Max-Planck-Institut
für Kohlenforschung

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dortmund

# Ringschluss-Alkin-Metathese / Semihydrierung von Eninen:

# Totalsynthesen von Leiodermatolide und Mandelalide A

## Dissertation

zur Erlangung des akademischen Grades eines

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vorgelegt von

**Jens Willwacher**

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in Leverkusen

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Hiermit versichere ich, dass ich die eingereichte Dissertation sebstständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, sowie Zitate kenntlich gemacht habe.

Mülheim an der Ruhr, 22.01.2015 Jens Willwacher

(Ort, Datum) (Unterschrift)

1. Berichterstatter: Prof. Dr. Alois Fürstner
2. Berichterstatter: Prof. Dr. Norbert Krause

Die vorliegende Arbeit entstand unter Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Oktober 2011 bis Januar 2015 am Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr. Teile dieser Arbeit wurden bereits in folgenden Beiträgen veröffentlicht:

"Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide"
J. Willwacher, N. Kausch-Busies, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 12041.

"Catalysis-based Total Synthesis of Putative Mandelalide A"
J. Willwacher, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, 53, 4217.

"Synthesis, Molecular Editing, and Biological Assessment of the Potent Cytotoxin Leiodermatolide"
D. Mailhol, J. Willwacher, N. Kausch-Busies, E. E. Rubitski, Z. Sobol, M. Schuler, M.-H. Lam, S. Musto, F. Loganzo, A. Maderna, A. Fürstner, *J. Am. Chem. Soc.* **2014**, 136, 15719.

Die Arbeiten erfolgten zum Teil in enger Zusammenarbeit mit Dr. Nina Kausch-Busies und Dr. Damien Mailhol (Kapitel 2); sowie Dipl. Ing. Berit Heggen und M. Sc. Katharina Holthusen (Kapitel 3). Um eine umfassende Beschreibung der Ergebnisse zu ermöglichen, wurden deren Ergebnisse in die Diskussion aufgenommen. Die von diesen Mitarbeitern erzielten Ergebnisse sind an den entsprechenden Stellen gekennzeichnet.

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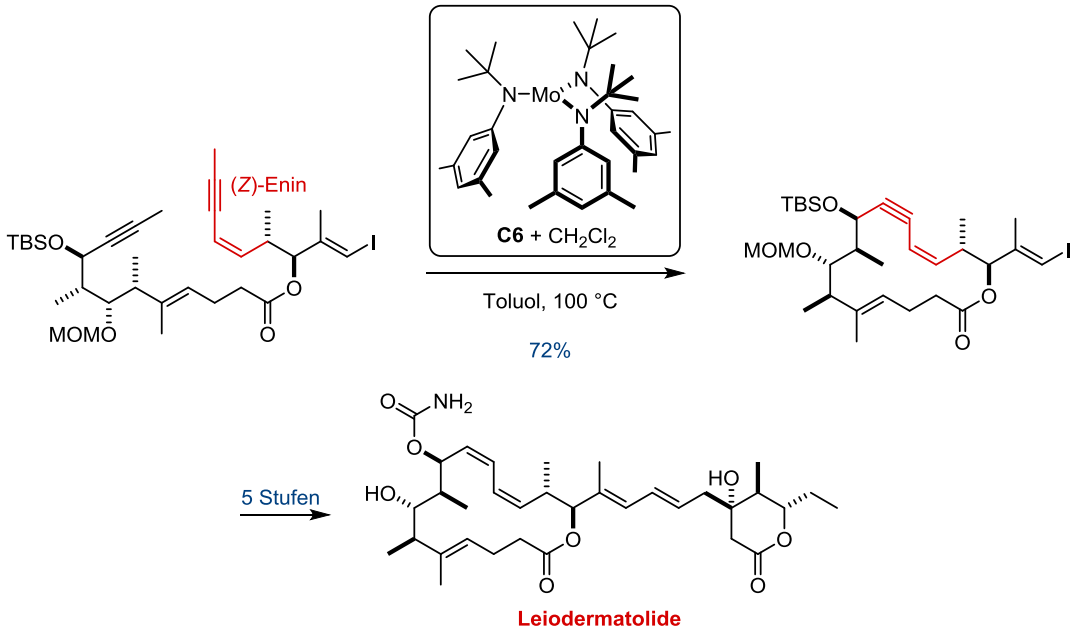
## Inhalt

Konjugierte Alkene sind allgegenwärtige Motive in Naturstoffen marinen Ursprungs, die die pharmazeutische Industrie auch weiterhin mit Leitstrukturen für die Entwicklung von neuen Arzneimitteln versorgen. Solche mehrfach-ungesättigten Doppelbindungen in einem makrozyklischen Gerüst stellen den synthetischen Chemiker vor eine große Herausforderung, da der selektive Zugang per Alkenmetathese bis dato nicht möglich ist.

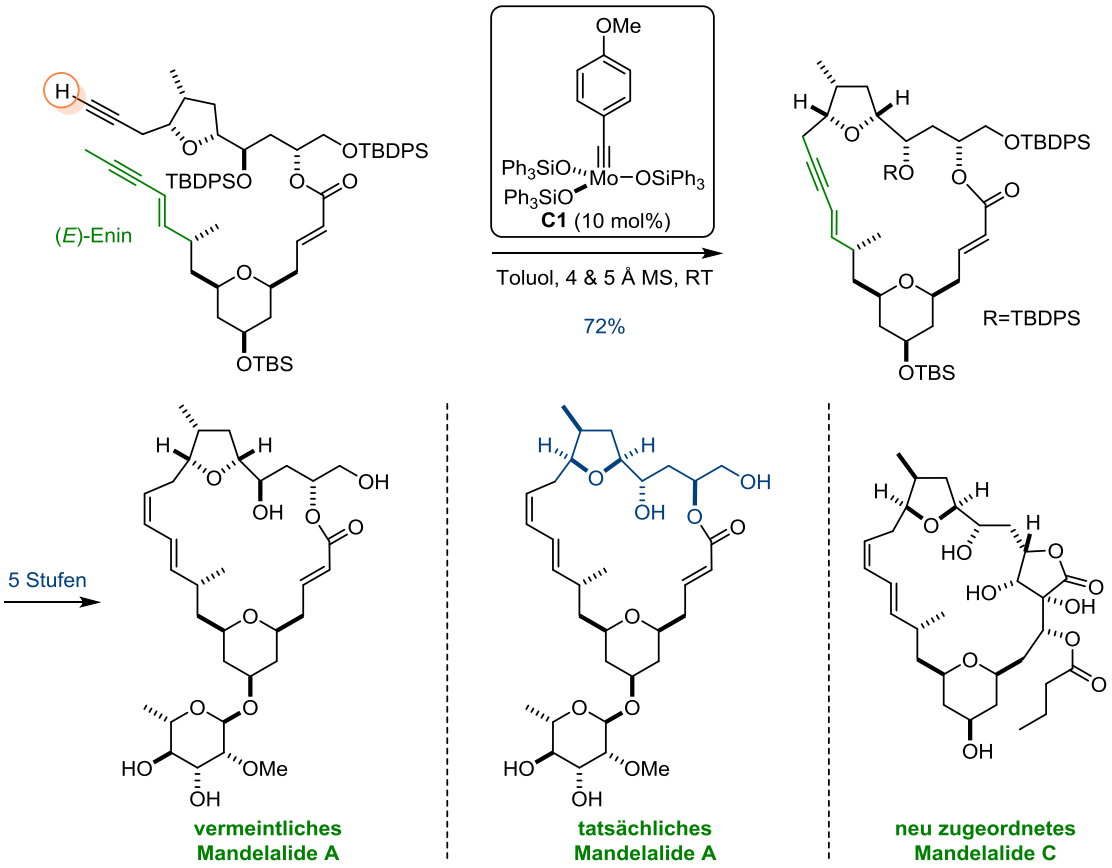
Die Ringschluss-Alkinmetathese (RCAM) bietet eine nunmehr unverzichtbare Alternative, da sie nicht nur eine Vielzahl funktioneller Gruppen toleriert, sondern auch strikt zwischen Alkinen und Alkenen zu unterscheiden vermag. Im Rahmen dieser Arbeit wurde die RCAM mit der *syn*-selektiven Semihydrierung kombiniert, was als Schlüsselsequenz für die Synthese der makrozyklischen Naturstoffe Leiodermatolide und Mandelalide A diente.

Leiodermatolide, ein Naturstoff aus dem Tiefseeschwamm *Leiodermatium*, zeigte in ersten Studien hohe antimitotische Aktivität ohne mit isoliertem Tubulin zu wechselwirken, was einen neuen Wirkmechanismus verspricht. Obwohl die Struktur von Leiodermatolide nicht vollständig aufgeklärt war, wurde eine Totalsynthese initiiert.




Der Naturstoff konnte im Rahmen dieser Arbeit erfolgreich synthesiert werden; ebenso gelang die Strukturzuordnung. Eine überarbeitete Synthese wurde anschließend entwickelt um die verbleibenden Schwachstellen der ersten Generation auszumerzen. Mit dieser verbesserten Route konnten sowohl signifikante Mengen des Naturstoffs als auch einige Analoga hergestellt werden, die für eine eingehende biologische Untersuchung genutzt wurden. Die bisher erhaltenen Ergebnisse sprechen für einen neuartigen Wirkmechanismus via "centrosome declustering".

Im Anschluss wurde die Synthese des Naturstoffs Mandelalide A verfolgt. Neben der noch komplexeren Struktur war die vermeintlich hohe biologische Aktivität erneut ein ausschlaggebendes Auswahlkriterium.



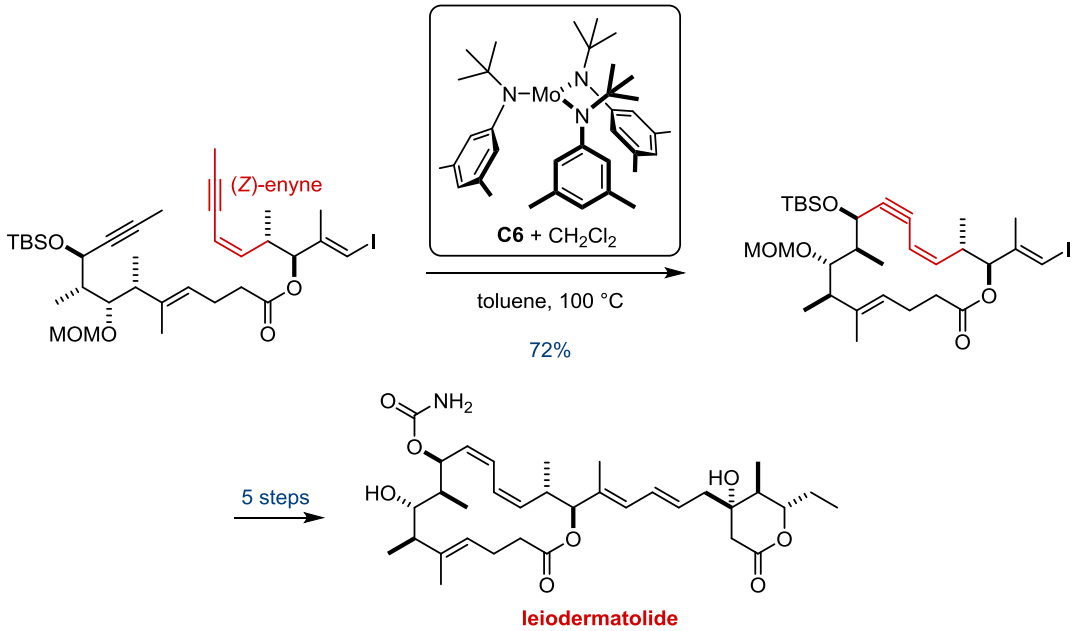

Nach der erfolgreichen Synthese aller benötigten Fragmente und deren Kupplung konnte, zum ersten Mal im Rahmen einer Naturstoffsynthese, ein terminales Alkin in der RCAM erfolgreich umgesetzt werden, vorausgesetzt das Molybdän-Alkylidin **C1** wurde als Katalysator eingesetzt. Das gebildete zyklische Enin wurde im Anschluss semi-reduziert und weiter in die angestrebte Struktur umgewandelt. Es stellte sich heraus, dass die Struktur des Naturstoffs falsch zugeordnet worden war; durch die Synthese des Isomers mit invertiertem Nordfragment konnte die korrekte Stereochemie aufgeklärt werden. Leider konnte die biologische Aktivität mit dem synthetischen Material nicht bestätigt werden. Trotzdem wurde das Projekt um die Synthese des verwandten Naturstoffs Mandelalide C erweitert.

## Abstract

Conjugated olefins are common motifs in natural products of marine origin, which continue to serve the pharmaceutical industry as lead structures for the development of novel drugs. Polyunsaturated sites within a macrocyclic framework pose a considerable challenge to synthetic organic chemists, since their selective assembly is not possible via the well-established olefin metathesis reaction.

Ring-closing alkyne metathesis (RCAM) offers an indispensable alternative, as it tolerates a variety of polar functional groups and the catalysts display unmet selectivity for alkynes over olefins. To further elaborate the scope of this transformation, RCAM was combined with *syn*-selective semi-hydrogenation to achieve the synthesis of the cyclodienes found in leiodermatolide and mandelalide A.

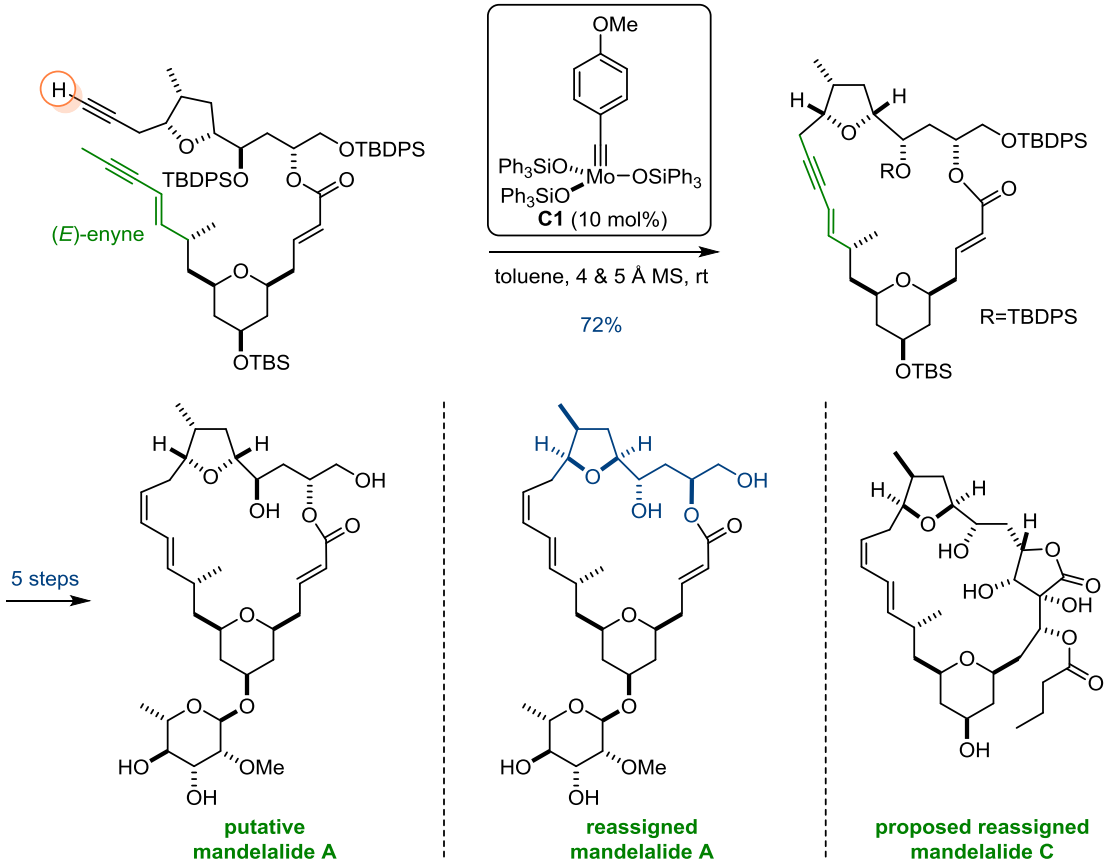
Leiodermatolide, a natural product derived from a deep-sea sponge, was chosen as a target as it displayed high antimitotic acitivity against a variety of differenct cancer cell lines without interfering with purified tubulin, thus indicating a novel mode of action. Moreover, the structure could not be fully secured by the isolation team and led us to consider two possible diastereomers.




In the event, the natural product could be successfully synthesized and its structure assigned based on subtle differences in the NMR spectra of two diastereomeric compounds. A second generation synthesis was in turn developed that addressed the remaining bottlenecks of the initial approach and features a catalytic asymmetric propargylation of a highly enolizable β-keto lactone. Substantial amounts of material and a set of analogues were thus synthesized to

allow for a deeper biological investigation. Until now, the acquired data points to centrosome declustering as the potential mode of action.

An even more challenging enyne-yne metathesis was pursued within the total synthesis of mandelalide A, a natural product isolated from a marine ascidian along with three related macrolides. Mandelalide A was chosen as the primary target for a synthetic endeavor as the most active member of the family.




After fragment synthesis and assembly, the RCAM reaction now engaged an enyne with a terminal alkyne, a structural motif that had been long beyond reach due to significant polymerization side-reactions. This was enabled by the use of the recently developed molybdenum alkylidynes bearing silanolate ligands. The resulting cycloenyne was subsequently semireduced and further transformed into the target molecule. However, the natural product had been misassigned by the isolation team, but was reassigned by inverting the whole northern fragment. Unfortunately, the promising biological activity could not be confirmed. Nevertheless, the project was extended to approach the closely related natural product mandelalide C.

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# Ring-Closing Alkyne Metathesis / Semihydrogenation of Enynes:

# Total Syntheses of Leiodermatolide and Mandelalide A

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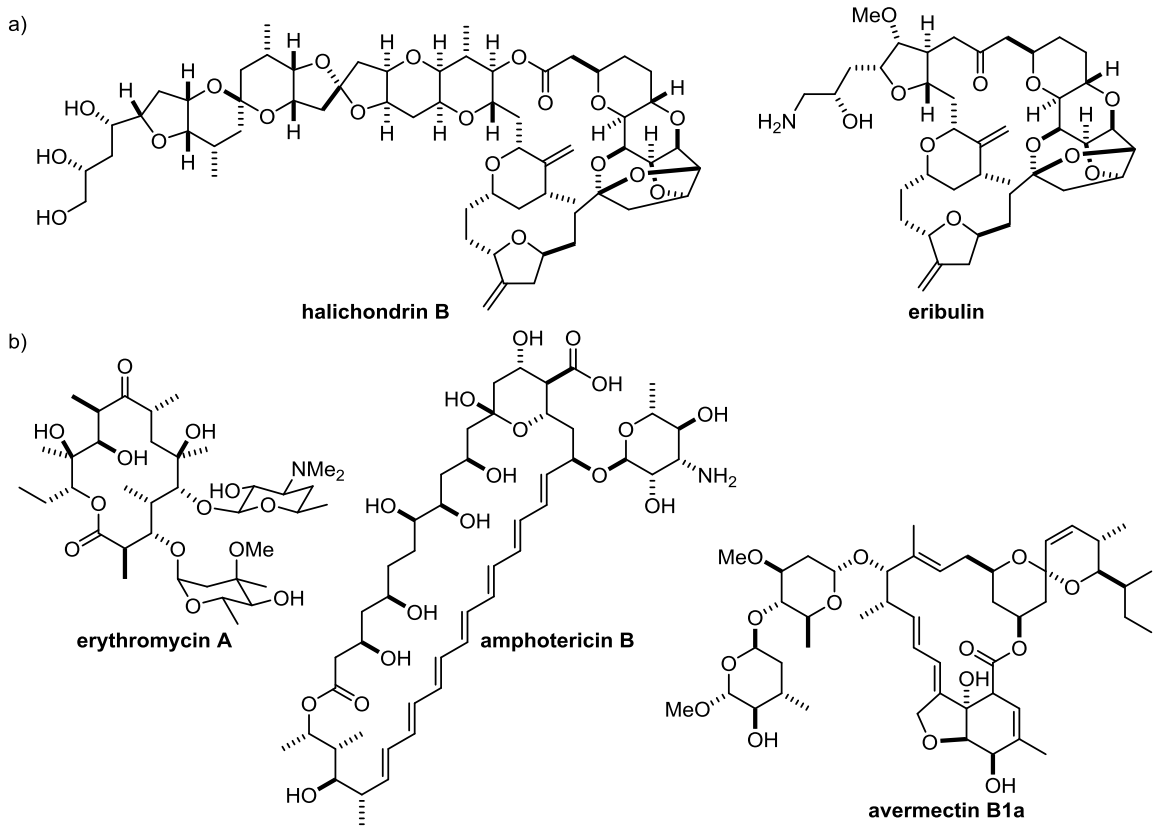
# 1 Introduction

Secondary metabolites are natural products produced by living organisms and are meant to undergo an interaction with an enzyme or a specific receptor protein.[1] The structures of such compounds can be interpreted as the result of an evolutionary process and display the outcome of a long optimization period. Therefore, these natural products often exhibit a remarkable biological activity,[2] even in completely remote contexts and are ideal starting points for drug discovery programs in the pharmaceutical industry.[3] The plethora of successfully developed and approved drugs derived from such metabolites maintains the high interest of both industrial and academic research. At the end of a discovery process, the natural product is not necessarily the most potent drug candidate, but rather a derivative thereof.[4] This is demonstrated by the textbook example of halichondrin B,[5] which was replaced during clinical evaluation by the truncated but more active synthetic congener eribulin (scheme 1.1a).[6]




*Scheme 1.1:* a) Naturally occurring halichondrin B; approved synthetic drug eribulin.
b) Selected macrocyclic polyketides with important biological activity.

The material supply from the natural sources, especially when dealing with those of marine origin, is frequently unreliable and only minute amounts of the target compound can be accessed. A modern total synthesis route should therefore be robust, scalable and hence

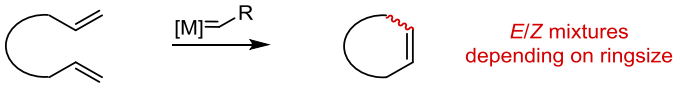
enable a steady supply of the target molecule to allow further evaluation of biological properties and record of structure activity relationships.[7]

The challenging structural motifs found in natural compounds have ever since inspired synthetic chemists toward the development of novel reactions and will likely continue to do so. Moreover, total synthesis serves as the ultimate setting for the testing and application of novel methodologies. The numerous polar functional groups and complex architecture found in natural products offer a tremendous challenge to most catalysts.

Finally, it is worth mentioning that, even in the age of ever more sophisticated spectroscopic methods, structure misassignments regularly come about.[8] In most cases, total synthesis has served as the ultimate tool to prove a proposed structure or to reassign the stereochemistry or even connectivity of a natural product.

Macrocyclic polyketides are an important class of natural products since they often display impressive biological activity.[9] Prominent examples are the anticancer agent epothilone (see chapter 2.10, scheme 2.52),[10] the approved antibiotic drug erythromycin,[11] the antifungal drug amphotericin B[12] and the insecticide and antihelmithic agent avermectin (see scheme 1.1b).[13]

Conjugated double bonds are common motifs of such macrocyclic compounds and occur with greater frequency than isolated double bonds for ring sizes between 16 and 24.[14] The selective assembly of these polyene units poses a considerable challenge for ring-closing olefin metathesis (RCM) reaction, which has become the method of choice for the synthesis of cycloolefins due to the high functional group tolerance, easy handling and reliability of Grubbs' ruthenium alkylidene complexes.[15] However, one considerable drawback of this approach is the lack of stereocontrol over the constructed double bond, especially during the formation of medium-[16] or macrocyclic rings (scheme 1.2).[17]

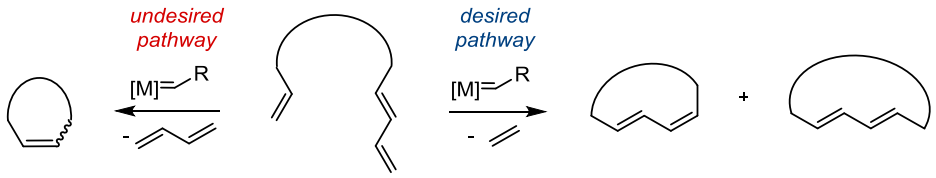



*Scheme 1.2:* General drawback of ring-closing olefin metathesis (RCM).

In general, the (*E*)-isomer is thermodynamically more stable and prevails in the product mixture over the corresponding (*Z*)-double bond;[18] yet, the product distribution can be influenced by the constraints of the macrocycle and is difficult to predict. At the outset of this thesis, (*Z*)-selective olefin metathesis was immature and far from being applicable to the synthesis of complex natural products.[19] During the course of this investigation, impressive progress has been made;[20] however, it still remains doubtful that this strategy would currently be applicable to the ring closing diene metathesis as needed within the natural

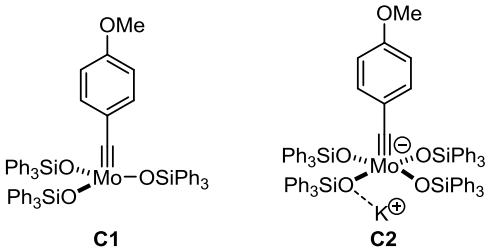
product syntheses addressed herein.[21] Moreover, (*E*)-selective olefin metathesis catalysts are not known to date and the metatheses of unhindered, non-polarized sites likely produce mixtures of isomers.

A second drawback comes into play, when one considers the construction of diene motifs. Not only does the olefin geometry need to be controlled, the catalyst must further differentiate between the different unsaturated sites to impede undesired ring-contraction reactions that are generally observed for such systems. Nevertheless, few successful outcomes of diene metathesis within the context of complex natural product synthesis are known.[22] For example, introducing a silyl substituent on the inner olefin of the diene was shown to enable selective diene-ene metathesis and produces selectively the (*E*,*Z*)-diene after protodesilylation.[23]



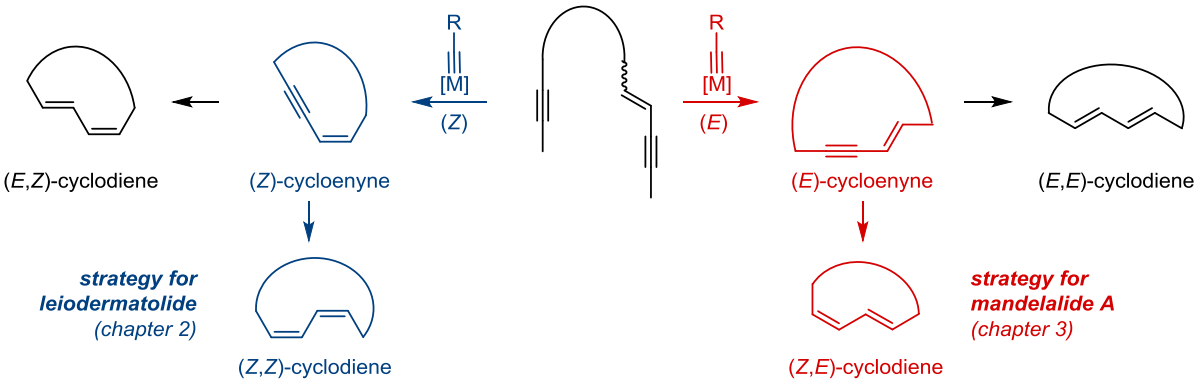

*Scheme 1.3:* General drawback of ring-closing olefin metathesis with dienes.

