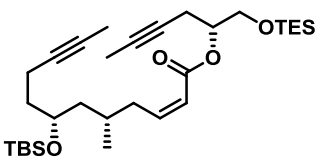
4.2, -4.3; **IR** (neat): 3340, 2953, 2928, 2857, 1472, 1462, 1378, 1361, 1253, 1064, 986, 939, 835, 773 cm^{-1}; **MS** (EI): *m/z* (%) 171 (13), 107 (13), 105 (12), 99 (11), 95 (11), 93 (19), 81 (14), 75 (100), 73 (21), 55 (11); **HRMS** (ESI-pos.) calcd. for $C_{17}H_{34}O_2SiNa$ $[M + Na]^+$ 321.22203, found 321.22219.

(3*R*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-methyldec-8-ynal (46)



$[Cu(CH_3CN)_4]BF_4$ (6.32 mg, 20.1 µmol, 5 mol%), 2,2'-bipyridyl (3.14 mg, 20.1 µmol, 5 mol%), TEMPO (3.14 mg, 20.1 µmol, 5 mol%) and 1-methylimidazole (3.30 mg, 40.2 µmol, 10 mol%), each as a solution in CH_3CN (400 µL), were consecutively added to a solution of compound **61** (120 mg, 0.402 mmol) in CH_3CN (400 µL). The mixture was stirred in a flask open to the air. After the addition was completed, the flask was closed with a septum and connected to balloon of O_2. The reaction was stirred for 7 h during which time the color changed from brown to green. The reaction was quenched with water, the aqueous layer was extracted with hexane, and the combined extracts were dried over $MgSO_4$, filtered and evaporated to afford the product as a yellow oil (117 mg, 98 %) which was used for the next step without further purification. $[\alpha]_D^{20}$ = +28.2 (*c* 0.85, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.75 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.85 (qd, *J* = 6.6, 4.8 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.32 – 2.10 (m, 4H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.74 – 1.53 (m, 2H), 1.49 – 1.33 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.7, 79.1, 75.9, 69.1, 51.3, 44.3, 36.1, 26.0, 24.9, 20.6, 18.2, 14.9, 3.57, -4.2, -4.3; **IR** (neat): 2954, 2929, 2857, 2712, 1726, 1472, 1462, 1380, 1253, 1066, 1006, 988, 834, 773 cm^{-1}; **MS** (EI): *m/z* (%) 239 (50), 211 (12), 147 (14), 145 (34), 143 (24), 119 (26), 105 (36), 101 (31), 93 (15), 91 (15), 79 (10), 77 (11), 75 (100), 73 (40), 59 (13), 41 (12); **HRMS** (ESI-pos.) calcd. for $C_{17}H_{32}O_2SiNa$ $[M + Na]^+$ 319.20638, found 319.20608.

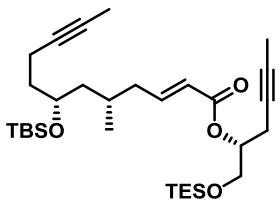
(*R*)-1-((Triethylsilyl)oxy)hex-4-yn-2-yl(5S,7*R*,*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-5-methyldodec-2-en-10-ynoate (47)



A solution of phosphonate **41** (200 mg, 0.388 mmol) in THF (0.4 mL) was slowly added to a solution of KHMDS (77.5 mg, 0.388 mmol) and 18-crown-6 (216.1 mg, 0.818 mmol) in THF (2.5 mL) at –78 °C. After stirring for 1 h at this temperature, a solution of aldehyde **46** (96 mg, 0.324 mmol) in THF (0.4 mL) was introduced and stirring continued for 5 h. The

solution was then poured onto hexane (100 mL) and sat. sol. NH_4Cl was added. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 98:2, with fine SiO_2) to afford the desired *Z*-isomer (102 mg, 57 %) along with the *E*-isomer (24.7 mg, 14 %), each as a colorless oil. *Z*-Isomer: $[\alpha]_D^{20}$ = +8.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.21 (dt, *J* = 11.6, 7.4 Hz, 1H), 5.84 (dt, *J* = 11.6, 1.6 Hz, 1H), 4.94 (p, *J* = 5.1 Hz, 1H), 3.90 – 3.78 (m, 1H), 3.78 (d, *J* = 5.6 Hz, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.50 (dddd, *J* = 19.5, 14.0, 9.0, 2.7 Hz, 2H), 2.22 – 2.12 (m, 2H), 1.77 (q, *J* = 2.6 Hz, 6H), 1.72 – 1.60 (m, 2H), 1.60 – 1.28 (m, 3H), 1.01 – 0.90 (m, 12H), 0.88 (s, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.8, 149.6, 120.8, 79.3, 77.6, 75.7, 74.5, 72.5, 69.3, 62.9, 44.4, 36.5, 36.4, 30.0, 26.1, 20.9, 20.0, 18.2, 14.9, 6.9, 4.5, 3.7, 3.6, -4.2, -4.3; **IR** (neat): 2954, 2927, 2877, 2857, 1721, 1642, 1461, 1415, 1379, 1252, 1172, 1089, 1062, 1006, 836, 808, 775, 744, 678 cm^{-1}; **MS** (EI): *m/z* (%) 519 (14), 492 (15), 491 (38), 396 (16), 395 (47), 321 (16), 293 (10), 263 (10), 261 (14), 212 (16), 211 (88), 197 (13), 189 (21), 184 (18), 183 (48), 161 (37), 156 (15), 155 (100), 147 (11), 117 (15), 116 (11), 115 (89), 105 (15), 103 (14), 95 (19), 87 (50), 79 (13), 75 (33), 73 (56), 59 (14); **HRMS** (ESI-pos.) calcd. for $C_{31}H_{56}O_4Si_2Na$ $[M + Na]^+$ 571.36094, found 571.36127.

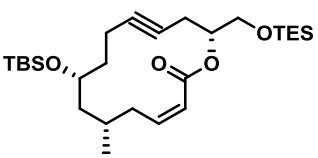
(*R*)-1-((Triethylsilyl)oxy)hex-4-yn-2-yl(5S,7*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-5-methyldodec-2-en-10-ynoate (70)



E-Isomer: $[\alpha]_D^{20}$ = +7.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.94 (ddd, *J* = 15.2, 8.0, 7.0 Hz, 1H), 5.84 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.96 (dq, *J* = 6.5, 5.1 Hz, 1H), 3.83 (dt, *J* = 6.5, 3.3 Hz, 1H), 3.79 (d, *J* = 4.6 Hz, 2H), 2.62 – 2.43 (m, 2H), 2.26 (dddd, *J* = 14.0, 6.9, 5.1, 1.6 Hz, 1H), 2.16 (ddt, *J* = 7.3, 4.9, 2.5 Hz, 2H), 2.00 (dtd, *J* = 14.2, 8.0, 1.4 Hz, 1H), 1.77 (q, *J* = 2.6 Hz, 6H), 1.74 – 1.57 (m, 2H), 1.47 – 1.28 (m, 3H), 1.00 – 0.84 (m, 21H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.0, 148.3, 122.8, 79.2, 77.7, 75.8, 74.5, 72.9, 69.2, 63.0, 44.4, 40.1, 36.3, 29.2, 26.1, 20.9, 20.1, 18.2, 14.9, 6.8, 4.5, 3.7, 3.6, -4.2, -4.3; **IR** (neat): 2954, 2929, 2877, 2857, 1722, 1654, 1462, 1379, 1316, 1256, 1166, 1087, 1005, 982, 835, 804, 774, 743 cm^{-1}; **MS** (EI): *m/z* (%) 519 (14), 492 (15), 491 (38), 396 (16), 395 (47), 321 (16), 293 (10), 263 (10), 261 (14), 212 (16), 211 (88), 197 (13), 189 (21), 184 (18), 183 (48), 161 (37), 156 (15), 155 (100), 147 (11), 117 (14), 116 (11), 115 (89), 105 (15),

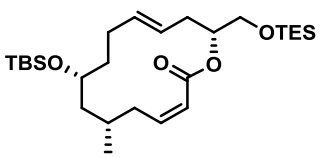
103 (14), 95 (19), 87 (50), 79 (13), 75 (33), 73 (56), 59 (14); **HRMS** (ESI-pos.) calcd. for $C_{31}H_{56}O_4Si_2Na$ $[M + Na]^+$ 571.36094, found 571.36054.

(6*S*,8*R*,14*R*,*Z*)-8-((*tert*-Butyldimethylsilyl)oxy)-6-methyl-14-(((triethylsilyl)oxy)methyl)oxacyclotetradec-3-en-11-yn-2-one (71)



A flame-dried flask was charged with freshly activated molecular sieves 5 Å (powder, 5.7 g), compound **47** (112.7 mg, 0.205 mmol) and toluene (120 mL). The suspension was stirred for 1 h and then heated to 80 °C before a solution of the alkylidyne complex **C1** (32.1 mg, 31 µmol, 15 mol%) in toluene (1.5 mL) was added in one portion. Stirring was continued for 10 min at this temperature before the suspension was allowed to reach ambient temperature. The mixture was filtered through a pad of SiO_2 which was rinsed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the product as a colorless oil (94.3 mg, 93 %). $[\alpha]_D^{20}$ = +27.1 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.32 (td, *J* = 11.0, 5.8 Hz, 1H), 5.89 (dd, *J* = 11.7, 1.2 Hz, 1H), 5.20 (dddd, *J* = 9.0, 5.9, 5.1, 4.0 Hz, 1H), 3.91 (dtd, *J* = 9.5, 6.0, 3.4 Hz, 1H), 3.71 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.64 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.30 (ddd, *J* = 15.9, 10.8, 5.7 Hz, 1H), 2.70 – 2.41 (m, 2H), 2.36 – 1.97 (m, 4H), 1.65 (dddd, *J* = 13.3, 9.4, 5.6, 3.8 Hz, 1H), 1.43 – 1.24 (m, 2H), 1.18 (ddd, *J* = 13.7, 9.6, 4.2 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.12 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.9, 146.7, 121.7, 81.7, 76.2, 71.4, 68.2, 63.8, 42.9, 37.2, 32.7, 28.6, 26.2, 21.8, 20.1, 18.3, 14.8, 6.8, 4.5, -4.1, -4.1; **IR** (neat): 2954, 2928, 2877, 2856, 1724, 1641, 1461, 1416, 1378, 1250, 1221, 1170, 1131, 1098, 1083, 1066, 1003, 832, 801, 774, 676 cm^{-1}; **MS** (EI): *m/z* (%) 466 (M^+–28, 19), 465 (49), 439 (13), 438 (36), 437 (100), 333 (13), 305 (12), 213 (12), 213 (12), 211 (13), 189 (18), 187 (11), 185 (31), 171 (31), 169 (11), 161 (26), 159 (14), 157 (11), 147 (11), 145 (33), 143 (17), 133 (15), 131 (13), 129 (14), 121 (12), 119 (11), 117 (36), 115 (50), 105 (18), 103 (24), 95 (28), 87 (60), 75 (55), 73 (50), 59 (20); **HRMS** (ESI-pos.) calcd. for $C_{27}H_{50}O_4Si_2Na$ $[M + Na]^+$ 517.31399, found 517.31413.

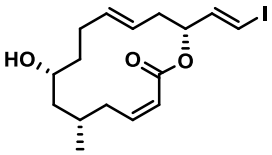
(3*Z*,6*S*,8*R*,11*E*,14*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-6-methyl-14-(((triethylsilyl)oxy)methyl) oxacyclotetradeca-3,11-dien-2-one (74).



A solution of Bu_3SnH (32.5 mg, 0.112 mmol) in CH_2Cl_2 (100 µL) was slowly added to a solution of alkyne **71** (46 mg, 93.0 µmol) and $[Cp^*Ru(CH_3CN)_3]PF_6$ (4.7 mg, 9.0 µmol, 10 mol%) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 1h before all volatile materials were evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford a colorless oil (69.5 mg, 95 %, *Z:E* > 20:1, mixture of regioisomers **72** and **73** = 1:1). **^{119}Sn NMR** (149 MHz, $CDCl_3$) δ: –51.5; –54.5 ppm; **HRMS** (ESI-pos.) calcd. for $C_{39}H_{78}O_4Si_2SnNa$ $[M + Na]^+$ 809.43522, found 809.43583.

$[(Ph_2PO_2)Cu]$ (44.7 mg, 159 µmol) was added in one portion to a solution of the alkenylstannanes (**72** and **73**) in DMF (1.8 mL). The mixture was stirred for 3 h before the reaction was quenched with sat. aq. NH_4Cl, water and *tert*-butyl methyl ether. The organic layer was separated and the aqueous phase was extracted with *tert*-butyl methyl ether. The combined extracts were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc – 99:1) to afford the product as a colorless oil (30.6 mg, 71 %, 67 % over two steps). $[\alpha]_D^{20}$ = +13.4 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.25 (td, *J* = 11.7, 4.6 Hz, 1H), 5.85 (dd, *J* = 11.7, 1.5 Hz, 1H), 5.48 – 5.28 (m, 2H), 5.17 (dtd, *J* = 10.7, 5.5, 2.7 Hz, 1H), 3.76 – 3.61 (m, 3H), 3.54 (ddd, *J* = 14.1, 11.6, 4.6 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.20 – 1.92 (m, 5H), 1.67 (dddd, *J* = 13.9, 9.2, 6.3, 2.8 Hz, 1H), 1.32 – 1.27 (m, 1H), 1.18 (ddd, *J* = 13.8, 10.4, 3.7 Hz, 1H), 1.10 (ddd, *J* = 13.8, 11.0, 2.9 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.13 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.9, 146.4, 133.4, 125.8, 121.9, 72.5, 67.9, 64.8, 43.2, 37.4, 35.2, 31.8, 28.1, 28.0, 26.2, 20.3, 18.4, 6.9, 4.5, -3.6, -3.7; **IR** (neat): 2954, 2930, 2877, 2856, 1722, 1642, 1461, 1417, 1377, 1250, 1174, 1134, 1097, 1072, 1004, 968, 835, 806, 774, 741 cm^{-1}; **HRMS** (ESI-pos.) calcd. for $C_{27}H_{52}O_4Si_2Na$ $[M + Na]^+$ 519.32964, found 519.32949.

(3*Z*,6*S*,8*R*,11*E*,14*R*)-8-Hydroxy-14-((*E*)-2-iodovinyl)-6-methyloxacyclotetradeca-3,11-dien-2-one (77)



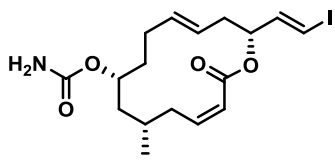
A solution of DMSO (55.0 mg, 0.704 mmol) in CH_2Cl_2 (300 µL) was added dropwise to a solution of oxalyl chloride (44.3 mg, 0.349 mmol) in CH_2Cl_2 (2.8 mL) at –70 °C. After stirring for 15 min, a solution of compound **74** (35.8 mg, 72.0 µmol) in CH_2Cl_2 (1 mL) was added dropwise and the resulting mixture was stirred at this temperature for 20 min and at –30°C for an additional 1 h. After cooling to –70 °C, triethylamine (116 mg, 1.15 mmol) was introduced and the solution warmed to room temperature within 1 h. *tert*-Butyl methyl ether was added, the organic phase was washed with sat. sol. NH_4Cl and sat. sol. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. A yellow oil (31.7 mg) was obtained that was used in the next step without further purification.

A solution of this crude aldehyde and CHI_3 (86.1 mg, 0.219 mmol) in 1,4-dioxane (2.4 mL) was slowly added to a suspension of $CrCl_2$·THF (288 mg, 1.48 mmol) in THF (2.4 mL) at 0 °C. The brown suspension was stirred for 16 h at this temperature and then quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 98:2) to afford the product as a colorless oil (27.1 mg, 75 % over two steps, *Z:E* = 12:1).

A solution of the product in CH_2Cl_2 (0.4 mL) was diluted with methanol (8 mL). A solution of CSA (3.7 mg, 15.9 µmol) in methanol (100 µL) was added and the resulting mixture stirred for 5 h before the reaction was quenched with triethylamine (1.60 mg, 15.9 µmol) in methanol (50 µL). The mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAc, 80:20) to afford the product as a colorless oil (15.0 mg, 53 % over three steps, containing ca. 4% of diastereoisomer at C1). mp = 115 – 116 °C; $[\alpha]_D^{20}$ = +109.9 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.58 (dd, *J* = 14.5, 6.0 Hz, 1H), 6.44 (dd, *J* = 14.6, 1.2 Hz, 1H), 6.33 (td, *J* = 12.4, 3.9 Hz, 1H), 5.89 (dd, *J* = 11.6, 2.4 Hz, 1H), 5.53 (dddd, *J* = 11.1, 6.0, 2.3, 1.2 Hz, 1H), 5.41 – 5.24 (m, 2H), 3.76 (ddd, *J* = 14.7, 12.7, 4.9 Hz, 1H), 3.44 (t, *J* = 10.5 Hz, 1H), 2.38 (ddd, *J* = 13.7, 4.6, 2.1 Hz, 1H), 2.23 – 1.96 (m, 5H), 1.64 (s, 1H), 1.47 (dddd, *J* = 14.1, 9.6, 6.1, 2.4 Hz, 1H), 1.35 (ddd, *J* = 14.9, 11.6, 4.0 Hz, 1H), 1.20 (ddt, *J* = 14.2, 11.8, 2.5 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.99 (ddd, *J* = 14.4, 12.3, 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.4, 147.4, 144.1, 134.1, 126.3, 121.4, 79.0, 73.0, 65.5,

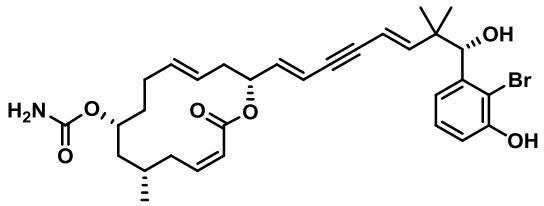
43.0, 39.1, 36.9, 31.6, 28.4, 27.7, 20.2; **IR** (neat): 3519, 2950, 2930, 2869, 1716, 1636, 1609, 1447, 1416, 1286, 1227, 1169, 1067, 1021, 967, 944, 835, 803 cm^{-1}; **MS** (EI): *m/z* (%) 263 (16), 245 (15), 208 (46), 180 (16), 179 (28), 167 (17), 165 (19), 163 (45), 162 (16), 152 (23), 148 (32), 139 (23), 135 (17), 133 (17), 123 (71), 122 (19), 121 (30), 113 (21), 111 (39), 109 (27), 108 (25), 107 (38), 97 (26), 96 (23), 95 (100), 94 (36), 55 (49), 54 (44), 41 (36); **HRMS** (ESI-pos.) calcd. for $C_{16}H_{23}O_3INa$ $[M + Na]^+$ 413.05841, found 413.05851.

(3*Z*,6*S*,8*R*,11*E*,14*R*)-14-((*E*)-2-Iodovinyl)-6-methyl-2-oxooxacyclotetradeca-3,11-dien-8-yl carbamate (48).



A solution of chlorosulfonyl isocyanate (7.0 mg, 49 µmol) in CH_2Cl_2 (50 µL) was slowly added to a solution of compound **77** (14.8 mg, 37.9 µmol) in CH_2Cl_2 (3.2 mL) at 0 °C. The mixture was stirred at this temperature for 30 min and the reaction was quenched with THF/H_2O (4:1, 400 µL). The resulting mixture was vigorously stirred at room temperature for 3.5 h before it was diluted with sat. aq. NH_4Cl. The aqueous phase was extracted with EtOAc, the combined organic layers were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 2:1) to afford the product as a colorless oil (15.7 mg, 95 %, containing ca. 4% of diastereoisomer at C1). $[\alpha]_D^{20}$ = +68.1 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.57 (dd, *J* = 14.6, 6.2 Hz, 1H), 6.43 (dd, *J* = 14.6, 1.2 Hz, 1H), 6.21 (td, *J* = 11.5, 4.7 Hz, 1H), 5.87 (dd, *J* = 11.6, 2.2 Hz, 1H), 5.58 (dddd, *J* = 10.3, 6.2, 2.8, 1.1 Hz, 1H), 5.49 (ddd, *J* = 15.5, 8.8, 5.3 Hz, 1H), 5.37 (dt, *J* = 14.7, 6.7 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.57 (s, 2H), 3.45 (ddd, *J* = 15.9, 11.3, 5.4 Hz, 1H), 2.49 – 2.32 (m, 1H), 2.27 – 2.08 (m, 2H), 2.01 (q, *J* = 6.4 Hz, 2H), 1.93 – 1.84 (m, 1H), 1.84 – 1.74 (m, 1H), 1.44 (ddd, *J* = 14.6, 11.5, 3.7 Hz, 1H), 1.28 (dtd, *J* = 12.6, 5.6, 5.0, 3.9 Hz, 1H), 1.18 (ddd, *J* = 14.2, 11.6, 2.6 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.0, 156.8, 145.4, 144.2, 133.3, 126.3, 121.9, 79.2, 73.2, 71.2, 40.7, 38.4, 34.2, 32.6, 28.2, 27.8, 20.3; **IR** (neat): 3483, 3380, 2953, 1922, 2870, 1714, 1638, 1604, 1385, 1330, 1169, 1046, 968, 943, 835, 802 cm^{-1}; **HRMS** (ESI-pos.) calcd. for $C_{17}H_{24}NO_4INa$ $[M + Na]^+$ 456.06423, found 456.06421.

(3*Z*,6*S*,8*R*,11*E*,14*R*)-14-((S,1*E*,5*E*)-8-(2-Bromo-3-hydroxyphenyl)-8-hydroxy-7,7-dimethylocta-1,5-dien-3-yn-1-yl)-6-methyl-2-oxo-oxa-cyclotetradeca-3,11-dien-8-yl carbamate (45)



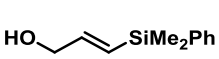
A solution of enyne **27** (6.5 mg, 22 µmol) and DIPEA (3.8 mg, 29 µmol) in THF (300 µL) was added dropwise to a solution of compound **48** (6.3 mg, 15 µmol), CuI (2.9 mg, 15 µmol) and $Pd(PPh_3)_4$ (1.7 mg, 1.0 µmol, 10 mol%) in degassed THF (1.5 mL). The mixture was stirred for 1.5 h during which time the color changed from yellow to orange. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 80:20 to 60:40) to afford the product as a colorless oil (6.4 mg, 74 %). $[\alpha]_D^{20}$ = +3.1 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.23 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.34 (d, *J* = 16.3 Hz, 1H), 6.21 (td, *J* = 11.4, 5.0 Hz, 1H), 6.11 (dd, *J* = 15.9, 6.1 Hz, 1H), 5.87 (dd, *J* = 11.8, 1.6 Hz, 1H), 5.84 (m, 1H), 5.74 (s, 1H), 5.69 (dddd, *J* = 9.1, 6.1, 3.0, 1.5 Hz, 1H), 5.55 (dd, *J* = 16.3, 2.2 Hz, 1H), 5.51 (dd, *J* = 8.7, 5.5 Hz, 1H), 5.39 (dt, *J* = 15.0, 6.8 Hz, 1H), 5.00 (s, 1H), 4.71 – 4.65 (m, 1H), 4.52 (s, 2H), 3.40 (ddd, *J* = 15.8, 11.0, 5.4 Hz, 1H), 2.42 (dddd, *J* = 14.3, 5.8, 3.0, 1.5 Hz, 1H), 2.23 (t, *J* = 9.2 Hz, 1H), 2.18 (ddd, *J* = 17.3, 5.3, 1.7 Hz, 1H), 2.02 (q, *J* = 6.2 Hz, 2H), 1.98 – 1.95 (m, 1H), 1.88 (qt, *J* = 7.0, 3.5 Hz, 1H), 1.80 (dddd, *J* = 14.0, 7.7, 6.1, 4.6 Hz, 1H), 1.45 (ddd, *J* = 14.6, 11.0, 3.8 Hz, 1H), 1.35 – 1.26 (m, 1H), 1.21 (ddd, *J* = 14.2, 11.3, 2.8 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 165.2, 156.7, 151.9, 150.0, 145.3, 141.2, 140.7, 133.1, 128.2, 126.5, 122.0, 121.5, 115.3, 112.8, 111.6, 109.1, 89.7, 87.1, 78.6, 71.5, 71.4, 43.7, 40.7, 38.7, 34.1, 32.8, 28.3, 27.8, 24.6, 22.0, 20.3; **IR** (neat): 3494, 3376, 2961, 2927, 2873, 1702, 1638, 1596, 1573, 1461, 1440, 1390, 1292, 1222, 1173, 1050, 911, 799, 757 cm^{-1}; **HRMS** (ESI-pos.) calcd. for $C_{31}H_{38}NO_6BrNa$ $[M + Na]^+$ 622.17748, found 622.17733.

6.3 First Synthetic Approach

The reactions described in the following Chapters (6.3.1 to 6.3.4), depicting the synthesis of the northern and southern fragment, their assembly as well as the following *trans*-hydroelementation studies, were carried out by Dr. Guillaume Mata.[58]

6.3.1 Synthesis of the Northern Fragment

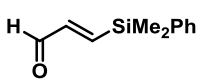
(*E*)-3-(Dimethyl(phenyl)silyl)prop-2-en-1-ol (79)[128]



Preparation of the catalyst: *t*-Bu_3P (82.5 mg) was added to the commercial sample of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (3.87 mL). The resulting mixture was stirred at 65 °C for 5 min, cooled to room temperature and used directly in the next step.

An aliquot of this catalyst solution (1.12 mL, 0.145 mmol, 0.1 mol%) was carefully added to a solution containing propargylic alcohol (8.5 mL, 146 mmol) and dimethylphenylsilane (23.5 mL, 153 mmol) in THF (275 mL). Sodium metal (40.3 mg, 1.75 mmol, 12 mol%) was then added and the resulting mixture was stirred at 72 °C for 16 h. All volatile materials were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 90:10 then 85:15) to afford the product as a colorless oil (21.3 g, 76 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 – 7.51 (m, 2H), 7.40 – 7.34 (m, 3H), 6.26 (dt, J = 18.8, 4.2 Hz, 1H), 6.07 (dt, J = 18.7, 1.8 Hz, 1H), 4.21 (ddd, J = 6.0, 4.2, 1.7 Hz, 2H), 1.61 (t, J = 5.9 Hz, 1H), 0.37 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 146.8, 138.5, 133.9, 129.2, 127.9, 127.3, 65.5, -2.5; **IR** (neat): 3320, 2955, 1621, 1427, 1247, 1114, 1081, 992, 817, 783, 728, 697 cm^{-1}; **MS** (EI): *m*/*z* (%) 177 (M^+–15), 135, 121, 99, 75 (100), **HRMS** (ESI-pos.) calcd. for $C_{11}H_{16}OSiNa$ $[M + Na]^+$ 215.08634, found 215.08626.