Recourse to alkyne metathesis allows these problems to be easily fixed.[17, 24] With the advent of the latest generation of alkyne metathesis catalysts such as **C1** and **C2** that combine user-friendliness, high activity and exceptional functional group tolerance, a competitive alternative to olefin metathesis has been established.[25] Like most metal alkylidyne complexes, these catalysts were shown to chemoselectively activate carbon-carbon triple bonds in the presence of olefins and enabled the construction of isolated and conjugated cycloalkyne units of highly functionalized products.[26]




*Scheme 1.4:* Recently developed alkyne metathesis catalyst.[25]

After successful ring-closing alkyne metathesis (RCAM), cycloenynes were shown to be selectively transformed into cyclodienes with complete control over the double bond geometry.[27] Previously, this approach was elegantly adopted to construct the macrocyclic frameworks of lactimidomycin[28] and latrunculin A;[29] yet, further applications were deemed desirable.




*Scheme 1.5:* Selective construction of diene motifs within a macrocyclic framework by RCAM / semireduction.

The application of ring closing alkyne metathesis followed by semi-hydrogenation for the selective generation of diene motifs within a macrocyclic polyketidic natural product will be described in the following chapters. In particular, employment of this strategy should produce the (*Z*,*Z*)- or (*Z*,*E*)-dienyl units within the total syntheses of leiodermatolide (scheme 1.5, blue) and mandelalide A (red), respectively. The results obtained during these synthetic endeavors are disclosed below.

# 2 Total synthesis of leiodermatolide

*Remark:* This project was initiated by postdoctoral researcher Dr. Nina Kausch-Busies and parts of this research were carried out in close collaboration. After completion of the first generation synthesis, the synthesis of leiodermatolide analogues and the development of a second generation synthesis was carried out in close collaboration with postdoctoral researcher Dr. Damien Mailhol. Their contributions are gratefully acknowledged and are indicated by references 42, 55 and 57.

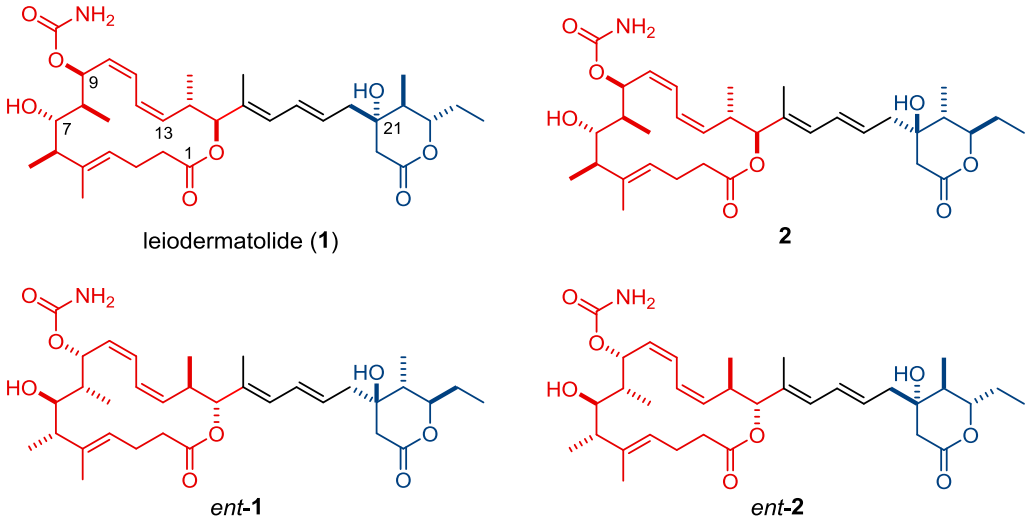
## 2.1 Isolation, structural discussion and biological activity

Leiodermatolide (**1**) was first detected in a *Leiodermatium sp.* off Wemyss Bight, Bahamas at a depth of 618 m. After further exploration, it was found in about 10-fold higher concentration in a *Leiodermatium sp.* at a depth of 401 m on the Miami Terrace, off Ft. Lauderdale.[30] Extraction of the collected sponge (1037 g) and chromatographic purifications along with bioassay-guided fractionation allowed 11.8 mg of the pure sample to be obtained as an amorphous white solid, which corresponds to 0.0011% wet weight. [30]

The structure was elucidated by careful analysis of the 2D-NMR spectra in combination with theoretical considerations (comparative DFT GIAO NMR shift calculations) and molecular modeling.[31] This ensured the assignment of the relative configuration of the macrocyclic portion (scheme 2.1, red) as well as the δ-lactone fragment (blue). Nevertheless, the

segregation of these two parts through a pentadienyl spacer (black) prohibited their stereochemical correlation. Therefore, two possible diastereomers of leiodermatolide had to be considered as the actual structure (**1** and **2**). Moreover, the absolute configuration was uncertain, tracing the structure of the natural compound back to four possible stereoisomers.

Overall, leiodermatolide possesses nine stereogenic centers, six of which are contained within the macrocyclic skeleton, while the remaining three can be found within the δ-lactone. The only quaternary stereogenic center of the molecule is a tertiary alcohol at C.21 that connects the δ-lactone with the (*E*,*E*)-configured dienyl linker. The pseudo-axial attachment at C.21 is quite unusual and has been questioned in the past.[32]




*Scheme 2.1*: The four possible structures of leiodermatolide.

Within the 16-membered macrocycle lies a (*Z*,*Z*)-diene between C.10 and C.13 along with an isolated (*E*)-configured trisubstituted double bond between C.4 and C.5. Three protic functional groups are found on the carbon skeleton of **1**; noteworthy is the carbamate at C.9, which is in close proximity to the secondary alcohol at C.7 but remote from the tertiary alcohol at C.21.

An initial bioassay revealed that leiodermatolide acts as an antimitotic agent and is strongly cytotoxic against several cancer cell lines. The tested cell lines along with the obtained $IC_{50}$ values are depicted in table 2.1. The reduced cytotoxicity towards Vero monkey kidney cells (entry 6) was interpreted as an indication of selectivity for malignant over healthy tissue.

Moreover, cell cycle analysis of the A549 and PANC-1 cell lines showed an arrest at the G2/M transition, which is a common effect of several known tubulin poisons.[31] Whereas no changes with interphase cells were observed, leiodermatolide caused abnormal spindle formation in mitotic cells at low two-digit nanomolar concentrations.

*Table 2.1:* Cytotoxicity of leiodermatolide as reported by the isolation team.[30-31]

| entry | cell line | $IC_{50}$ /nM |
|---|---|---|
| 1 | A549 lung adenocarcinoma | 3.3 |
| 2 | PANC-1 pancreatic carcinoma | 5.0 |
| 3 | DLD-1 colorectal carcinoma | 8.3 |
| 4 | NCI/ADR-Res ovarian adenocarcinoma | 233 |
| 5 | P388 murine leukemia | 3.3 |
| 6 | Vero monkey kidney | 211 |

However, no noteworthy effect on purified tubulin could be detected *in vitro*, even at concentrations as high as 20 µM.[31] This observation is remarkable since all approved drugs interfere with microtubule assembly upon contact with the target protein; the ultimate consequence is cell-cycle arrest, which eventually causes cell death. It was concluded that **1** acts through a distinct mechanism when compared to well-established antimitotic agents such as the taxanes, the vinca alkaloids vincristine, vinblastine and vindesine, the epothilones and discodermolide (see chapter 2.10).[33] The severe side-effects of these compounds and the development of drug resistances are the reasons for the need of alternative drugs that are ever more selective and effective.[34]

With this in mind, leiodermatolide (**1**) appeared to be an ideal target since a divergent total synthesis based on ring-closing alkyne metathesis would

(1) allow both stereoisomers of leiodermatolide to be synthesized and the structure of the natural product to be assigned,

(2) open a sustainable and reliable path to significant amounts of material required for additional biological tests, and

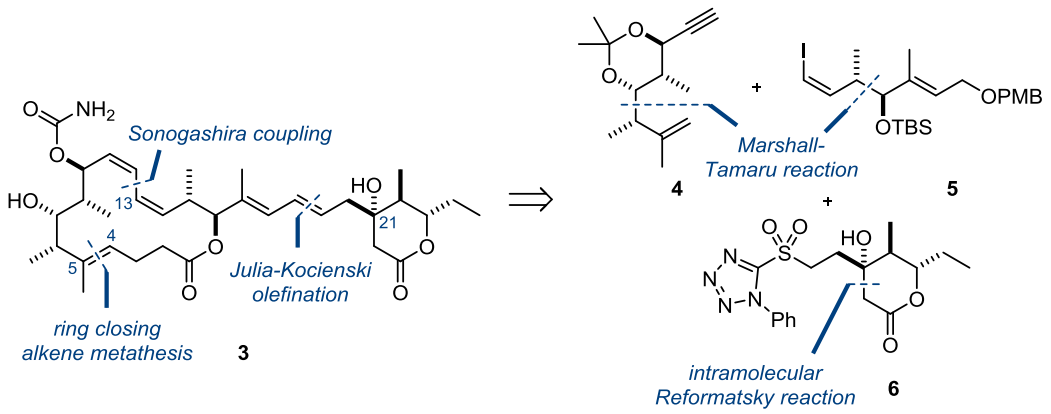
(3) provide a challenging setting for the application of a RCAM for the synthesis of the (*Z*,*Z*)-diene within the macrocyclic segment of **1**.

## 2.2 Previous synthetic approaches by other groups

Due to the interesting structural and biological features, leiodermatolide attracted the interest of several research groups. At the outset of this thesis, the groups of Prof. Maier and Prof. Paterson had already published their results describing synthetic studies towards a total synthesis of **1**. Their strategies as well as the lessons learned from these reports are outlined below.

The initial publication from Maier and co-workers[32] features fragment syntheses for the macrocycle and the δ-lactone region. Since only the flat structure of leiodermatolide was depicted in the isolation patents,[30] the relative stereoinformation was obtained from the

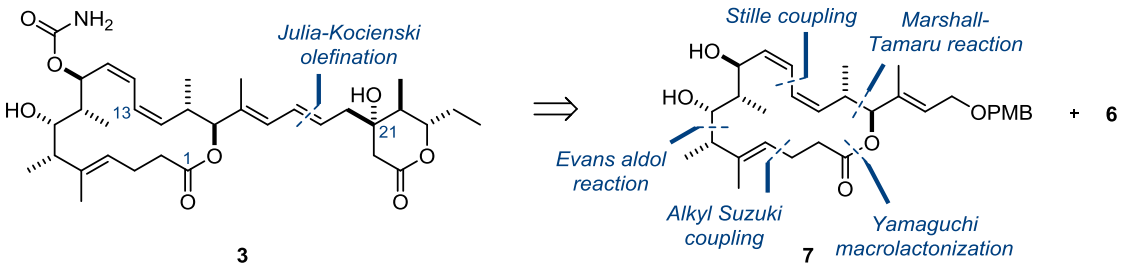
webpage of the isolation team. However, this structure (scheme 2.2) was later corrected to be as drawn in scheme 2.1.[31]




*Scheme 2.2:* Maier's initial strategy for the synthesis of a leiodermatolide isomer.[32]

Their key disconnection relied on a ring closing alkene-metathesis (RCM) reaction of the trisubstituted alkene at C.4 / C.5 for the closure of the macrocycle and a Sonogashira coupling between C.12 and C.13 to join the two fragments **4** and **5** (scheme 2.2). Although it was later shown that the two fragments could be fused and semi-reduced to give the (*Z*,*Z*)-diene, the RCM failed under a variety of conditions.[35] The synthesis of the δ-lactone **6** was envisioned to proceed via an intramolecular Reformatsky reaction, which, in the event, yielded only the wrong diastereomer with the side chain attached in the pseudo-equatorial position at C.21. Moreover, the sulfone failed to undergo the projected Julia-Kocienski olefination for the creation of the required dienyl linker, even with simple aldehydes.[36]

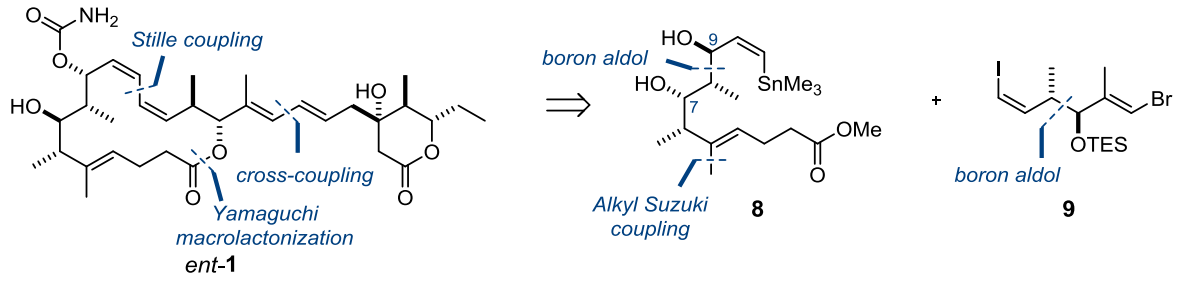
A second approach by Maier *et al.* based on a Stille fragment coupling and Yamaguchi macrolactonization allowed the macrocyclic segment **7** to be synthesized in 26 steps along the longest linear sequence.[37] Yet, no attempt was made to install the missing carbamate functionality or to attach the δ-lactone fragment **6**.




*Scheme 2.3:* Second generation approach by Maier culminating in a synthesis of the macrocyclic core of **3**.[37]

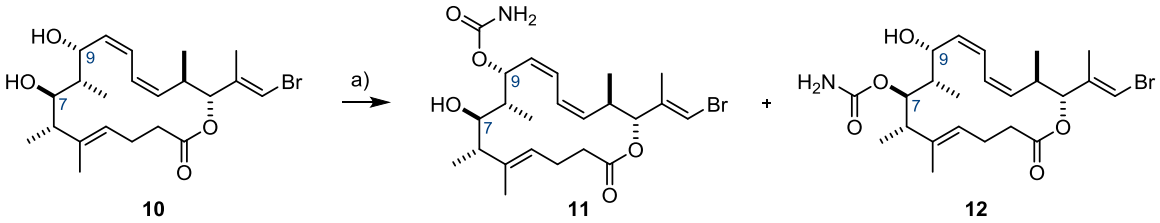
A similar strategy based on Stille fragment coupling and Yamaguchi macrolactonization was independently pursued by the group of Paterson.[38] The stereogenic centers of the macrolide sector were mainly created by boron-mediated aldol reactions (scheme 2.4). Although no

attempt was made to prepare the δ-lactone fragment of **1**, the synthesis served as a confirmation of the predicted stereochemistry within the macrocycle.[31]




*Scheme 2.4:* Key disconnections of the synthetic strategy by the Paterson group.[38]

A result of paramount importance for the strategic considerations in the Fürstner group was the attempted carbamoylation of the unprotected macrocyclic 1,3-diol **10**. Even when performed at −78 °C, no preference for the allylic alcohol at C.9 (**11**) was observed; rather, the alcohol at C.7 (3:2 ratio of **11**:**12**, scheme 2.5) was favorably transformed into the corresponding carbamate.[38] Additionally, the observation that reactions at the C.10/C.11 double bond were difficult as long as the allylic alcohol was protected as its silyl ether turned out to be a precious hint for the synthetic adventures described below.




*Scheme 2.5:* Carbamoylation.Conditions: a) $Cl_3(CO)NCO$, $CH_2Cl_2$, −78 °C; then $Al_2O_3$, 35% **11**, 52% **12**.

Only after the completion and publication of the total synthesis by our group in 2012,[39] the Paterson group achieved the total synthesis of **1** in early 2014 with similar key steps as outlined in scheme 2.4.[40] Though finally successful, their strategy required 24 steps in the longest linear sequence and produced only 0.6 mg of the natural product.

Besides the above mentioned groups, Roush and co-workers are currently addressing a total synthesis of **1**, although no details of their strategy have been made available.[41]

## 2.3 Objectives

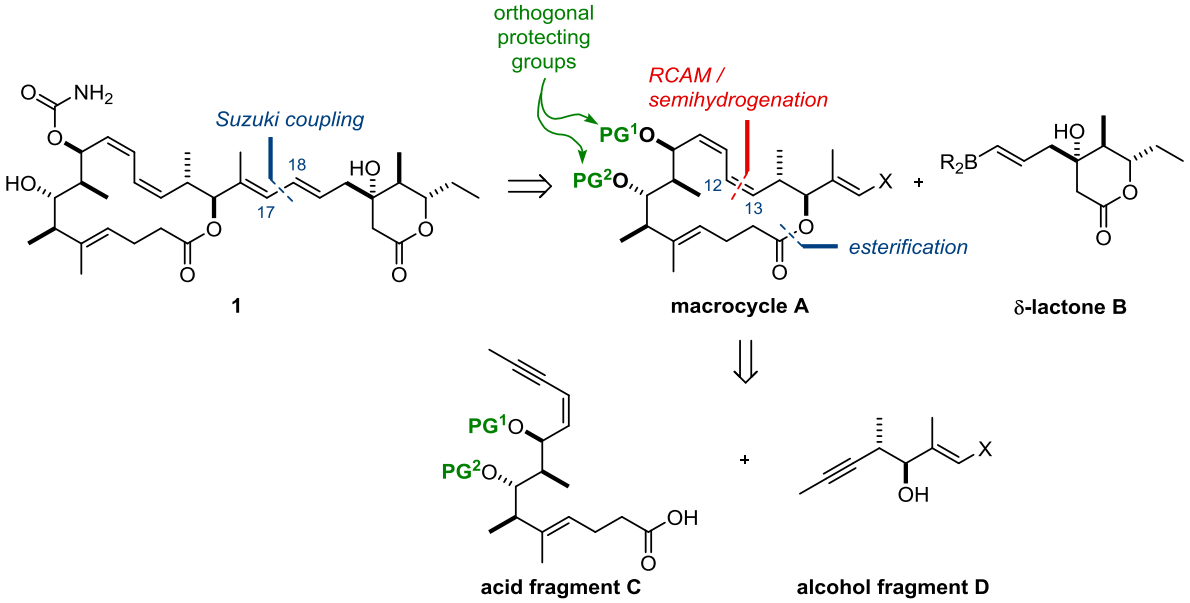
None of the synthetic studies described above addressed the problem of assigning the stereochemistry of the macrocycle in relation to the δ-lactone. Furthermore, the fascinating biological profile and the low, as well as fluctuating, natural abundance of leiodermatolide served as reasonable arguments to engage in a total synthesis program. The resulting synthetic plan should be short, efficient and flexible in order to allow both antipodal δ-lactone segments

to be attached to the macrocycle. After structure assignment and confirmation of the biological activity, such a divergent strategy would further allow the facile synthesis of analogues of the parent natural product. In light of these challenging goals, a robust and scalable synthesis was required in order to provide sufficient material for the synthesis of the natural product itself and analogues thereof.

The (*Z*,*Z*)-diene within the macrocyclic core of leiodermatolide was deemed as an ideal setting not only to apply the previously developed latest generation of ring closing alkyne metathesis catalysts, but to expand their known limits with an intriguingly challenging substrate.

## 2.4 Retrosynthetic Analysis

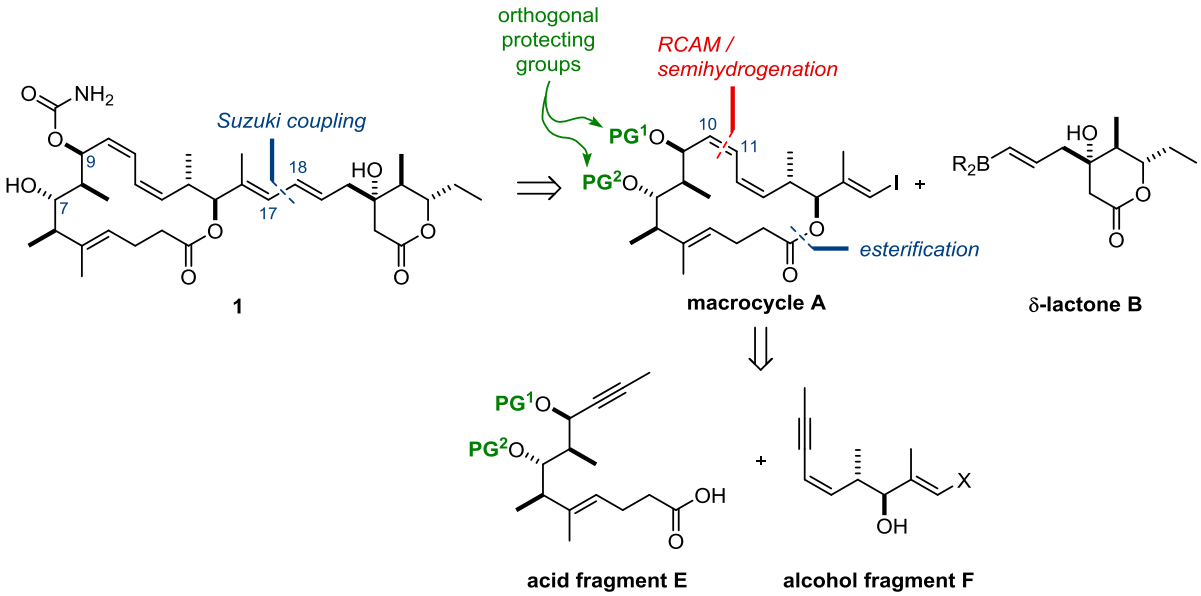
The retrosynthetic considerations were based on the desire to apply a ring closing alkyne metathesis reaction to access the macrocyclic framework. This specific transformation had proven reliable when dealing with complex natural product precursors and brings several advantages over its more famous relative, the olefin metathesis reaction. This is particularly true when a specific olefin geometry is required in the presence of other sites of unsaturation (see chapter 1). The (*Z*,*Z*)-dienyl unit was chosen as the key retrosynthetic disconnection, since this motif was impossible to generate by metathesis otherwise at the outset of this investigation. The disconnection between C.17 and C.18 would allow a late-stage Suzuki coupling of two advanced fragments, the δ-lactone fragment **B** and its macrocyclic counterpart **A**.




*Scheme 2.6:* Retrosynthetic analysis with key disconnection between C.12 and C.13.

The two olefins of the diene between C.10 and C.13 allowed for two distinct approaches. Disconnection between C.12 and C.13 (scheme 2.6, red) was initially targeted, since the resulting alkyne metathesis reaction between an enyne bearing a protected allylic alcohol **C** and an internal alkyne found in **D**, which is branched in the propargylic position, was deemed more feasible. The steric bulk around both alkynes was believed to be rather small and should therefore not pose a significant challenge for the latest generation of alkyne metathesis catalysts. Although enynes tend to be less reactive than unconjugated alkynes, their successful engagement in RCAM boded well.[28a] These promises outweighed the concern of having two fragments of different size, which clearly diminished the convergence of the route.

Alternatively, disassembly of the olefin between C.10 and C.11 (scheme 2.7, red) led to metathesis precursors bearing a protected propargylic alcohol on one side (**E**) and an enyne on the other side (**F**).




*Scheme 2.7:* Alternative retrosynthetic analysis with key disconnection between C.10 and C.11.

In this scenario, the alkyne metathesis would not only suffer from lower reactivity of the enyne, but the protected propargylic alcohol puts a severe steric and electronic demand on the alkyne metathesis reaction, since it deactivates the alkyne through σ-electron withdrawal. The propargylic alcohol could further provide a potential pathway for unwanted side reactions, since it could serve as a leaving group next to a nucleophilic Schrock alkylidyne unit that is necessarily generated during the metathesis reaction. Furthermore, it was unclear at the outset of the study whether the potentially reactive vinyl iodide unit would be tolerated during the alkyne metathesis.

Both approaches rely on an esterification of an alcohol fragment with an acid fragment to set the stage for the RCAM reaction. What is more, the difficulty to selectively carbamoylate the

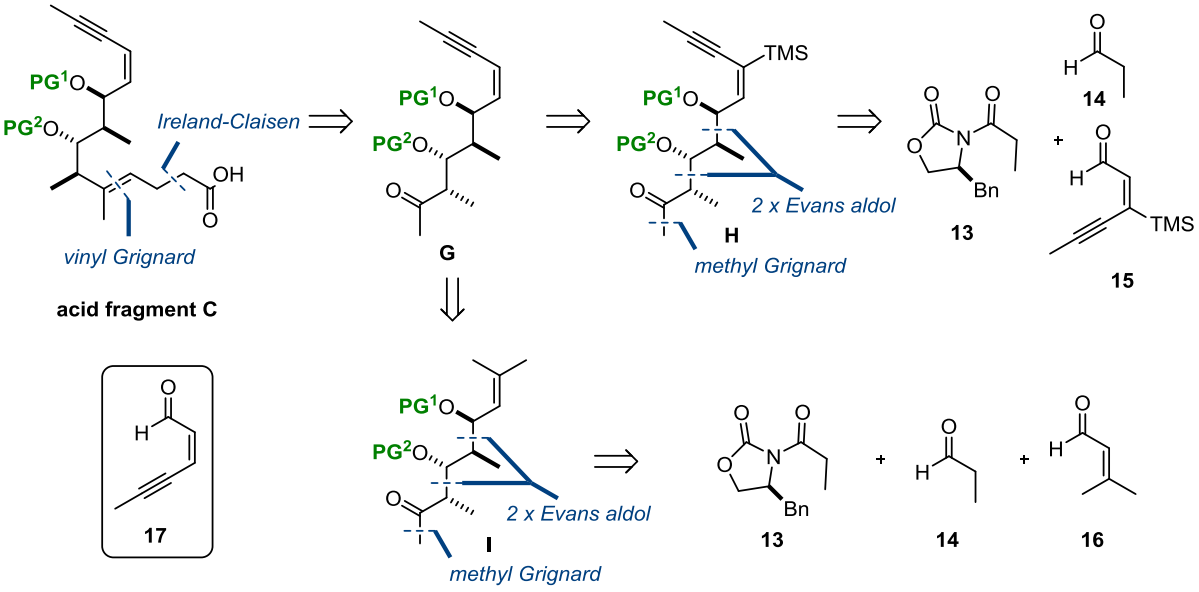
allylic alcohol at C.9 (see chapter 2.2) over the secondary alcohol at C.7 was thought to be addressed by using two orthogonal protecting groups. In the event, the deprotection of **PG$^1$** must proceed without interference of **PG$^2$**. Carbamoylation of the umasked allylic alcohol at C.9 followed by deprotection of **PG$^2$** should then release the natural product **1**.

## 2.5 The C.12 / C.13 disconnection approach[42]

All experiments described in this chapter were carried out by Dr. Nina Kausch-Busies.

### 2.5.1 Attempted Synthesis of the acid fragment C

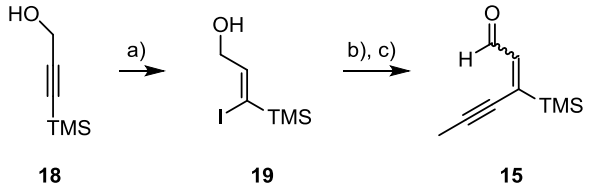
The initial approach targeted acid fragment **C** since it was believed to result in a more reliable RCAM. The carboxylate moiety of **C** would derive from an Ireland-Claisen rearrangement[43] of a tertiary allylic alcohol, which after acetylation and rearrangement as reported by Overman[44] would create both, the carbonyl functionality and the unsaturation in γ,δ-position (scheme 2.8). This is traced back to ketone intermediate **G**, which could be accessed from enyne **H** by desilylation or from allylic alcohol **I** by ozonolysis and subsequent Julia-Kocienski reaction.[45] The stereotetrad of the acid fragment could be built up by two Evans *syn*-aldol reactions followed by an *anti*-selective Evans-Saksena reduction.[46] In case of **H**, this would require the starting materials **13**, **14** and **15**, whereas in case of **I**, aldehyde **15** would be exchanged for its more stable analogue **16**.




*Scheme 2.8:* Retrosynthetic analysis of acid fragment **C**.

The use of aldehyde **17** would avoid further functional group conversions, but this compound is reported to be unstable; the isomerization of the (*Z*)-double bond to the more stable (*E*)-form occurs at temperatures above −78 °C due to conjugation to both alkyne and aldehyde.[47]

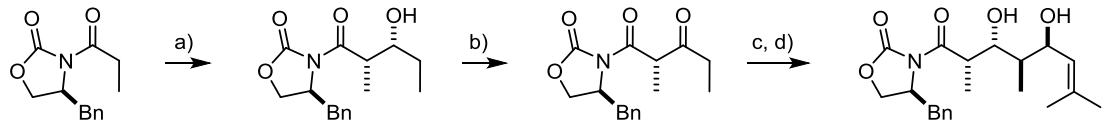
In order to explore the route via **H**, propargylic alcohol **18** was subjected to hydroalumination/iodination of the triple bond.[48] After Negishi cross-coupling to the desired enyne **19**,[49] the route via **H** was quickly abandoned since it was realized that oxidation of the corresponding alcohol precursor even under mild conditions ($MnO_2$, rt) led to substantial amounts of the isomerized aldehyde (*Z*)-**15**.




**18** **19** **15**

*Scheme 2.9:* Attempted synthesis of aldehyde **15**. Conditions: a) DIBAl-H, $Et_2O$, reflux; then $I_2$, −78 °C, 81%; b) propynyl lithium, $ZnBr_2$, $Pd(PPh_3)_4$ (8 mol%), THF, 0 °C, quant.; c) $MnO_2$, $Et_2O$, rt, *E*/*Z* = 1:1.[42]

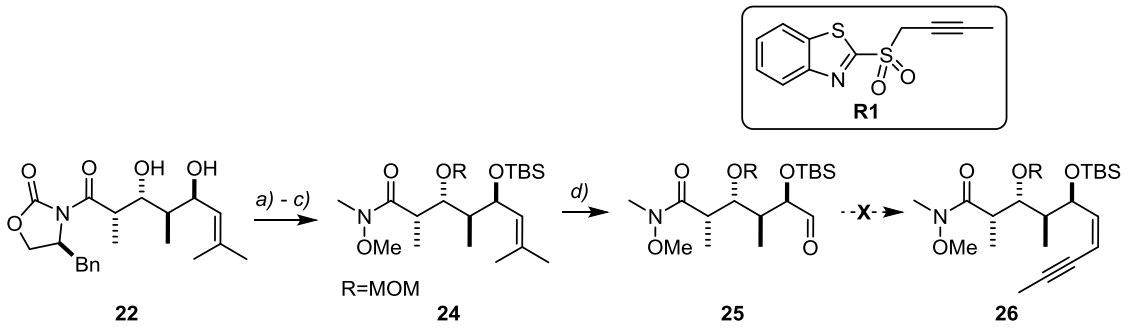
The path via dimethylacrolein (**16**) seemed more promising. The *syn*-aldol reaction of oxazolidinone **13** with propanal (**14**) proceeded as expected with high yield and selectivity. Subsequent Parikh-Doering oxidation[50] gave the literature known ketone **21**, which was engaged in a second *syn*-aldol reaction mediated by a combination of $Sn(OTf)_2$ and triethylamine.[51] After some optimization, the *anti*-reduction under Evans-Saksena conditions employing $Me_4NBH(OAc)_3$ proceeded smoothly and with high diastereoselectivity to install the fourth stereogenic center found on the rim of the macrocycle.[46]




**13** **20** **21** **22**

*Scheme 2.10:* Synthesis of diol **22**. Conditions: a) propanal (**14**), $(n\text{-Bu})_2BOTf$, $NEt_3$, $CH_2Cl_2$, −78 °C to 0 °C, 88%; b) $SO_3 \cdot Pyr$, DMSO, $CH_2Cl_2$, 0 °C, 85%; c) dimethylacrolein, $Sn(OTf)_2$, $NEt_3$, $CH_2Cl_2$, −20 °C, 72-87%; d) $Me_4NBH(OAc)_3$, AcOH, MeCN, −50 to 0 °C, 89% (92:8 d.r.).[42]

Attempted Evans-Tishchenko reactions[52] that would simultaneously discriminate between the two secondary alcohols failed under a variety of conditions due to retro-aldol side reactions. However, the crucial discrimination could be achieved by selective silylation of the allylic alcohol of diol **22** at low temperatures. After elaboration into the corresponding Weinreb amide, the remaining secondary alcohol was masked as its MOM ether to give **24**. The subsequent ozonolysis proceeded without complication and gave aldehyde **25**.

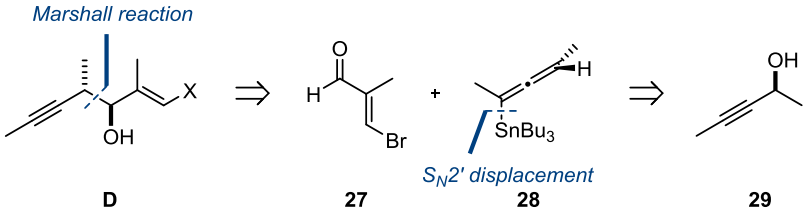



*Scheme 2.11:* Attempted synthesis of enyne **26**. Conditions: a) TBSOTf, $NEt_3$, $CH_2Cl_2$, −78 °C, 84%; b) $AlMe_3$, MeONHMe·HCl, THF, 0 °C to rt, 62%; c) MOMCl, DIPEA, DMF, 50 °C, 83%; d) $O_3$, $CH_2Cl_2$, −78 °C; then $Me_2S$, rt, quant.[42]

Somewhat unexpectedly, the Julia-Kocienski reaction of sulfone **R1** with **25** failed under a variety of conditions to give the desired product **26** with acceptable yields or selectivity.[42] This was the main reason why the C.12 / C.13 disconnection approach was abandoned.

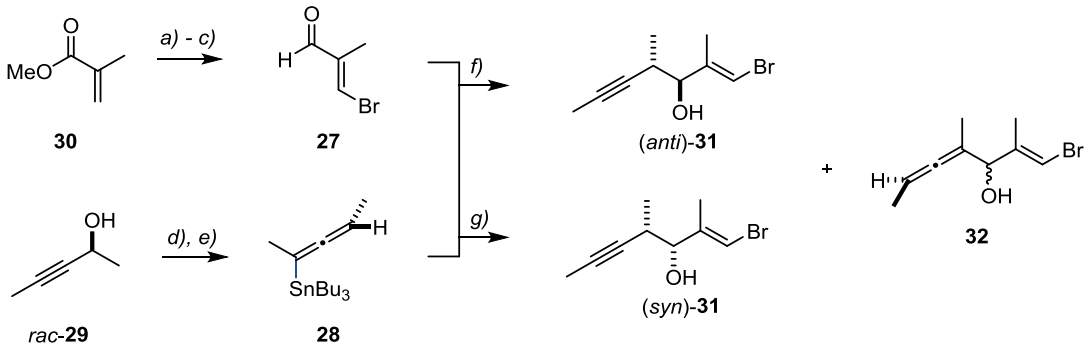
### 2.5.2 Synthesis of the alcohol fragment D[42]

In parallel to the findings described in the previous chapter, an approach to the alcohol fragment **D** had been developed. As outlined in scheme 2.12, the key disconnection was a Marshall reaction of aldehyde **27** and allene **28** in order to set the two stereogenic centers. Compound **28** was proposed to derive from propargylic alcohol **29**, whereas aldehyde **27** is literature known.[53]




*Scheme 2.12:* Retrosynthetic Analysis of the alcohol fragment **D**.[42]

In the forward direction, methyl methacrylate (**30**) served as the starting material for the synthesis of compound **27**. A sequence of dibromination and base-mediated elimination followed by reduction and oxidation gave aldehyde **27** in good yield.[22a] The initial studies were carried out with racemic alcohol **29**, which was transformed into allene **28** upon treatment of the corresponding mesylate with $LiSnBu_3$ in the presence of copper bromide. Although not fully optimized, the key Marshall reaction gave either the *anti*- or *syn*-product **31** depending on the Lewis acid employed.[54] The obtained yields were rather moderate, mainly due to low diastereoselectivity and formation of an allenic addition product (**32**).




*Scheme 2.13:* Synthesis of alcohol fragment **D**. Conditions: a) $Br_2$, $NEt_3$, $CH_2Cl_2$, 0 °C; then DBU, reflux, 92%; b) DIBAl-H, $CH_2Cl_2$, −78 °C, 60%; c) $MnO_2$, $Et_2O$, rt, 62%; d) MsCl, $NEt_3$, $CH_2Cl_2$, −78 °C; e) LDA, (*n*-Bu)$_3$SnH, $CuBr_2 \cdot SMe_2$, THF, −78 °C, 79% over 2 steps; f) $SnCl_4$, $CH_2Cl_2$, −78 °C, **31**: 60% (d.r. 9:1 *anti*/*syn*) + **32**: 30%; g) $BF_3 \cdot Et_2O$, $CH_2Cl_2$, −78 °C, **31**: 75% (d.r. 4:1 *syn*/*anti*) + **32**: 10%.[42]

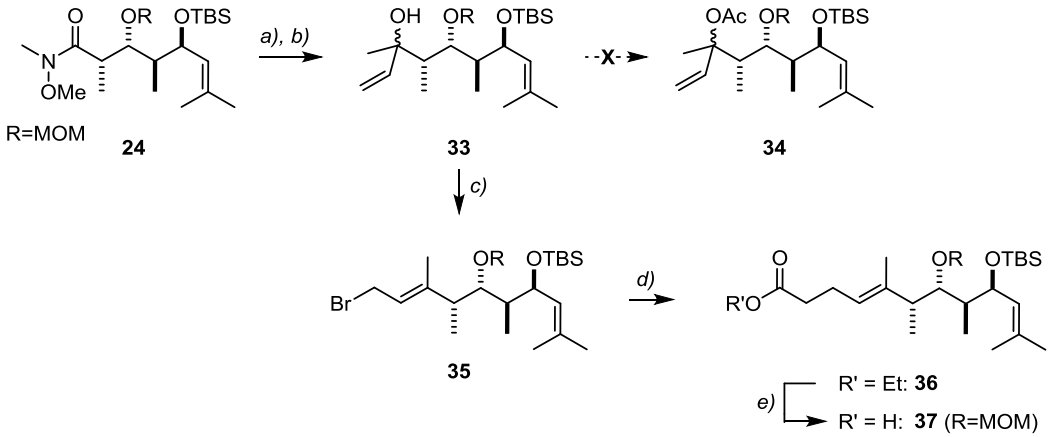
A short and convenient route to the alcohol fragment **D** was thus developed, although it was not fully optimized. The C.12 / C.13 disconnection approach was eventually abandoned because of the above mentioned problems faced during the synthesis of the acid fragment **C**.[42]

## 2.6 The C.10 / C.11 disconnection approach (first generation)

### 2.6.1 Synthesis of the acid fragment E

Since the synthesis of key fragments of the C.12 / C.13 disconnection approach turned out to be a formidable obstacle, our efforts were focused on the C.10 / C.11 disconnection.

For this purpose, compound **24** was used as a model system in order to evaluate the remaining steps required for the introduction of the C.1 – C.5 framework. With this in mind, **24** was treated subsequently with methylmagnesium chloride and vinylmagnesium bromide to give the tertiary alcohol **33** (scheme 2.14).[42]

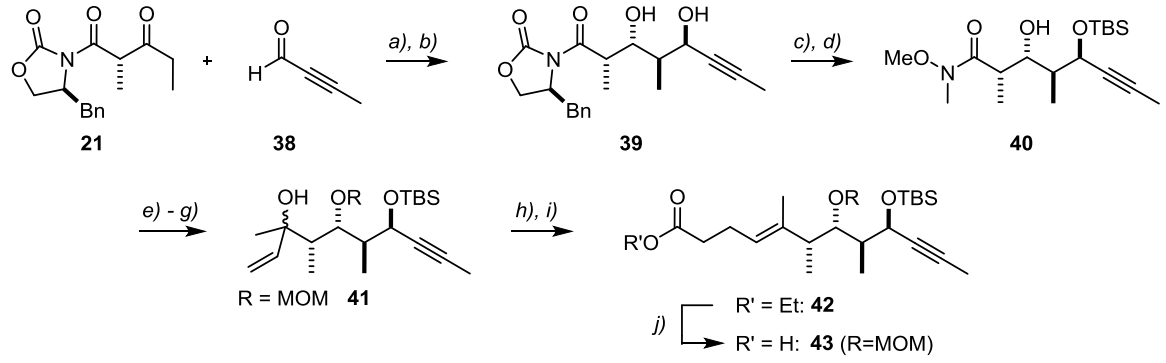



*Scheme 2.14:* Model system for the synthesis of the acid fragment. Conditions: a) MeMgCl, $Et_2O$, 0 °C, 93%; b) vinylMgBr, THF, −78 °C; 52%; c) $PBr_3$, pyridine, $Et_2O$; d) EtOAc, LDA, CuI, THF, −110 to −30 °C, 40-60% over 2 steps; e) TMSOK, $Et_2O$, rt, 90%.[42]

The formation of the tertiary acetate **34** required for the projected Ireland-Claisen rearrangement failed under a variety of conditions, including classical Steglich conditions, *in situ* acetylation after Grignard reaction and Yamamoto's Lewis acid catalysis. However, an alternative two-step process consisting of allylic displacement by bromide and subsequent alkylation allowed for the clean transformation into ethyl ester **36**.[42] Finally, hydrolysis of the ethyl ester under mild conditions using TMSOK at ambient temperature furnished the desired acid **37**; the reaction was slow, but efficient.[42]

With optimized conditions in hand, the synthesis of acid fragment **E** terminating in a methyl-capped alkyne was addressed. Compound **21** was thus treated with freshly prepared 2-butynal (**38**) to produce the desired aldol product in moderate yield, with the remaining mass balance consisting of reisolated starting material.[55] Later studies by Dr. Damien Mailhol showed that the yield could be dramatically improved by using rigorously dry $Sn(OTf)_2$. Subsequent 1,3-*anti* reduction completed the stereotetrad with high selectivity and yield. Selective silylation of the propargylic alcohol and conversion into the corresponding Weinreb amide **40** preceded the protection of the secondary alcohol with MOMCl.

In light of previous experiences in the group, in which difficulties in cleaving methoxymethyl ethers from highly functionalized substrates were encountered, several alternatives were investigated at this stage. However, the secondary alcohol could not be converted into the corresponding PMB ether regardless of the conditions employed. Moreover, this alcohol failed to undergo silylation with TBDPSCl or TBDPSOTf. Although it could be transformed under forcing conditions (50 °C) into the triisopropylsilyl ether, the yield of this reaction was unsatisfactory (49%). Therefore, the synthesis was continued with the MOM group in place.

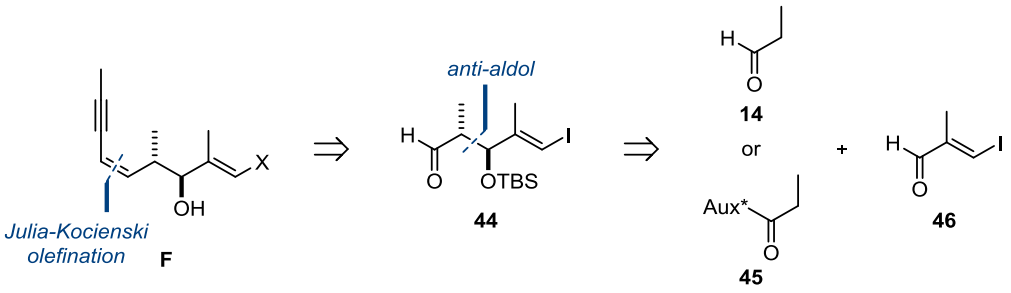



*Scheme 2.15:* Synthesis of the acid fragment **E**. Conditions: a) $Sn(OTf)_2$, $NEt_3$, $CH_2Cl_2$, −20 °C, 55% (88% brsm); b) $Me_4NBH(OAc)_3$, HOAc, MeCN, −50 °C, 98%; c) TBSOTF, $NEt_3$, $CH_2Cl_2$, −78 to 0 °C, 89%; d) (MeO)NHMeHCl, $AlMe_3$, THF, 0 °C to rt, 90%; e) MOMCl, (*i*-Pr)$_2$NEt, DMF, 50 °C, 89%; f) MeMgCl, $Et_2O$, 0 °C, 97%; g) vinylMgBr, THF, −78 °C to rt, 87% 2:1 d.r.; h) $PBr_3$, pyridine, $Et_2O$, 0 °C; i) EtOAc, LDA, CuI, −110 to −30 °C, 63% over 2 steps; j) TMSOK, $Et_2O$, rt, quant.[55]

Two Grignard additions as described above for the model system gave the tertiary alcohol **41** as an inconsequential mixture of diastereomers. The allylic alcohol **41** was then treated with $PBr_3$ to furnish the rather unstable allylic bromide, which was immediately added to the lithium enolate of ethyl acetate in the presence of CuI resulting in a clean alkylation. Again, the saponification of ethyl ester **42** was achieved with TMSOK to give the desired acid **43** in high yield. The acid segment **E** was thus produced in 12 steps in the longest linear sequence.[55] During the first generation synthesis, batches of 347 mg and 415 mg of acid **43** were produced, highlighting the robustness and scalability of this fragment synthesis.

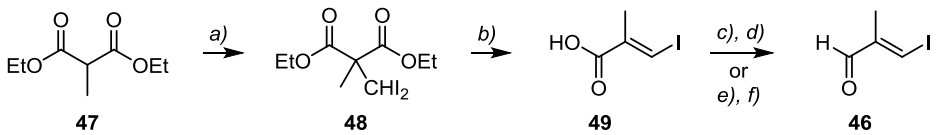
### 2.6.2 Synthesis of the alcohol fragment F

The retrosynthetic analysis of the alcohol fragment **F** centered on a Julia-Kocienski reaction for the construction of the required (*Z*)-enyne. Aldehyde **44** was thought to originate from an *anti*-selective aldol reaction of either propanal (**14**) or an ester or amide of type **45** with aldehyde **46** to enable the creation of the *anti*-scaffold of the two stereogenic centers.




*Scheme 2.16:* Retrosynthetic analysis of the alcohol fragment **F**.

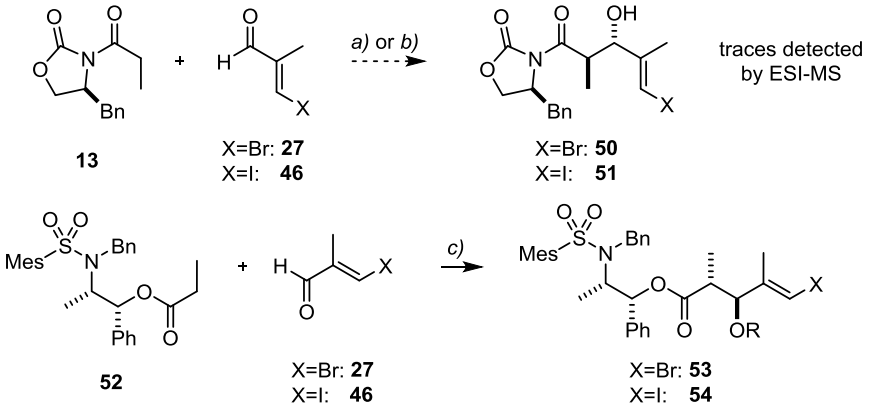
The literature known aldehyde **46** was synthesized in 4 steps from commercially available diethyl methylmalonate (**47**).[56] After deprotonation with sodium hydride and alkylation with iodoform, the diiodoalkyl species **48** was obtained in excellent yield. Treatment with potassium hydroxide in aqueous ethanol led to the saponification of both esters, decarboxylation of one of the two carboxylates, and elimination of iodide to afford 3-iodomethacrolein (**49**) in good yield. The acid was reduced with lithium aluminum hydride to give a primary alcohol that was oxidized on demand with manganese dioxide to yield the rather unstable aldehyde **46**.




*Scheme 2.17:* Synthesis of aldehyde **46**. Conditions: a) NaH, $CHI_3$, $Et_2O$, 0 °C to reflux, 99%; b) KOH, $EtOH/H_2O$, reflux, 72%; c) $LiAlH_4$, $Et_2O$, 0 °C to rt, 49%; d) $MnO_2$ (10 eq.), $CH_2Cl_2$, rt, 98%; e), $BH_3$·THF, THF, −30 °C to rt, f) $[Cu(MeCN)_4]OTf$ (5 mol%), bipyridine (5 mol%), TEMPO (5 mol%), NMI (10 mol%), air, MeCN, 55% over 2 steps.

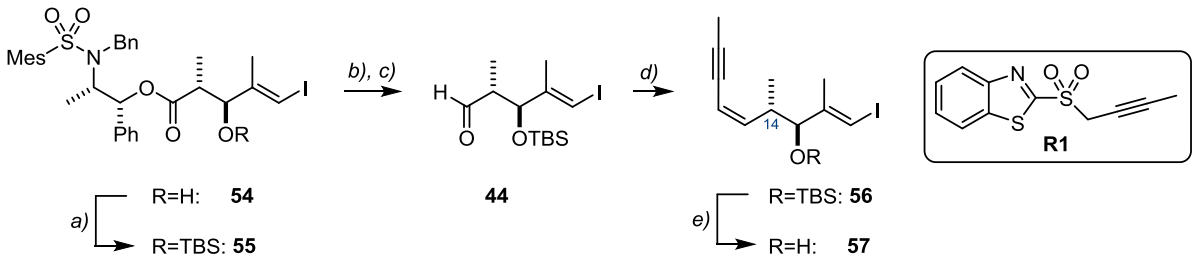
More reproducible results were later obtained by replacing $LiAlH_4$ with $BH_3 \cdot THF$.[57] Moreover, a copper catalyzed air oxidation[58] was found to be more practical than the use of excess $MnO_2$ during a second generation synthesis.[57]

Aldehyde **46** and its brominated congener **27** were first subjected to Evans *anti*-aldol conditions employing $MgCl_2$,[59] but only traces of the desired adducts **50** and **51** were detected by mass spectrometry after workup. On the other hand, resorting to ester **40**,[60] derived from norephedrine[61] according to Masamune and Abiko, secured good yields and stereoselectivity as previously reported.[62] Since the outcome with iodo-aldehyde **46** was superior when compared to the bromo-aldehyde **27**, the former was used for scale-up and the synthesis continued with the vinyl iodide in place.




*Scheme 2.18:* Attempted *anti*-aldol reactions. Conditions: a) **27** or **46** (1.2 eq), $NEt_3$, TMSCl, $MgCl_2$ (20 mol%), EtOAc, rt; b) **27**, $NEt_3$, TMSCl, $MgCl_2$ (10 mol%), $NaSbF_6$ (30 mol%), EtOAc, rt; c) **27** or **46**, $Cy_2B(OTf)$, $NEt_3$, $CH_2Cl_2$, −78 °C, **53** (X=Br): 58% (10:1 d.r.), **54** (X=I): 76% (12:1 d.r.).

The secondary alcohol was converted into the corresponding TBS-ether and the auxiliary reductively cleaved by using DIBAl-H. Aldehyde **44** was then obtained by oxidation of the primary alcohol with Dess-Martin periodinane[63] and immediately submitted to the Julia-Kocienski reaction.[45] In the initial experiments, substantial isomerization at C.14 was observed, although the (*E*/*Z*)-selectivity was high.

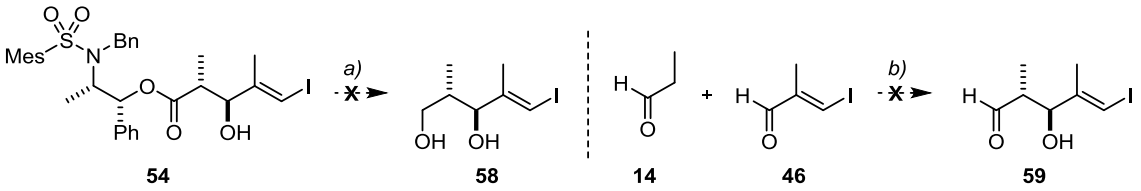



*Scheme 2.19:* Completion of the synthesis of the alcohol fragment **F**. Conditions: a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −10 °C; b) DIBAl-H, toluene, −78 °C, 83% over 2 steps; c) DMP, $CH_2Cl_2$, 0 °C; d) **R1**, KHMDS, THF, −55 °C, 56% over 2 steps, (E/Z > 24:1); e) TBAF, THF, 0 °C, 99%.

This problem could be circumvented by stirring sulfone **R1**[28a] with KHMDS for 30 min before the deprotonated sulfone was transferred to a cooled solution of aldehyde **44** via

canula. A longer reaction time for the deprotonation did not improve the outcome of the reaction further. Finally, removal of the silyl group occurred readily with TBAF to give alcohol **57** in excellent yield.

Attempts to shorten the synthesis of alcohol fragment **F** by performing the reactions without silyl protecting group failed (scheme 2.20). Upon treatment of **54** with DIBAl-H, only traces of the reduced product **58** were obtained, mainly due to retro-aldol side reactions. Likewise, the attempted shortcut on the way to **57** via a proline-catalyzed cross-aldol reaction[64] between propanal (**14**) and aldehyde **46** was unsuccessful.[57] Instead of the cross-aldol product **59**, only homocoupling of propanal (**14**) was observed.