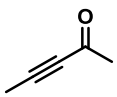
(*E*)-3-(Dimethyl(phenyl)silyl)acrylaldehyde (80)[128]



PCC (19.0 g, 88.38 mmol) was added over 10 min to a slurry of Celite (19.0 g). in CH_2Cl_2 (171 mL). A solution of alcohol **79** (8.50 g, 44.2 mmol) in CH_2Cl_2 (20 mL) was then slowly introduced and the resulting mixture was stirred for 45 min. Insoluble materials were filtered off over a pad of silica which was carefully rinsed with CH_2Cl_2. The combined filtrates were evaporated and the residue was purified by flash

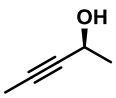
chromatography (hexane/EtOAc, 95:5 to 90:10) to afford the product as a colorless oil (7.61 g, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.54 (d, J = 7.6 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.46 – 7.37 (m, 3H), 7.30 (d, J = 18.7 Hz, 1H), 6.56 (dd, J = 18.7, 7.6 Hz, 1H), 0.49 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.7, 156.7, 145.1, 135.7, 133.9, 129.8, 128.2, -3.3; **IR** (neat): 2959, 2800, 1688, 1428, 1251, 1115, 1084, 991, 821, 787, 731, 697 cm^{-1}; **MS** (EI): *m/z* (%) 189 (M^+–1, 17), 176 (16), 175 (100), 147 (29), 145 (24), 135 (32), 131 (14), 121 (45), 115 (21), 105 (24), 91 (10), 75 (33), 43 (14); **HRMS** (ESI-pos.) calcd. for $C_{11}H_{14}OSiNa$ $[M + Na]^+$ 213.07066, found 213.07061.

Pent-3-yn-2-one (84)



3-Pentyn-2-ol (2.27 g, 27.0 mmol) was added to a suspension of MnO_2 (46.91 g, 540 mmol) in CH_2Cl_2 (210 mL) and the resulting mixture was stirred for 4 h. For work-up, the mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2. The combined filtrates were evaporated and the residue was purified by distillation under reduced pressure (bp = 58 °C and p = 65 mbar) to afford the product as a colorless oil (1.44 g, 65 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 185.0, 89.9, 80.8, 32.8, 4.13; **IR** (neat): 2216, 1671, 1421, 1359, 1239, 962, 658 cm^{-1}; **MS** (EI): *m/z* (%) 82 (M^+, 14), 67 (100), 39 (17); **HRMS** (ESI-pos.) calcd. for C_5H_6O $[M]^+$ 82.04176, found 82.04187.

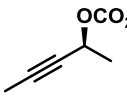
(*S*)-Pent-3-yn-2-ol (85)[86]



RuCl[(*S*,*S*)-Ts-DPEN](η^6-cymene) (0.753 g, 1.18 mmol) was added in portions to a solution of pent-3-yn-2-one (8.83 g, 107.5 mmol) in degassed CH_2Cl_2 (358 mL). Next, a mixture of formic acid and triethylamine (5:2, 10.2 mL) was added and stirring continued for 14 h. The reaction was quenched with sat. aq. $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by distillation under reduced pressure (bp = 66 °C and p = 55 mbar) to afford the product as a colorless oil (4.03 g, 45 % over two steps, 93% *ee*). **GC** (Lipodex AG 717), t_R (*R*) = 10.56 min, t_R (*S*) = 11.26 min (major); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.39 (d, J_1 = 6.6 Hz, 3H), 1.81-1.80 (m, 3H), 2.17 (br, s, 1H), 4.48-4.45 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 81.5, 80.2, 58.6, 24.7, 3.6; **IR** (neat): 3346, 2981, 2922, 2255, 1667, 1369,

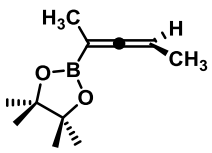
1286, 1158, 1071, 998, 885 cm^{-1}; **MS** (EI): *m/z* (%) 69 (M^+–15 , 100), 43 (29), 41 (29), 40 (14), 39 (46), 29 (11); **HRMS** (ESI-pos.) calcd. for C_5H_9O $[M + H]^+$ 85.06534, found 85.06540.

(*S*)-Methyl pent-3-yn-2-yl carbonate (86)[84]



Methyl choloroformate (7.40 mL, 95.8 mmol) was added dropwise to a solution of pyridine (11.6 mL, 143.7 mmol) and alcohol **85** (11.6 mL, 143.7 mmol) in CH_2Cl_2 (94.0 mL) at 0 °C. The resulting mixture was stirred for 2 h and the reaction was quenched with with aq. HCl (1 M). The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the product as a colorless and volatile oil (6.20 g, 91 %, 93% *ee*). $[\alpha]_D^{20}$ = –130.4 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.30-5.23 (m, 1H), 3.78 (s, 3H), 1.83 (d, J_1 = 2.1 Hz, 3H), 1.49 (d, J_1 = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.1, 82.2, 77.1, 65.0, 54.9, 21.8, 3.8; **IR** (neat): 2993, 2959, 2254, 1747, 1442, 1317, 1258, 1174, 1053, 991, 938 cm^{-1}; **MS** (EI): *m/z* (%) 127 (M^+-15, 50), 83 (48), 68 (16), 67 (76), 66 (100), 65 (48), 59 (15), 55 (14), 43 (17), 41 (29), 40 (10), 39 (21); **HRMS** (ESI-pos.) calcd. for $C_7H_{10}O_3Na$ $[M + Na]^+$ 165.0522, found 165.0524.

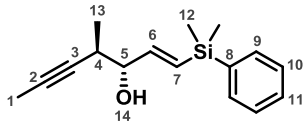
4,4,5,5-Tetramethyl-2-(penta-2,3-dien-2-yl)-1,3,2-dioxaborolane (81)[84]



A mixture of CuCl (0.651 g, 6.58 mmol), XantPhos (2.86 g, 4.93 mmol) and freshly sublimed *tert*-BuONa (0.791 g, 8.23 mmol) in THF (27 mL) was stirred for 15 min at room temperature before a solution of bis(pinacolato)diboron (16.7 g, 65.8 mmol) in THF (10 mL) was added. The resulting dark red solution warmed to –50 °C before propargylic carbonate **86** (4.68 g, 32.9 mmol) was added and stirring continued for 18 h at this temperature. Next, all volatile materials were evaporated and the residue was purified by flash chromatography (hexane/*tert*-butyl methyl ether, 97:3) to afford the product as a colorless and volatile oil (2.2 g, 35 %). (*Note: The flash chromatography was completed within 10 min as the product readily hydrolyzes on silica gel*). $[\alpha]_D^{20}$ = –37.0 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.99-4.97 (m, 1H), 1.69 (d, J_1 = 2.9 Hz, 3H), 1.65 (d, J_1 = 7.0 Hz, 3H), 1.27 (d, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 213.2, 83.7, 80.8, 24.9, 24.8, 16.3, 13.6; **IR** (neat): 2979, 2927, 1945, 1450, 1410, 1394, 1370, 1346, 1307, 1146, 1100, 854 671 cm^{-1}; **MS** (EI): *m/z* (%) 194 (M^+, 31), 179 (35), 150 (25), 139 (13), 138 (88), 137 (44), 136 (24), 135 (100), 123 (11), 121 (31), 119 (15), 111 (30), 108 (14), 107 (22),

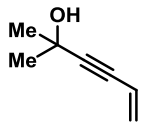
101 (32), 95 (16), 94 (26), 93 (56), 91 (11), 85 (15), 84 (16),83 (40), 82 (11), 81 (17), 80 (16), 79 (38), 70 (20), 69 (23), 68 (15), 67 (82), 66 (29), 57 (12), 55 (23), 43 (16), 41 (23), 39 (11).

(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhept-1-en-5-yn-3-ol (82)



Aldehyde **80** (0.469 g, 2.46 mmol) was added to a solution of (*R*)-TRIP (92.8 mg, 0.123 mmol, 5 mol%) and molecular sieves 4 Å (0.7 g) in toluene (12 mL). The mixture was stirred for 15 min at 0 °C before a solution of allenylboronate **81** (0.456 g, 0.235 mmol) in toluene (3 mL) was added dropwise. Stirring was continued for 18 h before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5 to 90:10) to afford the product as a colorless oil (0.492 g, 81 %, dr > 20:1). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +12.1 (*c* 0.59, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.58 – 7.48 (m, 2H, H9), 7.40 – 7.31 (m, 3H, H10 and H11), 6.13 (dd, *J* = 18.7, 4.4 Hz, 1H, H6), 6.06 (d, *J* = 18.8 Hz, 1H, H7), 3.94 (dd, *J* = 5.8, 4.3 Hz, 1H, H5), 2.60 – 2.51 (m, 1H, H4), 2.14 (br. s, 1H, H14), 1.81 (d, *J* = 2.4 Hz, 3H, H1), 1.16 (d, *J* = 6.9 Hz, 3H, H13), 0.36 (s, 6H, H12); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.8 (d, C6), 138.6 (s, C8), 134.0 (s, C9), 129.5 (d, C7), 129.1 (d, C11), 127.9 (d, C10), 79.5 (s, C3), 79.1 (s, C2), 77.5 (d, C5), 33.4 (d, C4), 17.6 (q, C13), 3.7 (q, C1), -2.5 (q, C12); **IR** (neat): 3422, 2956, 1621, 1427, 1248, 1113, 990, 842, 824, 731, 699 cm^{-1}; **MS** (EI): *m*/*z* (%) 243 (12), 191 (13), 190 (19), 175 (12), 173 (12), 165 (12), 145 (15), 137 (23), 135 (34), 117 (19), 113 (51), 106 (18), 105 (14), 98 (17), 91 (10), 77 (12), 75 (62), 68 (21), 67 (100), 65 (22), 45 (10), 43 (12), 41 (29), 39 (15); **HRMS** (ESI-pos.) calcd. for $C_{16}H_{22}OSiNa$ $[M + Na]^+$ 281.13321, found 281.13306.

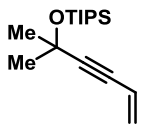
2-Methylhex-5-en-3-yn-2-ol (85)[88]



CuI (0.317 g, 1.66 mmol) and $Pd(PPh_3)_4$ (0.274 g, 0.238 mmol) were added to a solution of diethylamine (56.6 mL, 547 mmol). Next, 2-methyl-3-butyn-2-ol (10.0 g, 119 mmol) and vinyl bromide (178 mL, 178 mmo, 1 M in THF) were added dropwise. After stirring for 3 h, the reaction was poured in ice water, the aqueous layer was extracted with *tert*-butyl methyl ether, washed with aq. HCl (2 M) and evaporated and the residue was distilled under reduced pressure (T = 55 °C and P = 13 mbar) to afford the product as colorless liquid (10.2 g, 78 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.75 (dd, *J* = 17.6,

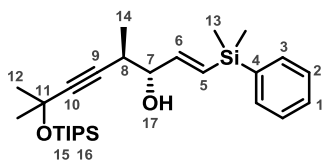
11.0 Hz, 1H), 5.56 (dd, *J* = 17.6, 2.3 Hz, 1H), 5.41 (dd, *J* = 11.1, 2.2 Hz, 1H), 2.73 (s, 1H), 1.49 (s, 6H); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 126.9, 116.8, 94.6, 80.8, 65.5, 31.4; **IR** (neat): 3346, 2982, 2934, 1609, 1455, 1411, 1363, 1238, 1163, 973, 941, 921, 845, 677, 650, 550 cm^{-1}; **MS** (EI): *m*/*z* (%) 95 (M^+–15, 86), 91 (14), 77 (10), 67 (15), 58 (16), 52 (43), 51 (34), 50 (26), 43 (100), 39 (10); **HRMS** (ESI-pos.) calcd. for $C_7H_{10}O_1Na$ $[M + Na]^+$ 133.06238, found 133.06246.

Triisopropyl((2-methylhex-5-en-3-yn-2-yl)oxy)silane (86)[88]



Compound **85** (9.5 g, 86.2 mmol) was added dropwise to a suspension of NaH (2.48 g, 104 mmol) in THF (285 mL). The resulting mixture was stirred for 30 min before TIPSCl (18.45 mL, 86.2 mmol) was added dropwise at 0 °C and stirring continued for 18 h. The reaction was quenched with water, the aqueous layer was extracted with *tert*-butyl methyl ether, and the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane) to afford the product as a colorless oil (19.1 g, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.68 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.46 (dd, *J* = 17.6, 2.3 Hz, 1H), 5.33 (dd, *J* = 11.1, 2.1 Hz, 1H), 1.43 (s, 6H), 1.14 – 1.00 (m, 3H), 1.00 – 0.90 (m, 19H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 126.4, 117.2, 95.8, 81.1, 66.5, 33.2, 18.5, 13.2; **IR** (neat): 2961, 2944, 2893, 2867, 1608, 1464, 1377, 1359, 1245, 1162, 1050, 1016, 971, 918, 882, 807, 738, 679, 659 cm^{-1}; **MS** (EI): *m*/*z* (%) 224 (M^+–42, 18), 223 (100), 181 (49), 171 (13), 166 (11), 165 (72), 138 (11), 137 (70), 123 (54), 109 (48), 103 (22), 95 (45), 91 (10), 77 (15), 75 (62), 73 (11), 61 (32), 59 (17), 45 (12); **HRMS** (ESI-pos.) calcd. for $C_{16}H_{31}O_1Si_1Na_1$ $[M + Na]^+$ 267.21387, found 267.21390.

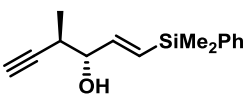
(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4,7-dimethyl-7-((triisopropylsilyl)oxy)oct-1-en-5-yn-3-ol (87)



A pressure Schlenk-flask was charged with aldehyde **80** (0.930 g, 4.887 mmol), enyne **86** (2.60 g, 9.77 mmol), $(Ir(cod)Cl)_2$ (0.082 g, 0.122 mmol), (*R*)-DM-Segphos (0.177 g, 0.244 mmol), Na_2SO_4 (0.694 g, 4.887 mmol), THF (5.55 mL) and HCO_2H (0.19 mL, 5.13 mmol). The vessel was closed and the mixture stirred at 70 °C for 40 h. For work up, all volatile materials were evaporated and the residue (dr = 8:1) was purified by flash chromatography (hexane/*tert*-butyl methyl ether, 99:1 to 98:2) to afford the *anti*-isomer as a colorless oil (1.23 g, 55 %, dr > 20:1) [*ee* = 82%, HPLC: 150 mm Chiralpak IA-3, 4.6 mm, *iso*-

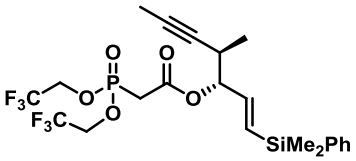
hexane/2-propanol = 99.9:0.1, 1.0 mL/min, 308K), t_R (*S,S*) = 17.26 min (minor), t_R (*R,R*) = 17.80 min (major)]. $[\alpha]_D^{20}$ = +3.0 (*c* 0.81, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 – 7.51 (m, 2H, H3), 7.40– 7.34 (m, 3H, H1 and H2), 6.15 (dd, *J* = 18.8, 4.1 Hz, 1H, H6), 6.09 (d, *J* = 18.8 Hz, 1H, H5), 3.99 (q, *J* = 6.0, 5.5 Hz, 4.1, 1H, H7), 2.64 (p, *J* = 7.0, 5.5 Hz, 1H, H8), 2.01 (d, *J* = 6.0 Hz, 1H, H17), 1.49 (s, 6H, H12), 1.20 – 1.13 (m, 6H, H15 and H14), 1.12 – 1.07 (m, 18H, H16), 0.38 (s, 6H, H13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.5 (C6), 138.4 (C4), 133.9 (C3), 129.4 (C5), 129.2 (C1), 127.9 (C2), 89.3 (C10), 82.2 (C9), 76.9 (C7), 66.3 (C11), 33.8 (C12), 33.7 (C12), 33.3 (C8), 18.5 (C16), 16.7 (C14), 13.2 (C15), -2.5 (C13); **IR** (neat): 3430, 3069, 2942, 2892, 2865, 1621, 1463, 1428, 1377, 1358, 1333, 1299, 1247, 1160, 1114, 1048, 1015, 946, 882, 840, 822, 730, 698, 679, 469 cm^{-1}; **MS** (EI): *m/z* (%) 458 (11), 223 (13), 211 (12), 205 (31), 195 (10), 189 (36), 177 (15), 169 (13), 163 (12), 161 (14), 147 (14), 137 (10), 136 (14), 135 (100), 133 (20), 131 (16), 119 (12), 105 (12), 103 (20), 94 (67), 75 (40), 61 (14), 59 (10); **HRMS** (ESI-pos.) calcd. for $C_{27}H_{46}O_2Si_2Na$ $[M + Na]^+$ 481.29286, found 481.29313.

(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhex-1-en-5-yn-3-ol (88)



TBAF (1 M in THF, 3.6 mL, 3.59 mmol) was added dropwise to a solution of compound **87** (1.1 g, 2.40 mmol) in THF (3.7 mL). The mixture was stirred for 18 h at room temperature before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in toluene and NaOH (powder, 0.287 g, 7.19 mmol) was added, and the resulting mixture was stirred at 110 °C for 1 h 30 min. All volatile materials were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 98:2 then 95:5) to afford the product as colorless oil (0.432 g, 74 %). $[\alpha]_D^{20}$ = +4.5 (*c* 0.9 $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.58 – 7.50 (m, 2H), 7.41 – 7.33 (m, 3H), 6.22 – 6.06 (m, 2H), 4.09 – 4.00 (m, 1H), 2.64 (qdd, *J* = 7.1, 5.6, 2.5 Hz, 1H), 2.16 (d, *J* = 2.5 Hz, 2H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.38 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.2, 138.4, 133.9, 129.9, 129.2, 127.9, 85.0, 76.9, 71.2, 33.0, 17.1, -2.5, -2.5; **IR** (neat): 3545, 3430, 3302, 3069, 3049, 2976, 2956, 1612, 1543, 1248, 1191, 1113, 991, 818, 730, 698, 634 cm^{-1}; **MS** (EI): *m/z* (%) 175 (11), 145 (12), 137 (13), 135 (31), 121 (16), 115 (12), 113 (23), 105 (12), 91 (15), 78 (10), 77 (12), 75 (100), 59 (13), 54 (16), 53 (17), 43 (20), 39 (15); **HRMS** (ESI-pos.) calcd. for $C_{15}H_{20}OSiNa$ $[M + Na]^+$ 267.11756, found 267.11772.

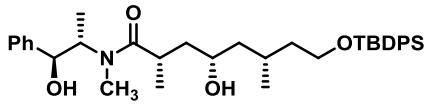
(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhept-1-en-5-yn-3-yl-2-(bis(2,2,2-trifluoroethoxy)-phosphoryl)acetate (23)



Phosphonoacetic acid **40**[61] (1.04 g, 3.41 mmol), HOBt·H_2O (0.092 g, 0.681 mmol) and EDCI·HCl (1.96 g, 10.2 mmol) were successively added to a solution of alcohol **82** (0.440 g, 1.70 mmol) in CH_2Cl_2 (85 mL). The mixture was stirred for 2 h before all volatile materials were evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1 to 8:2) to afford the ester as a colorless oil (0.65 g, 70 %). $[\alpha]_D^{20}$ = +9.2 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52-7.49 (m, 2H), 7.37 – 7.34 (m, 3H), 6.09 (d, *J* = 18.8 Hz, 1H), 6.03 (dd, *J* = 18.8, 4.4 Hz, 1H), 5.31 (dd, *J* = 5.4, 4.5 Hz, 1H), 4.49-4.40 (m, 4H), 3.23 (d, $^2J_{H,P}$ = 20.9 Hz, 2H), 2.77-2.69 (m, 1H), 1.76 (d, *J* = 2.4 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.35 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.9 (d, $^2J_{C,P}$ = 4.0 Hz), 141.7, 138.0, 133.9, 132.6, 129.2, 127.9, 122.5 (qd, $^1J_{C,F}$ = 275.8 Hz, $^3J_{C,P}$ = 8.2 Hz), 80.0, 78.9, 78.4, 62.5 (qd, $^2J_{C,F}$ = 38.0 Hz, $^2J_{C,P}$ = 5.4 Hz), 34.1 (d, $^1J_{C,P}$ = 144.1 Hz), 30.6, 16.7, 3.4, -2.7, -2.7; **^{31}P NMR** (162 MHz, $CDCl_3$) δ: 22.97; **IR** (neat): 2975, 1739, 1427, 1263, 1166, 1098, 1066, 961, 886, 824, 732, 700, 653 cm^{-1}; **MS** (EI): *m*/*z* (%) 423 (11), 362 (11), 361 (80), 319 (15), 287 (100), 267 (10), 135 (18), 75 (12); **HRMS** (ESI-pos.) calcd. for $C_{22}H_{27}F_6O_5PNa$ $[M + Na]^+$ 567.11662, found 567.11618.

6.3.2 Synthesis of the Southern Fragment

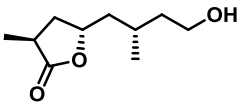
(2*S*,4*S*,6*S*)-8-((*tert*-Butyldiphenylsilyl)oxy)-4-hydroxy-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2,6-trimethyloctanamide (90)



*n*BuLi (1.6 M in hexanes, 29.7 mL, 47.8 mmol) was added over 10 min to a solution of anhydrous LiCl (5.70 g, 134.5 mmol) and *N*,*N*-diisopropylethylamine (7.13 mL, 50.9 mmol) in THF (50 mL) at –78 °C. The resulting suspension was warmed to 0 °C for 5 min before it was cooled again to –78 °C. A solution of compound **89**[90] (5.0 g, 22.6 mmol) in THF (50 mL) was added over 10 min and the resulting mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and room temperature for 5 min. Next, a solution of epoxide **54** (10.0 g, 27.1 mmol) in THF (100 mL) was added at 0°C and stirring was continued at this temperature for 1 h and at room temperature for 18 h. The reaction was quenched with a sat. aq. of NH_4Cl, the aqueous layer was extracted with EtOAc (3 x) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 8:2 then 5:5) to afford the product as a colorless oil (9.30 g, 70 %, dr > 20:1, mixture of rotamers) and recovered epoxide **54** (2.88 g). $[\alpha]_D^{20}$ = +64.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_6D_6, signals of the major rotamer only) δ: 7.86 – 7.74 (m, 4H, H26 and H30), 7.34 – 7.30 (m, 2H, H13), 7.29 – 7.23 (m, 6H, H27, H31, H28, H32), 7.18 – 7.13 (m, 2H, H14 underneath solvent peak), 7.10 – 7.05 (m, 1H, H15), 4.61 – 4.35 (m, 2H, H10 and H11), 3.87 – 3.81 (m, 1H, H5), 3.81 – 3.69 (m, 2H, H1), 2.92 (ddd, J = 10.4, 6.8, 3.4 Hz, 1H, H7), 2.50 (s, 3H, H20), 2.10 (ddd, J = 13.3, 10.3, 2.7 Hz, 1H, H6), 1.96 – 1.83 (m, 1H, H3), 1.75 (dtd, J = 13.9, 6.9, 5.0 Hz, 1H, H2), 1.41 – 1.24 (m, 4H, H2, H4, H6), 1.20 (s, 9H, H34), 1.03 (d, J = 6.9 Hz, 3H, H18), 0.92 – 0.87 (m, 6H, H16 and H21); **^{13}C NMR** (100 MHz, CD_6D_6, signals of the major rotamer only) δ: 178.7 (s, C8), 143.4 (s, C12), 136.1 (d, C26), 136.1 (d, C30), 134.4 (s, C25) 134.4 (s, C29), 130.0 (d, C28), 130.0 (d, C32), 128.4 (d, C14), 128.1 (d, C27), 128.1 (d, C31) 127.6 (d, C15), 127.1 (d, C13), 76.4 (d, C11), 67.4 (d, C5), 62.6 (t, C1), 58.5 (d, C10), 46.0 (t, C4), 42.1 (t, C6), 39.9 (t, C2), 33.0 (d, C7), 32.7 (q, C20), 27.2 (q, C34), 26.8 (d, C3), 20.5 (q, C16), 19.5 (s, C33), 18.3 (q, C18), 14.5 (q, C21); **IR** (neat): 3371, 2957, 2930, 2857, 1739, 1613, 1427, 1107, 1083, 1047, 882, 737, 699 cm^{-1}; **MS** (EI): *m*/*z* (%) 533 (17), 532 (41), 514 (13), 367 (22), 347 (26), 289 (20), 269 (11), 200 (14), 199 (75), 197 (11), 183 (11), 151 (12),

148 (23), 139 (12), 135 (17), 107 (12), 99 (11), 95 (11), 81 (14), 58 (100); **HRMS** (ESI-pos.) calcd. for $C_{36}H_{52}N_1O_4Si$ $[M + H]^+$ 590.36601, found 590.36602.

(3*S*,5*S*)-5-((*S*)-4-Hydroxy-2-methylbutyl)-3-methyldihydrofuran-2(3*H*)-one (91)



H_2SO_4 (1.64 mL, 30.7 mmol) in H_2O (15.5 mL) was added over 5 min to a solution of compound **90** (9.06 g, 15.4 mmol) in 1,4-dioxane (52 mL). The mixture was stirred at reflux temperature for 1 h before it was cooled to 0 °C. The reaction was carefully quenched with sat. aq. $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 4:6) to afford the product as a colorless oil (2.58 g, 90 %). $[\alpha]_D^{20}$ = –47.1 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.59 (tt, J = 8.2, 7.3, 5.8, 5.2 Hz, 1H), 3.80 – 3.49 (m, 2H), 2.65 (dp, J = 9.0, 7.3 Hz, 1H), 2.16 (s, 1H), 2.06 (ddd, J = 12.8, 8.8, 5.2 Hz, 1H), 1.97 (dt, J = 12.8, 7.3 Hz, 1H), 1.76 (dhd, J = 8.2, 6.7, 5.0 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.49 (ddd, J = 13.9, 6.6, 5.8 Hz, 1H), 1.38 (dddd, J = 13.5, 8.2, 6.8, 5.9 Hz, 1H), 1.23 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.4, 77.0, 60.4, 42.6, 39.2, 35.7, 34.0, 26.7, 19.9, 15.9; **IR** (neat): 3423, 2960, 2933, 2878, 1766, 1457, 1379, 1361, 1192, 1056, 1001 cm^{-1}; **MS** (EI): *m*/*z* (%) 99 (100), 95 (19), 83 (11), 82 (11), 81 (30), 71 (74), 70 (17), 69 (38), 68 (22), 67 (32), 57 (10), 56 (13), 55 (38), 44 (11), 43 (57), 42 (21), 41 (55), 39 (22), 31 (17), 29 (13), 28 (47), 27 (36); **HRMS** (ESI-pos.) calcd. for $C_{10}H_{18}O_3Na$ $[M + Na]^+$ 209.11476, found 209.11481.