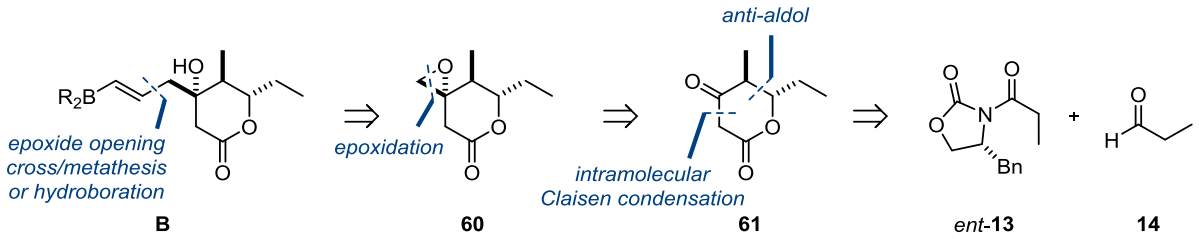

*Scheme 2.20:* Attempted shortcuts. Conditions: a) DIBAl-H, toluene, −78 °C to rt; b) (*L*)-proline (10 mol%), DMF, 4 °C.

Overall, synthetic access to alcohol fragment **F** was established with 10 steps in the longest linear sequence starting from commercially available malonyl diester **47**.

### 2.6.3 Synthesis of the δ-lactone fragment B

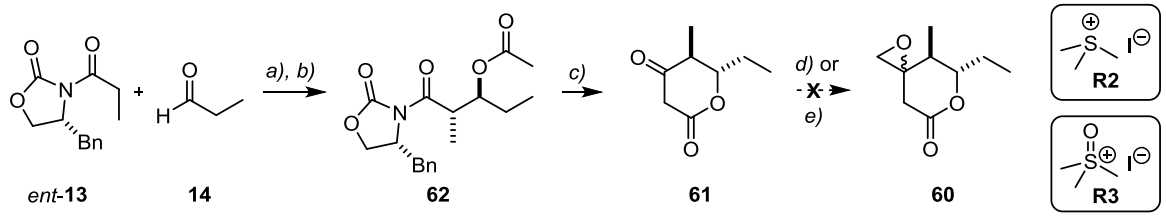
The δ-lactone fragment of leiodermatolide (**1**) is unique for its three contiguous stereogenic centers, one of which is a tertiary alcohol. The allylic substituent of this site connects to the macrolide segment, segregated through a pentadienyl linker.

Several strategies based on the cyclic β-keto ester **61** as a key intermediate were investigated and will be discussed in this chapter. The initial strategy was based on a nucleophilic opening of the exocyclic epoxide **60** with an ethynyl or vinyl metal reagent followed by cross metathesis with a vinyl boronate or hydroboration, respectively. Epoxide **60** should be accessed either directly from **61** via a Corey-Chaykovsky reaction or by a two-step sequence involving methylenation and epoxidation. The cyclic β-keto ester **61** is literature known and can be assembled through an intramolecular Claisen condensation of the acetylated *anti*-aldol product of *ent*-**13** with propanal (**14**).[65]



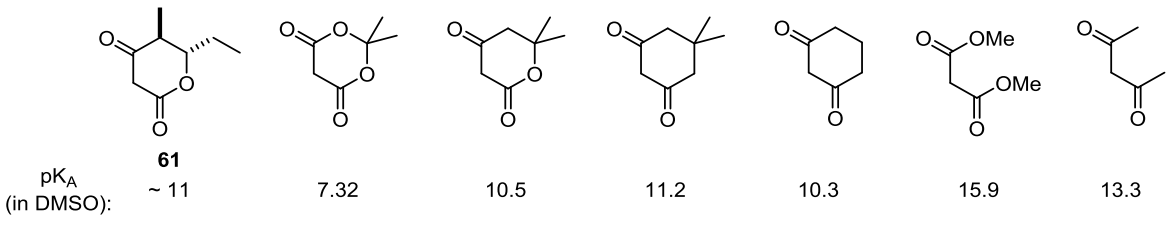

*Scheme 2.21:* Retrosynthetic analysis of δ-lactone fragment **B**.

In the event, the synthesis of **61** proceeded as reported and furnished the desired compound on gram scale.[65] The aldol reaction with two equivalents of dibutylboron triflate as described by Heathcock led to the *anti*-product **62** with acceptable selectivity (11:1 d.r.).[66] Acetylation with acetic anhydride set the stage for a Dieckmann-type condensation, which, when mediated by LiHMDS at low temperatures, gave the desired product in 83% yield.



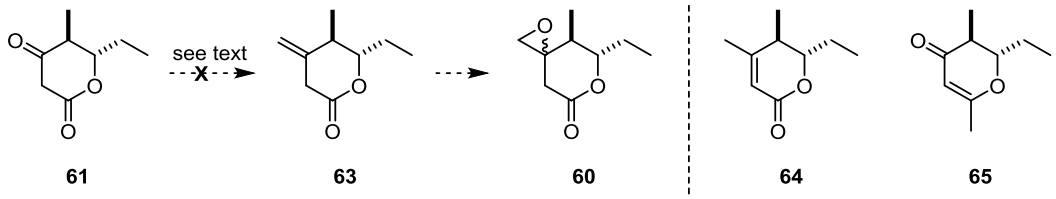

*Scheme 2.22:* Synthesis of key β-keto ester **61** and attempted epoxidation. Conditions: a) $(n\text{-Bu})_2$BOTf, $NEt_3$, $Et_2O$, −78 °C, 74% (11:1 d.r.); b) $Ac_2O$, $NEt_3$, DMAP (cat.), $CH_2Cl_2$, 0 °C, 82%; c) LiHMDS, THF, −78 °C, 83%; d) KHMDS, **R2**, THF, 0 °C; e) NaH, **R3**, THF, 0 °C.

The projected Corey-Chaykovsky epoxidation with sulfonium salt **R2** or sulfoxonium salt **R3** failed due to the high acidity of the α-protons of **61**.[67] Although no starting material could be detected by TLC analysis during the reaction, it reappeared after a slightly acidic workup. These initial results already indicated the major problem that had to be overcome with **61**. Comparison of literature known $pK_A$ values for Meldrum's acid or other cyclic β-dicarbonyl compounds allowed for an estimation of the $pK_A$ value of **61** (scheme 2.23).[68] With a forecasted $pK_A$ value of slightly less than 11, the acidity of **61** is similar to protonated amines ($Et_3NH^+$ $pK_A$ = 9.1; $BnNH_3^+$ $pK_A$ = 10.2; $n$-$BuNH_3^+$ $pK_A$ = 11.1, all values for DMSO).[69] It is interesting to note that the acidities of cyclic β-dicarbonyl compounds are significantly lower than those of their acyclic counterparts.



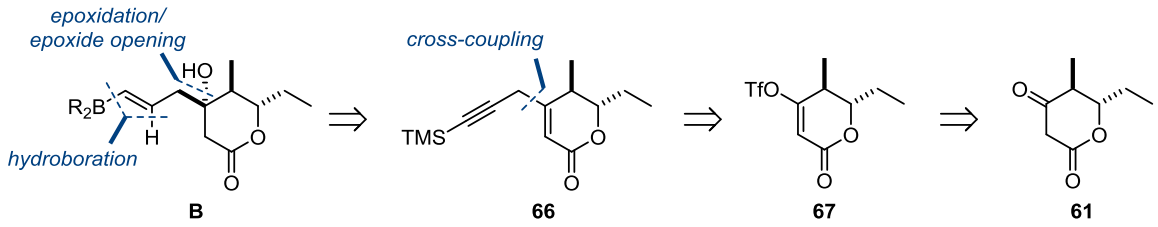

*Scheme 2.23:* Comparison of $pK_A$ values of several β-dicarbonyl compounds.[68]

This was attributed to preferred orbital overlap of the $\sigma^*_{C\text{-}H}$ with the $\pi^*_{C\text{-}O}$ of an adjacent carbonyl that is maximized in cyclic systems according to calculations.[70] This lowers the overall energy of the $\sigma^*_{C\text{-}H}$ LUMO and facilitates the overlap with a lone-pair of a base. NMR analysis of **61** revealed that the keto form is the only observed species in $CDCl_3$ and [$D_6$]-benzene, whereas the enol form dominates in [$D_6$]-DMSO.




*Scheme 2.24:* Attempted methylenation of **61**; observed products **64** and **65**.

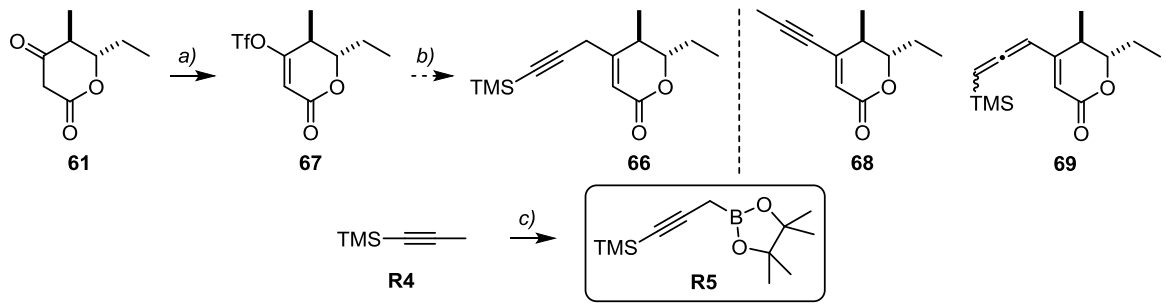
As the direct epoxidation of **61** had failed, a two-step sequence was envisioned. Methylenation should precede the epoxidation of the generated exocyclic double bond. Although the former transformation proceeded readily with the expected regioselectivity for the ketone using the Tebbe reagent at low temperatures, the exocyclic double bond of **63** isomerized quickly into conjugation with the ester upon contact with either $H_2O$, $SiO_2$ or, over time, in $CH_2Cl_2$ solution. At temperatures above 0 °C, the methylenation of the ester carbonyl took place preferentially and product **65** was detected. Resorting to other mild methylenating agents did not help to overcome this hurdle. No reaction occurred with the Lombardo reagent generated *in situ* from Zn, $CH_2Br_2$ and $TiCl_4$,[71], whereas the Nystedt[72] reagent reacted slowly, but only the isomerized product **64** with an endocyclic double bond was observed after workup. A different retrosynthetic analysis was therefore mandatory.




*Scheme 2.25:* Revised retrosynthetic analysis of the δ-lactone segment **B**.

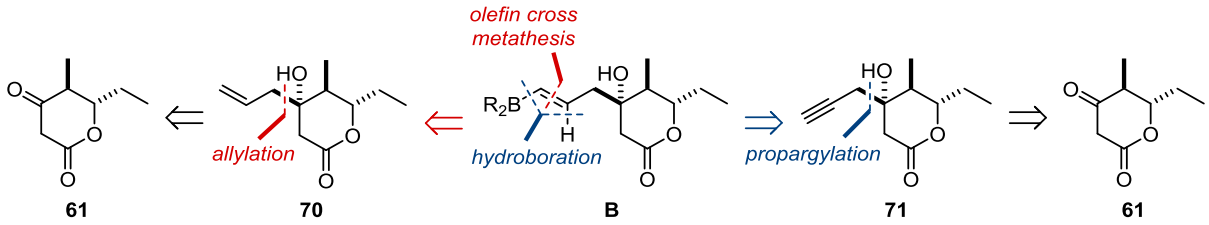
It was envisioned that the alcohol functionality could be introduced by a nucleophilic epoxidation of an unsaturated lactone of type **66** followed by radical epoxide opening. The precursor was thought to be derived from vinyl triflate **67**, which should be readily accessible from **61**.

Indeed, trapping of the enol form of **61** with triflic anhydride occurred without difficulty to give the stable vinyl triflate **67**. The envisioned palladium catalyzed cross-coupling was only tried with propargylic pinacolborolane **R5** and furnished either allene **69** or the conjugated alkyne **68** as the major product depending on the reaction temperature.



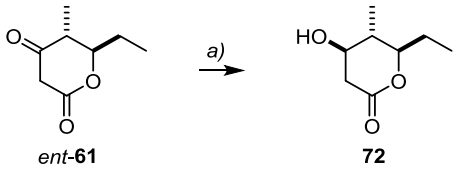

*Scheme 2.26:* Attempted cross-coupling approach. Conditions: a) $Tf_2O$, $NEt_3$, $CH_2Cl_2$, −78 °C, 91%; b) **R4**, $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$, $Cs_2CO_3$, $THF/H_2O$ 10:1, for **68**: reflux, HCl workup, 33%, for **69**: rt, neutral workup: 60%, 18:1 d.r.; c) *n*-BuLi, THF, then $MgCl_2$, (pin)B(OiPr), −40 °C, 83%.

The formation of alkyne **68** is noteworthy and it remains unclear, whether the forcing conditions led to a Hiyama coupling of **R5** with concurrent protodeborylation or if it was the result of an isomerization process. At this stage, the more promising Stille coupling with an allyl or propargyl tin reagent was not investigated,[73] since an alternative strategy was explored simultaneously and was found to be much more efficient in terms of step count.




*Scheme 2.27:* Retrosynthetic analysis of δ-lactone segment **B** based on direct allylation or propargylation.

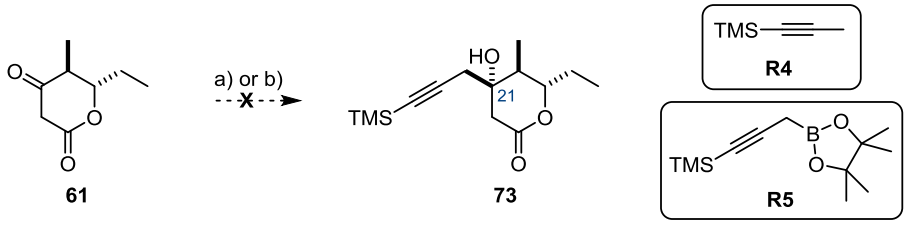
This strategy was based on the direct propargylation (scheme 2.27, blue) or allylation (red) of the previously described β-keto ester **61**. It was inspired by the report of Hinterding, who had shown that a hydride could be delivered with high selectivity from the face *syn* to the adjacent methyl group (scheme 2.28).[65] If this outcome could be translated to a carbon nucleophile in a propargylation or allylation reaction, this strategy would allow the δ-lactone with the axial C-branch to be synthesized in only five steps from commercial material.




*Scheme 2.28:* Reported reduction of β-keto lactone *ent*-**61**.[65] Conditions: a) *t*-$BuNH_2\cdot BH_3$, citric acid, MeOH, $H_2O$, 0 °C, 73%.

Due to the high acidity of the α-protons, a reactive but non-basic nucleophile had to be employed. Therefore, a variety of conditions were screened for the identification of suitable reagents.[74] The propargylation of compound **61** was initially tried with an organocerium compound[75] generated from 1-trimethylsilyl-1-propyne (**R4**) and the organozinc reagent

generated from **R5**.[76] In both cases, no addition occurred due to the pronounced enolization of **61** and the starting material was reisolated (scheme 2.29).




*Scheme 2.29:* Attempted propargylation of **61**. Conditions: a) **R4**, *n*-BuLi, $CeCl_3$, THF, −78 to 0 °C; b) **R5**, $Et_2Zn$, THF, −78 °C to rt.

An early result proved that an allylindium reagent generated *in situ* from allyl bromide and elemental indium[77] could afford the allylated compound **70** when the reaction was carried out in water (table 2.2, entry 2).[78] However, the analysis of the NOESY spectra did not allow for a stereochemical assignment of the newly created stereogenic center.

Fortunately, crystals of the major isomer suitable for X-ray analysis were obtained by slowly cooling a saturated $CH_2Cl_2$/hexane solution to −40 °C. The crystal structure revealed that the allyl group was attached in the pseudo-equatorial position and the product was assigned to *epi*-**70** (figure 2.1). This meant that the allylation took place from the bottom face *anti* to the adjacent methyl group at C.22 and therefore mainly delivered the undesired diastereomer.

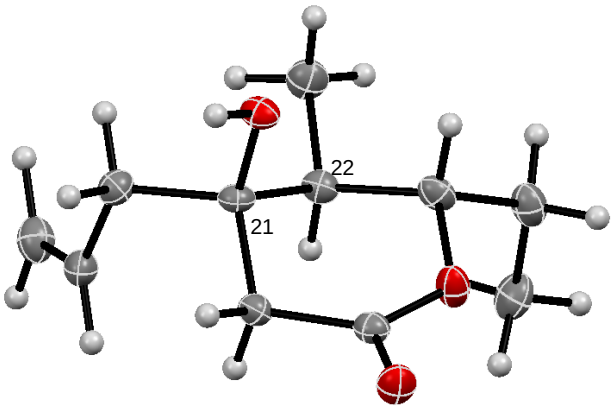


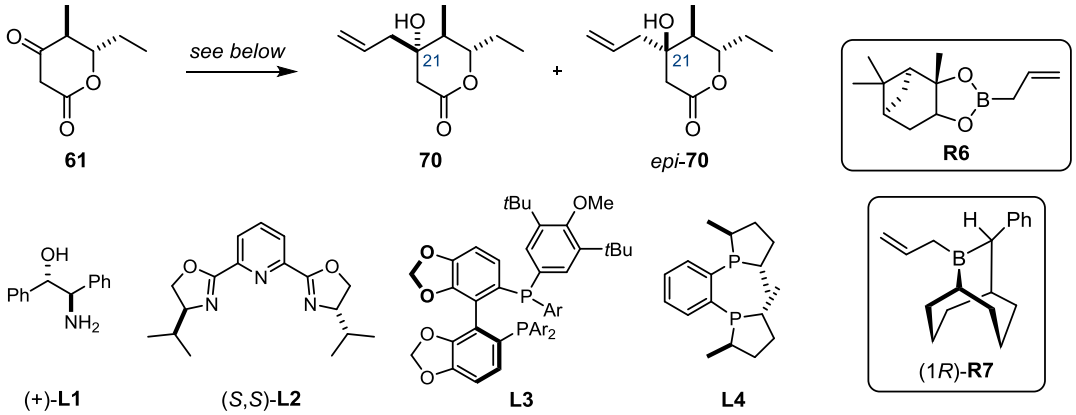

*Figure 2.1*: Crystal structure of *epi*-**70**

A short solvent screen revealed THF to be beneficial in terms of both conversion and diastereoselectivity, but the stereochemical outcome could not be inverted (entry 3). No reaction was observed with the solvent employed for the reduction that consisted of a mixture of aqueous citric acid and methanol as solvent (entry 4).[65]

In order to invert the facial selectivity, several chiral ligands and additives were screened. None of these modifiers was able to cause a switch in diastereoselection. For instance, (+)-**L1** improved the rate and diastereomeric ratio of the products, but the enantiomeric ligand (–)-**L1** was not able to override the substrate bias (entry 5).[79] At best, an almost 1:1 mixture of diastereomers was obtained with moderate yield when the PyBOX ligand **L2** was employed (entry 6).

Other metal mediated allylations including allyltin (entries 7 – 9),[80] allylsamarium (entry 10)[81] and allylboron reagents (entries 11 – 14)[82] under Lewis acid catalysis were screened, but none of these was fruitful.

*Table 2.2:* Selected results towards the allylation of **61**.

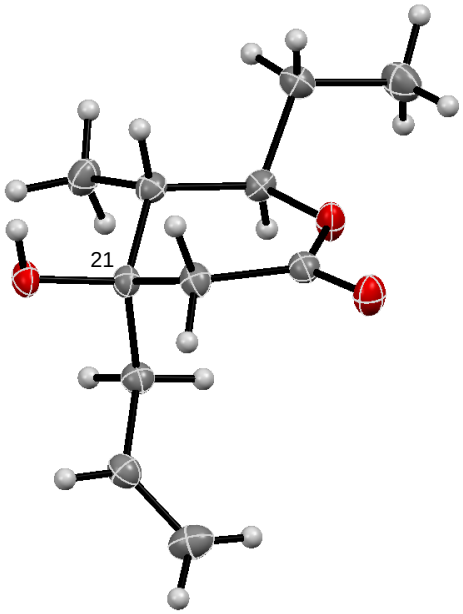



| entry | conditions | conv.[1)] (yield) | 70 : *epi*-70 [1)] |
|---|---|---|---|
| 1 | allylbromide, In, DMF, rt to 50 °C | complex mixture | - |
| 2 | allylbromide, In, $H_2O$, 50 °C | 65 (42%) | 1:6 |
| 3 | allylbromide, In, THF, rt | 79 | 1:1.9 |
| 4 | allylbromide, In, MeOH, citric acid, rt | no reaction | - |
| 5 | allylbromide, In, **L1**, THF, rt | (+): 95 (−): 69 | (+): 1:10; (−): 1:3.5 |
| 6 | allylbromide, In, $Sc(OTf)_3$, (*S*,*S*)-**L2** | 64 | 1:1.3 |
| 7 | allylbromide, Sn, $NaBF_4$, $H_2O$, rt | 18 | 1:3.9 |
| 8 | $Sn(allyl)_4$, $Ti(OiPr)_4$, BINOL, *i*-PrOH/$CH_2Cl_2$, rt | (*R*): 23 (*S*): 15 | (*R*): 1:12; (*S*): 1:10 |
| 9 | $Bu_3Sn(allyl)$, $InBr_3$, BINOL, $CH_2Cl_2$, 4 Å MS, rt to 40 °C | (*S*): 56 (*R*): - | (*S*): 1:5.3; (*R*): - |
| 10 | allylbromide, Sm, $I_2$ (cat.), THF, 40 °C | 26 | 1:7.8 |
| 11 | (pin)B(allyl), $PCy_3$, Cu(OAc), **L3**, THF, 50 °C | no reaction | - |
| 12 | (pin)B(allyl), $CuF_2$, **L4**, La(O*i*-Pr)$_3$, DMF, rt | no reaction | - |
| 13 | $(Ipc)_2B(allyl)$, $Et_2O$, 0 °C | complex mixture | - |
| 14 | **R6**, w/o $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, rt | no reaction | - |
| 15 | 9-allyl-9-BBN, THF, 0 °C | 78 (72%) | 1 : 1.9 |
| 16 | (*1S*)-**R7**, $CH_2Cl_2$, −78 °C | 100 (88%) | 1:7.5 |
| 17 | (1*R*)-**R7** (1.1 eq.), $CH_2Cl_2$, 0 °C to rt | 100 (58%) | 4.1:1 |
| 18 | (1*R*)-**R7** (1.1 eq.), $CH_2Cl_2$, 0 °C (inverse order of add.) | 100 (86%; 73% **70**) | 5.5:1 |

1) in %; determined by $^1$H NMR analysis of a crude sample.

Even though several reactions with allylboron reagents failed, the allylboration with 9-allyl-9-BBN[83] was quite clean and yielded the allylated product as a 1:1.9 mixture of diastereomers (entry 15). For this reason, the chiral reagent **R7** reported by Soderquist was synthesized and explored (entries 16 – 18).[84] Fortunately, the (1*R*)-isomer was able to override the parent substrate control and furnished the allylated product with a diastereomeric ratio of 4.1:1 favoring the desired isomer **70**.

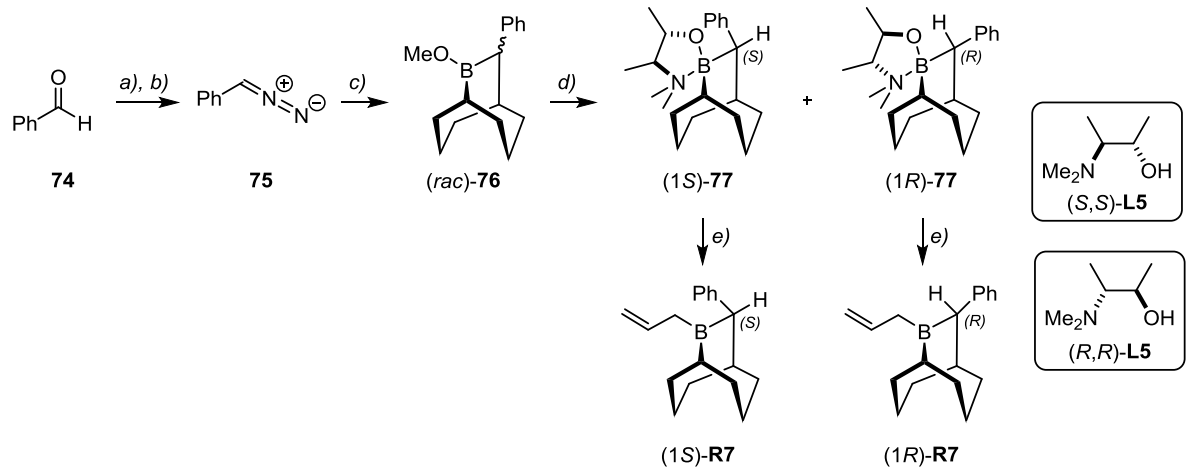
*Figure 2*: Crystal structure of *ent*-**70**




After a short optimization process, best results were obtained by using a slight excess of (1*R*)-**R7** and reversing the order of addition when compared to the originally reported conditions; dropwise addition of the reagent to a chilled solution of **61** ensured a rather low local concentration of (1*R*)-**R7** and suppressed the otherwise observed double and triple allylation products. This protocol allowed the reaction to be performed at 0 °C and increased the diastereomeric ratio to 5.5:1. Repeated column chromatography on fine silica gel allowed the desired isomer **70** to be separated from its counterpart *epi*-**70** and to be isolated with a yield of 73% (86% combined yield).[85] With an efficient and reliable protocol developed, the allylation was similarly performed on *ent*-**61** with the enantiomeric reagent (1*S*)-**R7** that allowed a crystal structure of *ent*-**70** to be grown. The crystal structure depicted in figure 2.2 highlights the rather unusual pseudo-axial attachment of the allyl moiety at C.21.

The synthesis of **R7** was performed as described in scheme 2.30 and is based on the insertion of the benzylic carbene generated from **75** into the C−B bond of 9-methoxy-9-BBN.[84] The diazo species **75** is literature known and was previously synthesized from the corresponding tosylhydrazone by vacuum pyrolysis.[86] A more convenient synthesis was chosen in the present case, since the handling of a potentially dangerous diazo compound at temperatures above 220 °C seemed hazardous.