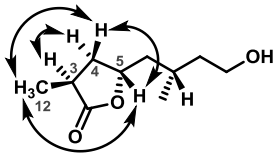
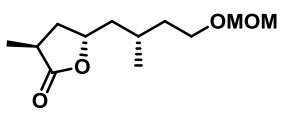


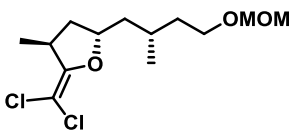
Figure 9: Observed NOE correlations in lactone ring.

(3*S*,5*S*)-5-((*S*)-4-(Methoxymethoxy)-2-methylbutyl)-3-methyldihydrofuran-2(3*H*)-one (92)



N,*N*-Diisopropylethylamine (9.82 mL, 56.4 mmol) and chloromethyl methylether (3.26 mL, 42.9 mmol) were successively added to a solution of alcohol **91** (2.5 g, 13.4 mmol) in CH_2Cl_2 (112 mL). After stirring for 18 h, the reaction was quenched with a sat. aq. NH_4Cl, the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 7:3) to afford the product as a colorless oil (3.02 g, 98 %). $[\alpha]_D^{20}$ = –40.7 (*c* 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.62 – 4.50 (m, 3H), 3.58 – 3.44 (m, 2H), 3.30 (s, 3H), 2.63 (dp, J = 8.8, 7.4 Hz, 1H), 2.04 (ddd, J = 12.8, 8.9, 5.2 Hz, 1H), 1.96 (dt, J = 12.8, 7.3 Hz, 1H), 1.75 (dqd, J = 8.2, 6.7, 5.2 Hz, 1H), 1.66 (dtd, J = 13.9, 6.9, 5.1 Hz, 1H), 1.57 (ddd, J = 13.9, 8.1, 7.2 Hz, 1H), 1.48 (dt, J = 14.0, 6.1 Hz, 1H), 1.39 (ddt, J = 13.8, 8.2, 6.3 Hz, 1H), 1.22 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.0, 96.4, 76.8, 65.5, 55.2, 42.6, 36.2, 35.7, 33.9, 27.0, 19.8, 15.9; **IR** (neat): 2933, 2879, 1770, 1458, 1380, 1174, 1151, 1109, 1053, 1036, 1002, 920 cm^{-1}; **MS** (EI): *m*/*z* (%) 185 (12), 169 (31), 168 (19), 167 (45), 123 (12), 99 (86), 97 (40), 95 (22), 85 (23), 81 (14), 74 (18), 71 (28), 55 (12), 45 (100); **HRMS** (ESI-pos.) calcd. for $C_{12}H_{22}O_4Na$ $[M + Na]^+$ 253.14081, found 253.14103.

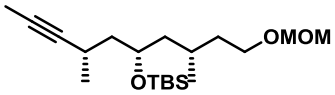
(3*S*,5*S*)-2-(Dichloromethylene)-5-((*S*)-4-(methoxymethoxy)-2-methylbutyl)-3-methyltetrahydrofuran (93)



PPh_3 (33.26 g, 126.80 mmol) was added to a solution of lactone **92** (2.92 g, 12.68 mmol) in THF (275 mL). The solution was stirred at reflux temperature while CCl_4 (73.4 mL, 760.8 mmol) was added dropwise over 6 h via a syringe pump. The mixture was cooled to room temperature and the reaction quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to a minimum volume of CH_2Cl_2. Pentane was added and the precipitate was filtered off. This precipitation cycle was repeated three times before the residue was purified by flash chromatography (hexane/EtOAc, 95:5 to 90:10) to afford the product as a colorless oil (2.57 g, 68 %) along with recovered starting material (0.60 g). $[\alpha]_D^{20}$ = +12.7 (*c* 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.64 – 4.52 (m, 3H), 3.55 (td, *J* = 6.7, 0.9 Hz, 2H), 3.34 (s, 3H), 3.16 – 3.04 (m, 1H), 1.91 – 1.82 (m, 2H), 1.79 – 1.61 (m, 3H), 1.54 (ddd, *J* = 13.6, 6.3, 5.3 Hz,

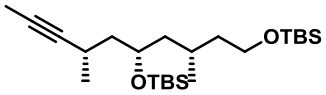
1H), 1.50 – 1.40 (m, 1H), 1.21 (d, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.2, 95.5, 92.5, 81.0, 64.7, 54.3, 41.4, 38.5, 36.0, 35.9, 26.6, 18.8, 16.3; **IR** (neat): 2930, 2877, 1659, 1459, 1380, 1225, 1152, 1109, 1052, 1030, 916 cm^{-1}; **MS** (EI): *m*/*z* (%) 296 (M^+, 6), 111 (8), 95 (13), 85 (8), 45 (100); **HRMS** (ESI-pos.) calcd. for $C_{13}H_{22}Cl_2O_3Na$ $[M + Na]^+$ 319.08382, found 319.08361.

(3*S*,5*S*,7*S*)-1-(Methoxymethoxy)-3,7-dimethyldec-8-yn-5-ol (94)



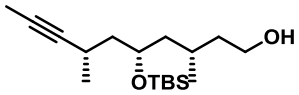
$Fe(acac)_3$ (0.354 g, 1.00 mmol, 12 mol%) and 1,2-diaminobenzene (0.225 g, 2.09 mmol, 25 mol%) were added to a solution of dichloro-olefin **93** (2.48 g, 8.34 mmol) in Et_2O (62.0 mL) at 0 °C before MeLi (1.6 M in Et_2O, 26.1 mL, 41.7 mmol) was slowly introduced at this temperature. Stirring was continued at room temperature for 3 h before the reaction was quenched with H_2O at 0 °C. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1 then 8:2) to afford the product as a colorless oil (1.48 g, 73 %). $[\alpha]_D^{20}$ = +21.0 (*c* 0.29, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.62 (d, *J* = 0.8 Hz, 2H), 4.08 – 3.95 (m, 1H), 3.66 – 3.51 (m, 2H), 3.37 (s, 3H), 2.68 (dttt, *J* = 16.4, 9.3, 4.7, 2.4 Hz, 1H), 1.95 (d, *J* = 2.4 Hz, 1H), 1.79 (d, *J* = 2.4 Hz, 3H), 1.77 – 1.70 (m, 1H), 1.52 – 1.34 (m, 5H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 96.5, 83.3, 76.5, 67.7, 66.1, 55.2, 45.4, 44.7, 36.3, 26.8, 22.7, 21.9, 20.4, 3.6; **IR** (neat): 3429, 2929, 2874, 1452, 1378, 1214, 1152, 1107, 1034, 943, 918, 847, 631, 515 cm^{-1}; **MS** (EI): *m*/*z* (%) 135 (10), 125 (11), 124 (11), 123 (28), 121 (14), 119 (12), 112 (12), 111 (40), 110 (11), 109 (25), 107 (29), 105 (17), 99 (68), 98 (15), 97 (21), 96 (15), 95 (56), 94 (12), 93 (34), 91 (22), 85 (17), 84 (13), 83 (27), 82 (24), 81 (58), 80 (17), 79 (43), 77 (25), 71 (21), 70 (17), 69 (68), 68 (21), 67 (90), 65 (21); **HRMS** (ESI-pos.) calcd. for $C_{14}H_{26}O_3Na$ $[M + Na]^+$ 265.17741, found 265.17728.

(5*S*,7*S*)-2,2,3,3,7,11,11,12,12-Nonamethyl-5-((*S*)-2-methylpent-3-yn-1-yl)-4,10-dioxa-3,11-disilatridecane (95)



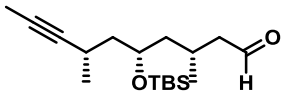
HCl conc. (4.6 mL) was added dropwise at 0 °C to a solution of alcohol **94** (1.38 g, 5.69 mmol) in MeOH (110 mL). The mixture was stirred at 60 °C for 2 h before the reaction was quenched with sat. aq. $NaHCO_3$ at 0 °C. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in CH_2Cl_2 (37 mL). 2,6-Lutidine (2.7 mL, 22.8 mmol) and TBSOTf (3.1 mL, 13.7 mmol) were added dropwise at 0 °C and stirring was continued for 1 h at room temperature before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99.3:0.7 to 99:1) to afford the product as a colorless oil (2.17 g, 89 %). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +49.5 (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.96 (tdd, *J* = 9.1, 4.5, 2.4 Hz, 1H), 3.69 – 3.56 (m, 2H), 2.56 (dtqd, *J* = 13.5, 6.8, 4.7, 2.5 Hz, 1H), 1.78 (d, *J* = 2.3 Hz, 3H), 1.61 – 1.40 (m, 4H), 1.40 – 1.33 (m, 1H), 1.29 (ddd, *J* = 13.3, 9.3, 5.0 Hz, 2H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.90-0.87 (m, 21H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.9, 76.1, 69.2, 61.3, 46.0, 44.9, 41.1, 26.5, 26.1, 23.1, 22.1, 19.9, 18.5, 18.3, 3.6, -4.0, -4.4, -5.1, -5.1; **IR** (neat): 2955, 2929, 2895, 2857, 1462, 1378, 1252, 1095, 1045, 1006, 833, 807, 772 cm^{-1}; **MS** (EI): *m/z* (%) 299 (11), 233 (11), 189 (31), 185 (11), 163 (14), 149 (19), 148 (16), 147 (99), 135 (12), 133 (19), 121 (31), 109 (32), 107 (56), 101 (13), 99 (10), 95 (48), 93 (31), 91 (10), 89 (11), 83 (17), 81 (29), 79 (14), 75 (96), 73 (100), 69 (84), 67 (31), 59 (15), 55 (21), 41 (14); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{50}O_2Si_2Na$ $[M + Na]^+$ 449.32416, found 449.32454.

(3*S*,5*S*,7*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyldec-8-yn-1-ol (96)



PPTS (1.48 g, 5.90 mmol) was added to a solution of silyl ether **95** (2.10 g, 4.92 mmol) in EtOH (35.6 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 4 d before the solvent was evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1 then 87:13) to afford the product as a colorless oil (0.926 g, 60 %) along with the completely deprotected material (0.302 g, 31 %). $[\alpha]_D^{20}$ = +61.4 (*c* 0.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.96 (tdd, *J* = 9.0, 4.5, 2.4 Hz, 1H), 3.71 – 3.58 (m, 2H), 2.54 (ttdt, *J* = 9.2, 6.8, 4.3, 2.3 Hz, 1H), 1.76 (d, *J* = 2.3 Hz, 3H), 1.65 – 1.49 (m, 3H), 1.49 – 1.34 (m, 3H), 1.30 (dddd, *J* = 13.4, 9.5, 4.2, 1.9 Hz, 2H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.10 – 0.03 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 82.8, 75.2, 68.1, 59.9, 44.9, 43.7, 39.9, 25.5, 25.1, 22.0, 21.1, 18.7, 17.2, 2.5, -5.0, -5.4; **IR** (neat): 3314, 2956, 2929, 2857, 1462, 1378, 1252, 1108, 1043, 1005, 926, 833, 807, 773 cm^{-1}; **MS** (EI): *m*/*z* (%) 255 (25), 225 (35), 186 (15), 185 (100), 173 (28), 171 (14), 169 (12), 167 (15), 163 (43), 145 (13), 137 (13), 135 (20), 121 (57), 119 (59), 107 (95), 105 (28), 99 (20), 95 (28), 93 (54), 91 (11), 83 (13), 81 (20), 79 (11), 75 (92), 73 (29), 69 (21), 67 (51); **HRMS** (ESI-pos.) calcd. for $C_{18}H_{36}O_2SiNa$ $[M + Na]^+$ 335.23768, found 335.23760.

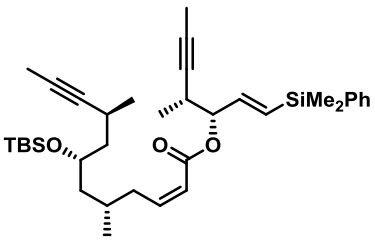
(3*R*,5*S*,7*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyldec-8-ynal (24)



Dess-Martin periodinane (2.04 g, 4.80 mmol) was added to a solution of alcohol **96** (0.500 g, 1.60 mmol) in CH_2Cl_2 (13.6 mL) at 0 °C. The resulting mixture was stirred for 3 h before the reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the product as a colorless, somwhat unstable oil (0.390 g, 79 %), which was used in the next step without further characterization.

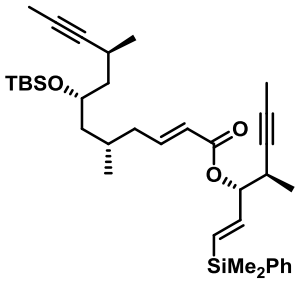
6.3.3 Fragment Assembly

(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhept-1-en-5-yn-3-yl-(5*S*,7*S*,9*S*,*Z*)-7-((*tert*-butyldimethyl-silyl)oxy)-5,9-dimethyldodec-2-en-10-ynoate (25)



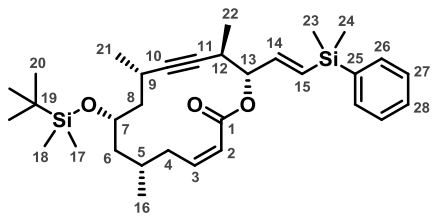
KHMDS (0.222 g, 1.11 mmol) was added at −78°C to a solution of phosphonate **23** (0.600 g, 1.102 mmol) and [18]-crown-6 (1.46 g, 5.51 mmol) in THF (14 mL). The mixture was stirred for 1 h before a solution of aldehyde **24** (0.326 g, 1.049 mmol) in THF (6 mL) was added dropwise. Stirring was continued at this temperature for 4 h before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 99.3:0.8) to afford the major *Z*-isomer (0.385 g, 62%) along with the minor *E*-isomer (ca. 0.030 g, 5%) as a colorless oil each. *Z*-isomer: $[\alpha]_D^{20}$ = +44.8 (*c* 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.62 – 7.45 (m, 2H), 7.34 (dd, *J* = 4.4, 1.3 Hz, 3H), 6.24 (ddd, *J* = 11.6, 8.0, 6.9 Hz, 1H), 6.14 (dd, *J* = 18.8, 5.1 Hz, 1H), 6.05 (dd, *J* = 18.8, 1.2 Hz, 1H), 5.89 (dd, *J* = 11.6, 1.8 Hz, 1H), 5.34 (td, *J* = 5.1, 1.3 Hz, 1H), 3.96 (tdd, *J* = 9.2, 4.8, 2.6 Hz, 1H), 2.75 (ddp, *J* = 7.3, 4.9, 2.4 Hz, 1H), 2.66 (dtd, *J* = 15.7, 7.7, 1.8 Hz, 1H), 2.61 – 2.50 (m, 2H), 1.82 – 1.74 (m, 6H), 1.70 – 1.62 (m, 1H), 1.48 (tdd, J = 13.4, 7.1, 3.6 Hz, 2H), 1.39-1.30 (m, 2H), 1.12 (dd, *J* = 7.0, 1.5 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.35 (d, *J* = 2.0 Hz, 6H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 165.6, 149.6, 143.2, 138.6, 134.0, 130.7, 129.1, 127.9, 120.7, 83.8, 79.6, 77.9, 77.2, 76.2, 69.1, 45.6, 45.0, 37.1, 30.7, 30.2, 26.1, 23.1, 22.1, 19.6, 18.2, 16.7, 3.7, 3.6, -2.43, -2.44, -4.0, -4.4; **IR** (neat): 2956, 2929, 2856, 1722, 1641, 1461, 1427, 1414, 1377, 1249, 1163, 1113, 1064, 1045, 1006, 989, 927, 834, 831, 773, 731, 699, 469 cm^{-1}; **MS** (EI): *m*/*z* (%) 429 (11), 335 (11), 295 (17), 277 (24), 241 (20), 225 (19), 203 (17), 175 (34), 161 (28), 159 (14), 147 (14), 136 (14), 135 (100), 133 (13), 121 (11), 119 (18), 115 (19), 107 (13), 105 (15), 97 (88), 95 (28), 91 (14), 75 (30), 73 (62), 59 (15); **HRMS** (ESI-pos.) calcd. for $C_{36}H_{56}O_3Si_2Na$ $[M + Na]^+$ 615.36602, found 615.36664.

(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhept-1-en-5-yn-3-yl-(5*S*,7*S*,9*S*,*E*)-7-((*tert*-butyldimethyl-silyl)oxy)-5,9-dimethyldodec-2-en-10-ynoate (97)



E-isomer: $[\alpha]_D^{20}$ = +16.5 (*c* 0.15, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.34 (m, 3H), 6.97 (ddd, *J* = 15.5, 7.5 Hz, 1H), 6.15 (dd, *J* = 18.8, 5.0 Hz, 1H), 6.05 (dd, *J* = 18.8, 1.2 Hz, 1H), 5.89 (ddd, *J* = 15.5, 1.4 Hz, 1H), 5.35 (td, *J* = 5.1, 1.2 Hz, 1H), 3.96 (dddd, *J* = 9.3, 8.3, 4.7, 2.6 Hz, 1H), 2.76 (qdq, *J* = 7.2, 5.0, 2.4 Hz, 1H), 2.55 (dqdq, *J* = 9.0, 6.9, 3.0, 2.4 Hz, 1H), 2.25 (dddd, *J* = 14.3, 7.6, 5.6, 1.4 Hz, 1H), 2.05 (dddd, *J* = 7.8, 1.4, -14.3 Hz, 1H), 1.78 (d, *J* = 2.4 Hz, 3H), 1.76 (d, *J* = 2.4 Hz, 3H), 1.71 (m, 1H), 1.46 (m, 2H), 1.34 (m, 2H), 1.12 (d, *J* = 6.9, 3H), 1.12 (d, *J* = 7.0, 3H), 0.93 (d, *J* = 6.6, 3H), 0.88 (s, 9H), 0.35 (s, 3H), 0.35 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 165.6, 148.4, 143.1, 138.5, 134.0, 130.6, 129.1, 127.9, 122.6, 83.7, 79.5, 77.9, 77.3, 76.2, 69.0, 45.5, 44.9, 40.6, 30.6, 29.4, 26.07, 26.06, 23.1, 22.1, 19.7, 18.2, 16.6, 3.6, 3.5, -2.45, -2.48, -4.0, -4.4; **IR** (neat): 2956, 2929, 2856, 1723, 1653, 1461, 1427, 1414, 1377, 1249, 1161, 1113, 1068, 1044, 956, 924, 853, 807, 773, 731, 699, 469 cm^{-1}; **MS** (EI): *m*/*z* (%) 429 (11), 335 (11), 295 (17), 277 (24), 241 (20), 225 (19), 203 (17), 175 (34), 161 (28), 159 (14), 147 (14), 136 (14), 135 (100), 133 (13), 121 (11), 119 (18), 115 (19), 107 (13), 105 (15), 97 (88), 95 (28), 91 (14), 75 (30), 73 (62), 59 (15); **HRMS** (ESI-pos.) calcd. for $C_{36}H_{56}O_3Si_2Na$ $[M + Na]^+$ 615.36602, found 615.36635.

(6*S*,8*S*,10*S*,13*R*,14*R*,*Z*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-((*E*)-2-(dimethyl(phenyl)silyl)vinyl)-6,10,13-trimethyloxacyclotetradec-3-en-11-yn-2-one (28)



A mixture comprising molecular sieves 5 Å (powder, 2.4 g) and diyne **25** (0.092 g, 0.155 mmol) in toluene (78 mL) was stirred for 30 min before a solution of alkylidyne catalyst **C1** (0.024 g, 0.023 mmol, 15 mol%) in toluene (2.5 mL) was added. The mixture was stirred at 70 °C for 1 h, cooled to room temperature and filtered through a pad of Celite that was carefully rinsed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford the product as a colorless oil (0.092 g, 80 %). $[\alpha]_D^{20}$ = +48.3 (*c* 0.52, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.49 (m, 2H, H26), 7.36 (m, 1H, H28), 7.34 (m, 2H, H27), 6.28 (ddd, *J* = 11.7, 10.8, 5.3 Hz, 1H, H3), 6.12 (dd, *J* = 18.7, 6.3 Hz, 1H, H14), 5.99 (dd, *J* = 18.7, 1.0 Hz, 1H, H15), 5.92 (ddd, *J* = 18.7, 2.3, 1.0 Hz, 1H, H2), 5.38 (ddd, *J* = 8.4, 6.3, 1.0 Hz, 1H, H13), 3.83 (dddd, *J* = 9.8, 8.7, 3.0, 1.3 Hz, 1H, H7), 3.35 (dddd, *J* = 14.3, 10.8, 6.5, 1.0 Hz, 1H, H4), 2.62 (dqd, *J* = 8.4, 7.0, 2.3 Hz, 1H, H12), 2.52 (qddd, *J* = 12.1, 6.9, 3.0, 2.9 Hz, 1H, H9), 2.30 (dddd, *J* = 14.8, 5.3, 2.7, 2.3 Hz, 1H, H4), 2.00 (qdddd, *J* = 11.5, 7.0, 6.5, 3.5, 2.7 Hz, 1H, H5), 1.43 (ddd, *J* = 13.9, 8.7, 3.5 Hz, 1H, H6), 1.41 (ddd, *J* = 13.2, 9.8, 3.0 Hz, 1H, H8), 1.27 (ddd, *J* = 13.2, 12.1, 1.3 Hz, 1H, H8), 1.17 (d, *J* = 7.0 Hz, 3H, H22), 1.13 (ddd, *J* = 13.9, 11.5, 3.0 Hz, 1H, H6), 1.09 (d, *J* = 6.9 Hz, 3H, H21), 1.03 (d, *J* = 7.0 Hz, 3H, H16), 0.88 (s, 9H, H20),0.34 (s, 3H, H23), 0.34 (s, 3H, H24), 0.15 (s, 3H, H17) 0.12 (s, 3H, H18); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.6 (s, C1), 146.2 (d, C3), 143.7 (d, C14), 138.2 (s, C25), 134.0 (d, C26), 132.5 (d, C15), 129.2 (d, C28), 128.0 (d, C27), 121.8 (d, C2), 86.3 (s, C10), 81.4 (s, C11), 78.3 (d, C13), 68.8 (d, C7), 48.4 (t, C8), 45.5 (t, C6), 32.5 (t, C4), 31.3 (d, C12), 28.6 (d, C5), 26.2 (q, C20), 23.4 (d, C9), 22.2 (q, C21), 20.5 (q, C16), 18.4 (s, C19), 18.3 (q, C22), -2.5 (q, C24), -2.6 (q, C23), -3.5 (q, C18), -4.2 (q, C17); **IR** (neat): 2955, 2930, 2903, 2855, 1720, 1638, 1461, 1415, 1374, 1249, 1167, 1114, 1072, 990, 824, 806, 773, 730, 698 cm^{-1}; **MS** (EI): *m*/*z* (%) 483 (17), 482 (40), 481 (98), 291 (21), 271 (10), 255 (12), 211 (17), 209 (30), 195 (11), 149 (24), 145 (11), 137 (10), 136 (14), 135 (100), 133 (16), 119 (11), 95 (21), 75 (29), 73 (23); **HRMS** (ESI-pos.) calcd. for $C_{32}H_{50}O_3Si_2Na$ $[M + Na]^+$ 561.31907, found 561.31954.

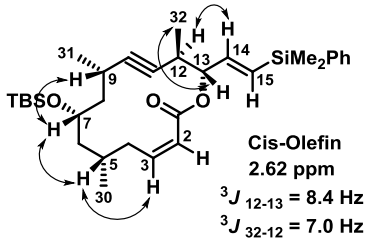
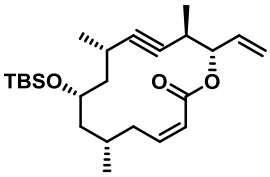


Figure 10: Observed NOE correlations in macrolactone ring.

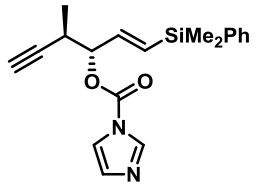
(4*S*,5*R*,8*S*,10*S*,12*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-5,8,12-trimethyl-4-vinyl-1,3-dioxacyclotetradec-6-yn-2-one (98)



AgF (56.6 mg, 0.45 mmol) was added to a solution of compound **28** (30 mg, 0.056 mmol) in MeOH, THF and H_2O (5:5:1, 11 mL) and the resulting mixture was stirred for 72 h in the dark. The suspension was filtered through a pad of Celite that was washed with EtOAc and *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 99.4:0.6) to afford the product as a colorless oil (20.8 mg, 92 %).$[\alpha]_D^{20}$ = +30.0 (*c* 2.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.26 (td, *J* = 11.3, 5.1 Hz, 1H), 5.90 (ddd, *J* = 11.8, 2.4, 1.1 Hz, 1H), 5.86 – 5.71 (m, 1H), 5.43 – 5.27 (m, 2H), 5.25 (ddd, *J* = 10.4, 1.5, 0.8 Hz, 1H), 3.82 (tdd, *J* = 9.3, 2.9, 1.5 Hz, 1H), 3.48 – 3.33 (m, 1H), 2.67 – 2.55 (m, 1H), 2.56 – 2.45 (m, 1H), 2.25 (ddt, *J* = 14.7, 4.9, 2.5 Hz, 1H), 2.00 (ddp, *J* = 17.0, 6.8, 3.5 Hz, 1H), 1.45 – 1.36 (m, 2H), 1.34 – 1.23 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.13 – 1.07 (m, 4H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.5, 146.2, 135.1, 121.8, 119.4, 86.3, 81.4, 77.0, 68.7, 48.4, 45.4, 32.3, 31.3, 28.5, 26.2, 23.4, 22.2, 20.5, 18.4, 18.2, -3.4, -4.2; **IR** (neat): 2955, 2931, 2855, 1722, 1639, 1461, 1415, 1374, 1293, 1253, 1169, 1105, 1073, 992, 935, 835, 806, 774 cm^{-1}; **MS** (EI): *m*/*z* (%) 348 (23), 347 (83), 329 (14), 291 (10), 237 (21), 227 (24), 213 (29), 212 (12), 211 (63), 209 (12), 188 (15), 187 (55), 185 (22), 183 (14), 173 (10), 171 (20), 169 (26), 159 (22), 157 (13), 147 (40), 146 (12), 145 (38), 143 (14), 138 (19), 133 (19), 131 (12), 129 (20), 121 (75), 119 (44), 107 (15), 105 (34), 95 (33), 93 (39), 91 (20), 81 (16), 79 (20), 77 (14), 73 (48), 59 (101), 55 (14); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{40}O_3SiNa$ $[M + Na]^+$ 427.26389, found 427.26369.

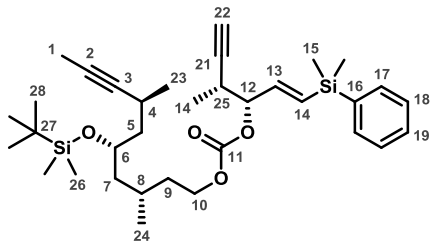
6.3.4 *trans*-Hydrostannation via Assisted Substrate Binding

(3*R*,4*R*,*E*)-1-(Dimethyl(phenyl)silyl)-4-methylhex-1-en-5-yn-3-yl 1*H*-imidazole-1-carboxylate (100)



1,1'-Carbonyldiimidazole (2.986 g, 18.41 mmol) was added to a solution of alcohol **88** (1.50 g, 6.137 mmol) in CH_2Cl_2 (24 mL) and the resulting mixture was stirred for 18 h. All volatile materials were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 85:15 then 80:20) to afford the carbamate as a colorless oil that solidified upon standing at –20 °C (1.67 g, 80%). $[\alpha]_D^{20}$ = –9.1 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.19 (t, *J* = 1.0 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.47 (t, *J* = 1.7, 1.2 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.09 (dd, *J* = 1.7, 0.9 Hz, 1H), 6.24 (dd, *J* = 18.8, 0.9 Hz, 1H), 6.13 (dd, *J* = 18.7, 5.8 Hz, 1H), 5.40 (td, *J* = 5.8, 0.9 Hz, 1H), 2.90 (qdd, *J* = 7.1, 5.7, 2.5 Hz, 1H), 2.13 (d, *J* = 2.4 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.38 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.9, 140.6, 137.5, 137.2, 134.6, 133.9, 130.8, 129.4, 128.0, 117.3, 83.3, 81.9, 71.2, 30.7, 16.8, –2.67, –2.69; **IR** (neat): 3294, 3069, 2981, 2957, 1760, 1471, 1428, 1391, 1315, 1287, 1239, 1174, 1115, 1094, 1058, 999, 829, 768, 734, 700, 648 cm^{-1}; **MS** (EI): *m*/*z* (%) 211 (30), 202 (14), 187 (25), 169 (10), 145 (22), 136 (16), 135 (100), 128 (12), 121 (44), 107 (10), 105 (21), 92 (11), 91 (26), 79 (15), 78 (18), 77 (14), 73 (16), 68 (75), 67 (19); **HRMS** (ESI-pos.) calcd. for $C_{19}H_{22}O_2SiNa$ $[M + Na]^+$ 361.13428, found 361.13451.

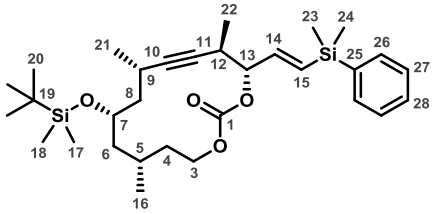
(3*S*,5*S*,7*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyldec-8-yn-1-yl-((3*R*,4*R*,*E*)-1-(dimethyl(phenyl)-silyl)-4-methylhex-1-en-5-yn-3-yl) carbonate (101)



A solution of alcohol **96** (0.282 g, 0.902 mmol) in THF (1.5 mL) was slowly added to a suspension of NaH (0.022 g, 0.902 mmol) in THF (7.5 mL) at 0 °C. After stirring for 30 min at room temperature, carbamate **100** (0.351 g, 1.038 mmol) was introduced and stirring continued for 18 h at room temperature. A standard extractive work up followed by flash chromatography (hexane/EtOAc, 99.4:0.6 then 99.3:0.7) furnished the product as a colorless oil (0.415 g, 79 %). $[\alpha]_D^{20}$ = +31.6 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.55 – 7.47 (m, 2H, H17), 7.38 – 7.33 (m, 2H, H18), 7.37 – 7.31 (m, 1H, H19), 6.17 (d, *J* = 18.8 Hz, 1H, H14),

6.11 (dd, *J* = 18.8, 4.4 Hz, 1H, H13), 5.15 (t, *J* = 5.5, 4.4 Hz, 1H, H12), 4.19 (t, *J* = 6.9 Hz, 2H, H10), 3.96 (tt, *J* = 9.4, 8.7, 4.9, 2.5 Hz, 1H, H6), 2.82 (qdd, *J* = 7.0, 5.5, 2.5 Hz, 1H, H20), 2.56 (dqdq, *J* = 10.7, 7.0, 4.1, 2.3 Hz, 1H, H4), 2.11 (d, *J* = 2.5 Hz, 1H, H22), 1.78 (d, *J* = 2.3 Hz, 3H, H1), 1.72 (dq, *J* = 13.8, 6.7 Hz, 1H, H9), 1.62 (dhept, *J* = 9.4, 6.5, 4.4 Hz, 1H, H8), 1.51 (dq, *J* = 13.8, 6.5 Hz, 1H, H9), 1.47 (ddd, *J* = 13.3, 10.7, 2.5 Hz, 1H, H5), 1.46 (ddd, *J* = 13.3, 8.7, 4.4 Hz, 1H, H7), 1.34 (ddd, *J* = 13.3, 9.4, 4.9 Hz, 1H, H7), 1.32 (ddd, *J* = 13.5, 9.4, 4.1 Hz, 1H, H5), 1.19 (d, *J* = 7.0 Hz, 3H, H25), 1.12 (d, *J* = 7.0 Hz, 3H, H23), 0.94 (d, *J* = 6.5 Hz, 3H, H24), 0.89 (s, 9H, H28), 0.36 (s, 6H, H15), 0.10 (s, 3H, H26), 0.07 (s, 3H, H26'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.7 (C11), 141.7 (C13), 138.0 (C16), 134.0 (C17), 132.5 (C14), 129.2 (C19), 127.9 (C18), 84.1 (C21), 83.7 (C3), 81.0 (C12), 76.2 (C2), 70.7 (C22), 68.9 (C6), 66.6 (C10), 45.8 (C7) 44.7 (C5), 36.5 (C9), 30.5 (C20), 26.6 (C8), 26.1 (C28), 23.0 (C4), 22.1 (C23), 19.4 (C24), 18.2 (C27), 16.2 (C25), 3.5 (C1), -2.6 (C15), -4.1 (C26), -4.4 (C26); **IR** (neat): 3311, 3296, 2957, 2930, 2857, 1746, 1461, 1428, 1390, 1378, 1249, 1114, 1070, 1045, 991, 953, 834, 775, 732, 699, 643 cm^{-1}; MS (EI): *m*/*z* (%); 227 (17), 225 (38), 211 (11), 199 (16), 163 (22), 136 (14), 135 (100), 133 (12), 121 (23), 107 (24), 75 (23), 73 (34), 59 (16); **HRMS** (ESI-pos.) calcd. for $C_{34}H_{54}O_4Si_2Na$ $[M + Na]^+$ 605.34529, found 605.34523.

(4*R*,5*R*,8*S*,10*S*,12*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-4-((*E*)-2-(dimethyl(phenyl)silyl)vinyl)-5,8,12-trimethyl-1,3-dioxacyclotetradec-6-yn-2-one (104)



A mixture comprising freshly activated molecular sieves 5Å (powder, ca. 5.4 g) and 4 Å (ca. 4.2 g) and diyne **101** (0.250 g, 0.429 mmol) in toluene (216 mL, stored over molecular sieves 5Å) was stirred for 45 min at room temperature before a solution of the alkylidyne catalyst **C1** (0.067 g, 0.0643 mmol, 15 mol%) in toluene was added. The mixture was then stirred at 70 °C for 1 h, cooled to room temperature and filtered through a pad of Celite which was rinsed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 99.5:0.5 to 99.45:0.55) to afford the product as a pale yellow oil (0.172 g, 74 %). $[\alpha]_D^{20}$ = +65.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52 – 7.45 (m, 2H, H26), 7.38 – 7.32 (m, 3H, H27 and H28), 6.20 (dd, *J* = 18.7, 1.0 Hz, 1H, H15), 5.95 (dd, *J* = 18.8, 6.8 Hz, 1H, H14), 4.86 (dd, *J* = 9.8, 6.8 Hz, 1H, H13), 4.47 (ddd, *J* = 11.7, 6.1, 3.0 Hz, 1H, H3a), 4.10 (ddd, *J* = 11.7, 9.3, 2.4 Hz, 1H, H3b), 3.90 – 3.79 (m, 1H, H7), 2.66 (dqd, *J* =

9.8, 7.0, 2.8 Hz, 1H, H12), 2.58 – 2.47 (m, 1H, H9), 2.04 (dddd, *J* = 15.5, 9.3, 4.0, 3.2 Hz, 1H, H4a), 2.00 – 1.92 (m, 1H, H5), 1.56 (dddd, *J* = 16.0, 9.0, 3.4, 1.5 Hz, 1H, H4b), 1.49 – 1.39 (m, 4H, H8 and H6), 1.14 (d, *J* = 6.0 Hz, 3H, H22), 1.12 (d, *J* = 6.0 Hz, 3H, H21), 0.98 (d, *J* = 7.0 Hz, 3H, H16), 0.88 (s, 9H, H20), 0.35 (s, 3H, H24), 0.35 (s, 3H, H23), 0.11 (s, 3H, H17), 0.09 (s, 3H, H18); **^{13}C NMR** (100 MHz, $CDCl_3$); δ: 154.5 (C1), 142.9 (C14), 138.0 (C25), 134.1 (C15), 133.9 (C26), 129.3 (C28), 128.0 (C27), 86.9 (C10), 83.5 (C13), 80.8 (C11), 70.3 (C7), 65.6 (C3), 48.6 (C8), 45.3 (C6), 33.0 (C4), 31.0 (C12), 27.1 (C5), 26.3 (C20), 23.6 (C9), 22.1 (C21), 21.1 (C16), 18.6 (C19), 17.7 (C22), -2.54 (C23), -2.61 (C24), -3.57 (C18), -3.95 (C17); **^{29}Si NMR** (100 MHz, $CDCl_3$) δ: 15.20, -10.97; **IR** (neat): 2955, 2907, 2856, 1743, 1451, 1361, 1296, 1249, 1114, 1067, 993, 945, 832, 773, 732, 700 cm^{-1}; **MS** (EI): *m*/*z* (%) 485 (12), 209 (14), 193 (12), 159 (10), 149 (30), 145 (11), 136 (13), 135 (100), 133 (13), 119 (16), 75 (24), 73 (18); **HRMS** (ESI-pos.) calcd. for $C_{31}H_{50}O_4Si_2Na$ $[M + Na]^+$ 565.31399, found 565.31405.

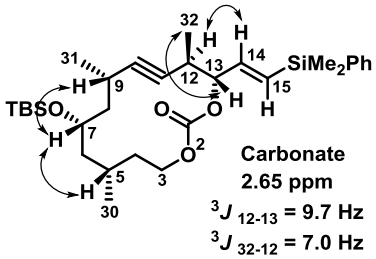
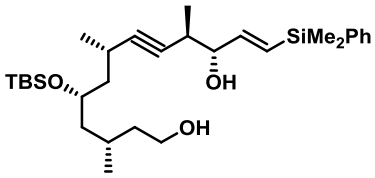


Figure 11: Observed NOE correlations in macrocyclic carbonate.

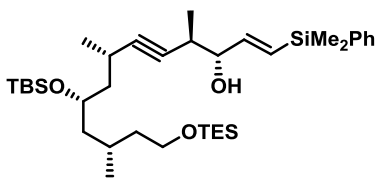
(3*S*,5*S*,7*S*,10*R*,11*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-13-(dimethyl(phenyl)silyl)-3,7,10-trimethyltridec-12-en-8-yne-1,11-diol (102a).



A mixture comprising carbonate **104** (0.138 g, 0.254 mmol) and K_2CO_3 (0.105 g, 0.763 mmol) in MeOH (3.0 mL) was stirred for at room temperature for 46 h. sat. aq. NH_4Cl was added and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 90:10 then 82:18) to afford the product as a colorless oil (0.118 g, 90 %). $[\alpha]_D^{20}$ = +59.8 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52 (ddt, *J* = 4.6, 3.7, 2.0 Hz, 2H), 7.38 – 7.29 (m, 3H), 6.18 – 6.01 (m, 2H), 4.00 – 3.89 (m, 2H), 3.72 – 3.61 (m, 2H), 2.66 – 2.54 (m, 2H), 2.03 – 1.63 (m, 2H), 1.62 – 1.30 (m, 7H), 1.14 (dd, *J* = 8.7, 6.9 Hz, 6H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.36 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.7, 138.5, 133.9, 129.6, 129.1, 127.9, 88.4,

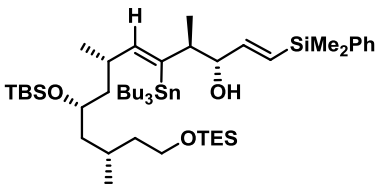
81.0, 77.4, 69.2, 60.9, 45.9, 44.9, 40.9, 33.5, 26.6, 26.1, 23.1, 22.2, 19.7, 18.2, 17.8, -2.4, -2.5, -3.9, -4.3; **IR** (neat): 3382, 2956, 2930, 2857, 1621, 1462, 1427, 1377, 1250, 1114, 1047, 999, 921, 835, 775, 733, 699 cm^{-1}; **MS** (EI): *m/z* (%) 269 (30), 212 (14), 194 (16), 187 (24), 177 (10), 175 (16), 173 (32), 159 (11), 149 (35), 147 (11), 145 (19), 143 (11), 137 (19), 136 (14), 135 (100), 133 (12), 121 (32), 119 (19), 117 (11), 113 (10), 109 (13), 108 (14), 107 (33), 105 (18), 99 (46), 95 (23), 93 (22), 91 (14), 83 (16), 81 (26), 80 (20), 79 (14), 75 (65), 73 (26), 69 (11), 55 (11); **HRMS** (ESI-pos.) calcd. for $C_{30}H_{52}O_3Si_2Na$ $[M + Na]^+$ 539.33472, found 539.33442.

(3*R*,4*R*,7*S*,9*S*,11*S*,*E*)-9-((*tert*-Butyldimethylsilyl)oxy)-1-(dimethyl(phenyl)silyl)-4,7,11-trimethyl-13-((triethylsilyl)oxy)tridec-1-en-5-yn-3-ol (102)



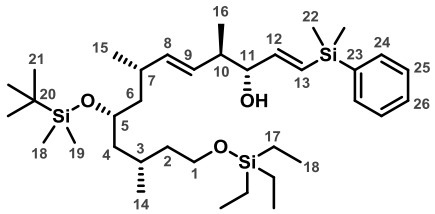
Et_3N (0.342 mmol, 0.048 mL) and TESCl (0.251 mmol, 0.042 mL) were added to a solution of diol **102a** (0.118 g, 0.228 mmol) in CH_2Cl_2 (3.2 mL) and the resulting mixture was stirred for 2 h. The reaction was quenched with a sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1 then 98:2) to afford the product as a colorless oil (0.129 g, 90 %). $[\alpha]_D^{20}$ = +47.0 (*c* 1.0, $CHCl_3$)**; ^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.58 – 7.48 (m, 2H), 7.41 – 7.30 (m, 3H), 6.18 – 6.01 (m, 2H), 3.94 (dtd, *J* = 18.4, 6.1, 5.6, 4.4 Hz, 2H), 3.69 – 3.58 (m, 2H), 2.67 – 2.53 (m, 2H), 2.14 (d, *J* = 5.4 Hz, 1H), 1.65 – 1.26 (m, 7H), 1.14 (dd, *J* = 7.6, 7.0 Hz, 6H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.89 (s, 12H), 0.66 – 0.54 (m, 6H), 0.36 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 147.8, 138.5, 134.0, 129.6, 129.1, 127.9, 88.5, 81.0, 77.4, 69.2, 60.9, 45.9, 44.8, 41.1, 33.6, 26.6, 26.1, 23.1, 22.3, 19.8, 18.2, 17.7, 7.0, 4.6, -2.4, -2.5, -3.9, -4.3; **IR** (neat): 3464, 2955, 2931, 2877, 2857, 1620, 1461, 1427, 1378, 1249, 1113, 1093, 1047, 1004, 922, 836, 774, 730, 699, 469 cm^{-1}; **MS** (EI): *m/z* (%) 630 (15), 574 (33), 573 (65), 383 (18), 301 (11), 251 (11), 213 (27), 212 (18), 209 (11), 189 (15), 185 (18), 177 (21), 175 (12), 161 (22), 149 (27), 147 (16), 145 (10), 137 (10), 136 (14), 135 (100), 133 (12), 121 (18), 119 (16), 117 (22), 115 (18), 107 (19), 105 (10), 95 (13), 87 (12), 81 (11), 75 (33), 73 (21); **HRMS** (ESI-pos.) calcd. for $C_{36}H_{66}O_3Si_3Na$ $[M + Na]^+$ 653.42120, found 653.42130.

(1*E*,3*S*,4*S*,5*Z*,7*S*,9*S*,11*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-1-(dimethyl(phenyl)silyl)-4,7,11-trimethyl-5-(tributylstannyl)-13-((triethylsilyl)oxy)trideca-1,5-dien-3-ol (105)



A solution of alkyne **102** (5 mg, 7.9 µmol) and $[Cp^*RuCl]_4$ (2.2 mg, 7.9 µmol) in CH_2Cl_2 (0.16 mL) was stirred for 10 min before the mixture was cooled to –50 °C. A solution of Bu_3SnH (2.3 µL, 8.7 µmol) in CH_2Cl_2 (0.5 mL) was added dropwise over 2 h at –50 °C via syringe pump. Upon completion of the reaction, tris(hydroxymethyl)phosphine (24.6 mg, 0.198 mmol) was added and stirring continued for 1 h at room temperature. Water was added and stirring continued for 0.5 h before the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford stannanes **105** (mixture of regioisomers α:β = 90:10, *Z:E* = 20:1) as a colorless oil that was used directly in the next step (5.2 mg, 71%,). **^{119}Sn NMR** (149 MHz, $CDCl_3$) δ: –54.4 ppm; **HRMS** (ESI-pos.) calcd. for $C_{48}H_{94}O_3Si_3SnNa$ $[M + Na]^+$ 945.54243, found 945.54285.

(1*E*,3*R*,4*R*,5*E*,7*S*,9*S*,11*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-1-(dimethyl(phenyl)silyl)-4,7,11-trimethyl-13-((triethylsilyl)oxy)trideca-1,5-dien-3-ol (106)

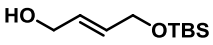


[$(Ph_2PO_2)Cu$] (3.4 mg, 12.2 µmol) was added in one portion to a solution of the stannanes **105** (mixture of regioisomers, 9.4 mg, 10.2 µmol) in DMF (0.12 mL) and the resulting mixture was stirred for 2 h. After dilution with *tert*-butyl methyl ether and water, the aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic layers were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 99/1 then 98.5/1.5 then 1.8) to afford the product as a colorless oil (4.5 mg, 70 %). $[\alpha]_D^{20}$ = +23.1 (*c* 0.45, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.54 – 7.49 (m, 2H, H24), 7.35 (t, *J* = 4.7 Hz, 1H, H26), 7.35 (d, *J* = 5.1 Hz, 2H, H25), 6.09 (d, *J* = 18.7 Hz, 1H, H13), 6.07 (t, *J* = 19.0 Hz, 1H, H12), 5.43 (dd, *J* = 15.5, 7.7 Hz, 1H, H8), 5.29 (dd, *J* = 15.5, 8.0 Hz, 1H, H9), 3.83 (td, *J* = 6.8, 5.9, 2.9 Hz, 1H, H11), 3.73 (tdd, *J* = 7.6, 5.5, 4.1 Hz, 1H, H5), 3.68 – 3.57 (m, 2H, H1), 2.33 (hept, *J* = 13.9, 7.0 Hz, 1H, H7), 2.21 (h, *J* = 7.1 Hz, 1H, H10), 1.83 (d, *J* = 3.7 Hz, 1H, H10), 1.62 (dd, *J* = 12.9, 6.5 Hz, 1H, H3), 1.57 (ddd, *J* = 25.9, 13.3, 6.4 Hz, 1H, H2b), 1.46 – 1.40 (m, 1H, H6b), 1.43 – 1.38 (m, 1H, H4b), 1.38 – 1.33 (m, 1H, H6a), 1.33 (ddd, *J* = 9.8, 4.9, 2.7 Hz, 1H, H2a), 1.32 – 1.23 (m, 1H, H4a), 0.97 (d, *J* = 6.8 Hz, 6H, H15, H16), 0.96 (t, *J* = 7.9 Hz, 9H, H18), 0.88 (s, 9H, H21), 0.86 (d, *J* = 6.5 Hz, 3H, H14), 0.59 (q, *J* = 8.0 Hz, 6H, H17), 0.35 (s, 6H, H22), 0.04 (s, 3H, H19), 0.04 (s, 3H, H19); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 148.4 (C12), 139.2 (C8), 138.7 (C23), 134.0 (C24), 130.0 (C9), 129.2 (C26), 129.1 (C13), 127.9 (C25), 78.1 (C11), 69.1 (C5), 61.0 (C1), 45.8 (C4), 44.8 (C6), 43.4 (C10), 40.7 (C2), 33.3 (C7), 26.5 (C3), 26.2 (C21), 22.0 (C15), 20.2 (C14), 18.3 (C20), 16.5 (C16), 7.0 (C18), 4.6 (C17), -2.4 (C22), -2.4 (C22), -3.7 (C19), -4.0 (C19). **IR** (neat): 3463, 2955, 2928, 2876, 1729, 1620, 1461, 1428, 1377, 1249, 1114, 1092, 1047, 1005, 835, 773, 731, 699 cm^{-1}; **MS** (EI): *m/z* (%) 310 (10), 281 (12), 229 (22), 189 (13), 185 (27), 178 (15), 177 (24), 161 (16) 149 (21), 136 (12), 135 (79), 123 (11), 121 (18), 117 (20), 115 (21), 109 (16), 107 (13), 103 (11), 99 (40), 95 (22), 87 (12), 83 (19), 82 (100), 81 (20), 75 (31), 73 (20), 67 (10), 55 (11); **HRMS** (ESI-pos.) calcd. for $C_{36}H_{68}O_3Si_3Na$ $[M + Na]^+$ 655.43685, found 655.43655.

6.4 Second Synthetic Approach

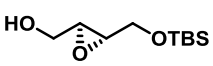
6.4.1 Synthesis of the Northern Fragment

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-ol (124)[108a]



(E)-2-Butene-1,4-diol (5.17 g, 58.7 mmol) in THF (15 mL) was slowly added to a suspension of NaH (1.55 g, 64.6 mmol) in THF (160 mL) at 0 °C. After stirring for 1.5 h at this temperature, a solution of TBSCl (10.6 g, 70.5 mmol) in THF (14 mL) was added dropwise. The mixture was stirred at room temperature overnight before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5 then 85:15) to afford the product as a colorless oil (8.21 g, 69 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.94 – 5.84 (m, 1H), 5.84 – 5.76 (m, 1H), 4.23 – 4.12 (m, 4H), 1.31 (t, *J* = 5.9 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 131.2, 129.0, 63.4, 63.2, 26.1, 18.6, -5.1; **MS** (EI): *m/z* (%) 127 (M^+–75, 11), 75 (100); **HRMS** (ESI-pos.) calcd. for $C_{10}H_{22}O_2SiNa$ $[M + Na]^+$ 225.12813, found 225.12817.

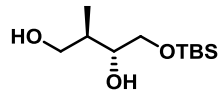
((2*S*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)oxiran-2-yl)methanol) (125)[108]



Ti(*i*PrO)$_4$ (2.8 mL, 9.46 mmol) and L-(+)-DET (2 mL, 11.7 mmol) were successively added to CH_2Cl_2 (370 mL) containing molecular sieves 4 Å (powder, 3.33 g) at –20 °C. The reaction was stirred for 15 min before a solution of alcohol **124** (7.83 g, 38.7 mmol) in CH_2Cl_2 (25 mL + 2 x 5 mL rinse) was added over 45 min. After 30 min *t*BuOOH (5.5 M in decane, 14 mL, 77.0 mmol) was added over 30 min and stirring continued for 18 h at –20 °C. The resulting mixture was poured into a freshly prepared solution of ferrous sulfate ($FeSO_4 \cdot 7\ H_2O$, 13.4 g) and Rochelle salt (4.26 g) in water (45 mL) at 0 °C. The solution was stirred for 10 min at room temperature before the organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were treated with a solution of NaOH (32.0 g) in sat. aq. NaCl (80 mL) at 0 °C and the solution was stirred for 2.5 h at this temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 84:16 then 80:20) to afford the product as a colorless oil (7.45 g, 88%, *ee*

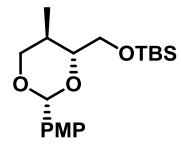
93 %). $[\alpha]_D^{20}$ = –22.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.96 (ddd, *J* = 12.5, 5.4, 2.2 Hz, 1H), 3.90 (dd, *J* = 12.1, 2.8 Hz, 1H), 3.74 – 3.69 (m, 1H), 3.69 – 3.62 (m, 1H), 3.20 – 3.09 (m, 2H), 1.67 (dd, *J* = 7.6, 5.4 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) 62.8, 61.4, 56.0, 55.8, 26.0, 18.5, -5.2, -5.2; **IR** (neat): 3414, 2954, 2929, 2886, 2857, 1472, 1389, 1362, 1254, 1141, 1110, 1069, 1006, 937, 871, 836, 778, 730, 667 cm^{-1}; **MS** (EI): *m*/*z* (%) 117 (M^+–101, 59), 101, (37), 89 (26), 75 (100), 73 (21), 59 (25); **HRMS** (ESI-pos.) calcd. for $C_{10}H_{22}O_3SiNa$ $[M + Na]^+$ 241.12304, found 241.12305. The *ee* was determined by GC (210 °C injector temperature, 100 °C for 75 min then 6 °C / min to 230 °C; flow rate: 0.2 bar H_2; minor enantiomer t_R = 69.9 min, major enantiomer t_R = 67.0 min).

(2*R*,3*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbutane-1,3-diol (126)[108b]



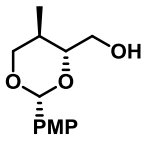
MeMgBr (34 mL, 102 mmol, 3.0 M in Et_2O) was added over 15 min to a suspension of CuI (1.95 g, 10.2 mmol) in Et_2O/THF (300 mL, 5:1) at –8 °C. The resulting grey precipitate was cooled to –40 °C and a solution of the epoxide **125** (7.46 g, 34.2 mmol) in Et_2O (15 mL + 2 x 5 mL rinse) was added dropwise over 20 min. After the mixture had been stirred at –40 °C for 2h, the reaction was warmed to –20 °C and stirring continued at this temperature overnight. The reaction was quenched with sat. aq. NH_4Cl and the organic phase was washed with sat. aq. NH_4Cl (until the aqueous layer was no longer blue). The aqueous layer was saturated with sat. aq. NaCl and then extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/*tert*-butyl methyl ether, 70:30 then 60:40) to afford the product as a colorless oil (7.27 g, 91 %). $[\alpha]_D^{20}$ = –14.7 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.72 – 3.68 (m, 1H), 3.63 (dd, *J* = 6.2, 5.1 Hz, 2H), 3.58 – 3.53 (m, 1H), 3.53 – 3.48 (m, 1H), 3.25 (t, *J* = 5.8 Hz, 1H), 2.99 (d, *J* = 3.5 Hz, 1H), 1.83 – 1.68 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 76.8, 67.3, 65.7, 37.4, 26.0, 18.4, 13.6, -5.3, -5.3; **IR** (neat): 3367, 2955, 2929, 2884, 2858, 1472, 1389, 1362, 1255, 1101, 1032, 995, 939, 836, 778, 669 cm^{-1}; **MS** (EI): *m*/*z* (%) 159 (M^+–75, 28), 141 (13), 117 (16), 105 (12), 89 (15), 85 (23), 75 (100), 73 (24), 57 (12), 43 (11); **HRMS** (ESI-pos.) calcd. for $C_{11}H_{26}O_3SiNa$ $[M + Na]^+$ 257.15434, found 257.15446.