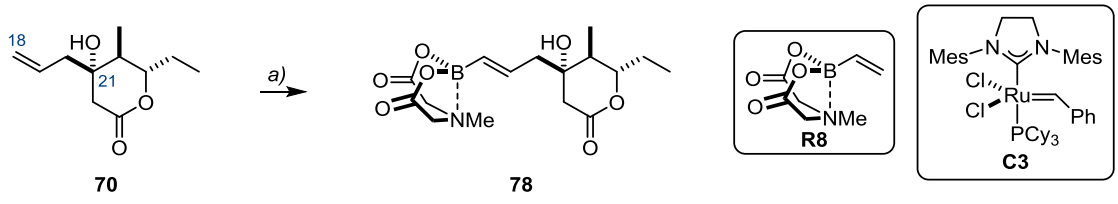
As it turned out, simple oxidation of benzaldehyde hydrazone (**74**) with $MnO_2$[87] worked well in the presence of molecular sieves to trap the generated water.[88] This oxidation proceeded at room temperature and delivered a solution of the diazo compound **75** after filtration, which was immediately used for the insertion step. No high-temperature operations were thus required, although the yield over the two steps was significantly lower than reported, most likely due to inefficient trapping of water during the diazo formation and side reactions with the ethereal solvent.[89]




*Scheme 2.30:* Synthesis of chiral allylboron reagent **R7**. Conditions: a) $H_2NNH_2 \cdot H_2O$, 100 °C, sealed tube, quant.; b) $MnO_2$ (5 eq.), $Et_2O$, 4 Å MS, rt; c) 9-MeO-9-BBN, pentane, 0 °C to rt, 37% over 2 steps; d) (*S*,*S*)-**L5**, pentane reflux, (1*S*)-**77**: 26%; then (*R*,*R*)-**L5**, pentane, reflux, (1*R*)-**R7**: 22%; e) allylMgBr, $Et_2O$, −78 °C to rt, 92%.

The racemic insertion product **76** was then resolved by fractional crystallization with the pseudoephedrine derivative **L5** to give the enantiopure adducts **77**. The order of crystallizations was reversed once it was shown that (1*R*)-**R7** gave the desired isomer **70**. Treatment with allyl magnesium bromide gave the desired allylboron compound **R7** after precipitation and filtration of the magnesium salt of **L5**.

Since the challenging construction of the quaternary stereogenic center was now accomplished, a functionalization at C.18 for the Suzuki coupling was required. Olefin cross-metathesis was initially explored with vinyl pinacolboronates, but the product suffered from rapid hydrolysis of the pinacol ester during workup and chromatography. Replacement by the more stable MIDA boronate ester readily solved this problem.[90] The cross metathesis catalyzed by Grubbs 2nd generation catalyst (**C3**) afforded the desired (*E*)-olefin in good yield and high selectivity (>19:1).[91] In contrast to the corresponding pinacol ester, product **78** was stable during flash chromatography and upon storage.



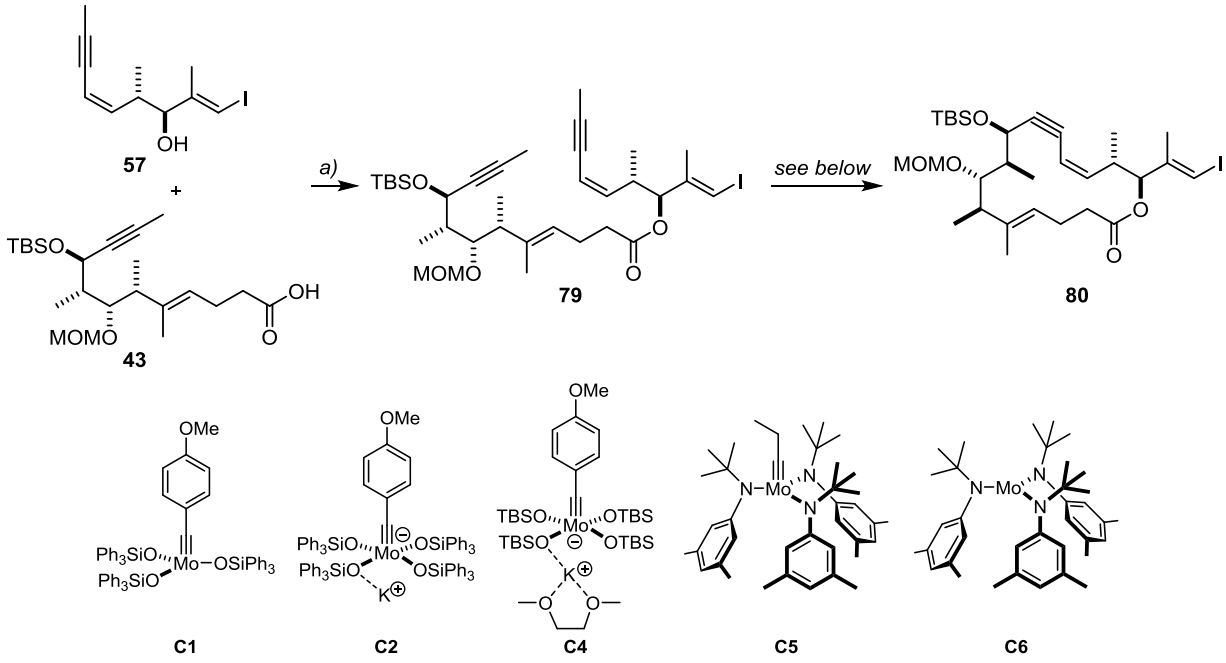

*Scheme 2.31:* Cross metathesis reaction. Conditions: a) **R8**, **C3** (5 mol%), $CH_2Cl_2$, reflux, 81% (*E*/*Z*>19:1).

A short five-step synthesis of the structurally challenging δ-lactone fragment **B** was successfully established. Although the allylation required the use of stoichiometric amounts of **R7**, the developed route was deemed satisfactory for a first generation synthesis. For further improvements, see chapter 2.9.

### 2.6.4 Fragment assembly, macrocyclization, endgame and structure assignment

With all three fragments in hand, the focus shifted to their assembly. The envisioned esterification of alcohol **57** with acid **43** proceeded efficiently when mediated by EDCI and DMAP. The stage was now set for the anticipated ring closure by alkyne metathesis (table 2.3). Surprisingly though, the highly active alkyne metathesis catalyst **C1** based on molybdenum bearing silanolate ligands[25] failed, giving exclusively an open dimer (entry 1).[42] On the basis of $^1$H NMR analysis and comparison with the spectra of diyne precursor **79**, the triple bond next to the silyl ether seemed to be inert to the catalyst and was not engaged in a metathesis reaction. This outcome was independent on the reaction temperature as similar results were obtained at 23 °C and 120 °C. Moreover, ring-closure was not achieved with either the ate-complex **C2** or with complex **C4** bearing supposedly smaller *tert*-butyldimethylsilanolate ligands.

*Table 2.3:* Optimization of the RCAM. Conditions: a) EDCI·HCl, DMAP, $CH_2Cl_2$, 0 °C to rt, 89%.




| entry | cat | conditions | result |
|---|---|---|---|
| 1 | **C1** (15 mol%) | toluene, 5 Å MS, rt or reflux | acyclic dimer (~80%) |
| 2 | **C2** (15 mol%) | toluene, 5 Å MS, reflux | acyclic dimer (~80%) |
| 3 | **C4** (50 mol%) | toluene, 5 Å MS, reflux | acyclic dimer (45%) |
| 4 | **C5** (50 mol%) | *p*-nitrophenol, toluene, 100 °C | no reaction |
| 5 | **C6** (50 mol%) | $CH_2Cl_2$, toluene, 100 °C, 0.006 M | 58% **80** + open & closed dimer |
| 6 | **C6** (40 mol%) | $CH_2Cl_2$, toluene, 100 °C, 0.0015 M | 72% **80** + traces dimer & s.m. |
| 7 | **C6** (4 x 10 mol%) | $CH_2Cl_2$, toluene, 100 °C, 0.0015 M | 68% **80** + traces dimer & s.m. |

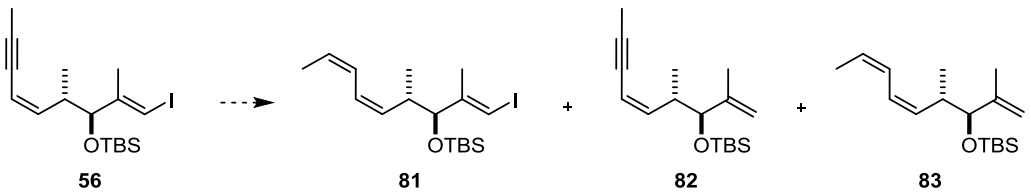
Substitution of the bulky silanolate ligands for sterically less demanding ligands on the molybdenum center was therefore evaluated. The catalyst derived *in situ* from **C5** and *p*-nitrophenol according to the protocol by Moore[92] did not induce any reaction. On the other

hand, the species generated *in situ* from Cummins precatalyst[93] **C6** and $CH_2Cl_2$ effected the desired transformation.[94]

In the initial experiment, stoichiometric amounts of **C6** were used due to the small scale;[42] on larger scale, a catalyst loading of 40 mol% was still required to obtain macrocyclic enyne **80** in a reproducible manner. Close inspection of the reaction progress by TLC and HPLC-MS revealed that a dimeric species was initially formed, which was then converted into monomeric cycloenyne **80**. The catalytic systems **C1** and **C6**/$CH_2Cl_2$ therefore seem to differ in their ability to activate the alkyne next to the propargylic silylether of this dimeric species.

The long reaction time and the high catalyst loading can be explained by considering the ring strain of the polyunsaturated macrocycle, the immense steric demand of the propargylic site and the slight electronic deactivation of the enyne. These individual factors combine to result in an extremely challenging overall transformation that required harsh conditions in order to proceed. As expected, the chemoselectivity was excellent and all other unsaturated sites of the molecule including the vinyl iodide survived the metathesis reaction unaltered.[95]

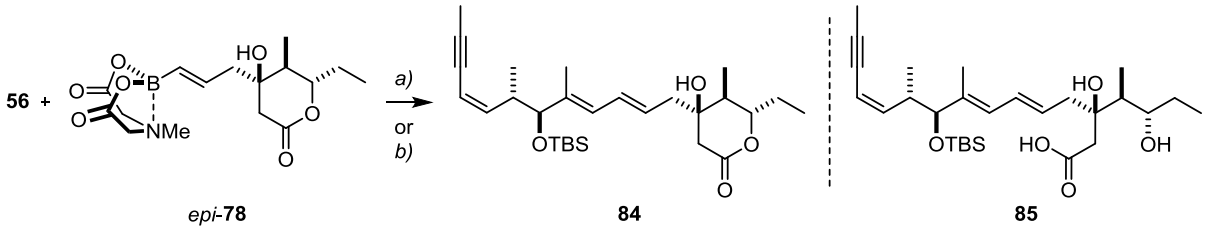
This functionality defined the order of the subsequent steps. Model studies with compound **56** showed that the vinyl iodide was not compatible with semihydrogenation conditions employing activated Zn (scheme 2.32).[42] Under the conditions reported by Boland[96] or Rieke[97] the deiodination was as fast as or faster than the semireduction and only product mixtures of the desired compound **81** and deiodinated products **82** and **83** were detected by GC-MS, ESI-MS, and $^1$H NMR. Activated Zn as described by Brandsma[98] failed to react with **56**; most likely, the activation of Zn was not achieved on the rather small scale. Upon Lindlar hydrogenation,[99] the vinyl iodide unit stayed intact,[100] but the reaction suffered from overreduction and resulted in a mixture of **81** and several other products.[42] Therefore, it was concluded that the Suzuki coupling of macrocycle **63** with δ-lactone **61** had to precede the semireduction of the enyne to consume the vinyl iodide.




*Scheme 2.32:* Attempted semihydrogenation and detected products.[42] Conditions: a) Zn(Cu/Ag), THF/$H_2O$/MeOH 1:1:1, 45 °C, mixture obtained; b) $ZnBr_2$, K, THF/$H_2O$/MeOH 1:1:1, 50 °C, mixture obtained; c) Zn, $(H_2BrC)_2$, CuBr, LiBr, EtOH/THF 1:1, 50 °C, no reaction; d) Pd/$CaCo_3$, $H_2$ (1 atm), pentane, rt, **81** + overreduced products.

Again, compound **56** served as a model system for the Suzuki cross coupling with *epi*-**78** (scheme 2.33). Despite its excellent functional group tolerance and the host of successful

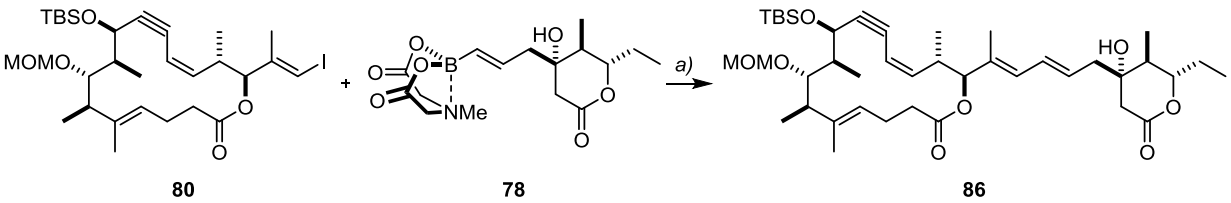
Suzuki couplings in the context of total synthesis,[101] this specific case turned out to be very demanding. The MIDA boronate ester required the use of an aqueous solvent mixture to allow the *in situ* release of the boronic acid.[102] Although the product was detected in trace amounts under classical conditions during an intensive screening process,[103] only the use of a thallium base[104] allowed the coupled product **84** to be isolated in 15% yield despite a high catalyst loading. Analysis of the crude reaction mixture by mass spectrometry enabled the identification of ring-opened diol **85** as a side-product.




*Scheme 2.33:* Suzuki cross-coupling model studies. Conditions: a) $[Pd(PPh_3)_4]$ (20 mol%), Tl(OEt), THF/$H_2O$ 9:1, 50 °C, **84**: 15% **85** detected in the crude mixture; b) $[Pd(PPh_3)_4]$ (20 mol%), Tl(OEt), THF/$H_2O$ 3:1, rt; then MTBE/0.5 M HCl, rt, 81%.

It seems likely that the rather basic conditions employed for the cross-coupling not only hydrolyzed the boronate ester but also the δ-lactone. The crude product was therefore treated overnight with diluted aqueous HCl to close the partially opened δ-lactone. This workup procedure significantly improved the yield (81%) without causing isomerization of the conjugated olefins or alcohol deprotection.

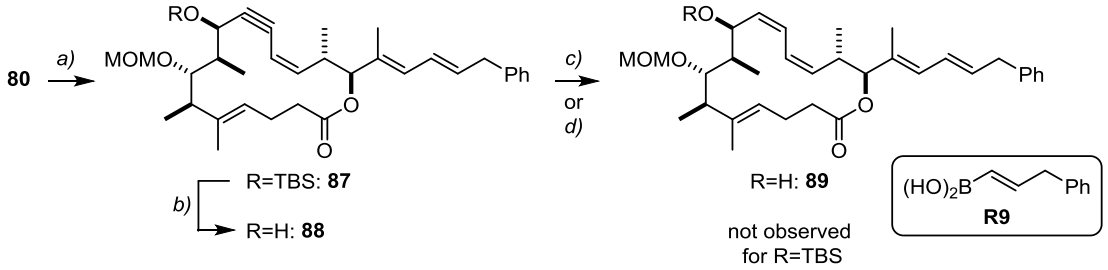
Application of these conditions to the macrocyclic vinyl iodide **80** gave the desired adduct **86** after a similar acidic workup in 49-56% yield. Although the outcome was only moderate, this reaction was reliable and served well for the material supply of a first generation synthesis. Nevertheless, it was kept in mind that a higher yielding alternative would be desirable for a later upscaling process.




*Scheme 2.34:* Suzuki cross-coupling. Conditions: a) $[Pd(PPh_3)_4]$ (20 mol%), Tl(OEt), THF/$H_2O$ 3:1, rt; then MTBE/0.5 M HCl, rt, 49-56%.

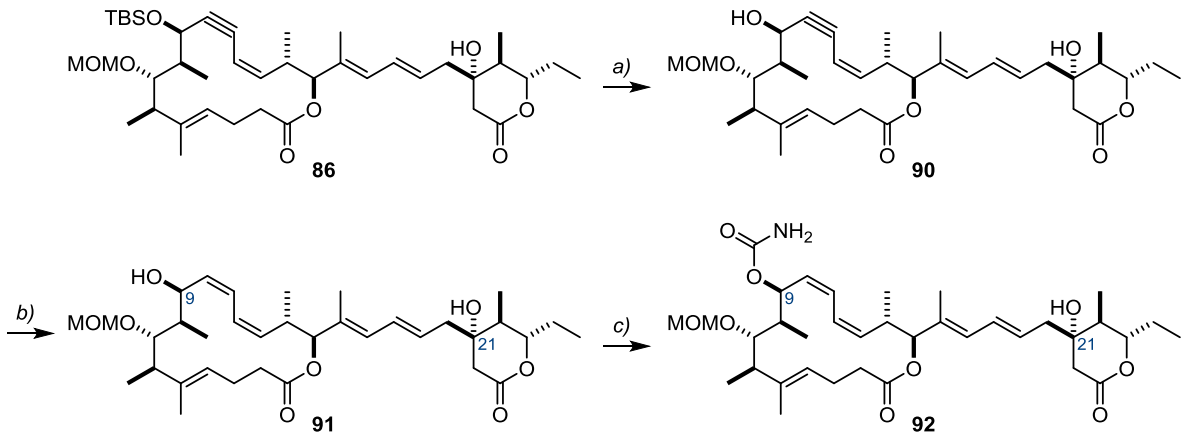
The semihydrogenation was now explored on a macrocyclic system. Initial experiments with model compounds **87** and **88**[105] bearing a truncated side chain revealed that only the deprotected propargylic alcohol **88** was successfully reduced with either Zn(Cu/Ag) as described by Boland[96] or activated zinc obtained by the Rieke method,[97] whereas the triple bond of silylether **87** was inert under identical conditions. As discussed above, this is likely

due to the steric hindrance imposed by the bulky *tert*-butyldimethylsilyl protecting group. Furthermore, White had previously described an activating effect of alcohol groups in proximity to the alkyne.[97c] It was speculated that the alcohol assists the coordination of the substrate to the heterogeneous metal surface.




*Scheme 2.35:* Model for the semihydrogenation. Conditions: a) **R9**, [$Pd(PPh_3)_4$], Tl(OEt), THF/$H_2O$ 3:1, rt, 56%; b) TBAF, THF, 0 °C, 96%; c) Zn(Cu/Ag), MeOH/$H_2O$ 1:1, 50 °C, 91%; d) $ZnBr_2$, K, THF/MeOH/$H_2O$, reflux, 85%.

These promising results were translated to the actual system (scheme 2.36). Thus, the propargylic silyl ether **86** was deprotected using TBAF in the presence of 4 Å MS to ensure short reaction times. Since the isolated yield was low when **90** was purified by column chromatography on silica gel, all chromatographic operations after this point were carried out on less acidic Florisil®. The stage was set for the semihydrogenation of the propargylic alcohol **90**.



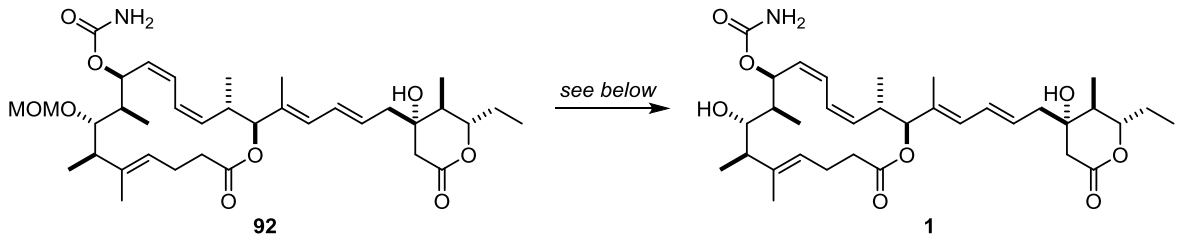

*Scheme 2.36:* Semihydrogenation and selective carbamoylation. Conditions: a) TBAF, THF, 4 Å MS, 0 °C, 85%; b) Zn(Cu/Ag), THF, $H_2O$/MeOH, 50 °C, 89%, c) $Cl_3C(O)NCO$, $CH_2Cl_2$, −78 °C, then $Al_2O_3$, 84%.

After treatment with freshly prepared Zn(Cu/Ag) at elevated temperature, the targeted (*Z*,*Z*)-diene **91** was isolated as a single olefin isomer in high yields. Although the reaction times fluctuated from batch to batch, the reaction always proceeded to full conversion. With an efficient and highly selective entry for the diene unit of the macrocycle in hand, the allylic alcohol at C.9 was carbamoylated with trichloroacetyl isocyanate in the presence of the more shielded tertiary alcohol at C.21. The primary adduct was hydrolyzed by prolonged contact

with basic alumina to release the desired allylic carbamate **92** in good yield.[106] Although the isolation team had reported that the tertiary alcohol easily undergoes esterification reactions during Mosher ester formation, the carbamoylation was completely selective for the secondary alcohol.[31] During this first generation synthesis, 38 mg of MOM-protected leiodermatolide were prepared in a single batch.

The cleavage of the MOM group as the last step of the synthesis posed another considerable hurdle. As can be seen from table 2.4, the reaction with a host of Brønsted (entry 1)[107] or Lewis acids[108] formed complex mixtures. Due to the small scale and the manifold by-products, the compounds could not be isolated from the crude mixture, which was hence analyzed by ESI-MS analysis. All detected side-products are depicted in scheme 2.37. Since no NMR data was available, the structures are only tentative. As eliminated species like **95** - **98** were often detected during this process, it was postulated that a conjugated and therefore stabilized carbocation was initially formed, which likely loses a proton to form elimination products. Indeed, when the reaction was carried out in the presence of a nucleophile like *n*-butylthiol, the adducts **94** were detected by ESI-MS in the crude mixture (entry 4). Treatment with *B*-bromocatechol borane[109] (entry 5) led, for the first time, to the detection of the desired signal in the crude ESI-MS sample.

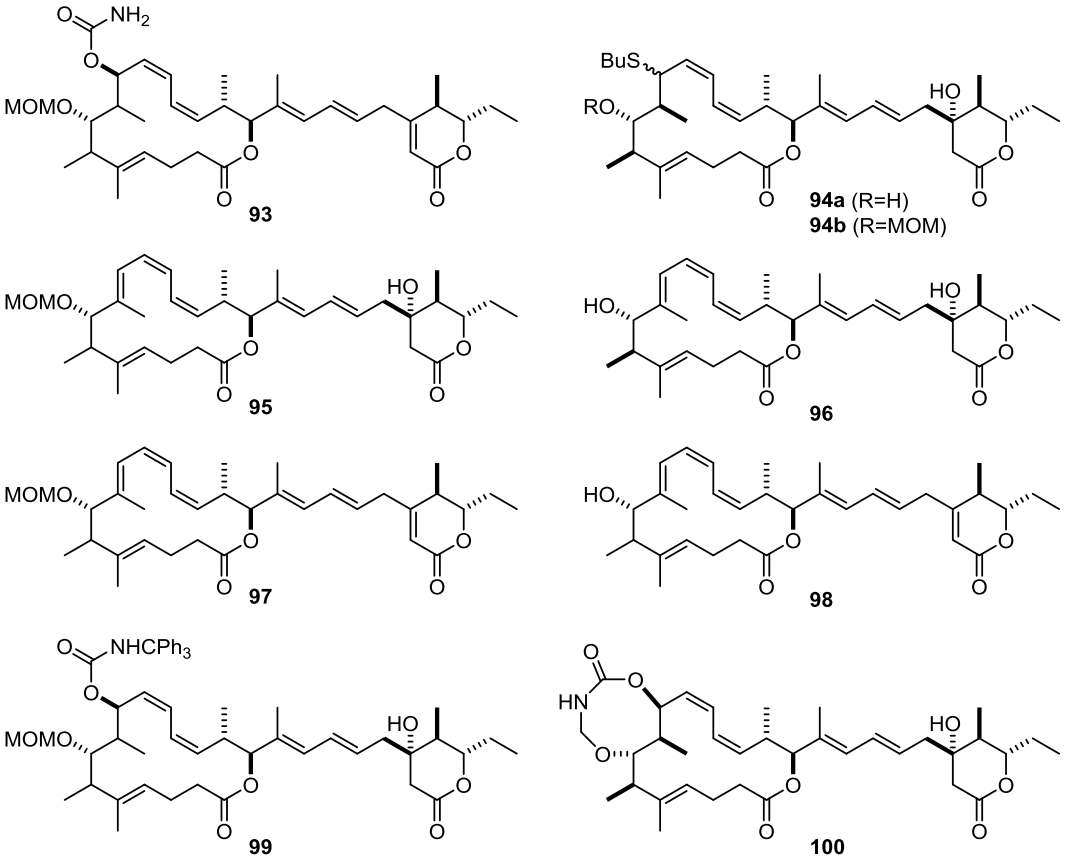
*Table 2.4:* Optimization of final MOM-deprotection. For structures of the by-products, see scheme 2.37.




| entry | reagent | conditions | result [1)] |
|---|---|---|---|
| 1 | AcCl, EtOH | $CH_2Cl_2$, 0 °C | mix of **95**, **97**, **98**, **100** |
| 2 | TMSCl, *n*-$Bu_4NBr$ | $CH_2Cl_2$, 0 °C | complex mixture |
| 3 | $Ph_3CBF_4$ | w/o 2,6-di(*t*-Bu)pyridine, $CH_2Cl_2$, −20 °C | mix of **99**, **95**, **96** |
| 4 | $ZnBr_2$, *n*-BuSH | $CH_2Cl_2$, 0 to 10 °C | mix of **94a**, **94b**, **98**, **96** |
| 5 | (catechol)BBr | w/o *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 to −35 °C | mix of **1** (traces), **95**, **96** |
| 6 | (catechol)BCl | $CH_2Cl_2$, −78 to −35 °C | **95**, **92**, unidentified product |
| 7 | 9-I-9-BBN | w/o *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 °C | mix of **97**, **1**, **100**, **96**, **92** |
| 8 | $Me_2BBr$ | $CH_2Cl_2$, −90 to −78 °C | clean reaction, 61% **1** isolated |

1) determined by ESI-MS of a crude sample.

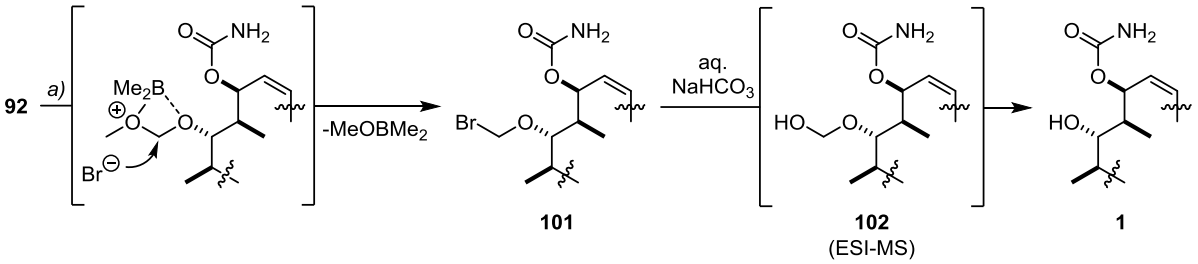
Based on this finding, several boron-based Lewis acids were screened in order to identify a reagent that would cleave the MOM group without causing undesired elimination. In some cases, these Lewis acids were combined with bulky bases to quench any Brønsted acid (entries 5, 7), but no effect was noticed.