***tert*-Butyl(((2*R*,4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methoxy)dimethylsilane (127)**



p-Anisaldehyde dimethyl acetal (5.89 g, 32.3 mmol) was added in one portion to a solution of diol **126** (7.19 g, 30.7 mmol) in CH_2Cl_2 (160 mL) at 0 °C. PPTS (0.771 g, 3.07 mmol) was added and the mixture stirred at room temperature for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the product as a colorless oil (9.15 g, 85 %) as a single diastereoisomer. $[\alpha]_D^{20}$ = –14.4 (*c* 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.47 – 7.38 (m, 2H), 6.95 – 6.84 (m, 2H), 5.45 (s, 1H), 4.10 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.87 – 3.76 (m, 5H), 3.55 – 3.42 (m, 2H), 2.05 (ddtd, *J* = 18.1, 10.0, 6.7, 4.9 Hz, 1H), 0.91 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.9, 131.4, 127.6, 113.6, 101.3, 84.0, 73.0, 64.8, 55.4, 30.8, 26.0, 18.5, 12.5, -5.1, -5.1; **IR** (neat): 2954, 2929, 2855, 1615, 1518, 1462, 1389, 1368, 1303, 1249, 1171, 1149, 1115, 1078, 1034, 984, 831, 778, 662, 615 cm^{-1}; **MS** (EI): *m/z* (%) 295 (M^+–57, 41), 207 (21), 160 (13), 159 (100), 137 (31), 136 (11), 135 (24), 129 (20), 121 (95), 117 (40), 115 (21), 89 (10), 75 (30), 73 (14); **HRMS** (ESI-pos.) calcd. for $C_{19}H_{33}O_4Si$ $[M + H]^+$ 353.21426, found 353.21391.

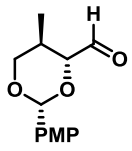
((2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methanol (128)



TBAF (1.0 M in THF, 19.5 mL, 19.5 mmol) was added dropwise to a solution of the compound **127** (4.50 g, 12.8 mmol) in THF (130 mL) at room temperature. The mixture was stirred for 2h and the reaction quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 95:5 then 85:15) to afford the product as a colorless oil (2.67 g, 88 %). $[\alpha]_D^{25}$ = –13.9 (*c* 1.1, benzene), (lit. $[\alpha]_D^{25}$ = –14.5,[109] *c* 1.0, benzene); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.46 – 7.38 (m, 2H), 6.94 – 6.86 (m, 2H), 5.48 (s, 1H), 4.11 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.84 – 3.80 (m, 1H), 3.79 (s, 3H), 3.66 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.55 (ddd, *J* = 10.1, 6.2, 2.6 Hz, 1H), 3.49 (t, *J* = 11.3 Hz, 1H), 2.27 (s, 1H), 2.03 (dddd, *J* = 18.0, 10.0, 6.7, 4.9 Hz, 1H), 0.80 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ: 160.1, 130.9, 127.5, 113.7, 101.2, 83.5, 72.7, 63.3, 55.4, 29.9, 12.2; **IR** (neat): 3448, 2957, 2933, 2875, 2838, 1614, 1589, 1518, 1462, 1391,

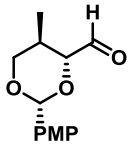
1368, 1303, 1246, 1172, 1144, 1117, 1073, 1005, 989, 827, 784, 628, 607 cm^{-1}; **MS** (EI): *m/z* (%) 237 (M^+–1, 14), 137 (20), 136 (58), 135 (100), 122 (21), 121 (26), 109 (14), 108 (14), 107 (35), 92 (18), 91 (10), 79 (14), 78 (15), 77 (59), 65 (15), 64 (10), 57 (17), 43 (10), 39 (11); **HRMS** (ESI-pos.) calcd. for $C_{13}H_{18}O_4Na$ $[M + Na]^+$ 261.10973, found 261.10981.

(2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxane-4-carbaldehyde (129)



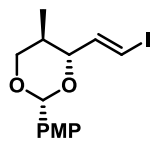
A solution of DMSO (1.7 mL, 23.9 mmol) in CH_2Cl_2 (12 mL) was added dropwise to a solution of oxalyl chloride (1.0 mL, 11.6 mmol) in CH_2Cl_2 (10 mL) at –78 °C. After stirring for 20 min, a solution of alcohol **128** (2.40 g, 10.1 mmol) in CH_2Cl_2 (10 mL + 2 x 2 mL rinse) was added dropwise and the resulting mixture was stirred at this temperature for 3 h. Triethylamine (7.0 mL, 50.2 mmol) was introduced and the solution warmed to room temperature within 1 h. The reaction was quenched with water and the phases were separated. The organic phase was washed with sat. aq. NH_4Cl and sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. A pale yellow solid (2.50 g) was obtained that was used in the next step without further purification. A small amount was purified by flash chromatography (hexane/EtOAc, 8:2 then 7:3) to afford the product as a white solid. $[\alpha]_D^{20}$ = +67.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.67 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.50 – 7.39 (m, 2H), 6.96 – 6.87 (m, 2H), 5.52 (s, 1H), 4.20 (dd, *J* = 11.5, 4.9 Hz, 1H), 3.89 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.81 (s, 3H), 3.56 (t, *J* = 11.3 Hz, 1H), 2.22 – 2.06 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ: 199.7, 160.3, 130.2, 127.6, 113.9, 100.8, 85.7, 72.7, 55.4, 29.6, 11.6; **IR** (neat): 2962, 2935, 2913, 2839, 1736, 1615, 1589, 1519, 1461, 1386, 1302, 1250, 1173, 1146, 1117, 1032, 1005, 831 cm^{-1}; **MS** (EI): *m/z* (%) 207 (M^+–29, 12), 137 (32), 136 (59), 135 (100), 121 (19), 109 (17), 107 (24), 100 (16), 92 (22), 78 (11), 77 (60), 65 (19), 64 (15), 63 (17), 51 (15), 50 (12), 43 (15), 42 (60), 41 (37), 39 (30); **HRMS** (ESI-pos.) calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.09408, found 259.09375.

(2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxane-4-carbaldehyde (129)[58, 109]



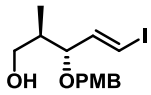
A solution of alcohol **128** (0.500 g, 2.10 mmol) in CH_2Cl_2 (2.0 mL) was added to a suspension of molecular sieves 4 Å (powder, 2.1 g), K_2CO_3 (2.90 g, 20.98 mmol) and NCS (0.308 g, 2.31 mmol) in CH_2Cl_2 (21.2 mL) at 0 °C. Next, a solution of *N*-*tert*-butylbenzenesulfenamide (38.0 mg, 0.210 mmol, 10 mol%) was added and stirring continued for 5 h at room temperature. For work-up, the mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2. Sat. aq. NH_4Cl was added to the combined filtrates and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 8:2 then 7:3) to afford the product as a white solid (0.365 g, 74%).
Characterizations are given on the previous page.

(2*R*,4*R*,5*R*)-4-((*E*)-2-Iodovinyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (130)[58]



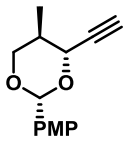
A solution of aldehyde **129** (0.334 g, 1.41 mmol) in THF and CHI_3 (3.34 g, 8.48 mmol) were added to a suspension of $CrCl_2$·THF (7.17 g, 36.8 mmol) in THF (17 mL). The mixture was stirred for 18 h at this temperature and then quenched with sat. aq. $Na_2S_2O_4$. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over Na_2SO_4, filtered and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 95:5) to afford the product as a white solid (0.306 g, 60%, *E*:*Z* = 5:1), which consisted of a mixture of isomers. Characterizations are given for the *E*-isomer. $[\alpha]_D^{20}$ = –26.8 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.47 – 7.38 (m, 2H), 6.92 – 6.85 (m, 2H), 6.65 (dd, *J* = 14.4, 6.6 Hz, 1H), 6.50 (dd, *J* = 14.4, 1.0 Hz, 1H), 5.48 (s, 1H), 4.14 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.80 (d, *J* = 2.0 Hz, 3H), 3.51 (t, *J* = 11.3 Hz, 1H), 1.97 – 1.85 (m, 1H), 0.81 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 160.1, 143.5, 127.6, 113.8, 101.2, 85.4, 80.3, 72.8, 55.4, 34.0, 12.3; **IR** (neat): 2958, 2931, 2837, 1614, 1518, 1460, 1390, 1301, 1249, 1172, 1130, 1108, 1073, 1032, 982, 946, 829 cm^{-1}; **MS** (EI): *m*/*z* (%) 360 (M^+ – 13), 273 (21), 233 (12), 107 (11), 194 (13), 187 (36), 137 (15), 136 (89), 135 (100), 108 (11), 81 (16); **HRMS** (ESI-pos.) calcd. for $C_{14}H_{17}O_3INa$ $[M + Na]^+$ 383.01146, found 383.01137.

(2*R*,3*R*,*E*)-5-Iodo-3-((4-methoxybenzyl)oxy)-2-methylpent-4-en-1-ol (131)[58]



DIBAL-H (8.3 mL, 8.32 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a solution of alkenyl iodide **130** (0.300 g, 0.833 mmol, *E:Z* = 5:1) in CH_2Cl_2 (9.1 mL) at –78 °C. After stirring for 1 h at –55 °C, DIBAL-H (4.15 mL, 4.15 mmol, 1.0 M in CH_2Cl_2) was added and the resulting mixture was stirred at –50 °C for 6 h. The reaction was quenched with MeOH, the aqueous layer was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1 then 8:2) to afford the product as a white oil (0.130 g, 43 %, 62 % brsm, *E:Z* = 4:1) along with the corresponding regioisomer **132** (47.0 mg, 14 %). Characterizations are given on page 134.

(2*R*,4*R*,5*R*)-4-Ethynyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (133)

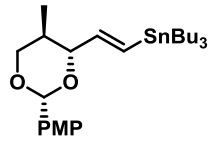


MeOH (4.6 mL, 114 mmol) was slowly added to a suspension of NaH (541 mg, 22.5 mmol) in THF (40.5 mL) at 0 °C. The reaction was stirred for 15 min at this temperature and 15 min at room temperature.

This freshly prepared solution of NaOMe (40 mL, 20 mmol, 3.0 M in THF) was slowly added to a solution of the Bestmann-Ohira reagent (4.96 g, 25.8 mmol) in THF (78 mL) at –78 °C. The resulting orange solution was stirred for 30 min at this temperature, followed by the dropwise addition of the crude aldehyde **129** (2.38 g, 10.1 mmol). Once the addition was complete, the mixture was warmed to –50 °C over 30 min; gas evolution was observed and a yellow suspension was formed. Stirring continued at this temperature for 19 h, before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1) to afford the product as a white solid (1.73 g, 74 % over 2 steps). m.p. 110.0 – 111.3 °C; $[\alpha]_D^{20}$ = +0.6 (*c* 1.3, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.49 – 7.36 (m, 2H), 6.93 – 6.82 (m, 2H), 5.43 (s, 1H), 4.23 – 4.13 (m, 2H), 3.79 (s, 3H), 3.51 (t, J = 11.4 Hz, 1H), 2.54 (d, J = 2.1 Hz, 1H), 2.25 – 2.10 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 160.2, 130.4, 127.7, 113.7, 101.6, 80.9, 74.4, 73.8, 72.8, 55.4, 35.2, 12.6; **IR** (neat): 3262, 2999, 2963, 2930, 2911, 2839, 2122, 1614, 1590, 1519, 1456, 1430, 1386, 1356, 1301, 1244, 1182, 1131, 1110, 1072, 1040, 1024, 997, 979, 936, 903, 876, 834 cm^{-1}; **MS** (EI): *m/z* (%) 187 (M^+–45, 7), 136 (45), 135 (100), 108 (17), 107 (13), 92

(12), 79 (24), 77 (34), 65 (15), 39 (13); **HRMS** (ESI-pos.) calcd. for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.11722, found 233.11740.

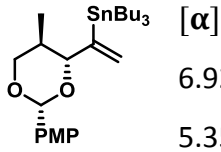
Tributyl((*E*)-2-((2*R*,4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)vinyl) stannane (134)



Bu_3SnH (4.2 mL, 15.6 mmol) and AIBN (85.6 mg, 0.521 mmol) were successively added to a solution of alkyne **133** (1.21 g, 5.21 mmol) in benzene (120 mL). The mixture was stirred at reflux temperature for 2 h before the solvent was evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 96:4) to afford the desired product (2.28 g, 84 %, *E*:*Z* = 8:1) along with the α-addition product (300 mg, 11 %), each as a colorless oil. Characterizations are given for the *E*-Isomer. $[\alpha]_D^{20}$ = –22.0 (*c* 1.1, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 – 7.39 (m, 2H), 6.93 – 6.85 (m, 2H), 6.26 (dd, J = 19.1, 0.9 Hz, J_{Sn-H} = 71.2 Hz, 1H), 6.00 (dd, J = 19.1, 6.7 Hz, J_{Sn-H} = 61.6 Hz, 1H), 5.50 (s, 1H), 4.16 (dd, J = 11.3, 4.7 Hz, 1H), 3.83 (dd, J = 9.9, 7.1 Hz, 1H), 3.80 (s, 3H), 3.53 (t, J = 11.2 Hz, 1H), 1.95 – 1.78 (m, 1H), 1.56 – 1.40 (m, 6H), 1.36 – 1.26 (m, 6H), 1.00 – 0.82 (m, 15H), 0.78 (d, J = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 145.7, 132.8, 131.3, 127.7, 113.7, 101.1, 87.8, 73.2, 55.4, 33.8, 29.2, 27.4, 13.8, 12.5, 9.6; **^{119}Sn NMR** (112 MHz, $CDCl_3$) δ: -47.5; **IR** (neat): 2954, 2925, 2871, 2842, 1615, 1518, 1461, 1388, 1301, 1249, 1171, 1124, 1073, 1036, 988, 829 cm^{-1}; **MS** (EI): *m*/*z* (%) 471 (17), 469 (17), 468 (24), 467 (M^+–57, 100), 466 (42), 465 (75), 464 (32), 463 (42), 301 (10), 245 (12), 189 (10), 187 (10), 177 (19), 175 (13), 136 (11), 135 (25), 121 (67), 97 (25); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{44}O_3SnNa$ $[M + Na]^+$ 547.22039, found 547.22105.

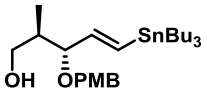
Tributyl(1-((2*R*,4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)vinyl)stannane (135)



$[\alpha]_D^{20}$ = –15.7 (*c* 1.2, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 – 7.34 (m, 2H), 6.92 – 6.77 (m, 2H), 5.80 (dd, J = 2.4, 1.0 Hz, J_{Sn-H} = 129.0 Hz, 1H), 5.50 (s, 1H), 5.35 (dd, J = 2.4, 0.8 Hz, J_{Sn-H} = 61.2 Hz, 1H), 4.16 (dd, J = 11.3, 4.7 Hz, 1H), 4.05 – 3.85 (m, 1H), 3.80 (s, 3H), 3.53 (t, J = 11.2 Hz, 1H), 1.78 (dddd, J = 11.3, 9.8, 6.8, 4.7 Hz, 1H), 1.54 – 1.36 (m, 6H), 1.27 (h, J = 7.2 Hz, 6H), 0.99 – 0.88 (m, 6H), 0.85 (t, J = 7.3 Hz, 9H), 0.72 (d, J = 6.8 Hz, 3H).; **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.9, 154.6, 131.4, 127.7, 126.8, 113.5, 101.0, 91.9, 73.2, 55.4, 33.4, 29.2, 27.5, 13.8, 12.5, 10.5; **^{119}Sn NMR** (112 MHz, $CDCl_3$) δ: -44.9; **IR** (neat): 2954, 2924, 2871, 2840, 1616, 1518, 1460, 1380, 1300, 1249, 1171, 1124,

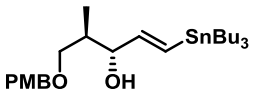
1111, 1073, 1037, 1021, 828 cm^{-1}; **MS** (EI): *m/z* (%) 467 (M^+–57, 14), 465 (10), 437 (11), 331 (39), 330 (15), 329 (31), 328 (12), 327 (17), 305 (17), 303 (14), 302 (14), 301 (100), 300 (36), 299 (73), 298 (28), 297 (42), 177 (25), 175 (21), 173 (12), 135 (11), 121 (18); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{44}O_3SnNa$ $[M + Na]^+$ 547.22039, found. 547.22097.

(2*R*,3*R*,*E*)-3-((4-Methoxybenzyl)oxy)-2-methyl-5-(tributylstannyl)pent-4-en-1-ol (136)



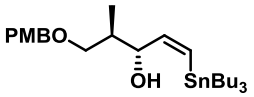
DIBAL-H (8.0 mL, 8.0 mmol, 1.0 M in CH_2Cl_2) was slowly added to a solution of compound **134** (2.10 g, 4.01 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After stirring for 3 h at this temperature, the reaction was quenched with sat. aq. Rochelle salt (40 mL) and the mixture was stirred for 1 h before the phases were separated. The aqueous phase was extracted with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1 then 7:3) to afford the desired product (1.43 g, 68 %, *E* isomer) along with *Z* isomer (124 mg, 6 %) and regioisomer (233 mg, 11 %), each as a colorless oil. $[\alpha]_D^{20}$ = +65.5 (*c* 2.3, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.25 – 7.19 (m, 2H), 6.91 – 6.81 (m, 2H), 6.15 (dd, J = 19.1, 0.7 Hz, J_{Sn-H} = 71.6 Hz, 1H), 5.83 (dd, J = 19.1, 7.7 Hz, J_{Sn-H} = 60.7 Hz, 1H), 4.55 (d, J = 11.4 Hz, 1H), 4.27 (d, J = 11.4 Hz, 1H), 3.80 (s, 3H), 3.66 – 3.54 (m, 3H), 3.09 (dd, J = 8.1, 3.6 Hz, 1H), 1.86 (dqd, J = 14.2, 7.2, 3.5 Hz, 1H), 1.62 – 1.42 (m, 6H), 1.33 (dq, J = 14.1, 7.2 Hz, 6H), 1.02 – 0.87 (m, 15H), 0.81 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.4, 147.3, 134.1, 130.3, 129.7, 114.0, 89.5, 70.0, 67.8, 55.4, 39.6, 29.3, 27.4, 14.0, 13.9, 9.7; **^{119}Sn NMR** (112 MHz, $CDCl_3$) δ: -47.8; **IR** (neat): 3447, 2955, 2924, 2871, 2852, 1613, 1513, 1464, 1246, 1172, 1037, 993, 820 cm^{-1}; **MS** (EI): *m/z* (%) 473 (12), 471 (12), 470 (17), 469 (M^+–57, 70), 468 (29), 467 (52), 466 (22), 465 (29), 413 (9), 122 (9), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{46}O_3SnNa$ $[M + Na]^+$ 549.23604, found 549.23667.

(3*R*,4*R*,*E*)-5-((4-Methoxybenzyl)oxy)-4-methyl-1-(tributylstannyl)pent-1-en-3-ol (regioisomer) (137)



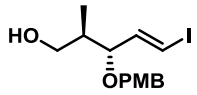
$[\alpha]_D^{20}$ = –6.6 (*c* 1.0, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.25 (d, J = 8.7 Hz, 2H), 6.96 – 6.80 (m, 2H), 6.17 (dd, J = 19.1, 1.1 Hz, J_{Sn-H} = 73.2 Hz, 1H), 5.96 (dd, J = 19.0, 6.0 Hz, J_{Sn-H} = 63.0 Hz, 1H), 4.44 (d, J = 2.6 Hz, 2H), 4.05 – 3.91 (m, 1H), 3.80 (s, 3H), 3.57 (dd, J = 9.2, 4.4 Hz, 1H), 3.44 (dd, J = 9.2, 7.1 Hz, 1H), 3.28 (d, J = 3.7 Hz, 1H), 1.89 (qd, J = 7.1, 4.4 Hz, 1H), 1.60 – 1.39 (m, 6H), 1.30 (dq, J = 14.2, 7.3 Hz, 6H), 0.99 – 0.79 (m, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.4, 149.5, 130.1, 129.4, 129.3, 114.0, 80.2, 74.5, 73.2, 55.4, 38.6, 29.3, 27.4, 13.9, 13.9, 9.6; **^{119}Sn NMR** (112 MHz, $CDCl_3$) δ: -47.2; **IR** (neat): 3461, 2955, 2925, 2871, 2854, 1613, 1513, 1463, 1248, 1173, 1090, 1039, 992, 820 cm^{-1}; **MS** (EI): *m*/*z* (%) 473 (10), 470 (14), 469 (M^+–57, 59), 468 (25), 467 (45), 466 (19), 465 (25), 177 (9), 137 (15), 122 (9), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{46}O_3SnNa$ $[M + Na]^+$ 549.23604, found 549.23661.

(2*R*,3*R*,*Z*)-3-((4-Methoxybenzyl)oxy)-2-methyl-5-(tributylstannyl)pent-4-en-1-ol (*Z* isomer)



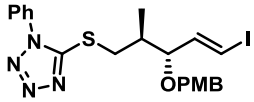
Sample contained 6 % of *E* isomer. $[\alpha]_D^{20}$ = –19.0 (*c* 0.8, $CHCl_3$), **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.25 – 7.19 (m, 2H), 6.98 – 6.83 (m, 2H), 6.45 (dd, J = 13.0, 9.0 Hz, 1H), 6.23 (d, J = 13.0 Hz, J_{Sn-H} = 133.8 Hz, 1H), 4.56 (d, J = 11.0 Hz, J_{Sn-H} = 59.2 Hz, 1H), 4.24 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.73 (ddd, J = 10.9, 7.5, 3.4 Hz, 1H), 3.64 (ddd, J = 11.1, 7.0, 4.1 Hz, 1H), 3.56 (dd, J = 9.2, 7.5 Hz, 1H), 3.09 (dd, J = 7.4, 4.0 Hz, 1H), 1.87 (hd, J = 7.2, 3.4 Hz, 1H), 1.60 – 1.39 (m, 6H), 1.31 (h, J = 7.3 Hz, 6H), 0.99 – 0.80 (m, 18H).; **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.3, 147.8, 134.6, 130.5, 129.2, 114.0, 88.8, 70.1, 67.4, 55.4, 40.1, 29.3, 27.5, 14.3, 13.8, 10.7; **^{119}Sn NMR** (112 MHz, $CDCl_3$) δ: -61.7; **IR** (neat): 3444, 2956, 2925, 2871, 2853, 1613, 1514, 1463, 1248, 1173, 1073, 1039, 821 cm^{-1}; **MS** (EI): *m*/*z*(%) 473 (12), 471 (12), 470 (17), 469 (M^+–57, 70), 468 (29), 467 (52), 466 (22), 465 (29), 413 (9), 122 (9), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{26}H_{46}O_3SnNa$ $[M + Na]^+$ 549.23604, found 549.23644.

(2*R*,3*R*,*E*)-5-Iodo-3-((4-methoxybenzyl)oxy)-2-methylpent-4-en-1-ol (131)



A solution of I_2 (986.4 mg, 3.89 mmol) in CH_2Cl_2 (40 mL) was added over 20 min to a solution of alcohol **136** (1.36 g, 2.58 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The mixture was stirred for 40 min at room temperature and the reaction quenched with sat. aq. $Na_2S_2O_3$ (50 mL). The mixture was stirred for 30 min and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (SiO_2 with 10 % KF, hexane/EtOAc, 7:3) to afford the product as a colorless oil (875.0 mg, 94%). $[\alpha]_D^{20}$ = +109.2 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.25 – 7.19 (m, 2H), 6.93 – 6.84 (m, 2H), 6.48 (dd, J = 14.6, 8.3 Hz, 1H), 6.34 (d, J = 14.7 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.27 (d, J = 11.4 Hz, 1H), 3.81 (s, 3H), 3.68 – 3.59 (m, 2H), 3.54 (dd, J = 11.1, 7.0 Hz, 1H), 2.63 (s, 1H), 1.94 – 1.79 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.5, 145.5, 129.7, 129.6, 114.1, 86.3, 79.7, 70.6, 66.8, 55.4, 39.6, 13.7; **IR** (neat): 3423, 2958, 2932, 2875, 2835, 1611, 1513, 1463, 1302, 1247, 1173, 1034, 953, 820 cm^{-1}; **MS** (EI): *m*/*z* (%) 137 (M^+–225, 11), 122 (9), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{14}H_{19}O_3INa$ [M + Na]$^+$ 385.02711, found 385.02723. The spectroscopic data are in agreement with those reported in the literature.[13a, 129]

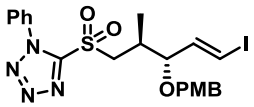
5-(((2*S*,3*R*,*E*)-5-Iodo-3-((4-methoxybenzyl)oxy)-2-methylpent-4-en-1-yl)thio)-1-phenyl-1H-tetrazole (138)[13a]



1-Phenyl-1*H*-tetrazole-5-thiol (315.0 mg, 1.77 mmol) and PPh_3 (463.5 mg, 1.77 mmol) were added to a solution of alcohol **131** (400.0 mg, 1.10 mmol) in THF (25 mL) at 0 °C. Next, DEAD (320 µL, 1.76 mmol) was slowly added and the resulting mixture was stirred for 2.5 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 8:2 then 7:3) to afford the product as a colorless oil (577.8 mg, quantitative yield). $[\alpha]_D^{20}$ = +39.9 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.61 – 7.48 (m, 5H), 7.27 – 7.16 (m, 2H), 6.89 – 6.79 (m, 2H), 6.47 (dd, J = 14.6, 7.9 Hz, 1H), 6.37 (d, J = 14.6 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.25 (d, J = 11.4 Hz, 1H), 3.78 (s, 3H), 3.64 (t, J = 7.4 Hz, 1H), 3.59 (dd, J = 12.9, 5.2 Hz, 1H), 3.41 (dd, J = 12.9, 6.9 Hz, 1H), 2.19 (hd, J = 6.9, 5.2 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.4, 154.7, 144.6, 133.8,

130.2, 129.9, 129.8, 129.7, 124.0, 113.9, 83.8, 80.1, 70.5, 55.4, 37.4, 36.6, 15.6; **IR** (neat): 3061, 2961, 2930, 2856, 1728, 1611, 1598, 1512, 1499, 1461, 1385, 1385, 1246, 1174, 1073, 1058, 1035, 953, 820, 761, 694 cm^{-1}; **MS** (EI): *m/z* (%) 259 (M^+–263, 42), 208 (11), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{21}H_{23}OISNa$ [M + Na]$^+$ 545.04786, found 545.04783.

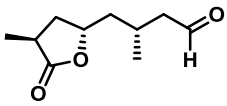
5-(((2*S*,3*R*,*E*)-5-Iodo-3-((4-methoxybenzyl)oxy)-2-methylpent-4-en-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (109)[13a]



H_2O_2 (35% *w/w* in water, 4.2 mL) was added over 5 min to a suspension of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.04 g, 0.841 mmol) and thioether **138** (879.4 mg, 1.68 mmol) in EtOH (20 mL) at 0 °C. The mixture was stirred at room temperature for 16 h and a yellow precipitate was observed. The reaction was quenched with water and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to afford the product as a colorless oil (671.0 mg, 72 %). $[\alpha]_D^{20}$ = +43.1 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.66 – 7.54 (m, 5H), 7.23 – 7.15 (m, 2H), 6.91 – 6.85 (m, 2H), 6.50 – 6.37 (m, 2H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 4.06 (dd, *J* = 14.6, 3.6 Hz, 1H), 3.81 (s, 3H), 3.67 (ddd, *J* = 6.8, 4.0, 3.0 Hz, 1H), 3.52 (dd, *J* = 14.6, 8.8 Hz, 1H), 2.52 – 2.39 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.5, 154.1, 143.6, 133.1, 131.6, 129.8, 129.6, 129.4, 125.3, 114.0, 83.2, 81.1, 70.6, 58.3, 55.4, 32.8, 16.3; **IR** (neat): 3064, 2956, 2926, 2854, 1726, 1611, 1513, 1498, 1461, 1341, 1247, 1174, 1152, 1065, 1035, 954, 822, 763, 689, 631, 529 cm^{-1}; **MS** (EI): *m/z* (%) 312 (M^+–242, 12), 137 (20), 121 (100); **HRMS** (ESI-pos.) calcd. for $C_{21}H_{23}N_4O_4ISNa$ [M + Na]$^+$ 577.03769, found 577.03725.

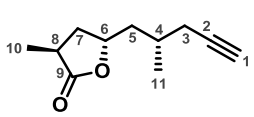
6.4.2 Synthesis of the Southern Fragment

(*R*)-3-Methyl-4-((2*S*,4*S*)-4-methyl-5-oxotetrahydrofuran-2-yl)butanal (139)



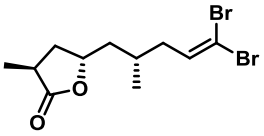
$[Cu(CH_3CN)_4]BF_4$ (59.1 mg, 0.188 mmol), 2,2'-bipyridyl (29.4 mg, 0.188 mmol), TEMPO (29.4 mg, 0.188 mmol) and 1-methylimidazole (30.9 mg, 0.376 mmol), each as a solution in CH_3CN (4 mL), were consecutively added to a solution of alcohol **91** (700 mg, 3.76 mmol) in CH_3CN (4 mL). The mixture was stirred in a flask open to air. After the addition was completed, the flask was closed with a septum and connected to a ballon of O_2. Stirring continued for 3 h during which time the color changed from brown to green. The reaction was quenched with water, the aqueous layer was extracted with hexane, and the combined extracts were dried over $MgSO_4$, filtered and evaporated to afford the product as an orange oil (673 mg, 97 %) was obtained that was used for the next step without any further purification. For characterization purposes, an analytical sample was obtained by flash chromatography (hexane/EtOAc, 7:3). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = –31.5 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.70 (dd, *J* = 2.2, 1.5 Hz, 1H), 4.53 (ddt, *J* = 8.5, 7.4, 5.3 Hz, 1H), 2.63 (dp, *J* = 9.0, 7.4 Hz, 1H), 2.48 (ddd, *J* = 16.6, 5.8, 1.5 Hz, 1H), 2.36 – 2.14 (m, 2H), 2.08 (ddd, *J* = 12.8, 8.9, 5.1 Hz, 1H), 1.97 (dt, *J* = 12.8, 7.4 Hz, 1H), 1.62 (ddd, *J* = 14.2, 8.6, 6.8 Hz, 1H), 1.56 – 1.47 (m, 1H), 1.22 (d, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.0, 179.8 76.3, 50.3, 42.0, 35.6, 33.8, 25.1, 20.2, 15.8; **IR** (neat): 2967, 2936, 2879, 2833, 2726, 1766, 1721, 1458, 1379, 1362, 1187, 1175, 1001, 924 cm^{-1}; **MS** (EI): *m*/*z* (%) 138 (M^+–46, 10), 99 (100), 97 (11), 96 (24), 95 (18), 93 (12), 83 (17), 81 (34), 71 (71), 70 (17), 69 (48), 67 (15), 57 (11), 56 (12); **HRMS** (ESI-pos.) calcd. for $C_{10}H_{16}O_3Na$ $[M + Na]^+$ 207.09916, found 207.09921.

(3*S*,5*S*)-3-Methyl-5-((*S*)-2-methylpent-4-yn-1-yl)dihydrofuran-2(3H)-one (140)[58]



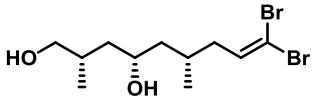
A freshly prepared solution of NaOMe (2.6 mL, 1.63 mmol, 0.5 M in THF) was slowly added to a solution of Bestmann-Ohira reagent (0.313 g, 1.63 mmol) in THF (4.5 mL) at –78 °C. The resulting mixture was stirred for 1 h at this temperature, followed by the dropwise addition of aldehyde **139** (0.100 g, 0.543 mmol). Once the addition was complete, the mixture was warmed to –65 °C and stirring continued at this temperature for 1.5 h, before the reaction was quenched with phosphate buffer (pH 7.0) and sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc, the combined extracts were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 91:9) to afford the product as a colorless oil (67 mg, 68 %). $[\alpha]_D^{20}$ = –69.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.58 (ddt, *J* = 8.8, 7.3, 5.2 Hz, 2H, H6), 2.69 (dp, *J* = 8.8, 7.4 Hz, 1H, H8), 2.26 (ddd, *J* = 16.9, 6.0, 2.6 Hz, 2H, H3a), 2.19 (ddd, *J* = 16.8, 5.5, 2.7 Hz, 1H, H3b), 2.10 (ddd, *J* = 12.8, 8.8, 5.0 Hz, 1H, H7a), 2.02 (dt, *J* = 12.8, 7.3 Hz, 1H, H7b), 1.97 (t, *J* = 2.7 Hz, 1H, H1), 1.91 (sept., *J* = 6.7, 6.0, 5.5 Hz, 1H, H4), 1.69 (ddd, *J* = 14.2, 7.3, 5.2 Hz, 2H, H5a), 1.61 (ddd, *J* = 14.2, 8.8, 6.7 Hz, 1H, H5b), 1.27 (d, *J* = 7.3 Hz, 3H, H10), 1.04 (d, *J* = 6.7 Hz, 3H, H11); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 179.84 (C9), 81.94 (C2), 76.45 (C6), 69.96 (C1), 40.97 (C5), 35.78 (C7), 33.82 (C8), 28.97 (C4), 24.87 (C3), 19.82 (C11), 15.79 (C10); **IR** (neat): 3287, 2965, 2933, 2877, 2116, 1768, 1457, 1379, 1362, 1191, 1054, 1001, 925, 647 cm^{-1}; **MS** (EI): *m/z* (%) 139 (M^+–41, 14), 109 (15), 107 (10), 99 (100), 95 (17), 93 (21), 91 (12), 81 (15) 79 (42), 71 (82), 69 (40), 68 (36), 67 (27), 66 (13), 55 (23), 43 (22), 41 (16); **HRMS** (ESI-pos.) calcd. for $C_{10}H_{16}O_3Na$ $[M + Na]^+$ 207.099164, found 207.099210.

(3*S*,5*S*)-5-((*S*)-5,5-Dibromo-2-methylpent-4-en-1-yl)-3-methyldihydrofuran-2(3H)-one (141)



A solution of PPh_3 (3.83 g, 14.6 mmol) in CH_2Cl_2 (25 mL) was added over 15 min to a solution of CBr_4 (2.42 g, 7.30 mmol) and aldehyde **139** (673 mg, 3.65 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The yellow mixture was stirred at this temperature for 2 h before hexane (60 mL) was introduced. The orange precipitate was filtered off and washed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to afford the product as a colorless oil (1.14 g, 92%). $[\alpha]_D^{20}$ = –30.6 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.40 (dd, J = 7.7, 6.9 Hz, 1H), 4.59 (ddt, J = 8.7, 7.2, 5.2 Hz, 1H), 2.69 (dp, J = 8.8, 7.3 Hz, 1H), 2.18 (ddd, J = 14.7, 7.0, 5.6 Hz, 1H), 2.11 – 1.99 (m, 3H), 1.87 (pd, J = 6.9, 5.6 Hz, 1H), 1.63 (ddd, J = 14.2, 8.7, 6.7 Hz, 1H), 1.50 (ddd, J = 14.2, 7.2, 5.1 Hz, 1H), 1.29 (d, J = 7.3 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 180.0, 136.7, 90.1, 76.6, 42.2, 39.5, 36.0, 34.1, 29.7, 20.2, 16.0; **IR** (neat): 2961, 2933, 2875, 1763, 1618, 1456, 1378, 1361, 1187, 999, 923, 777 cm^{-1}; **MS** (EI): *m/z* (%) 228 (31), 226 (M^+–112, 63), 224 (33), 201 (14), 199 (28), 197 (14), 147 (13), 145 (14), 139 (100), 119 (18), 117 (15), 99 (22), 71 (20), 69 (25), 65 (14), 43 (38), 41 (34), 39 (20); **HRMS** (ESI-pos.) calcd. for $C_{11}H_{16}O_2Br_2Na$ $[M + Na]^+$ 360.94095, found 360.94097.

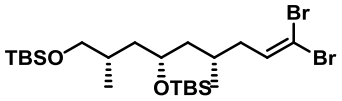
(2*S*,4*S*,6*S*)-9,9-Dibromo-2,6-dimethylnon-8-ene-1,4-diol (142)



$LiBH_4$ (4 M in THF, 2.1 mL, 8.40 mmol) was added dropwise to a solution of MeOH (200 µL, 4.94 mmol) and lactone **141** (1.14 g, 3.35 mmol) at 0 °C. After stirring for 1.5 h, the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 1:1) to afford the product as a colorless oil (1.11 g, 97 %). $[\alpha]_D^{20}$ = –5.7 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.41 (dd, J = 7.7, 6.9 Hz, 1H), 3.89 (tt, J = 7.4, 5.5 Hz, 1H), 3.58 (dd, J = 10.5, 4.4 Hz, 1H), 3.49 (dd, J = 10.5, 7.0 Hz, 1H), 2.61 (s, 2H), 2.16 (ddd, J = 14.6, 6.9, 5.3 Hz, 1H), 2.06 – 1.89 (m, 2H), 1.83 (dq, J = 12.6, 7.1 Hz, 1H), 1.55 – 1.44 (m, 2H), 1.44 – 1.34 (m, 2H), 0.95 (t, J = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 137.4, 89.4, 68.2, 67.2, 44.4, 42.7, 39.8, 32.2, 29.4, 20.4, 17.7. **IR** (neat): 3322, 2954, 2925, 2871, 1620, 1458, 1379, 1035, 778 cm^{-1}; **MS** (EI): *m/z* (%) 228 (50), 226 (M^+–116, 100), 224 (51), 199 (15), 143 (52), 125 (63),

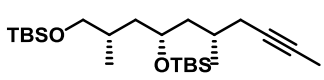
109 (11), 103 (18), 85 (75), 81 (18), 71 (15), 69 (38), 67 (23), 65 (16), 58 (13), 57 (51), 56 (21), 55 (25); **HRMS** (ESI-pos.) calcd. for $C_{11}H_{20}O_2Br_2Na$ $[M + Na]^+$ 364.97225, found 364.97233.

(5*S*,7*S*)-5-((*S*)-5,5-Dibromo-2-methylpent-4-en-1-yl)-2,2,3,3,7,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodecane (143)



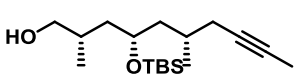
TBSOTf (1.8 mL, 7.84 mmol) was slowly added to a solution of diol **142** (1.05 g, 3.06 mmol) and 2,6-lutidine (1.8 mL, 15.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred for 2 h at room temperature, the reaction was quenched with methanol (4.5 mL) and the resulting solution poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford the product as a colorless oil (1.72 g, 98 %). $[\alpha]_D^{20}$ = –8.0 (*c* 2.6, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 6.38 (dd, J = 7.8, 6.7 Hz, 1H), 3.80 (p, J = 6.6 Hz, 1H), 3.45 (dd, J = 9.7, 5.3 Hz, 1H), 3.37 (dd, J = 9.7, 6.2 Hz, 1H), 2.14 (ddd, J = 14.8, 6.8, 5.2 Hz, 1H), 1.96 (dt, J = 14.7, 7.8 Hz, 1H), 1.79 (dtd, J = 13.6, 6.9, 5.6 Hz, 1H), 1.67 (dt, J = 18.9, 6.2 Hz, 1H), 1.54 (dt, J = 12.6, 6.6 Hz, 1H), 1.42 (ddd, J = 13.9, 7.1, 5.4 Hz, 1H), 1.31 (dt, J = 13.7, 6.7 Hz, 1H), 1.20 (ddd, J = 13.7, 7.8, 6.1 Hz, 1H), 0.94 – 0.87 (m, 24H), 0.08 – 0.02 (m, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 137.6, 89.2, 69.0, 68.2, 44.3, 41.2, 40.1, 32.5, 28.9, 26.1, 20.6, 18.5, 18.2, 17.6, -4.0, -4.1, -5.2; **IR** (neat): 2954, 2928, 2885, 2856, 1471, 1462,1388, 1361, 1251, 1068, 1005, 833, 806, 771 cm^{-1}; **MS** (EI): *m*/*z* (%) 459 (M^+–111, 11), 199 (19), 189 (39), 149 (15), 148 (16), 147 (100), 81 (11), 75 (21), 73 (40); **HRMS** (ESI-pos.) calcd. for $C_{23}H_{48}O_2Si_2Br_2Na$ $[M + Na]^+$ 593.14521, found 593.14539.

(5*S*,7*S*)-2,2,3,3,7,10,10,11,11-Nonamethyl-5-((*S*)-2-methylhex-4-yn-1-yl)-4,9-dioxa-3,10-disiladodecane (144)



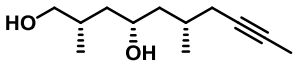
*n*BuLi (1.6 M in hexane, 4.2 mL, 6.72 mmol) was slowly added at -78 °C to a solution of compound **143** (1.65 g, 2.89 mmol) in THF (27 mL). The mixture was stirred for 1 h at this temperature before methyl iodide (0.9 mL, 14.5 mmol) was added dropwise. The resulting solution was allowed to reach room temperature overnight, before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 99:1) to afford the product as a colorless oil (1.18 g, 96 %). $[\alpha]_D^{20}$ = –15.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.80 (tt, J = 7.1, 5.5 Hz, 1H), 3.46 (dd, J = 9.7, 5.3 Hz, 1H), 3.35 (dd, J = 9.6, 6.3 Hz, 1H), 2.13 (ddq, J = 16.4, 5.1, 2.5 Hz, 1H), 2.04 (ddq, J = 16.4, 6.6, 2.5 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.77 (t, J = 2.5 Hz, 3H), 1.69 (ddt, J = 12.1, 8.0, 6.6 Hz, 1H), 1.59 – 1.48 (m, 2H), 1.24 (dddd, J = 21.6, 13.7, 7.7, 6.0 Hz, 2H), 0.97 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 5.4 Hz, 21H), 0.05 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 77.7, 76.6, 69.2, 68.4, 43.5, 41.4, 32.6, 29.1, 26.1, 25.9, 20.6, 18.5, 18.2, 17.4, 3.6, -4.0, -4.2, -5.2; **IR** (neat): 2955, 2928, 2856, 1472, 1462, 1388, 1376, 1361, 1251, 1061, 1006, 833, 806, 771 cm^{-1}; **MS** (EI): *m/z* (%) 226 (M^+–57, 3), 313 (26), 199 (16), 189 (13), 163 (11), 149 (15), 148 (14), 147 (85), 133 (10), 107 (100), 75 (25), 73 (38); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{50}O_2Si_2Br_2Na$ $[M + Na]^+$ 449.32416, found 449.32434.

(2S,4S,6S)-4-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethyldec-8-yn-1-ol (145)



HF-pyridine (2.8 mL, 108 mmol) was slowly added at 0 °C to a solution of compound **144** (500 mg, 1.17 mmol) in pyridine (15 mL, 185 mmol) and THF (28 mL). The mixture was stirred for 2.5 h at room temperature before it was poured into cold sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 9:1) to afford the desired product (230.6 mg, 63 %, 77% brsm) along with fully deprotected diol (40.4 mg, 17%), each as a colorless oil. $[\alpha]_D^{20}$ = –5.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.91 (tt, J = 7.0, 4.5 Hz, 1H), 3.52 – 3.37 (m, 2H), 3.33 (t, J = 8.5 Hz, 1H), 2.09 (ddq, J = 16.3, 5.2, 2.5 Hz, 1H), 2.00 (ddq, J = 16.4, 6.6, 2.5 Hz, 1H), 1.95 – 1.81 (m, 1H), 1.76 (t, J = 2.5 Hz, 3H), 1.74 – 1.68 (m, 1H), 1.63 (td, J = 12.3, 5.9 Hz, 1H), 1.51 (dt, J = 14.6, 4.8 Hz, 1H), 1.44 (ddd, J = 14.5, 8.8, 4.6 Hz, 1H), 1.34 (ddd, *J* = 13.3, 7.2, 6.5 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.89 – 0.83 (m, 12H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 77.5, 76.8, 69.7, 68.8, 42.3, 42.2, 31.8, 29.5, 26.5, 26.0, 19.9, 18.5, 18.2, 3.6, -4.4, -4.5; **IR** (neat): 3349, 2955, 2928, 2857, 1471, 1462, 1377, 1255, 1044, 835, 807, 773 cm^{-1}; **MS** (EI): *m/z* (%) 199 (M^+–113, 44), 145 (22), 107 (100), 85 (14), 75 (62), 73 (24); **HRMS** (ESI-pos.) calcd. for $C_{18}H_{37}O_2Si$ $[M + H]^+$ 313.25573, found 313.25525.

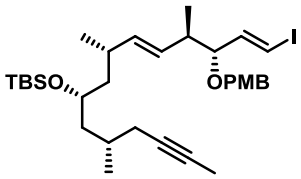
(2*S*,4*S*,6*S*)-2,6-Dimethyldec-8-yne-1,4-diol (146)



$[\alpha]_D^{20}$ = –12.7 (*c* 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.91 (ddt, J = 8.3, 6.7, 5.0 Hz, 1H), 3.55 (dd, J = 10.6, 4.6 Hz, 1H), 3.48 (dd, J = 10.6, 7.0 Hz, 1H), 2.76 (s, 2H), 2.19 – 2.02 (m, 2H), 1.93 (dpd, J = 13.9, 6.9, 4.7 Hz, 1H), 1.87 – 1.72 (m, 1H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.56 – 1.43 (m, 3H), 1.40 (ddd, J = 13.9, 8.3, 6.2 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 77.8, 76.9, 68.2, 67.2, 43.9, 42.4, 32.3, 29.6, 25.8, 20.6, 17.6, 3.6; **IR** (neat): 3327, 2954, 2920, 2871, 1456, 1434, 1377, 1032, 989, 966, 828 cm^{-1}; **MS** (EI): *m/z* (%) 125 (M^+–73, 44), 109 (12), 107 (20), 103 (15), 99 (10), 98 (10), 95 (17), 93 (20), 91 (19), 85 (67), 82 (41), 81 (47), 80 (48), 79 (59), 77 (21), 71 (21), 69 (100), 68 (13), 67 (76), 65 (13), 58 (15), 57 (76), 56 (24), 55 (83), 54 (15), 53 (36), 43 (68), 41 (72), 39 (26); **HRMS** (ESI-pos.) calcd. for $C_{12}H_{22}O_2Na$ $[M + Na]^+$ 221.15120, found 221.15130.

6.4.3 Endgame

tert-Butyl(((5_S_,7_S_,9_S_,10_E_,12_R_,13_R_,14_E_)-15-iodo-13-((4-methoxybenzyl)oxy)-5,9,12-trimethylpentadeca-10,14-dien-2-yn-7-yl)oxy)dimethylsilane (147)

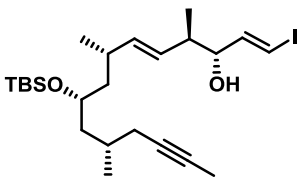


A solution of DMSO (65 µL, 0.915 mmol) in CH_2Cl_2 (500 µL) was added dropwise to a solution of oxalyl chloride (39 µL, 0.454 mmol) in CH_2Cl_2 (12.5 mL) at –78 °C. After stirring for 20 min, a solution of alcohol **145** (110 mg, 0.352 mmol) in CH_2Cl_2 (500 µL + 500 µL rinse) was added dropwise and the resulting mixture was stirred at this temperature for 2 h. DIPEA (300 µL, 1.72 mmol) was introduced and the mixture was stirred for 30 min at this temperature before warming to room temperature within 1 h. *tert*-Butyl methyl ether was added, the organic phase was washed with sat. sol. NH_4Cl and sat. sol. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to afford the corresponding aldehyde as a yellow oil (112 mg) which was used directly in the next step without further purification.

*n*BuLi (1.52 M in hexane, 0.34 mL, 0.517 mmol) was slowly added at 0 °C to a solution of hexamethyldisilazane (120 µL, 0.576 mmol) in THF (0.24 mL). The resulting solution of LiHMDS (0.517 mmol) was added dropwise over 10 min to a colorless solution of sulfon **109** (286.0 mg, 0.516 mmol) in DMF (3 mL) at –78 °C, causing a color change to orange. After stirring for 20 min at this temperature, a solution of aldehyde **108** (110.0 mg, 0.354 mmol) in THF (600 µL) was introduced and stirring continued for 4 h, before the reaction was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 98.5:1.5) to afford the product as a colorless oil (128.9 mg, 57 %, over two steps), which consisted of a mixture of isomers (*E*:*Z* = 15:1). $[\alpha]_D^{20}$ = +35.4 (*c* 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: δ 7.27 – 7.18 (m, 2H), 6.91 – 6.83 (m, 2H), 6.45 (dd, J = 14.5, 7.9 Hz, 1H), 6.23 (d, J = 14.5 Hz, 1H), 5.41 – 5.25 (m, 2H), 4.52 (d, J = 11.6 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.66 (m, 1H), 3.56 (dd, J = 7.9, 5.4 Hz, 1H), 2.35 (dt, J = 12.5, 6.7 Hz, 1H), 2.26 (h, J = 6.6 Hz, 1H), 2.12 (ddq, J = 16.4, 5.2, 2.4 Hz, 1H), 2.02 (ddq, J = 16.3, 7.0, 2.4 Hz, 1H), 1.78 (t, J = 2.5 Hz, 3H), 1.71 (dt, J = 13.4, 6.8 Hz, 1H), 1.54 (dt, J = 13.3, 6.6 Hz, 1H), 1.47 – 1.20 (m, 3H), 0.96 (t, J = 6.7 Hz, 9H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.2, 145.4, 137.2, 130.5, 129.8, 129.3, 113.9, 85.1, 78.5, 77.8, 76.7, 70.3, 69.1, 55.4, 45.0, 44.1, 40.9, 33.2, 29.4, 26.4, 26.1, 21.6, 20.3,

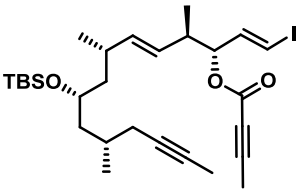
18.2, 16.2, 3.6, -3.9; **IR** (neat): 2955, 2927, 2856, 1612, 1513, 1462, 1376, 1302, 1248, 1172, 1061, 1039, 977, 950, 834, 806, 773 cm^{-1}; **MS** (EI): *m/z* (%) 399 (M^+–239, 4), 181 (2), 149 (2), 122 (7), 121 (100), 75 (11), 73 (4); **HRMS** (ESI-pos.) calcd. for $C_{32}H_{51}O_3ISiNa$ $[M + Na]^+$ 661.25444, found 661.25454.

(1*E*,3*R*,4*R*,5*E*,7*S*,9*S*,11*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-4,7,11-trimethylpentadeca-1,5-dien-13-yn-3-ol (148)



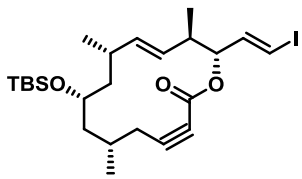
DDQ (71.1 mg, 0.313 mmol) was added to a mixture of compound **147** (100 mg, 0.157 mmol) in CH_2Cl_2 (7 mL) and phosphate buffer (pH 7.4, 0.1 M, 0.7 mL) at 0 °C. The resulting suspension was stirred at this temperature for 1 h while the color changed from green to yellow. Stirring was continued at room temperature for 3.5 h, before the reaction was quenched by addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with *tert*-butyl methyl ether, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc 95:5 then second column with fine silica gel, hexane/EtOAc 96:4) to afford the product as a colorless oil (50.8 mg, 63 %, single isomer). $[\alpha]_D^{20}$ = +34.2 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.54 (dd, J = 14.4, 6.5 Hz, 1H), 6.35 (dd, J = 14.5, 1.1 Hz, 1H), 5.46 (ddd, J = 15.5, 7.8, 0.9 Hz, 1H), 5.25 (ddd, J = 15.5, 8.2, 0.9 Hz, 1H), 3.79 (td, J = 6.8, 2.0 Hz, 1H), 3.78 – 3.66 (m, 1H), 2.33 (hept, J = 7.0 Hz, 1H), 2.20 (dt, J = 14.3, 7.0 Hz, 1H), 2.10 (ddq, J = 16.6, 5.4, 2.7 Hz, 1H), 2.02 (ddq, J = 16.4, 6.6, 2.5 Hz, 1H), 1.89 (d, J = 3.3 Hz, 1H), 1.78 (t, J = 2.6 Hz, 3H), 1.69 (dq, J = 13.0, 6.5 Hz, 1H), 1.56 (dt, J = 13.2, 6.6 Hz, 1H), 1.47 – 1.35 (m, 2H), 1.30 (ddd, J = 13.6, 7.6, 6.1 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 146.6, 140.0, 129.2, 78.2, 78.0, 77.7, 76.7, 69.2, 44.7, 43.9, 43.4, 33.3, 29.5, 26.5, 26.1, 21.7, 20.2, 18.3, 16.5, 3.6, -3.9, -3.9; **IR** (neat): 3460, 2956, 2927, 2856, 1608, 1460, 1377, 1254, 1169, 1063, 977, 948, 835, 806, 773 cm^{-1}; **MS** (EI): *m/z* (%) 239 (M^+–279, 11), 203 (11), 199 (31), 183 (22), 181 (10), 161 (23), 147 (12), 145 (15), 133 (12), 121 (11), 119 (16), 109 (26), 108 (12), 107 (100), 105 (14), 95 (18), 93 (13), 83 (14), 82 (23), 81 (13), 80 (11), 79 (11), 75 (94), 73 (53)67 (12), 55 (13); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{43}O_2ISiNa$ $[M + Na]^+$ 541.19693, found 541.19732.