*Scheme 2.37:* Putative structures of the by-products detected in the crude mixtures by ESI-MS.

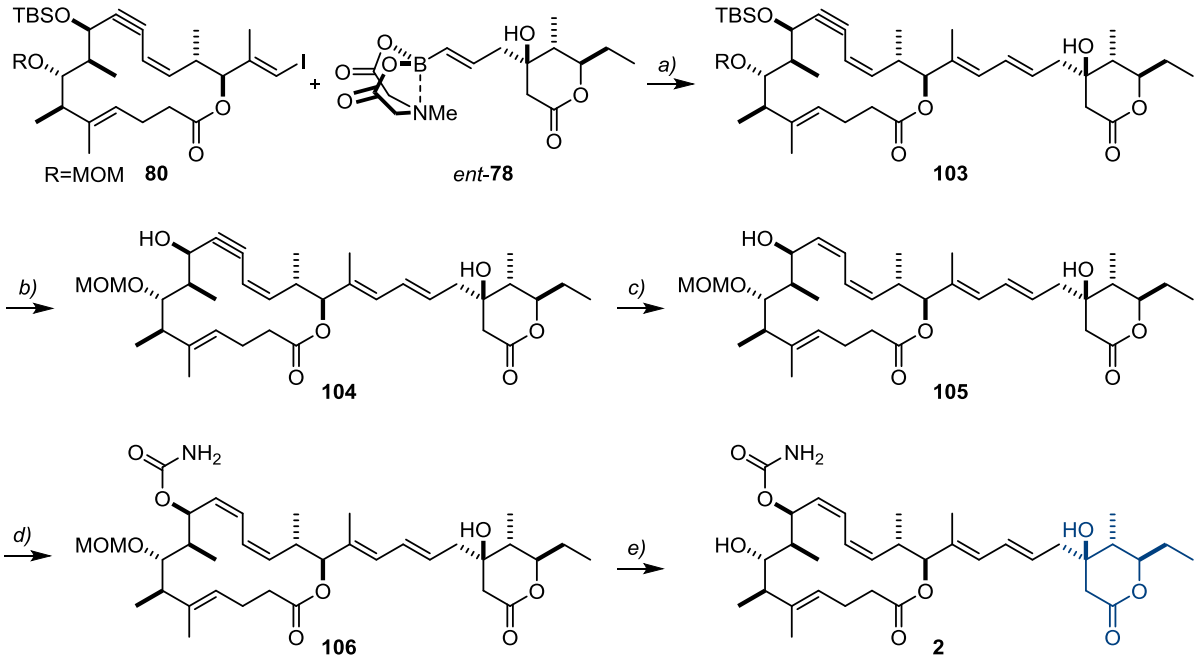
Although the MOM group was cleaved on some occasions, as can be concluded from the formation of **94a**, **96** and **98**, the reactions were often accompanied by a substantial amount of elimination side reactions. Fortunately, the use of the slim but highly Lewis acidic $Me_2BBr$[110] as a last resort enabled the clean deprotection of **92** and allowed the isolation of **1** in 61% isolated yield after preparative TLC.

Due to its high volatility (bp. 29 °C) and violent reaction with moisture, dimethylboron bromide is no longer commercially available and was freshly prepared prior to use from tetramethyltin and borontribromide for optimal results. This practical drawback notwithstanding, this reagent accomplished its task reliably by first transforming the MOM ether into the corresponding bromo-acetal **101** either directly by nucleophilic attack as outlined (scheme 2.38) or via the corresponding oxonium ion as proposed by Guindon and co-workers.[111] Upon aqueous $NaHCO_3$ workup, this intermediate is converted into the hemi-acetal **102**, which collapses to give the targeted compound **1**. Quite surprisingly, the hemi-acetal **102** was stable enough to be detected by mass spectrometry after purification by preparative TLC.




*Scheme 2.38:* Proposed mechanism and detected hemi-acetal. Conditions: a) $Me_2BBr$, $CH_2Cl_2$, −90 to −78 °C.

The diastereomeric compound **2** bearing the antipodal δ-lactone fragment was synthesized analogously (scheme 2.39) in order to allow for a stereochemical assignment of the natural product. Hence, the enantiomeric δ-lactone *ent*-**78** was engaged in the Suzuki coupling with **80** to give **103**. As described before, fluoride-induced desilylation preceded the semihydrogenation, which yielded allylic alcohol **105**. Selective introduction of the yet missing carbamate and deprotection of the MOM-acetal under the previously established conditions afforded the targeted compound **2**. The low yield of 18% is likely a consequence of the preparative HPLC purification that was necessary with this isomer after the MOM deprotection. It can be assumed that a significant amount of product got lost during the purification process due to the small scale.




*Scheme 2.39:* Total synthesis of diastereomeric compound **2**. Conditions: a) $[Pd(PPh_3)_4]$, Tl(OEt), THF/$H_2O$ 3:1, rt, 56% b) TBAF, THF, 4 Å MS, 0 °C, 76%; c) Zn(Cu/Ag), THF, $H_2O$/MeOH, 50 °C, 81%, d) $Cl_3C(O)NCO$, $CH_2Cl_2$, −78 °C, then $Al_2O_3$, 63%, e) $Me_2BBr$, $CH_2Cl_2$, −90 to −78 °C, 18%.

Nevertheless, the isolated material allowed for a direct comparison of both $^1H$ and $^{13}C$ NMR data of the two compounds with those of the natural product (see appendix for full spectra). The recorded $^{13}C$ NMR spectra of the two diastereomers were almost identical, and

juxtaposition with the spectrum of the natural product (see figure 2.3) did not allow for a conclusive assignment. In both cases, marginal deviations from the peaks of the natural product were observed that were within the experimental error of 0.1 – 0.2 ppm. To exclude concentration effects, the spectra of **1** were recorded at different molarities, though no significant differences were observed.

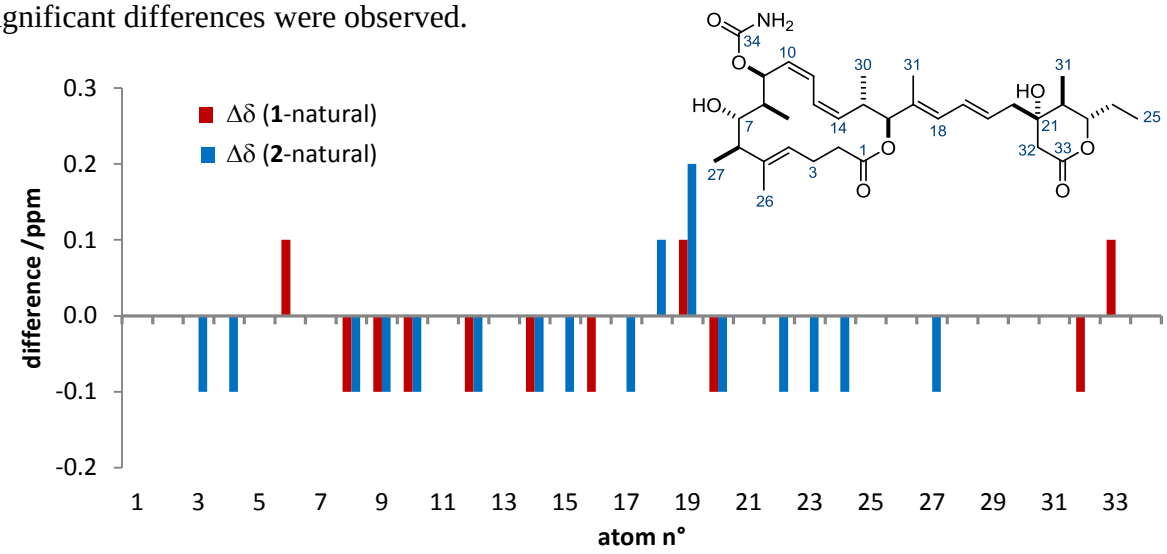



*Figure 2.3:* Differences in $^{13}C$ shifts (Δδ) of **1** (red) and **2** (blue) with the natural product.

A similar situation was encountered for the $^{1}H$ NMR spectra, which were indistinguishable except for the region between 2.20 and 2.50 ppm. The subtle differences found within this region were characteristic and did not change upon lowering the concentration of the sample solution. Therefore, it was used for the comparison with the natural product. The pattern of **1** (figure 2.4, red) was essentially identical with the spectrum of the natural product (black, extracted from the isolation paper[31]), whereas the spectrum of **2** showed a subtle but distinct dissimilarity.

The comparison of the recorded optical rotation of **1** ($[\alpha]_D^{24}$ = –74.3, c = 0.41, MeOH) and **2** ($[\alpha]_D^{24}$ = –58, c = 0.09, MeOH) with the one reported for the natural product ($[\alpha]_D^{24}$ = –84.2, c = 0.34, MeOH)[31] indicated that the absolute configuration of the synthetic material was identical to that of natural leiodermatolide. As a consequence, the structure of leiodermatolide is correctly represented by formula **1**. This assignment was later independently confirmed by the total synthesis of the Paterson group[40] and by the biological tests summarized in chapter 2.10.

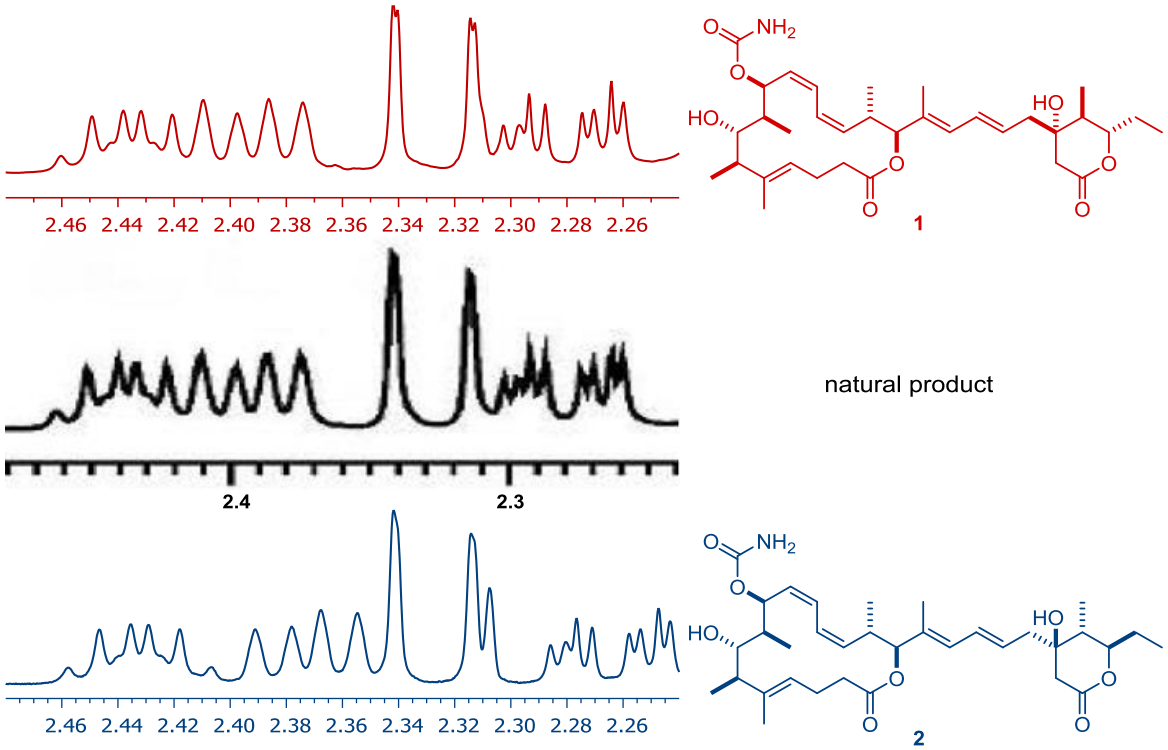



*Figure 2.4:* Extract from the $^{1}$H NMR spectra of **1** (red), natural leiodermatolide (black) and **2** (blue). All spectra were recorded in $CD_2Cl_2$ on a 600 MHz spectrometer. The full spectra can be found in the appendix.

As outlined in this chapter, the first total synthesis of the scarce marine natural product leiodermatolide was achieved in 19 steps along the longest linear sequence. The synthesis of both possible isomers allowed the structure to be assigned based on subtle differences in the $^{1}$H NMR spectra.[39] This short and flexible route delivered approximately 13 mg of the natural product and enabled a detailed biological investigation (see chapter 2.10). A significantly larger amount of the natural product was later prepared during a second generation synthesis (for details, see chapter 2.9).

## 2.7 Structural considerations

During the deprotection of the MOM-protected precursor **92** to give **1**, a perspicuous change in the $^{1}$H NMR spectra was noticed. Specifically, the spectra of all MOM-protected precursors of **1** show a significant line broadening for the atoms on the periphery of the macrocycle, regardless of the solvent ($CDCl_3$, $CD_2Cl_2$, $C_6D_6$) or concentration. This line broadening vanishes once the MOM group has been removed. It is postulated that the unmasking of the hydroxyl group at C.7 enables the formation of a hydrogen bond with the carbamate moiety at C.9. Due to this stabilizing effect, it is believed that the conformational freedom is reduced and the signals on the macrocycle become better resolved. Figure 2.6 illustrates this spectral feature and shows a juxtaposition of the spectra of **92** and **1**. Both spectra were recorded on a 600 MHz spectrometer with $CD_2Cl_2$ as the solvent.

Although the isolation team had described leiodermatolide as an amorphous white solid, a crystal structure could be obtained by slowly evaporating a $CH_2Cl_2/Et_2O$ solution of leiodermatolide (**1**).[57] The collected single crystals turned out to be the monohydrate of **1**, which crystallized in the $P2_12_12_1$ space group. The structure of **1** in the solid state as represented in figure 2.5 reveals several characteristic structural features of the macrocycle.

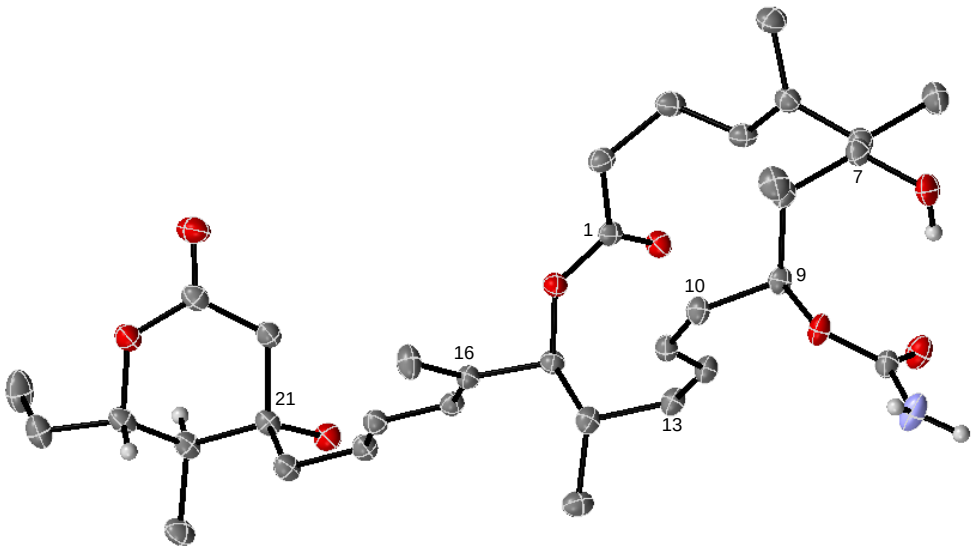



*Figure 2.5:* Crystal structure of leiodermatolide (**1**).
Hydrogen atoms and the co-crystallized water molecule are omitted for clarity.

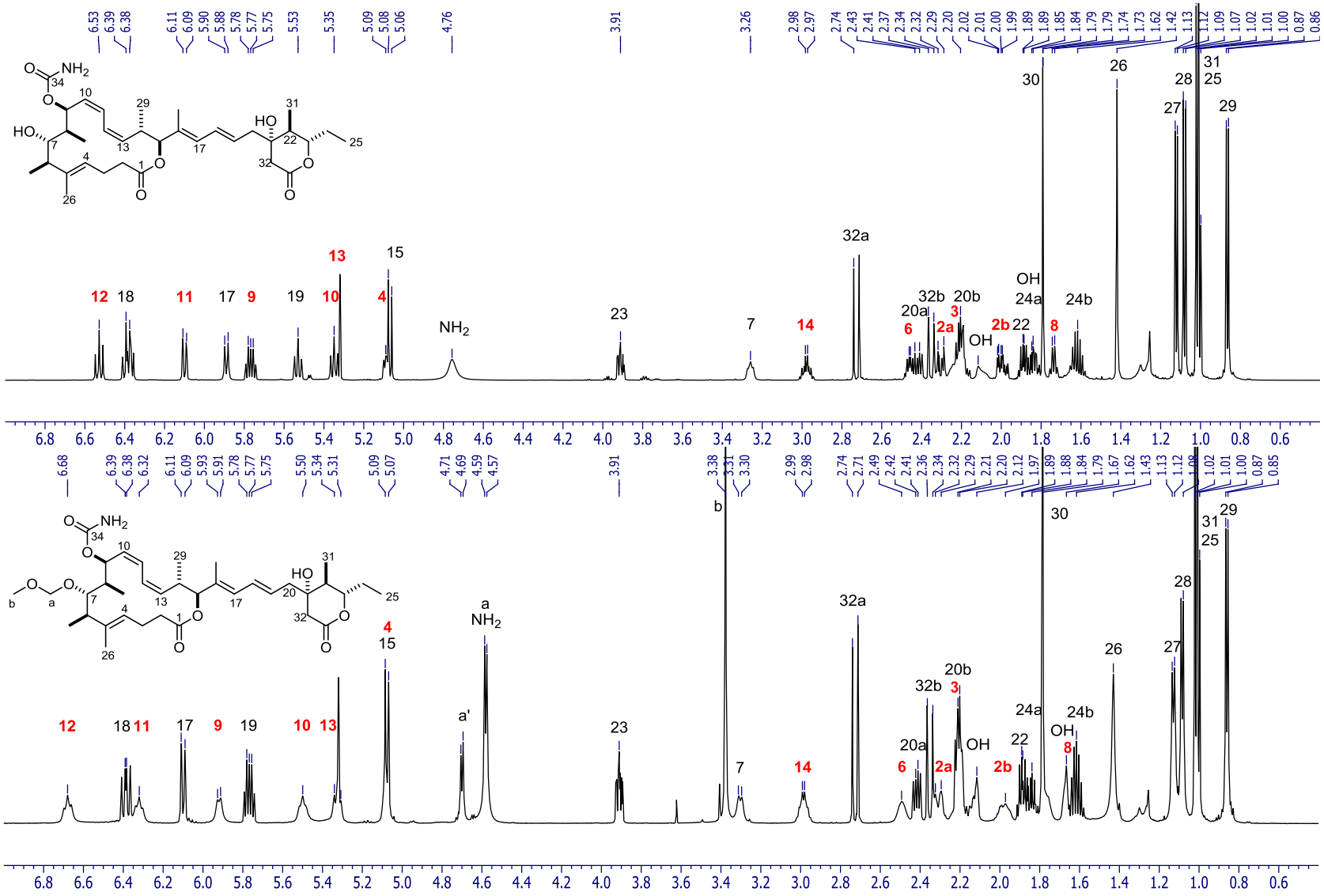


*Figure 2.6:* Comparison of the $^{1}$H NMR spectra (600 MHz, $CD_2Cl_2$) of **1** (top) and **92** (bottom). Signals that resolve after deprotection are highlighted in red.

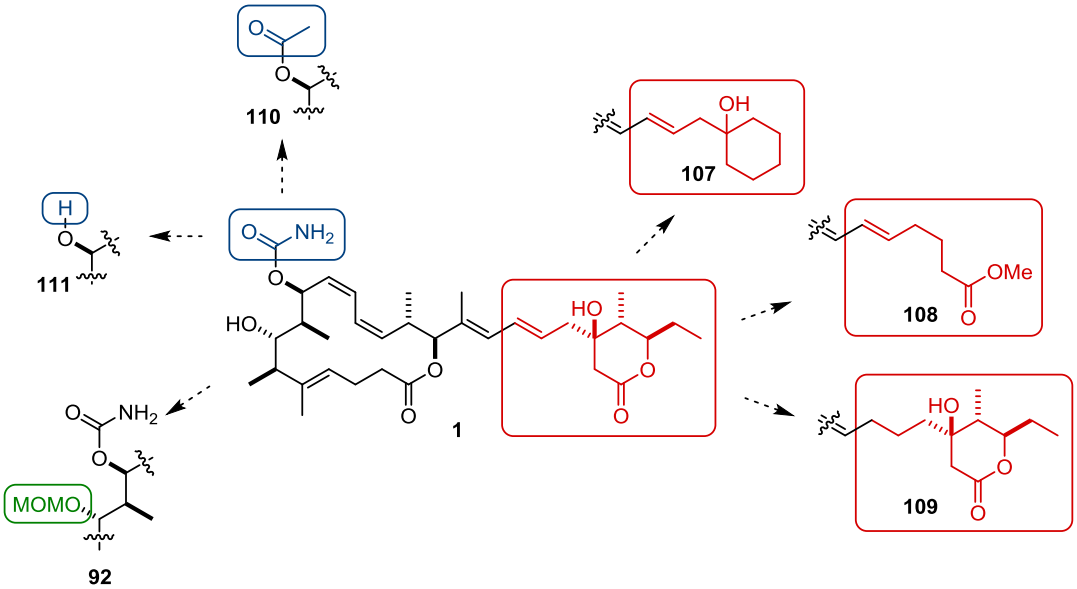
For instance, the (*Z*,*Z*)-diene is almost orthogonal to the macrocyclic framework; a feature that was previously observed during the iejimalide project.[112] The proximity of the carbamate moiety at C.9 and the alcohol functionality at C.7 confirms the previously proposed stabilizing hydrogen bond. Although the bridging proton could not be localized in a differential Fourier map, the calculation puts it only 2.116 Å away from the carbonyl group. Moreover, the relative configuration of both groups is deemed indicative, since they point into the very same direction, which is sterically and electronically disfavored otherwise.

The olefins of the pentadienyl spacer are in parallel orientation for maximal orbital overlap and populate the energetically favored *s*-trans configuration. Therefore, the δ-lactone side chain is spatially remote from the macrocycle, which is in line with the observation that these two substructures could not be correlated by spectroscopic means and the diastereomeric counterparts **1** and **2** show only minimally distinct spectral signatures.

## 2.8 Synthesis of leiodermatolide analogues

### 2.8.1 Motivation

The promising biological profile inspired the pursuit of several leiodermatolide analogues to shed light on the pharmacophore of leiodermatolide, which was unknown at the outset of this study. Specifically, the δ-lactone side chain was systematically varied to disclose whether this rather unusual motif is required for biological activity. In addition to the previously synthesized compound **2** bearing an antipodal head group, several modifications with respect to the structure of the natural product were targeted (scheme 2.40). Thus, the δ-lactone was replaced by a cyclohexanol ring (as in **107**) to maintain the tertiary alcohol while simultaneously lacking the hydrolysis-prone lactone, or by a linear methyl ester group (as in **108**), which retained only the ester carbonyl group. Both compounds preserved the pentadienyl linker that keeps this functional handle at distance to the macrocycle. As a less profound variation, compound **109** lacks one site of saturation within the spacer and should thus provide more structural flexibility. The replacement of the carbamate moiety allows to evaluate whether the postulated hydrogen bond is necessary for biological activity. Thus, an acetate group (**110**) was envisioned to take its place as a slightly less potent hydrogen bond acceptor. Furthermore, the free diol **111** was an interesting target, since a possible engagement in hydrogen bonding would from a six- instead of an eight-membered ring. The MOM-protected compound **92** was further submitted to the assay, since all functional groups were present except for the hydrogen bond donor at C.7.

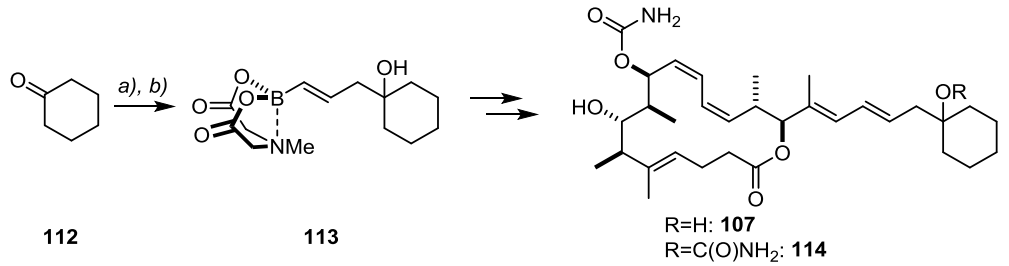



*Scheme 2.40:* Targeted derivatives of **1**: carbamate modification (blue) and δ-lactone side chain variations (red).

### 2.8.2 Modifications of the side chain

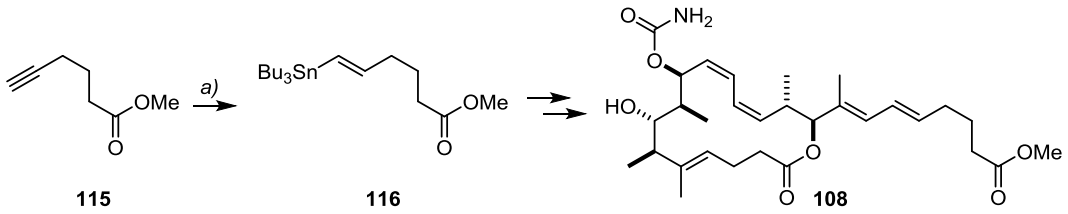
*Remark:* All experiments described in this chapter were carried out by Dr. Damien Mailhol; details can be found elsewhere.[113] Although the transformations leading to analogues **107**, **108** and **109** were not fully optimized, sufficient material for a preliminary cytotoxicity evaluation was obtained.

The analogues bearing different side chains were synthesized according to the same logic as outlined above. The cyclohexanol derivative **113** was prepared by allylation of cyclohexanone (**112**)[114] and ensuing cross-metathesis with vinyl MIDA boronate ester (**R8**). The endgame according to the sequence described for the natural product delivered the target compound **107**, albeit in slightly reduced yield since the carbamoylation was no longer selective for the secondary allylic alcohol.