(1*E*,3*R*,4*R*,5*E*,7*S*,9*S*,11*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-1-iodo-4,7,11-trimethylpentadeca-1,5-dien-13-yn-3-yl but-2-ynoate (110)



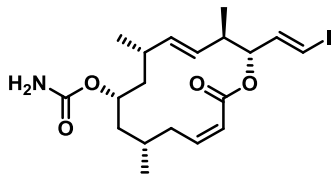
A solution of 2-butynoic acid (24.3 mg, 0.289 mmol) in CH_2Cl_2 (1 mL) and a solution of DMAP (1.73 mg, 14.2 µmol) in CH_2Cl_2 (100 µL) were consecutively added to a solution of alcohol **148** (50 mg, 96.4 µmol) in CH_2Cl_2 (2.7 mL) at 0 °C before DIC (45 µL, 0.291 mmol) was added dropwise. The resulting yellow suspension was stirred at room temperature for 2 h, leading to the formation of an orange solution. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (hexane/EtOAc – 98:2) to afford the product as a colorless oil (49.0 mg, 87 %). $[\alpha]_D^{20}$ = –1.0 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.55 – 6.38 (m, 2H), 5.39 (dd, J = 15.5, 7.6 Hz, 1H), 5.25 (dd, J = 15.7, 7.9 Hz, 1H), 5.13 (dt, J = 6.2, 3.2 Hz, 1H), 3.72 (qd, J = 6.6, 5.1 Hz, 1H), 2.41 (h, J = 7.1 Hz, 1H), 2.27 (hept, J = 6.8 Hz, 1H), 2.12 (ddq, J = 16.3, 5.0, 2.6 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.99 (s, 3H), 1.78 (t, J = 2.5 Hz, 3H), 1.72 (dq, J = 13.1, 6.6 Hz, 1H), 1.54 (dt, J = 13.2, 6.5 Hz, 1H), 1.48 – 1.24 (m, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.9, 141.5, 138.9, 128.1, 86.2, 81.6, 80.3, 77.8, 76.7, 72.5, 69.0, 44.8, 44.1, 40.4, 33.2, 29.3, 26.4, 26.1, 21.5, 20.3, 18.2, 16.2, 4.0, 3.6, -3.9, -3.9; **IR** (neat): 2956, 2928, 2856, 2242, 1713, 1609, 1461, 1377, 1248, 1182, 1062, 976, 947, 916, 835, 807, 774 cm^{-1}; **MS** (EI): *m*/*z* (%) 527 (M^+–57, 2), 239 (10), 203 (11), 202 (11), 185 (10), 161 (37), 159 (21), 147 (12), 142 (12), 141 (100), 133 (13), 121 (12), 120 (22), 119 (18), 109 (25), 107 (43), 105 (13), 97 (30), 95 (16), 93 (13), 81 (11), 80 (12), 75 (57), 73 (41), 67 (63); **HRMS** (ESI-pos.) calcd. for $C_{28}H_{45}O_3ISiNa$ $[M + Na]^+$ 607.20749, found 607.20726.

(6*S*,8*S*,10*S*,13*R*,14*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-14-((*E*)-2-iodovinyl)-6,10,13-trimethyloxacyclotetradec-11-en-3-yn-2-one (112)



A flame dried flask was charged with freshly activated molecular sieves 5 Å (powder, 2.7 g), diyne **110** (49.0 mg, 83.8 µmol) and toluene (46.0 mL). The suspension was stirred for 1 h at room temperature before a solution of the molybdenum alkylidyne complex **C1** (13.1 mg, 12.6 µmol, 15 mol%) in toluene (1 mL) was added in one portion. Stirring was continued for 1 h at this temperature. For work-up, the mixture was filtered through a pad of silica gel, which was rinsed with *tert*-butyl methyl ether. The combined filtrates were evaporated and the residue was purified by flash chromatography (hexane/EtOAc, 98:2) to afford the product as a colorless oil (42.8 mg, 96 %). $[\alpha]_D^{20}$ = +28.4 (*c* 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.56 (d, J = 14.6 Hz, 1H), 6.47 (dd, J = 14.6, 7.7 Hz, 1H), 5.22 (dd, J = 15.0, 9.3 Hz, 1H), 5.06 (dd, J = 15.0, 9.4 Hz, 1H), 4.77 (dd, J = 10.5, 7.7 Hz, 1H), 4.12 (ddt, J = 11.1, 8.6, 2.1 Hz, 1H), 2.44 – 2.24 (m, 3H), 2.19 – 2.06 (m, 1H), 1.99 (dd, J = 16.4, 10.7 Hz, 1H), 1.55 – 1.34 (m, 3H), 1.29 – 1.21 (m, 1H), 0.97 – 0.91 (m, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.7, 142.4, 140.3, 130.1, 90.7, 82.8, 80.5, 74.8, 70.9, 48.2, 48.0, 42.6, 34.8, 28.6, 27.0, 26.2, 24.0, 23.6, 18.5, 17.2, -2.8, -3.0; **IR** (neat): 2955, 2928, 2855, 2233, 1715, 1610, 1460, 1374, 1241, 1068, 972, 944, 835, 804, 773 cm^{-1}; **MS** (EI): *m*/*z* (%) 473 (M^+–57, 2), 253 (12), 247 (26), 225 (15), 211 (26), 195 (13), 169 (12), 168 (16), 167 (100), 133 (10), 121 (14), 120 (12), 119 (11), 105 (10), 93 (19), 75 (74), 73 (31); **HRMS** (ESI-pos.) calcd. for $C_{24}H_{39}O_2ISiNa$ $[M + Na]^+$ 553.16054, found 553.16082.

(2*R*,3*R*,4*E*,6*S*,8*S*,10*S*,12*Z*)-2-((*E*)-2-Iodovinyl)-3,6,10-trimethyl-14-oxooxacyclotetradeca-4,12-dien-8-yl carbamate (26)



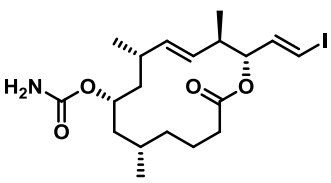
A solution of $NaBH_4$ (5.3 mg, 0.140 mmol) in ethanol (1 mL, not dry) was added in one portion to a solution of $Ni(OAc)_2 \cdot 4H_2O$ (35.2 mg, 0.141 mmol) in ethanol (4 mL). The resulting black suspension was vigorously stirred for 1 h at room temperature. Ethylenediamine (4 µL, 0.598 mmol) and ethyl *cis*-3-iodoacrylate (18 µL, 0.141 mmol) were added. An aliquot of this mixture (2.1 mL) was transferred into a solution of alkyne **112** (10.4 mg, 19.6 µmol) in ethanol (2.1 mL) at 0 °C. The flask was sealed with a septum and connected to a balloon of H_2. The mixture was stirred at 0 °C for 1 h, followed by stirring at room temperature for 14 h. The reaction was carefully quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with *tert*-butyl methyl ether, and the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was passed through a pad of silica gel, which was rinsed with EtOAc. The combined filtrates were evaporated to afford the crude product **111** as a yellow oil (10.8 mg) which was used in the next step without further purification.

A solution of crude **111** in CH_2Cl_2 (0.16 mL) was diluted with methanol (2.3 mL). A solution of CSA (4.5 mg, 19.4 µmol) in methanol (100 µL) was added and the resulting mixture stirred at room temperature for 5 h, before the reaction was quenched with DIPEA (3.4 µL, 19.5 µmol) in methanol (100 µL). The mixture was concentrated in vacuo and the residue was filtered through a pad of silica gel, which was rinsed with EtOAc. The combined filtrates were evaporated to afford the corresponding alcohol **149** as a yellow oil (11.0 mg), which was used in the next step without further purification.

A solution of chlorosulfonyl isocyanate (2.3 µL, 26.4 µmol) in CH_2Cl_2 (100 µL) was slowly added to a solution of this alcohol in CH_2Cl_2 (1.6 mL) at 0 °C. The mixture was stirred at this temperature for 30 min and the reaction was quenched with THF/H_2O (4:1, 260 µL). The resulting mixture was vigorously stirred at room temperature for 5 h before it was diluted with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc, the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (fine silica gel, hexane/EtOAc, 8:2 then 7:3) to afford the product as colorless oil (6.9 mg, 76 % over three steps).

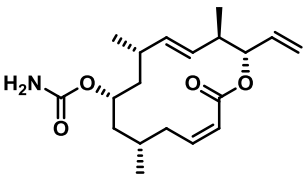
$[\alpha]_D^{20}$ = +103.6 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.53 – 6.44 (m, 2H), 6.13 (td, J = 12.3, 3.4 Hz, 1H), 5.87 (dd, J = 11.6, 2.4 Hz, 1H), 5.28 (dd, J = 15.0, 9.4 Hz, 1H), 5.18 (ddd, J = 10.4, 5.2, 2.4 Hz, 1H), 5.04 (dd, J = 15.0, 9.3 Hz, 1H), 4.58 (t, J = 10.8 Hz, 1H), 4.48 (s, 2H), 3.66 (ddd, J = 14.9, 12.9, 4.9 Hz, 1H), 2.23 (tq, J = 9.8, 6.9 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.96 (dq, J = 14.9, 3.1 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.55 – 1.43 (m, 2H), 1.12 – 1.03 (m, 2H), 1.01 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.7, 156.7, 143.8, 143.5, 137.0, 132.5, 122.4, 81.6, 77.8, 71.1, 44.4, 42.4, 41.5, 34.1, 31.7, 27.4, 22.4, 20.3, 17.5; **IR** (neat): 3494, 3370, 2957, 2925, 2870, 1715, 1603, 1454, 1382, 1326, 1172, 1046, 974, 947, 835, 799, 734 cm^{-1}; **MS** (EI): *m*/*z* (%) 461 (M^+, 1), 273 (12), 218 (25), 198 (16), 137 (15), 122 (10), 109 (10), 107 (13), 105 (10), 95 (58), 93 (19), 82 (100), 81 (16), 79 (10), 68 (14), 67 (20), 55 (18), 41 (12); **HRMS** (ESI-pos.) calcd. for $C_{19}H_{28}NO_4INa$ $[M + Na]^+$ 484.09553, found 484.09547. The spectroscopic data are in agreement with those reported in the literature.[13c]

(2*R*,3*R*,6*S*,8*S*,10*S*,*E*)-2-((E)-2-Iodovinyl)-3,6,10-trimethyl-14-oxooxacyclotetradec-4-en-8-yl carbamate (26a, overreduced product)



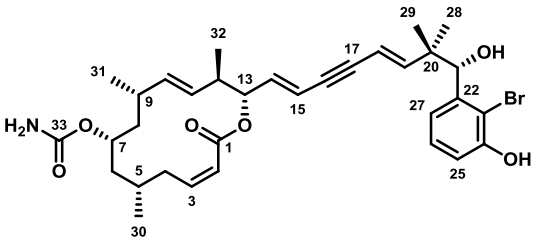
$[\alpha]_D^{20}$ = +76.0 (*c* 0.1, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 6.48 (dd, *J* = 14.5, 0.5 Hz, 1H), 6.34 (dd, *J* = 14.5, 8.4 Hz, 1H), 5.39 (dd, *J* = 15.1, 9.2 Hz, 1H), 5.12 (dd, *J* = 15.1, 9.0 Hz, 1H), 4.87 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.83 (ddt, *J* = 11.0, 9.7, 1.6 Hz, 1H), 4.45 (s, 2H), 2.42 (dt, *J* = 13.9, 5.3 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.24 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 1.78 – 1.69 (m, 2H), 1.62 – 1.48 (m, 4H), 1.26 – 1.17 (m, 2H), 1.16 (ddd, *J* = 14.5, 11.6, 1.5 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.3, 156.7, 143.5, 136.1, 133.0, 82.2, 79.4, 71.8, 44.0, 41.1, 41.1, 35.8, 34.2, 31.9, 27.3, 21.9, 20.6, 18.6, 18.2; **IR** (neat): 3460, 3357, 2922, 2851, 1720, 1607, 1457, 1382, 1341, 1321, 1249, 1161, 1047, 986, 946 cm^{-1}; **MS** (ESI): *m*/*z* $[M + Na]^+$ 486; **HRMS** (ESI-pos.) calcd. for $C_{19}H_{30}NO_4INa$ $[M + Na]^+$ 486.11118, found 486.11149.

(2*S*,3*R*,4*E*,6*S*,8*S*,10*S*,12*Z*)-3,6,10-Trimethyl-14-oxo-2-vinyloxacyclotetradeca-4,12-dien-8-yl carbamate (26b, dehalogenated product)



$[\alpha]_D^{20}$ = +28.1 (*c* 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.11 (ddd, *J* = 12.5, 11.5, 3.6 Hz, 1H), 5.89 (dd, *J* = 11.6, 2.6 Hz, 1H), 5.77 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H), 5.37 – 5.28 (m, 2H), 5.26 – 5.17 (m, 2H), 5.04 (dd, *J* = 15.0, 9.2 Hz, 1H), 4.61 (ddt, *J* = 11.7, 10.0, 1.6 Hz, 1H), 4.49 (s, 2H), 3.70 (ddd, *J* = 14.9, 12.6, 5.0 Hz, 1H), 2.26 – 2.06 (m, 2H), 2.01 – 1.83 (m, 2H), 1.56 – 1.44 (m, 2H), 1.08 (dddd, *J* = 14.3, 12.2, 3.8, 1.6 Hz, 2H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.0, 156.7, 143.3, 136.5, 135.8, 133.2, 122.8, 118.9, 77.4, 71.4, 44.4, 42.8, 41.5, 34.1, 31.7, 27.5, 22.5, 20.3, 17.7; **IR** (neat): 3496, 3368, 2957, 2926, 2871, 1714, 1643, 1601, 1456, 1382, 1324, 1225, 1186, 1046, 973, 835, 797, 741 cm^{-1}; **MS** (ESI): *m/z* $[M + Na]^+$ 358; **HRMS** (ESI-pos.) calcd. for $C_{19}H_{29}NO_4INa$ $[M + Na]^+$ 358.19888, found 358.19891.

(+)-Callyspongiolide (*ent*-1)



A solution of enyne **27** (11.4 mg, 38.6 µmol) and DIPEA (9.0 µL, 51.7 µmol) in degassed THF (400 µL + 200 µL rinse) was added dropwise to a suspension of alkenyl iodide **26** (11.9 mg, 25.8 µmol), CuI (4.9 mg, 25.7 µmol) and $Pd(PPh_3)_4$ (3.0 mg, 2.6 µmol, 10 mol%) in degassed THF (2.5 mL). The mixture was stirred for 1.5 h at room temperature, while its color changed from yellow to orange and eventually to brown. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (fine silica gel, hexane/EtOAc, 7:3 then 6:4) to afford the product as pale yellow amorphous solid (13.0 mg, 80 %). $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +24.4 (*c* 0.3, MeOH), (lit. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = –12.5,[11] –13.0,[13a] –25.5,[13b, 13c] –13.1,[13d] *c* 0.1, MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.24 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 1.6 Hz, 1H), 6.98 (dd, J = 8.0, 1.6 Hz, 1H), 6.35 (d, J = 16.3 Hz, 1H), 6.12 (td, J = 12.2, 3.5 Hz, 1H), 6.02 (dd, J = 15.8, 8.0 Hz, 1H), 5.91 – 5.83 (m, 2H), 5.77 (br. s, 1H), 5.55 (dd, J = 16.3, 2.1 Hz, 1H), 5.31 (dd, J = 14.9, 9.3 Hz, 1H), 5.26 (dd, J = 10.0, 8.0 Hz, 1H), 5.04 (dd, J = 15.0, 9.3 Hz, 1H), 5.00 (s, 1H), 4.60 (t, J = 10.7 Hz, 1H), 4.49 (br. s, 2H), 3.67 (ddd, J = 14.9, 12.6, 5.0 Hz, 1H), 2.23 (tq, J = 10.0, 6.8 Hz, 1H), 2.16 – 2.02 (m, 1H), 2.02 – 1.91 (m, 2H), 1.91 – 1.83 (m, 1H), 1.56 – 1.45 (m, 2H), 1.14 (s, 3H), 1.13 – 1.06 (m, 2H), 1.04 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.8, 156.7, 151.9, 150.0, 143.6, 141.2, 139.7, 136.8, 132.9, 128.2, 122.6, 121.4, 115.3, 114.1, 112.8, 109.1, 89.7, 87.2, 78.6, 76.3, 71.3, 44.4, 43.7, 42.9, 41.5, 34.1, 31.7, 27.4, 24.6, 22.4, 21.9, 20.3, 17.7; **IR** (neat): 3498, 3381, 2963, 2926, 2872, 1701, 1641, 1593, 1573, 1461, 1388, 1331, 1293, 1227, 1182, 1111, 1051, 967, 910, 835, 798, 774, 733 cm^{-1}; **MS** (EI): *m*/*z* 441 (31), 384 (M^+–243, 21), 203 (22), 202 (49), 201 (69), 200 (49), 199 (61), 197 (22), 185 (29), 171 (21), 159 (22), 157 (23), 149 (22), 147 (21), 145 (27), 143 (24), 119 (21), 109 (21), 107 (21), 105 (22), 95 (57), 94 (25), 93 (27), 91 (25), 84 (23), 83 (26), 82 (100), 81 (27), 71 (24), 69 (29), 67 (26), 59 (21), 57 (35), 55 (39); **HRMS** (ESI-pos.) calcd. for $C_{33}H_{42}BrN\,O_6Na$ $[M + Na]^+$ 650.20878, found 650.20915.

^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.06 (s, 1H), 7.13 (t, J = 7.9 Hz, 1H), 6.85 – 6.81 (m, 2H), 6.36 (d, J = 16.4 Hz, 1H), 6.13 (td, J = 12.0, 3.3 Hz, 1H), 6.06 (dd, J = 15.8, 7.7 Hz, 1H), 5.97 – 5.92 (m, 2H), 5.51 (d, J = 4.4 Hz, 1H), 5.46 (dd, J = 16.4, 2.2 Hz, 1H), 5.22 (dd, J = 15.0, 9.4 Hz, 1H), 5.09 (ddd, J = 10.6, 7.9, 0.9 Hz, 1H), 5.05 (dd, J = 15.0, 9.1 Hz, 1H), 4.89 (d, J = 4.4 Hz, 1H), 4.47 (t, J = 10.7 Hz, 1H), 3.42 (ddd, J = 14.8, 12.3, 4.9 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.04 – 1.96 (m, 1H), 1.89 – 1.82 (m, 1H), 1.80 – 1.69 (m, 1H), 1.44 – 1.33 (m, 2H), 1.07 – 1.00 (m, 2H), 1.04 (s, 3H), 0.97 (d, J = 7.1 Hz, 3H), 0.95 (s, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 164.2, 156.7, 153.3, 151.6, 143.2, 142.5, 139.6, 136.4, 132.0, 126.9, 122.3, 120.1, 114.3, 113.4, 111.7, 106.8, 90.4, 86.4, 76.6, 75.7, 68.3, 44.1, 43.1, 41.8, 41.1, 33.3, 31.3, 26.9, 24.1, 22.4, 22.0, 19.9, 17.4.

Table 8: Comparison of the ^{1}H NMR (600 MHz, DMSO-d_6) data of isolated callyspongiolide with synthesized product.

Atom-number	Callyspongiolide*[11]	Synthetic Callyspongiolide*
2	5.93 (dd, J = 12.0, 2.6)	5.97 – 5.92 (m, 2H)
3	6.13 (td, J= 12.0, 3.4)	6.13 (td, J = 12.0, 3.3 Hz, 1H)
4a	3.41 (ddd, J = 14.8, 12.6, 4.8)	3.42 (ddd, J = 14.8, 12.3, 4.9 Hz, 1H)
4b	1.86 (dq, J = 14.8, 3.0)	1.89 – 1.82 (m, 1H)
5	1.75 (m)	1.80 – 1.69 (m, 1H)
6a	1.37 (ddd, J = 14.2, 11.4, 3.0)	1.44 – 1.33 (m, 2H)
6b	1.01, overlapped	1.07 – 1.00 (m, 2H)
7	4.47 (br. dd, J = 11.4, 10.1)	4.47 (t, J = 10.7 Hz, 1H)
8a	1.41 (ddd, J = 14.4, 10.1, 1.6)	1.44 – 1.33 (m, 2H)
8b	1.03 (overlapped)	1.07 – 1.00 (m, 2H)
9	2.00 (m)	2.04 – 1.96 (m, 1H)
10	5.06 (dd, J = 15.0, 9.1)	5.05 (dd, J = 15.0, 9.1 Hz, 1H)
11	5.22 (dd, J = 15.0, 9.3)	5.22 (dd, J = 15.0, 9.4 Hz, 1H)
12	2.24 (m)	2.27 – 2.20 (m, 1H)
13	5.09 (dd, J = 10.3, 7.7)	5.09 (ddd, J = 10.6, 7.9, 0.9 Hz, 1H)
14	6.06 (dd, J = 15.8, 7.7)	6.06 (dd, J = 15.8, 7.7 Hz, 1H)
15	5.94 (dd, J = 15.8, 2.2)	5.97 – 5.92 (m, 2H)
18	5.46 (dd, J = 16.4, 2.2)	5.46 (dd, J = 16.4, 2.2 Hz, 1H)
19	6.36 (d, J = 16.4)	6.36 (d, J = 16.4 Hz, 1H)
21	4.89 (d, J = 4.4)	4.89 (d, J = 4.4 Hz, 1H)
25	6.83 (dd, J = 7.9, 1.6)	6.85 – 6.81 (m, 2H)
26	7.13 (t, J = 7.9)	7.13 (t, J = 7.9 Hz, 1H)
27	6.84 (dd, J = 7.9, 1.6)	6.85 – 6.81 (m, 2H)
28	1.04 (s)	1.04 (s, 3H)
29	0.96 (s)	0.95 (s, 3H)
30	0.97 (d, J = 7.1)	0.97 (d, J = 7.1 Hz, 3H)
31	0.87 (d, J = 6.8)	0.87 (d, J = 6.9 Hz, 3H)
32	0.89 (d, J = 6.8)	0.89 (d, J = 6.9 Hz, 3H)
OH-21	5.49 (dd, J = 4.4)	5.51 (d, J = 4.4 Hz, 1H)
OH-24	10.04 (s)	10.06 (s, 1H)

* δ_H [ppm], mult. (J in Hz)

Table 9: Comparison of the ^{13}C NMR (DMSO-d_6) data (δ_C in ppm) of callyspongiolide with those reported in the literature.

Atom-number	Isolated Callyspongiolide[11] (100 MHz)	Ye *et al.*[13a] (100 MHz)	Ghosh *et al.*[13b, 13c] (125 MHz)	Harran *et al.*[13d] (125 MHz)	This Work (150 MHz)
1	164.2	164.1	164.2	164.2	164.2
2	122.3	122.2	122.3	122.3	122.3
3	142.5	142.4	142.5	142.5	142.5
4	31.3	31.2	31.3	31.3	31.3
5	26.9	26.8	26.9	26.9	26.9
6	41.1	41.0	41.1	41.1	41.1
7	68.3	68.2	68.3	68.3	68.3
8	44.1	44.1	44.2	44.2	44.1
9	33.2	33.2	33.3	33.3	33.3
10	136.4	136.3	136.4	136.4	136.4
11	132.0	131.9	132.0	132.0	132.0
12	41.8	41.7	41.8	41.8	41.8
13	75.7	75.6	75.7	75.7	75.7
14	139.6	139.5	139.6	139.7	139.6
15	113.4	113.3	113.4	113.4	113.4
16	86.3	86.3	86.4	86.4	86.4
17	90.4	90.3	90.5	90.5	90.4
18	106.8	106.7	106.8	106.8	106.8
19	151.6	151.6	151.6	151.7	151.6
20	43.0	43.0	43.1	43.1	43.1
21	76.5	76.5	76.6	76.6	76.6
22	143.2	143.1	143.2	143.2	143.2
23	111.7	111.6	111.7	111.7	111.7
24	153.3	153.2	153.3	153.3	153.3
25	114.3	114.3	114.4	114.4	114.3
26	126.9	126.8	126.9	126.9	126.9
27	120.1	120.0	120.1	120.1	120.1
28	24.1	24.0	24.1	24.1	24.1
29	22.4	22.3	22.4	22.4	22.4
30	19.9	19.8	19.9	19.9	19.9
31	22.0	21.9	22.0	22.0	22.0
32	17.4	17.3	17.5	17.5	17.4
33	156.7	156.6	156.7	156.7	156.7

7 List of Abbreviations

Å	Ångström, 10^{-10} m
Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BBN	9-borabicyclo(3.3.1)nonane
Bn	benzyl
br	broad
Brown's P2-Ni catalyst	nickel boride
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic
CDI	1,1'-carbonyldiimidazol
cm	centimeter
cod	cyclooctadienyl
conc.	concentrated
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAl-H	diisobutylalumnium hydride
DIC	*N,N*'-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	*N*,*N*-dimethyl 4-aminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
(*R*)-DM-Segphos	(*R*)-(+)-5,5'−bis[di(3,5-xylyl)phosphino]-4,4'-bi-1,3-benzodioxole
DMS	dimethyl sulfide

DMSO	dimethylsulfoxide
DPEN	1,2-diphenyl-1,2-ethylenediamine
DTS	diverted total synthesis
EDC	*N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
ent	enantiomeric
epi	epimeric
Et	ethyl
et al.	et alii / et aliae
g	gram
GC	gas chromatography
h	hour
hep	heptet
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso* (branched)
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium hexamethyldisilazide
l	liter
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar (mol/L)
m	multiplet
Me	methyl
Mes	mesityl
mg	miligram
MIDA	*N*-methyliminodiacetic acid
min	minute
mL	mililiter
MOM	methoxy methyl
mp.	melting point
MS	mass spectrometry
MS	molecular sieves
Ms	methanesulfonyl
MTBE	*tert*-butylmethylether
µg	microgram
µL	microliter
n	normal (linear)
n.d.	not determined
NaHMDS	sodium hexamethyldisilazide
NCS	*N*-chlorosuccinimide
NMI	*N*-Methylimidazole
NMR	nuclear magnetic resonance

NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
PCC	pyridiniumchlorochromat
PG	protecting group
Ph	phenyl
Ph	phenyl
pin	pinacol
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet
quant	quantitative
R	arbitrary organic substituent
rac	racemic
RCAM	ring closing alkyne metathesis
RCM	ring closing (olefin) metathesis
ROESY	rotating frame nuclear overhauser effect spectroscopy
rt	room temperature
s	singlet
sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	dimethyltert-butylsilyl
TC	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*ortho*-tolyl
Tos	toluenesulfonyl
(R)-TRIP	*(R)*-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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9 Appendix

9.1 Supporting Crystallographic Information

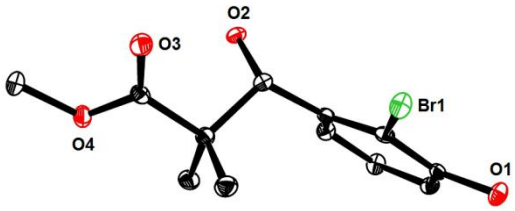


Figure 12: Structure of (*S*)-ester **64** in the solid state.

X-ray Crystal Structure Analysis of Compound 64: C_{12} H_{15} Br O_4, M_r = 303.15 g · mol^{-1}, colorless prism, crystal size 0.423 x 0.298 x 0.030 mm^3, trigonal, space group $P3_121$, a = 7.7155(2) Å, b = 7.7155(2) Å, c = 35.5487(8) Å, V = 1832.66(10) $Å^3$, T = 100(2) K, Z = 6, D_{calc} = 1.648 g · cm^3, λ = 1.54178 Å Å, $\mu(Cu\text{-}K_\alpha)$ = 4.618 mm^{-1}, Gaussian absorption correction (T_{min} = 0.36, T_{max} = 0.87), Bruker-AXS-X8-Proteum diffractometer, 3.730 < θ < 67.382°, 80621 measured reflections, 2201 independent reflections, 2197 reflections with $I > 2\sigma(I)$, Structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.016 [$I > 2\sigma(I)$], wR_2 = 0.040, 165 parameters, absolute structure parameter = -0.009(6), H atoms riding, S = 1.152, residual electron density 0.3 (0.82 Å from C2)/ -0.3 e $Å^{-3}$. **CCDC-1545687**.

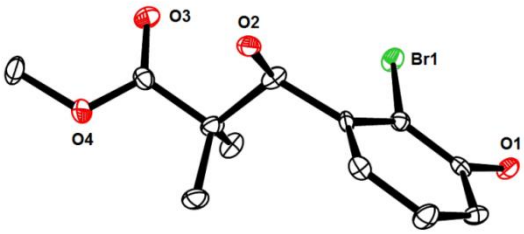
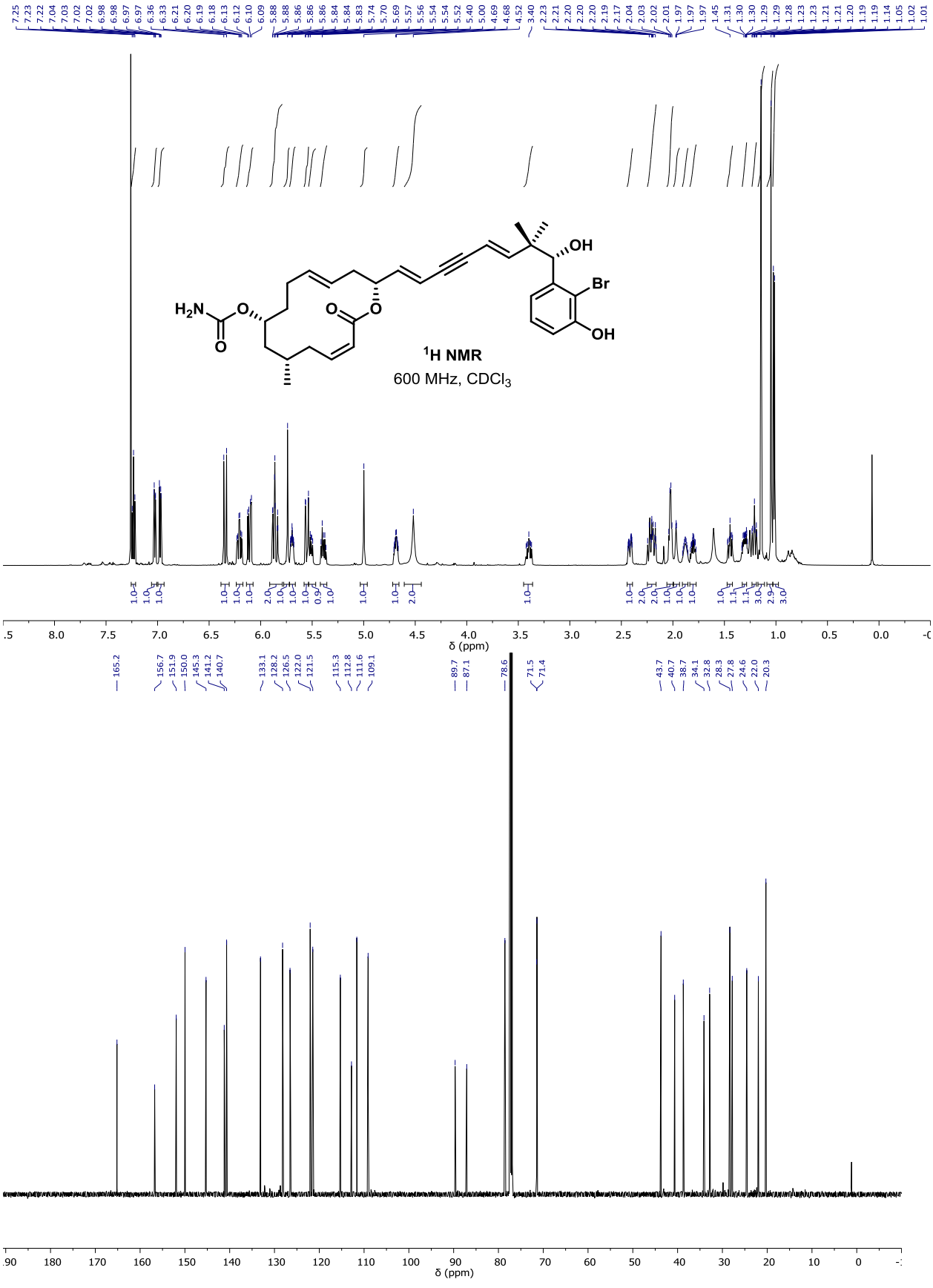
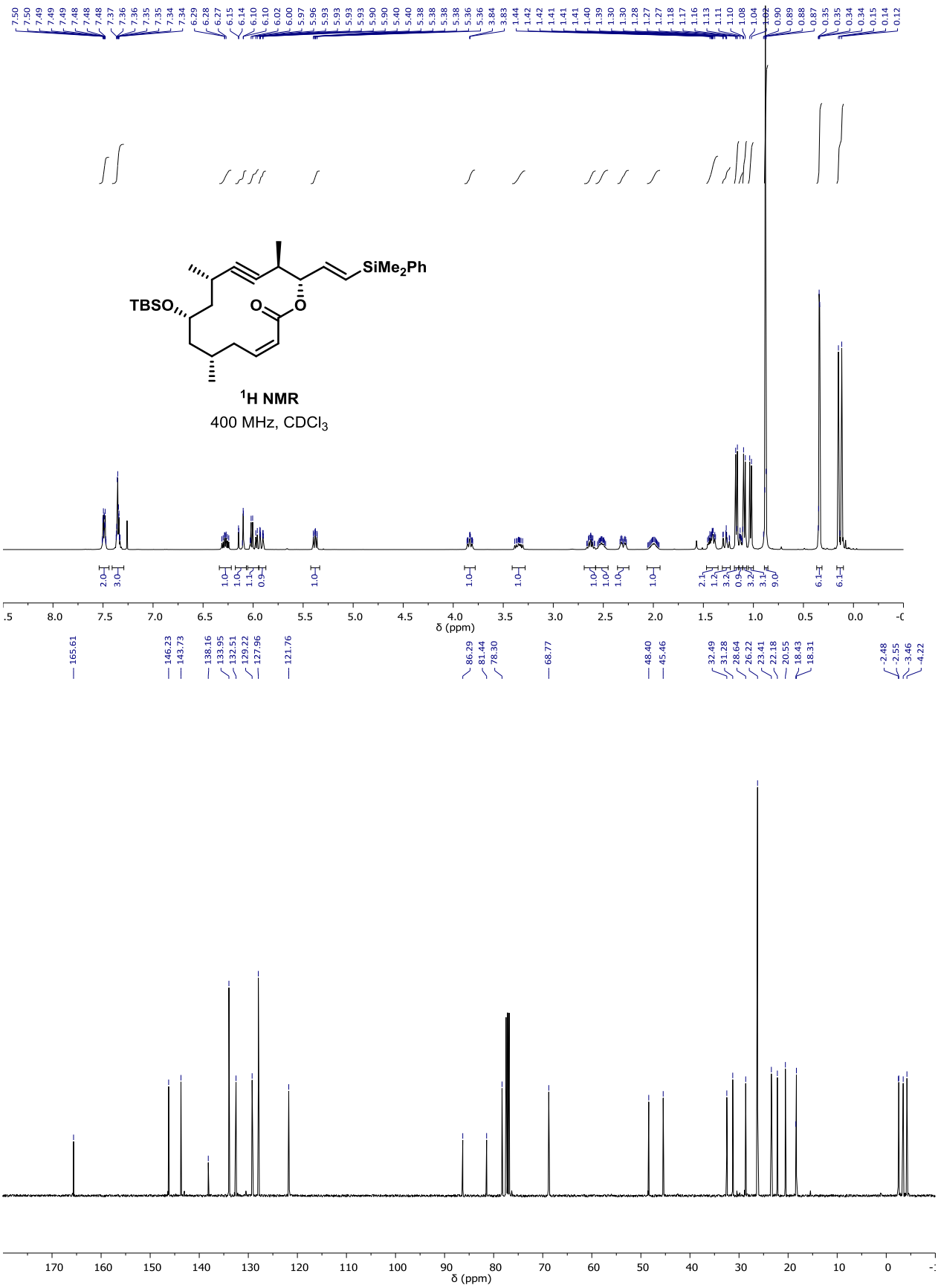


Figure 13: Structure of (*R*)-ester ***ent*-64** in the solid state.

X-ray Crystal Structure Analysis of Compound *ent*-64: C_{12} H_{15} Br O_4, M_r = 303.15 g · mol^{-1}, colorless prism, crystal size 0.14 x 0.14 x 0.06 mm^3, trigonal, space group $P3_221$, a = 7.7233(3) Å, b = 7.7233(3) Å, c = 35.5443(15) Å, V = 1836.14(16) Å^3, T = 100(2) K, Z = 6, D_{calc} = 1.645 g·cm^3, λ = 1.54178 Å Å, μ(*Cu-K*$_\alpha$) = 4.609 mm^{-1}, Gaussian absorption correction (T_{min} = 0.50, T_{max} = 0.77), Bruker-AXS-X8-Proteum diffractometer, 3.731 < θ < 67.520°, 82523 measured reflections, 2203 independent reflections, 2203 reflections with $I > 2\sigma(I)$, Structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.024 [$I > 2\sigma(I)$], wR_2 = 0.089, 161 parameters, absolute structure parameter = –0.001(9), H atoms riding, S = 0.905, residual electron density 0.3 (0.57 Å from C12)/ –1.1 e Å^{-3}. **CCDC-1540317**.

9.2 Spectra of Selected Compounds

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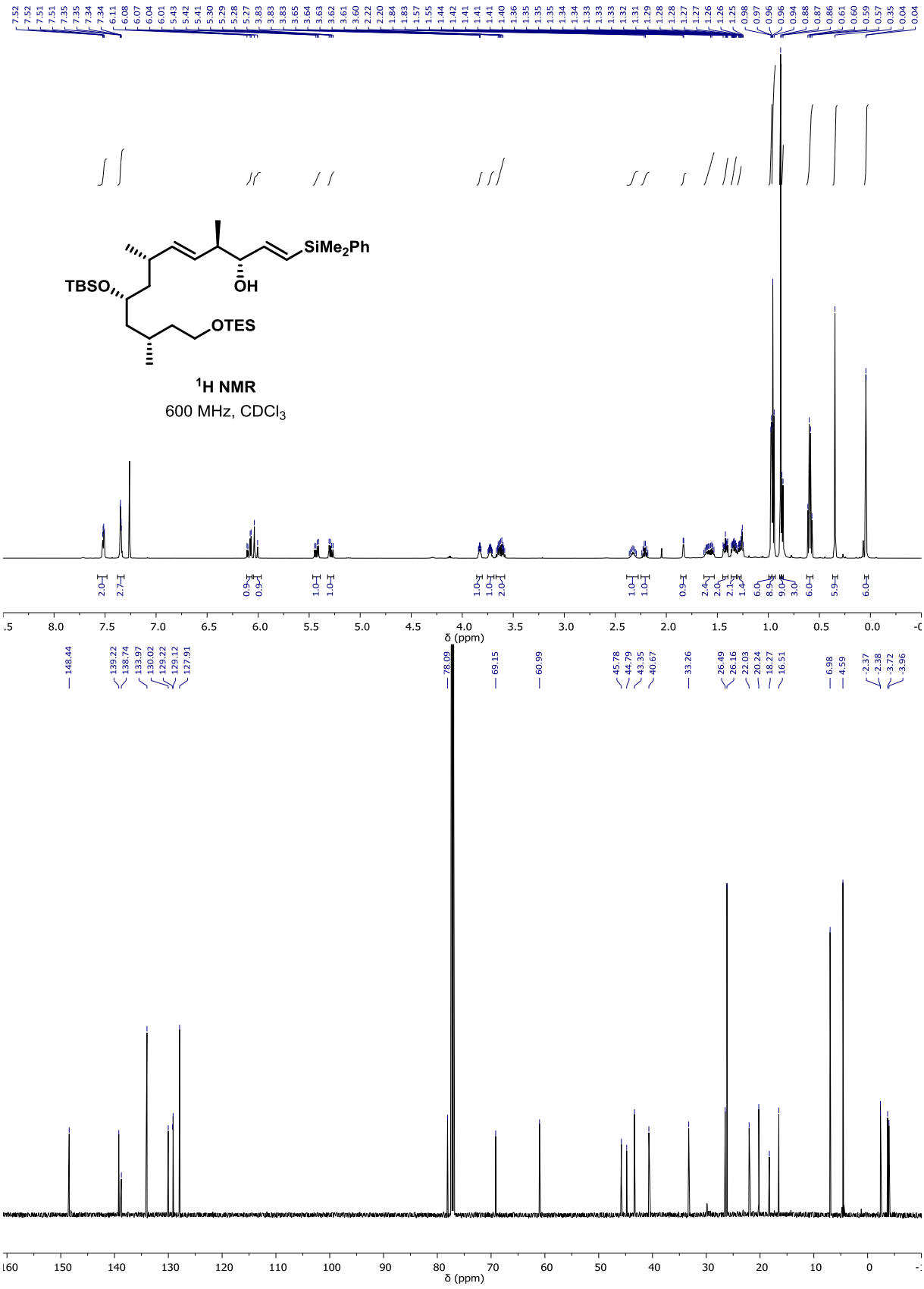
TBSO
O
O
1H NMR
400 MHz, CDCl3
δ (ppm)
δ (ppm)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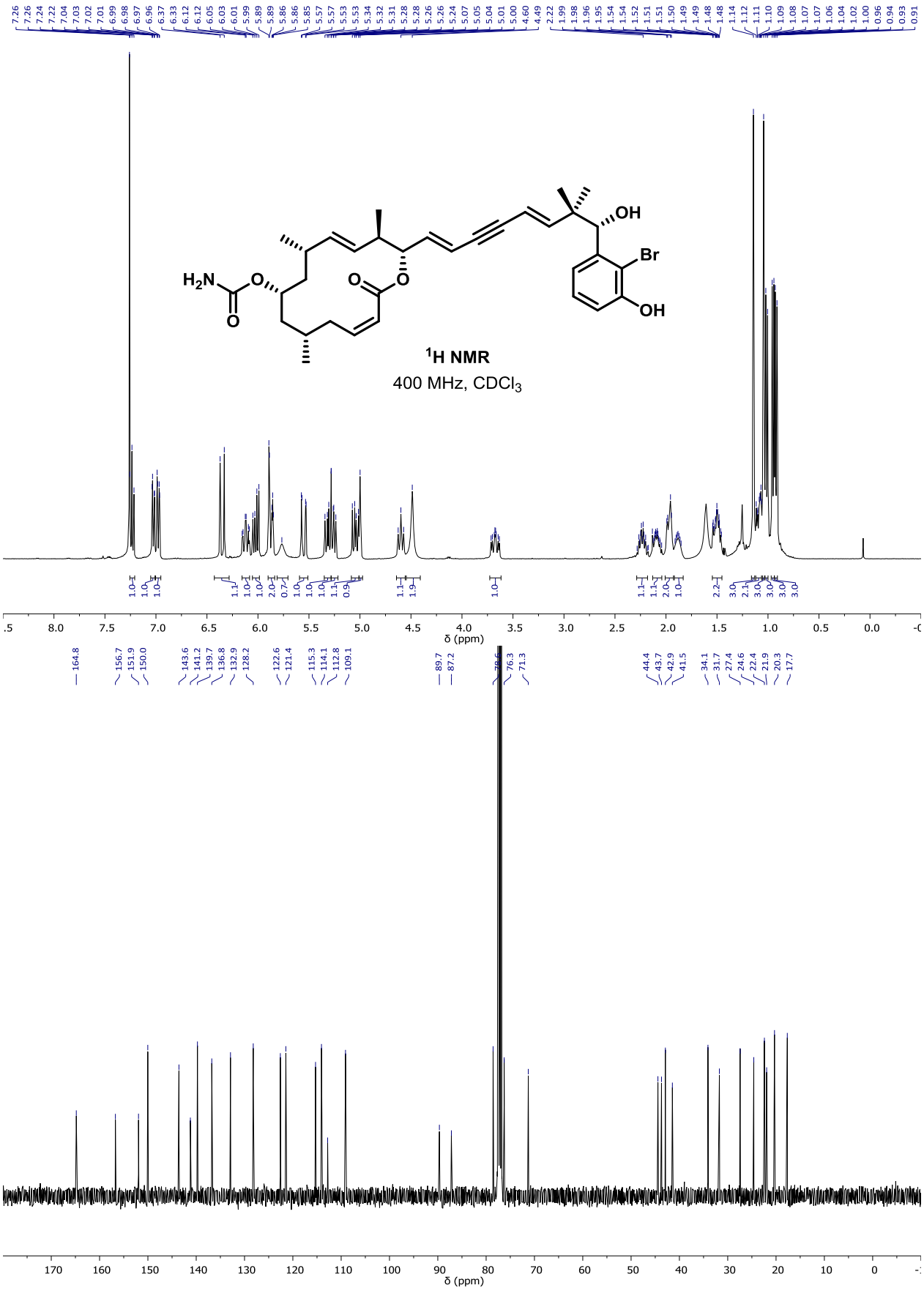
TBSO
OH
OTES
1H NMR
600 MHz, CDCl3
δ (ppm)
δ (ppm)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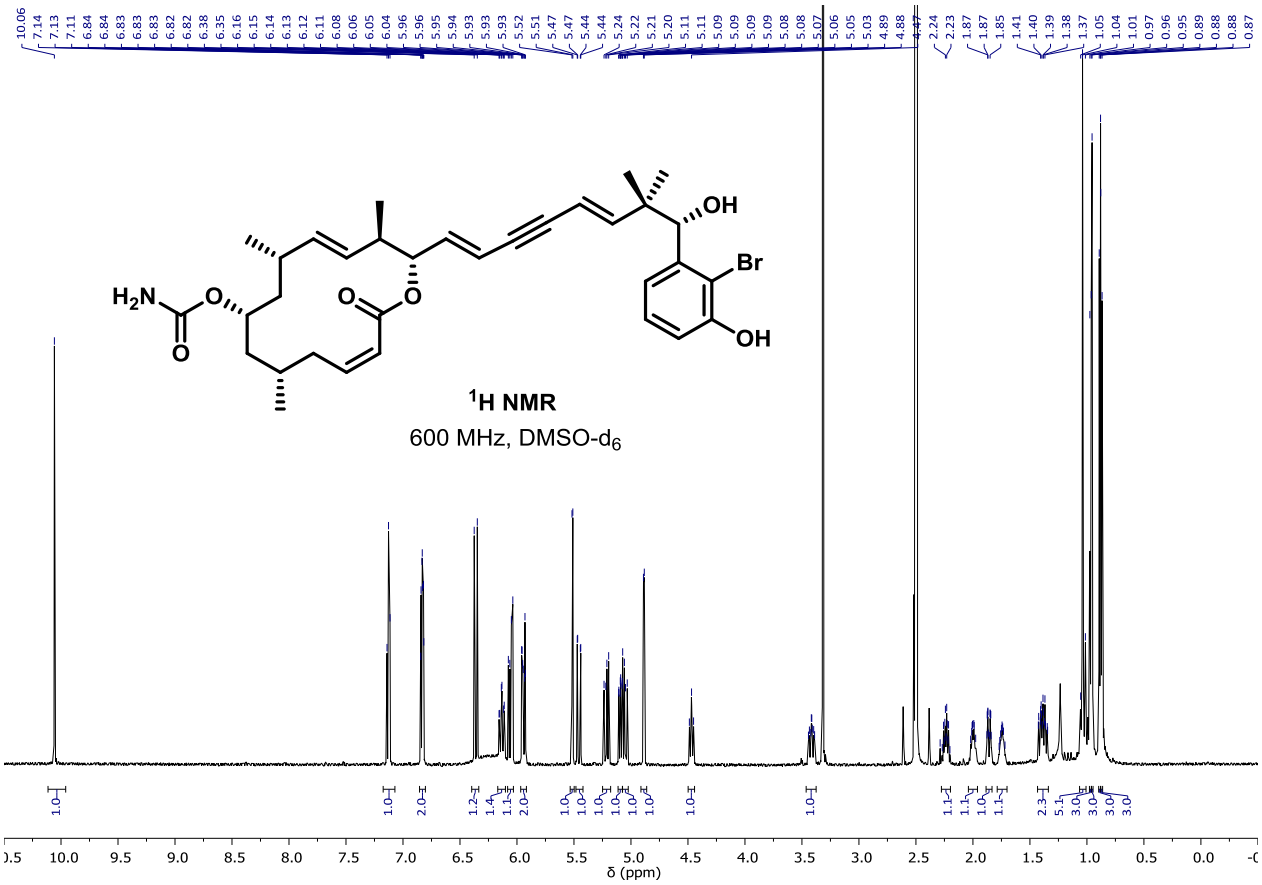
Br
OH
H_2N
O
O
O
O
^{1}H NMR
400 MHz, $CDCl_3$
δ (ppm)
δ (ppm)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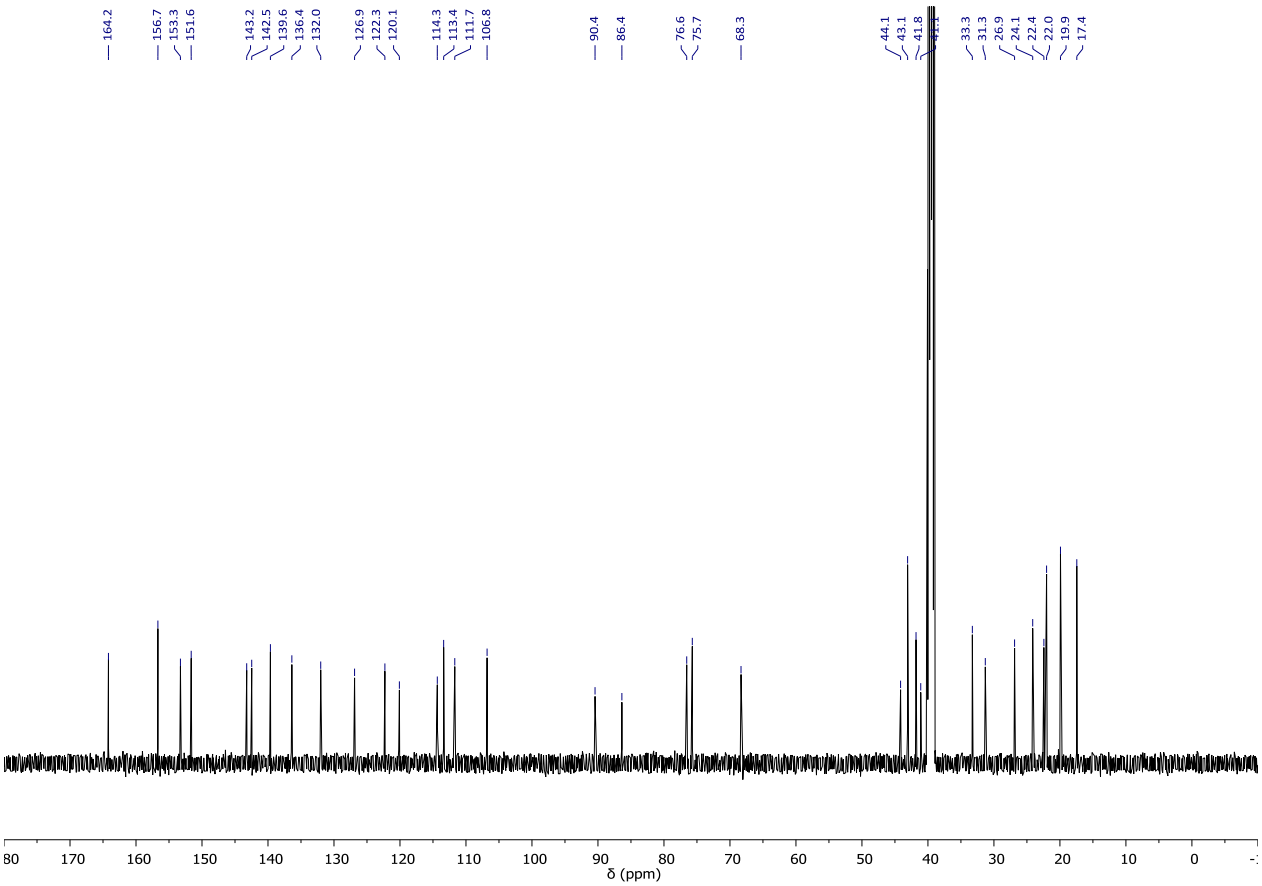
Br
OH
H_2N
O
O
O
O
^{1}H NMR
600 MHz, DMSO-d_6
δ (ppm)


δ (ppm)