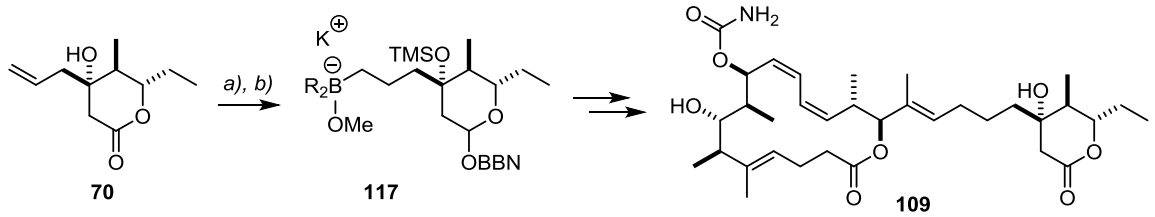

*Scheme 2.41:* Preparation of cyclohexanol analogue **107**. Conditions: a) (allyl)B(pin), $In^0$ (3 mol%), $H_2O$, rt, 90%; b) vinylB(MIDA) (**R8**), **C3** (10 mol%), $CH_2Cl_2$, 40 °C, 69% (*E*/*Z* > 20:1).[57]

Hydroboration of commercial methyl 5-hexynoate (**115**) followed by copper-catalyzed boron-tin exchange[115] set the stage for the Stille coupling envisioned for the introduction of the methyl ester side chain of analogue **108**. The coupling proceeded in 80% yield and enabled the rapid access to this derivative after carrying out the sequence of semihydrogenation, carbamoylation and protecting group manipulations.




*Scheme 2.42:* Synthesis of methyl ester analogue **108**. Conditions: a) $Cy_2BH$, THF, 0 °C, then aq. NaOH, rt, then $Cu(acac)_2$ (5 mol%), (*n*-Bu)$_3$SnCl, −15 °C to rt, 28% (d.r. > 20:1).[57]

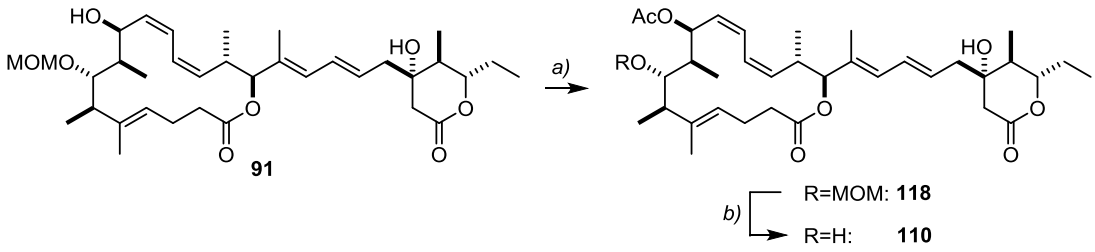
Lastly, the δ-lactone side chain **70** was TMS protected before being subjected to a sequence of hydroboration, alkyl Suzuki coupling and oxidation of the partially reduced lactone. Although the yields were rather moderate and the subsequent silyl deprotection was plagued by elimination of the trimethylsilyl ether, enough material of analogue **109** could be secured for a first biological assessment.




*Scheme 2.43:* Preparation of side chain analogue **109**. Conditions: a) imidazole, TMSCl, DMAP, $CH_2Cl_2$, 0 °C to rt, 76%; b) 9-BBN, THF, 50 °C, then KOMe, rt, 2h, then **80**, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (20 mol%), $AsPh_3$ (50 mol%), 70 °C; then PCC, $CH_2Cl_2$, rt, 47% over 2 steps.[57]

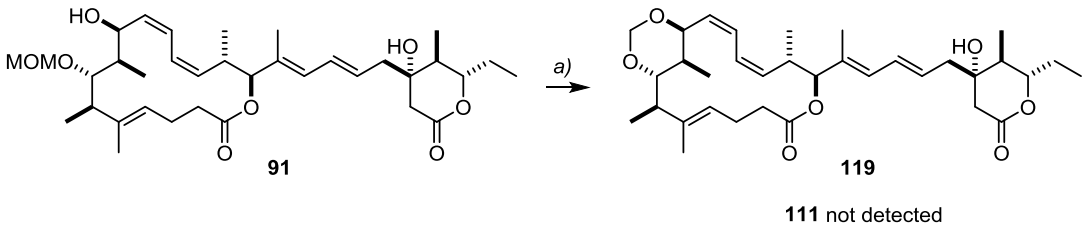
### 2.8.3 Modifications on the macrocycle

The synthesis of analogues bearing modifications of the carbamate moiety started from the macrocyclic diene **91**. In line with the result of the carbamoylation, the acetylation of compound **91** occurred preferentially at C.9, although formation of the bis-acetylated compound (27%, not shown) could not be avoided, most likely due to the higher reaction temperatures required for the acetylation (0 °C vs. −78 °C). Nevertheless, acetate **118** was isolated in sufficient amounts and was subsequently deprotected using the conditions developed for the natural product. The reaction required multiple additions of dimethylboron bromide, but afforded the targeted analogue **110** in moderate yield.




*Scheme 2.44:* Synthesis of acetate analogue **110**. Conditions: a) $Ac_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C to rt, 54%; b) $Me_2BBr$, $CH_2Cl_2$, −90 to −78 °C, 54%.

It was originally planned to access diol **111** from the very same intermediate **91** by direct deprotection of the MOM group. In the event, the desired product could not be detected in the complex crude mixture. Rather, the formation of cyclic acetal **119** was observed, which could be isolated in 18% yield by preparative TLC. Its formation can be explained by intramolecular trapping of the oxonium ion generated from the MOM-ether at C.7 by the alcohol at C.9. The more rigid 1,3-dioxane derivative itself was deemed structurally interesting, since the hydrogen bonding array of **1** was replaced by a more rigid covalently bridged acetal. Further experiments to obtain diol **111** were therefore not carried out.




*Scheme 2.45:* Attempted synthesis of analogue **111**. Conditions: a) $Me_2BBr$, $CH_2Cl_2$, −90 to −78 °C, 20%.

Studies to optimize the yields for compounds **110** or **119** were not performed since it was unclear at the time how these compounds would perform in the biological assays.

## 2.9 Development of a second generation synthesis

### 2.9.1 Motivation

After the successful first generation synthesis, which permitted the structure assignment and delivered sufficient material for more thorough biological testing, a continuing and reliable material supply of this otherwise scarce natural product was deemed necessary. Therefore, the bottlenecks of the first generation were to be replaced by more efficient steps. Three problematic transformations were identified for which more practical and more reliable operations had to be found:

(i) The allylation of β-keto ester **61** was performed with stoichiometric amounts of the chiral allylating agent **R7**. Since the preparation of this reagent was inconvenient and required the generation and use of diazo compounds as well as isolation by fractional crystallization, a more efficient catalytic alternative was desirable.

(ii) With an isolated yield of no more than 55%, the Suzuki coupling of the macrocycle **80** with the δ-lactone fragment **78** was arguably the major bottleneck of the first generation synthesis. Since no starting material could be reisolated, every coupling reaction resulted in loss of half of the precious material. Furthermore, the rather acidic conditions required for closure of the partially opened δ-lactone had to be carefully controlled, since further material loss was suspected from prolonged exposure.

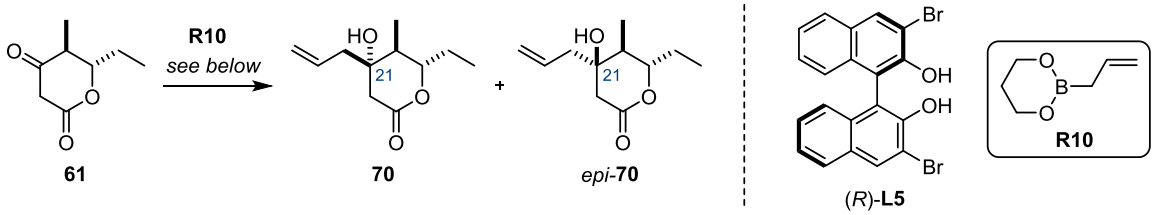
(iii) The RCAM required the handling of the extremely sensitive precatalyst **C6**, which entailed that all solvents had to be rigorously dried and degassed prior to use. Furthermore, *t*-butyl-dimethylaniline, resulting from hydrolysis of the amido ligand, was always isolated along with the desired product and could only be removed by applying high vacuum at 60 °C. The more convenient and user-friendly catalyst **C1** was unable to mediate ring-closure. A more detailed analysis of this reaction was therefore intended to shed light on the reasons for the failure of **C1**.

Slight modifications were also required during the scale-up syntheses of the alcohol fragment **F** and the acid fragment **E**. Since these modifications were only minor, they have been already mentioned in chapter 2.6.

### 2.9.2 Catalytic installation of the C.21 stereogenic center

After a long screening process, the stereogenic center of the δ-lactone moiety at C.21 was installed by a reagent controlled allylation of cyclic β-keto ester **61**. Although the reaction itself was reliable and successfully repeated with up to 180 mg of **61**, the tedious and low-yielding preparation of the reagent **R7** stimulated the search for a more convenient catalytic alternative. It was speculated that allylboronates would exhibit similar reactivity and may therefore be applicable to the challenging substrate **61**. Although allylboronates were originally decorated with bidentate ligands in a stoichiometric manner,[116] Schaus later showed that catalytic amounts of 2,2'-binaphthol ligands work well for the asymmetric allylation of ketones.[117] Furthermore, a single example of a successfully allylated acyclic β-keto ester was reported. During the screening of conditions for the first generation synthesis, a promising result was obtained by combining allyl-donor **R10** with catalytic amounts of 3,3'-dibromo 2,2'-binaphthol (**L5**) in the presence of *t*-BuOH. Although the conversion reached only 44%, the preference for the desired adduct **70** over the epimer *epi*-**70** suggested that optimization of the reaction conditions might eventually result in a satisfactory outcome (table 2.5, entry 2).

*Table 2.5:* Optimization of the catalytic asymmetric allylation of **61**.



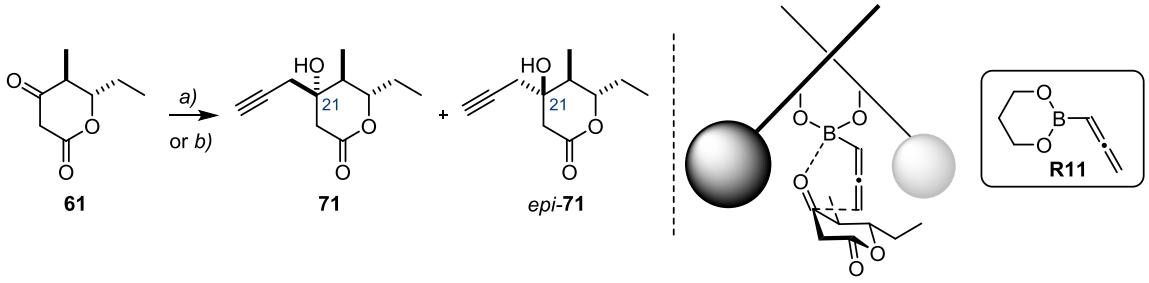

| entry | catalyst (10 mol%) | conditions | yield [%] (conv.)[1)] | 70 : *epi*-70 [1)] |
|---|---|---|---|---|
| 1 | (*S*)-**L5** | *t*-BuOH, toluene, rt | (39) | 1:10 |
| 2 | (*R*)-**L5** | *t*-BuOH, toluene, rt | (10-44) | 4:1 |
| 3 | (*R*)-**L5** | *t*-BuOH, $H_2O$, toluene, rt | (6) | 4:1 |
| 4 | (*R*)-**L5** | *t*-BuOH, rt (neat) | (5) | 4:1 |
| 5[57] | (*R*)-**L5** | *t*-BuOH, toluene, microwave, 130 °C | 84 | 6.1 |
| 6[57] | (*R*)-**L5** | toluene, microwave, 130 °C | 95 | 6:1 |
| 7[57] | (*S*)-**L5** | t-BuOH, toluene, microwave, 130 °C | 88 | 1:9 |

1) Determined by $^1$H NMR analysis of a crude sample.

However, all attempts to reproduce or improve this result failed for unknown reasons. Various experiments with modified reaction parameters such as solvent or water content led to no more than 15% conversion (entries 2, 3, 4).

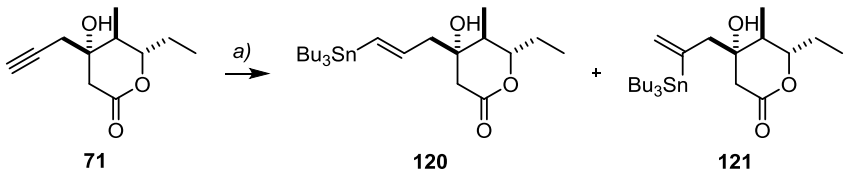
After an extensive literature survey, it was found that microwave irradiation at 130 °C[118] ensured reliable conversion of **61** into the allylated product **70**.[57] Surprisingly, the diastereomeric ratio was improved despite the high reaction temperature. The addition of *t*-BuOH was found to be irrelevant and its omission simplified the experimental procedure.

In order to replace the Suzuki coupling with a Stille coupling that had proven quite efficient during the synthesis of analogue **108**, the propargylation of **61** with allenylboronate **R11** under otherwise identical condition was explored.[118] The selectivity of this reaction was even better and provided the desired homopropargylic alcohol **71** with a diastereomeric ratio of 7.6:1 and excellent yield. The stereochemical outcome was confirmed by X-ray diffraction of the minor isomer *epi*-**71**.[57] Moreover, the control experiment with (*S*)-**L5** indicated that the addition is catalyst- rather than substrate-controlled.




*Scheme 2.46:* Synthesis of homopropargylic alcohol **71**. Conditions: a) **R11**, (*R*)-**L5** (10 mol%), toluene, microwave, 130 °C, 94% (7.6:1 d.r.); b) **R11**, (*S*)-**L5** (10 mol%), toluene, microwave, 130 °C, 87%, (1:15 d.r.).[57]

According to the calculated transition state structure by Goodman,[119] the boronate undergoes full ligand exchange with **L5,** releasing 1,3-propanediol. This was supported by the fact that *t*-BuOH was neither necessary nor beneficial for the reaction. The substrate resides in the chiral pocket formed by the binaphthol derivative through coordination of the ketone carbonyl to the Lewis acidic boron center (scheme 2.46). To avoid steric repulsion with the bulky π-systems of the ligand, the substituents on the six-membered ring are oriented towards the open quadrant in the back. This prepositioning of the substrate explains the high selectivity encountered during the allylation and propargylation process, placing the newly introduced substituent in a pseudo-axial position.

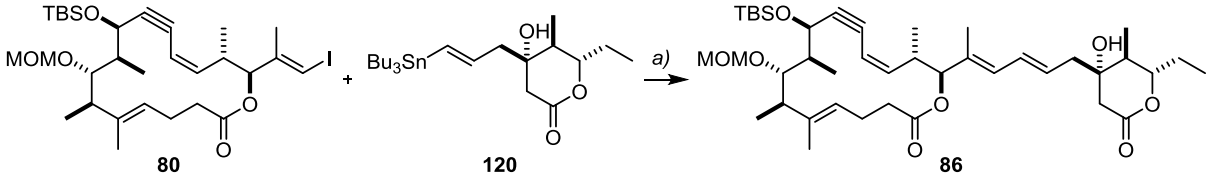



*Scheme 2.47:* Preparation of the modified δ-lactone fragment **120**. Conditions: a) *n*-$Bu_3SnH$ (added over 15 min), $Pd_2(dba)_3$ (1 mol%), $PCy_3HBF_4$ (4 mol%), *i*-$PrNEt_2$ (8 mol%), $CH_2Cl_2$, rt, **120**: 72%, **121**: 15%.[57]

The subsequent hydrostannation was achieved with $Pd_2(dba)_3$ as the precatalyst, $PCy_3$ as the ligand and dropwise addition of tin hydride to ensure full conversion.[120] Small amounts of the undesired regioisomer **121** were removed by column chromatography.[57]

### 2.9.3 Stille cross coupling reaction[57]

Next, the modified coupling partner **120** was engaged in a Stille-Migita coupling with vinyl iodide **80**. Under conditions previously developed in the group, the reaction was clean and the formation of **86** was complete after 1 min, thus minimizing the contact time of the sensitive compounds with transition metals.[121] The virtually neutral reaction conditions allowed the desired adduct **86** to be isolated in excellent 93% yield, which could be reproduced on a 100 mg scale.[57]




*Scheme 2.48:* Stille cross coupling reaction. Conditions: a) $[Pd(PPh_3)_4]$ (5 mol%), CuTC, $[NBu_4][Ph_2PO_2]$, DMF, rt, 93%.[57]

Although 1.4 equivalents of vinyl stannane **111** had to be engaged due to competing proto-destannylation, the low-yielding Suzuki coupling from the first generation synthesis was replaced by a very efficient Stille coupling, allowing for a significantly higher material throughput.

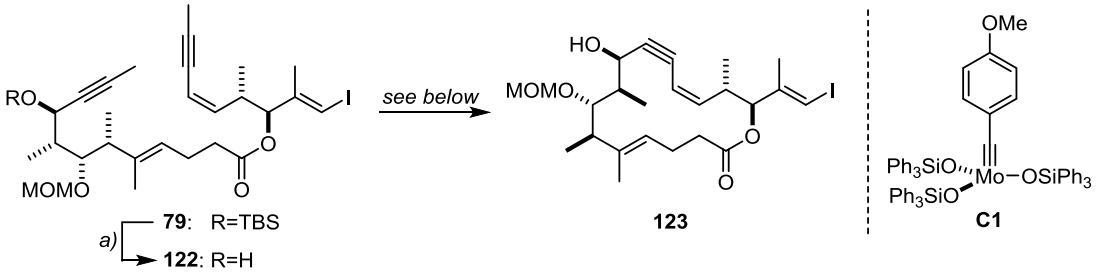
### 2.9.4 Further investigation of the RCAM reaction

The RCAM of **79** proceeded only under forcing conditions with **C6** activated by $CH_2Cl_2$ as catalyst. At the time, it was speculated that the failure to activate the alkyne was due to the steric demand of the flanking propargylic silyl ether. The results obtained during the semihydrogenation, which occurred only once the silyl ether was cleaved, further indicated a pronounced steric shielding of the alkyne by the bulky silyl ether.

Based on these observations, the TBS group of **79** was cleaved with the aid of TBAF and the resulting product **122** engaged in the RCAM reaction. Since it was well known that the

extremely sensitive system **C6**/$CH_2Cl_2$ would not tolerate an alcohol group, the silanolate bearing molybdenum catalyst **C1** was examined again. Under the conditions previously used for the protected congener **79**, the ring closure of **122** now occurred with only trace amounts of dimeric species detectable in the reaction mixture (entry 1). It was soon realized that the catalyst loading could be lowered to 15 mol% (entries 2, 3) and the reaction was similarly effective even at ambient temperature (entry 3) when carried out in the presence of 5 Å MS to sequester the released 2-butyne. Finally, adjustment of the concentration minimized the formation of dimeric species and allowed cycloenyne **123** to be isolated in 61% yield with 15 mol% of **C1** (entry 4).

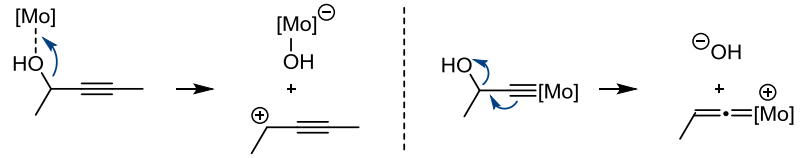
*Table 2.6:* Further investigation of the RCAM. Conditions: a) TBAF, THF, 0 °C to rt, 85%.




| entry | catalyst | conc. | conditions | result |
|---|---|---|---|---|
| 1 | **C1** (30 mol%) | 0.003 M | toluene, 100 °C, | 65% |
| 2 | **C1** (10 mol%) | 0.003 M | toluene, 100 °C, | s.m.:prod 1:4[1)] |
| 3 | **C1** (15 mol%) | 0.003 M | toluene, 5 Å MS, rt | 52% + 18% dimer |
| 4 | **C1** (15 mol%) | 0.0016 M | toluene, 5 Å MS, rt | 61% |

1) determined by $^1$H NMR analysis of a crude sample.

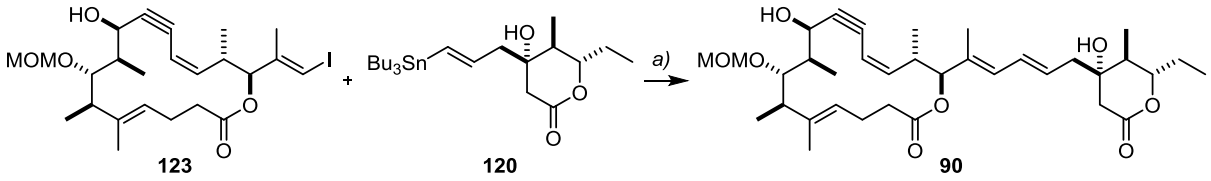
The tolerance of a propargylic alcohol during an alkyne metathesis reaction was largely unprecedented, and only simultaneously were successful examples reported by our group.[122] On one hand, such substrates can simply coordinate to the Lewis acidic molybdenum center through the oxygen lone-pair. This ligation might either tune down the catalytic activity of the molybdenum catalyst or could eventually end up in carbon-oxygen bond cleavage of the substrate under formation of a stabilized propargylic cation (scheme 2.49, left).[122a] On the other hand, the alkylidyne formed from a propargylic alcohol and the metal catalyst possesses highly nucleophilic character at the α-carbon and is likely to induce elimination of the alcohol. (scheme 2.49, right).[122a]




*Scheme 2.49:* Possible side reactions of propargylic alcohols and molybdenum alkylidynes.

It is for these reasons that alkyne metathesis with substrates bearing functional groups in the propargylic position remained largely unexplored and was enabled only by the introduction of the latest generation of alkyne metathesis catalysts.[25] The findings described herein will likely encourage further applications of this strategy in sterically demanding cases.[122b]

With an alternative procedure for the crucial ring-closure established, the optimized Stille cross-coupling reaction was executed with the macrocyclic vinyl iodide **123** bearing a free propargylic alcohol.[57] As expected, the additional protic functionality did not interfere with this protocol and the cross-coupled product **90** was obtained without incident while converging with the route described for the first generation synthesis.




*Scheme 2.50:* Interception of the first generation synthesis by Stille cross-coupling. Conditions: a) $[Pd(PPh_3)_4]$ (5 mol%), CuTC, $[NBu_4][Ph_2PO_2]$, DMF, rt, 90%.[57]

In conclusion, all supply-limiting steps of the first generation synthesis were replaced by more efficient and convenient synthetic manipulations. The revised synthesis of the δ-lactone features a catalytic asymmetric propargylation of a highly enolizable substrate. The low-yielding Suzuki coupling was replaced by a more efficient Stille coupling that ensured excellent yields for this critical fragment-assembling step. Finally, a closer investigation of the RCAM opened an alternative pathway to achieve the generation of the macrocyclic framework.

## 2.10 Investigation of the biological properties

The results described in this chapter were obtained in collaboration with Pfizer Drug Safety Research and Development, Pfizer Oncology and Pfizer Oncology Medicinal Chemistry. The contributions of Xingzhi Tan, Weidong Ding, Elizabeth E. Rubitski, Zhanna Sobol, Maik Schuler, My-Hanh Lam, Sylvia Musto, Frank Loganzo and Andreas Maderna are gratefully acknowledged.

### 2.10.1 Cytotoxicity

In order to confirm the biological activity reported by the isolation team, synthetic leiodermatolide (**1**) was tested against seven different human cancer cell lines. In all cases, $GI_{50}$ values in the low single-digit nanomolar scale were obtained (table 2.7) after an incubation period of four days. Impressively, this high antiproliferative activity was maintained when HEL92.1.7 leukemia cells were treated with leiodermatolide (entry 4). This human erythroleukemia cell line is known to express the permeability glycoprotein (Pgp) efflux transporter, also known as multidrug resistance protein 1, which is often believed to be the main reason for the development of resistances of leukemia cells against the treatment with chemotherapeutic agents.[123] It acts by pumping the cytotoxic agent out of the cell and therefore lowers its bioavailability.[124] This process is believed to be an evolutionary adaption to the threat imposed upon cells by potentially toxic substances.[125] It seemed reasonable to assume that leiodermatolide (**1**) is therefore not an effective efflux substrate, although more evidence has to be acquired in the future.

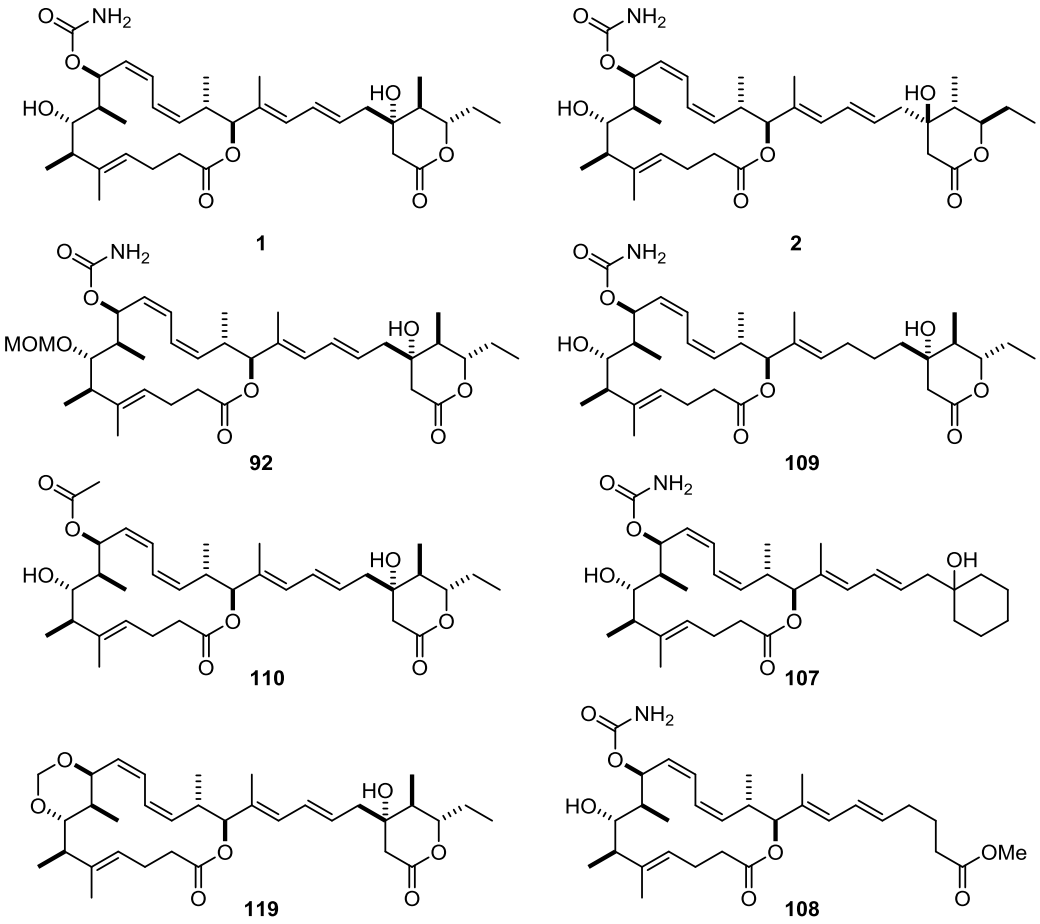
*Table 2.7:* Cytotoxic effect of synthetic leiodermatolide on a select panel of cancer cells.

| entry | cell line | histotype | $GI_{50}$ [nM] |
|---|---|---|---|
| 1 | HL60 | leukemia | 1.0 |
| 2 | NB4 | leukemia | 0.4 |
| 3 | Raji | leukemia | 1.0 |
| 4 | HEL92.1.7 | leukemia | 0.9 |
| 5 | N87 | gastric | 2.4 |
| 6 | MDA-MB-361-DYT2 | breast | 3.5 |
| 7 | HT29 | colon | 2.5 |

As a second step, the set of synthesized analogues (see overview in scheme 2.51) was tested for antiproliferative activity against the same panel of cancer cell lines.

All compounds underwent a prescreening to select those with a detectable proliferative activity at concentrations below 1 µM. During this prescreening process, the analogue **119** containing a rigid cyclic acetal and compound **108**, in which the δ-lactone was replaced by a simple methyl ester were excluded from further testing. Apart from these, some synthetic intermediates en route to the natural product (**91**) or to its derivatives as well as a variety of δ-lactone isomers

(**70**, *epi*-**70**, *ent*-**70**, *ent,epi*-**70**) did not meet the generous cutoff of 1 µM. Nevertheless, six compounds made it into the next round and were tested on the very same cell lines as the natural product (table 2.8).




*Scheme 2.51:* Selected leiodermatolide analogues submitted to the biological evaluation.

Not surprisingly, the natural product itself was the most potent of the tested compounds. The immediate MOM-protected precursor **92** was rather inactive, except for two cell lines, where the potency is roughly tenfold reduced. However, acetate derivative **110** is only slightly less cytotoxic towards the indicated cancer cell lines than **1**.

*Table 2.8: Cytotoxic effect of leiodermatolide analogues on cancer cells (96 h incubation, $GI_{50}$ in nM).*

| | HL60 | NB4 | Raji | HEL92.1.7 | N87 | MDA-361 | HT29 |
|---|---|---|---|---|---|---|---|
| **1** | 1.0 | 0.4 | 1.0 | 0.9 | 2.4 | 3.5 | 2.5 |
| **92** | >100 | >100 | >100 | >100 | 50.4 | 44.6 | >100 |
| **110** | 13.0 | 17.5 | 67.9 | 1.4 | 8.0 | >10 | 5.9 |
| **2** | n.d. | n.d. | n.d. | n.d. | 144.9 | 306.5 | 199.3 |
| **109** | 35.8 | 14.8 | 66.5 | 51.0 | 41.1 | 52.6 | 40.6 |
| **107** | n.d. | n.d. | n.d. | n.d. | 288.6 | 422.3 | 480.2 |

Taken together, these data indicate that a hydrogen bond between C.7 OH and the proximal carbonyl is not only of structural but also of functional relevance. Nevertheless, these initial results suggest that the carbamate is not essential and therefore interchangeable. This might

gain importance when considering the opportunity of using this position as a possible anchoring site for attaching a monoclonal antibody. Antibody-drug conjugates are receiving massive attention in light of the possibility to further increase the selectivity of anticancer drugs by attaching them to selective carrier proteins.[126]

Compound **2** bearing the enantiomeric δ-lactone side chain was less active by a factor of more than 50. Although the spectral differences of the diastereomeric compounds **1** and **2** were only subtle, they can be clearly distinguished by their biological activity. As a consequence, these biological results served as an ultimate proof of the original structure assignment. Since both ends of the molecule tend to have a strong influence on the activity, they are deemed crucial for obtaining high activity. The supposedly more flexible derivative **109** bearing only one olefin within the linking unit showed slightly reduced potency, although it remained reasonably active.

In light of these findings, the retained activity of compound **107** for some of the cancer cell lines is remarkable, although it is significantly reduced when compared to the parent molecule **1**. Bearing only a truncated cyclohexanol moiety, structural stability and hydrophobic interactions seem to be the predominant structural feature for high activity, whereas the necessity to have an ester moiety as hydrogen bond acceptor appears non-critical. In line with this analysis, compound **108** was ruled out during the prescreening.

### 2.10.2 Investigation of the mode of action

For a better understanding of the cell cycle analysis carried out with leiodermatolide, it is essential to recall the general function of the cell cycle and the terms used for its description.[127] In general, the cell cycle describes the process of cell division, in which a cell replicates into two identical daughter cells. It can be split into three individual phases, namely the interphase, the mitotic phase and the cytokinesis phase. The interphase is further divided into three parts, Gap1 (G1) phase, Synthesis (S) phase, and Gap2 (G2) phase. The first stage of the interphase (G1) is responsible for increasing the amount of centrioles, which are mainly composed of tubulin. After the G1 phase, the cell can either reversibly enter the G0 phase, which is an inactive idling or move on into the S phase. During the S phase, the replication of the genetic material in the form of DNA occurs until all chromosomes have been duplicated. In the subsequent G2 phase, the enzymes involved in cell duplication are produced.[127]

The cell then enters the mitosis phase, which can further be partitioned into prophase, metaphase, anaphase and telophase.

i) During the **prophase**, all chromosomes assemble in pairs which are held together at the centromere. The centrioles then occupy positions at opposite poles of the cell and simultaneously install a network of microtubules, which is also known as the spindle apparatus.

ii) At the end of this stage, the centromeres connect via their proteins to the end of the microtubules thereby causing an alignment at the equator of the cell; this is called the **metaphase**.

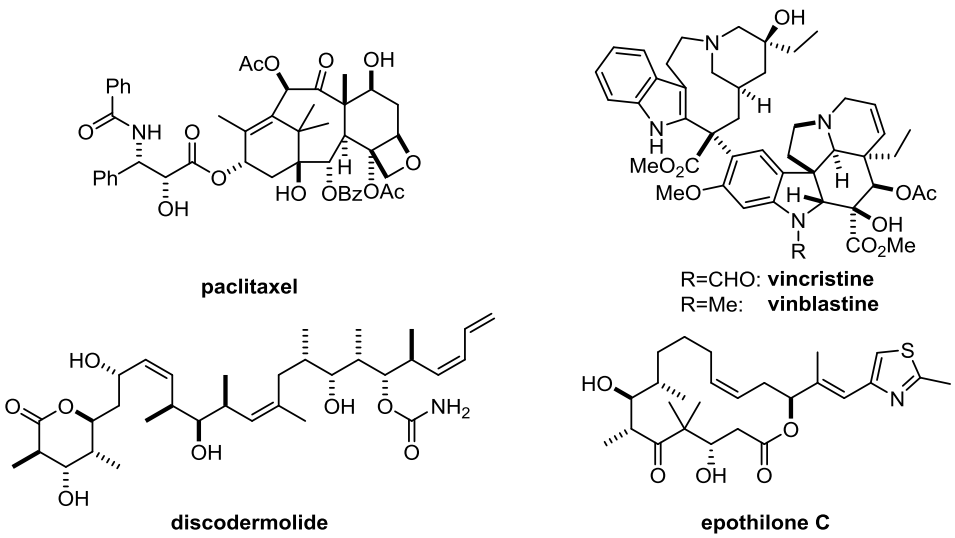
iii) The **anaphase** starts with the degradation of the protein, which holds the sister chromatids together, causing them to migrate to opposite poles.

iv) During the **telophase**, the stretching of the cell continues due to the ongoing lengthening of microtubules. A new membrane forms around the now separated chromosomes from the former cell membrane, although the final cell division takes place only during cytokinesis and involves vesicles from the Golgi apparatus.[127]

The microtubules involved in this process are dynamic species, which are formed by polymerization of a heterodimeric species consisting of α- and β-tubulin.[128] Although their dynamics differ throughout the cell cycle, they are key proteins involved in the process of mitosis. This has made them an attractive target for cancer therapy. Two different concepts to interfere with tubulin dynamics are known:

(1) destabilizing the microtubules causing depolymerization, as in the case of the vinca alkaloids[129] or

(2) stabilizing the microtubules by co-polymerization, as in the case of paclitaxel, discodermolide and the epothilones.[130]




*Scheme 2.52:* Structures of selected previously reported antimitotic agents.

For both cases, the target binding pockets have been identified by co-crystallization in the past.[131] Although the underlying mechanisms are different, the most potent effect of both cancer agent groups is the suppression of microtubule dynamics.[132]

As described above, the exact mode of action of leiodermatolide was unknown at the outset of the project. Therefore, high content imaging analysis was performed in order to obtain information on cell cycle distribution, micronucleus induction, centrosome enumeration and interaction with tubulin.[133] For the present study, human U2OS cells from a 15-year old female patient suffering from bone cancer were used for the image analysis. The cell cycle analysis was carried out by measuring the DNA content of DAPI-stained U2OS cells after exposure to leiodermatolide for 24 h. Figure 2.7 shows the relative changes in cell cycle population after treatment with **1** in direct comparison with cells treated only with DMSO as the negative control. The population of the subG1 phase, which accommodated less than two pairs of chromosomes, increased steadily between 0.9 and 4 nM, but decreased prior to the commencement of the G2/M phase. Strangely, the raise of subG1 population did not show a correlation to the cytotoxicity either; this was indicated by the fact that small cells were identified during the image analysis rather than the expected debris (figure 2.8). The G0/G1 population started to decrease at concentrations above 8 nM, which can be interpreted as a reduction of the overall cell cycle activity. The same concentration caused a shift to high population of the S phase, which decreased upon increasing concentrations. Cells in G2/M phase were accumulated at concentrations of and above 18 nM in a dose-dependent way.

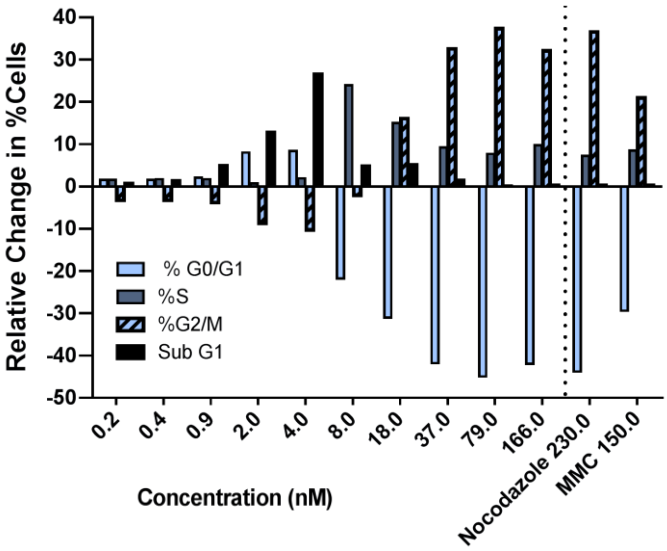



*Figure 2.7*: Cell cycle distribution of treated cells compared to control after 24 h incubation.

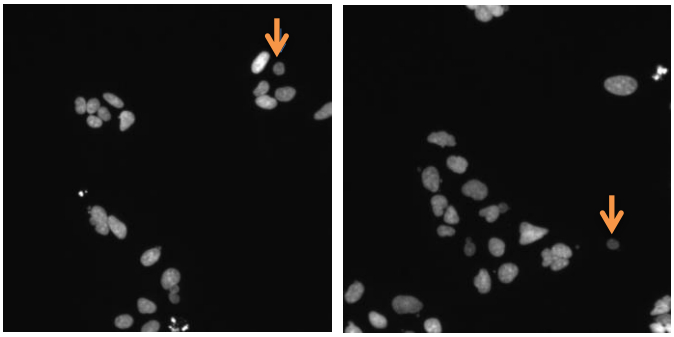


*Figure 2.8*: Representative images during cell cycle analysis. Arrows indicate cells in subG1 (<2N DNA).

Another indication for tubulin disruption is the measure of micronuclei that form upon treatment with a chemical substance. Micronuclei can form throughout the anaphase of mitosis; they are characteristic for chemicals that damage DNA strands or disrupt the mitosis process in general. Between 4 nM and 8 nM concentrations, **1** commenced to initiate the formation of micronuclei. It reached a maximum at concentrations of 37 nM with fivefold more micronucleated cells being observed when compared to the negative control. The absolute value is comparable to the positive control nocodazole. Even higher concentrations did not lead to a continuing rise in micronuclei formation, most likely due to increasing toxicity, which ultimately led to apoptosis.

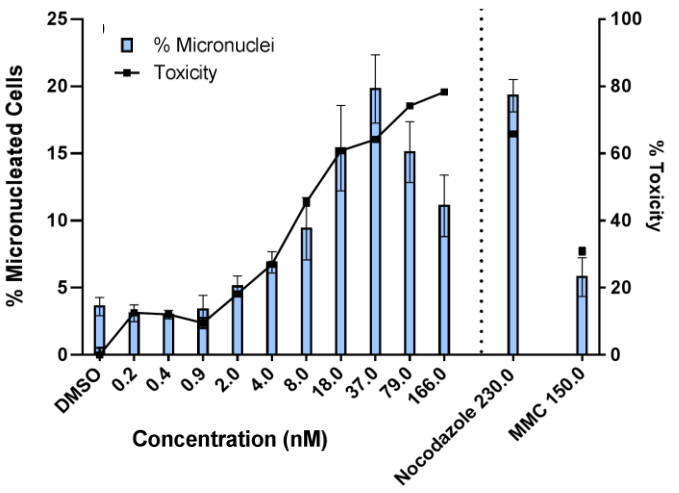



*Figure 2.9:* Micronuclei induction after 24 h incubation

Furthermore, the effect on centrosome amplification was measured. Centrosome amplification can occur when the replication process is stimulated and thus decoupled from the cell cycle.[134] The duplication sequence usually occurs during S phase, but can continue during the subsequent steps, when stimulated by chemical agents. Moreover, significant levels of centrosome amplification have been observed with untreated cancer cells.[135] These stand in sharp contrast to healthy human cells, which generally do not exhibit agglomeration of centrosomes. Thus, healthy tissue is far less sensitive than malignant cells to therapeutics acting by centrosome declustering.

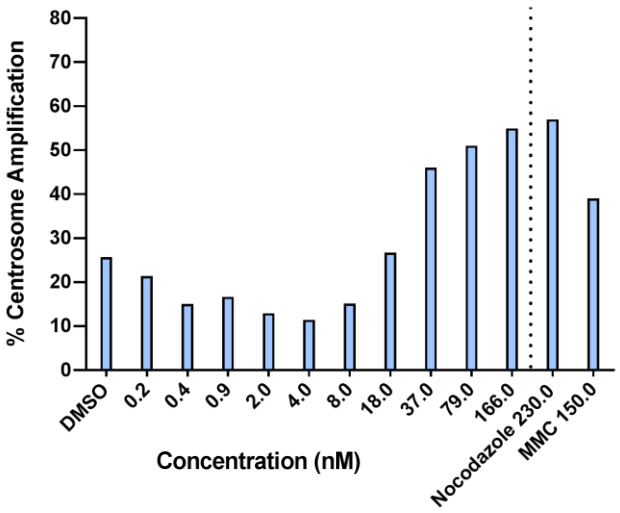



*Figure 2.10*: Centrosome amplification after 24 h.

Figure 2.10 details the concentration-dependent occurrence of amplified centrosomes, which is the percentage of cells containing more than two centrosomes. Unexpectedly, treatment of U2OS cells with leiodermatolide at levels below any observed toxicity induced a slight regression of amplified centrosomes when compared to the negative control. The maximum

effect was seen at 4 nM, for which the amount of amplified centrosomes was halved. In contrast, at concentrations above 8 nM, a significant concentration-dependent accumulation was noticed culminating in similar levels as the positive control nocodazole, which showed the highest concentration as evaluated during this study.

Finally, immunofluorescence imaging was carried out with an antibody specific to α-tubulin. Intriguingly, leiodermatolide caused abnormal spindle formation only above 8 nM concentration. Below this level, the recorded images do not show any effect on morphology with respect to α-tubulin or on the shape and size of cell nuclei. Furthermore, the supernumerary occurrence of centrosomes (green, figure 2.11) confirms the observations made before.

Taken together, all acquired data resemble the mode of action of a typical tubulin poison for concentrations above 8 nM. The observed effects induced by **1** at high concentrations are consistent with those observed for well-established tubulin-interfering drugs like nocodazole, colchicine, vinblastine and paclitaxel.

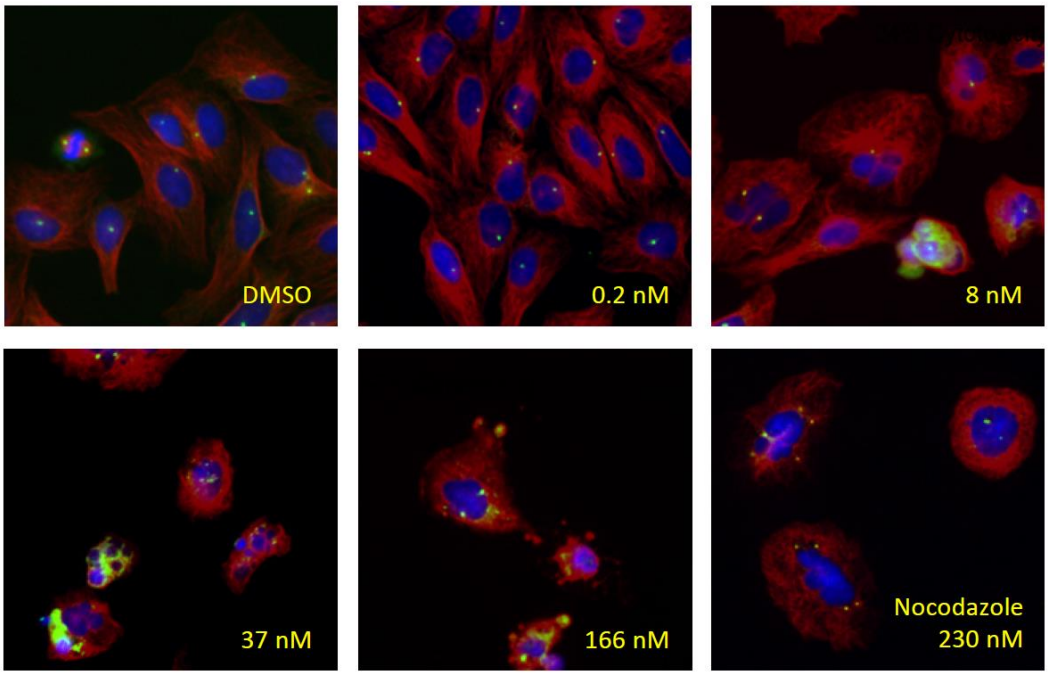



*Figure 2.11*: Fluorescence imaging of tubulin disruption (α-tubulin: red, nuclei: blue, centrosomes: green).

In this context, it is of particular importance to note that leiodermatolide did not cause any effect on purified tubulin. Thus, the previously reported outcome of the tubulin polymerization assay,[31] which showed no evidence for tubulin binding, was confirmed. Likewise, other biophysical assays like size exclusion chromatography (SEC LC-MS), tubulin-tryptophan quenching, an indicative test for the colchicine and vinca binding sites,[136] and isothermal titration calorimetry[137] did not indicate any interaction with purified tubulin. Since none of

these studies indicated a direct contact between tubulin and leiodermatolide, initially designed co-crystallization experiments were not carried out.

In order to establish a possible alternative target, a broad panel screen with 50 different kinases was performed (figure 2.12). However, no significant inhibition was observed for the investigated kinases, even at 1 µM concentration of the natural product. The direct binding target of leiodermatolide therefore remains unknown.

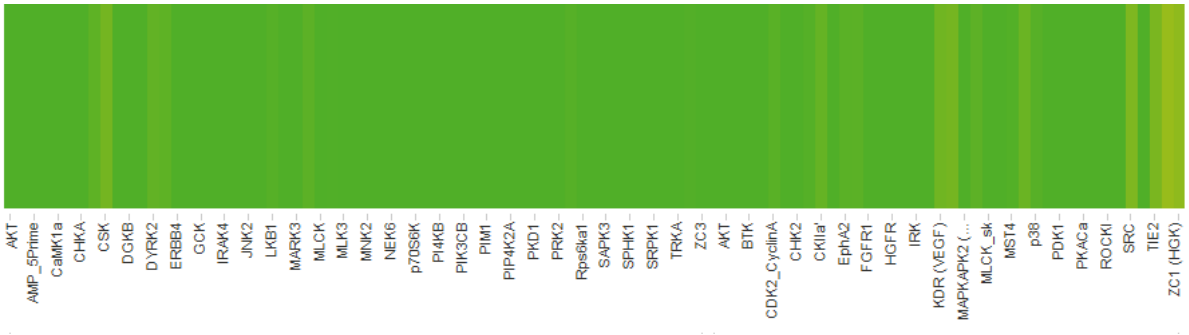



*Figure 2.12:* Kinase panel screen (c = 1 µM). green: 0% inhibition; yellow: 50% inhibition

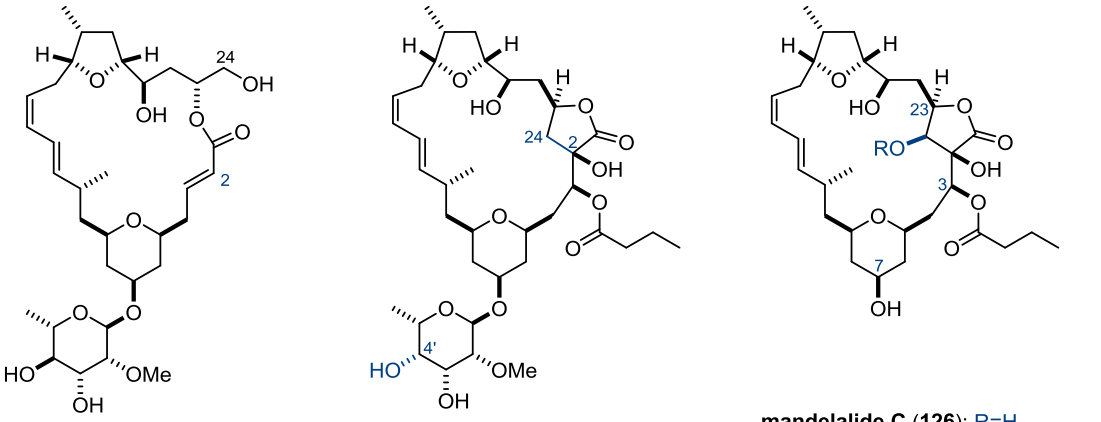
However, the behavior at concentrations below the 8 nM limit is unprecedented for an antimitotic agent and likely represents a novel mode of action. At these concentrations, no detectable toxicity for the employed cell line was observed. Nevertheless, leiodermatolide caused a significant drop of centrosome amplified cells compared to control. Similarly, the very same concentration caused an accumulation of subG1 cells with less than 2N DNA content. Taken together, the recorded data are suggestive of an arrest of the cell cycle prior to S phase but after completion of mitosis. Additionally, the replicated cells lack the full array of chromosomes and hypodiploidy was often recognized. The careful analysis of the samples obtained during the imaging studies showed that these cells are not debris and were correctly considered as small cells.

The data acquired so far point at centrosome declustering as leiodermatolide's potential mode of action. The observed spindle dysfunctioning leading to mitotic arrest followed by a peak in the subG1 cell population are common features of previously described centrosome declustering drugs.[138] Nevertheless, additional experiments including the staining for γ-tubulin and centrin2 as well as the measurement of phosphorylation of TACC3 as an indication for centrosome disruption in the subG1 population[139] should be performed to obtain more insight. If this mode of action is confirmed in future studies, it seems likely that the enormous potential offered by this specific mechanism offers will encourage more research with this unique natural product.[140] It should display a very high selectivity for tumor over healthy cells and may therefore reduce the side-effects commonly encountered with established anticancer agents.

# 3 Total synthesis of mandelalide A

## 3.1 Isolation, structural discussion and biological activity

Mandelalide A (**124**) was isolated along with three congeners, namely the mandelalides B, C, and D, from a *Lissoclinum* species found off the South African coast near Algoa Bay. The ascidian was collected by hand at a depth of 18 m from a white sand reef. After extraction of the raw material (15.1 g), bioassay-guided fractionation by reversed phase HPLC enabled the isolation of four novel natural products: mandelalides A (0.8 mg), B (0.5 mg), C (0.8 mg) and D (0.6 mg).[141] Their structures (scheme 3.1) were proposed based on the analysis of 2D-NMR data. The relative configuration was established by analyzing the ROESY as well as homonuclear ($^3J_{H,H}$) and heteronuclear ($^2J_{C,H}$) coupling constants. The absolute configuration could be assigned after acidic cleavage of the sugar moiety and co-injection of the bis-silylated methanolysis product with both enantiomeric glycosides of known configuration.

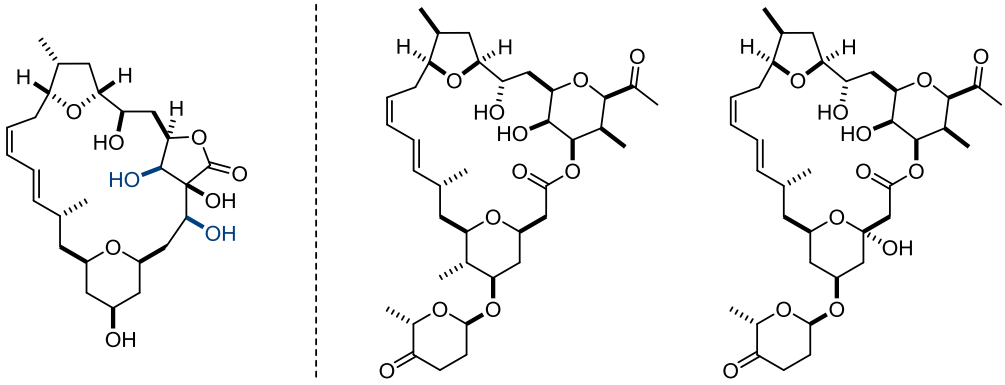



*Scheme 3.1*: Structures of mandelalides A – D as proposed by the isolation team. [141]

Bridging oxygen atoms lead to the occurrence of an all-*cis* substituted THF as well as an all-*cis* substituted THP ring within the macrocyclic framework and reduce the actual ring size of mandelalide A to 21. Mandelalide A possesses 14 stereogenic centers, nine of which decorate the macrocyclic scaffold; additional five reside on the sugar moiety. Within the macrocycle lies a diene of (*E,Z)*-configuration and an α,β-unsaturated ester. The carbon-carbon bond between C.24 and C.2 distinguishes mandelalides B, C and D (**125**, **126** and **127**) from mandelalide A (**124**), and installs a supplementary γ-lactone characteristic for these compounds. Furthermore, the former double bond between C.2 and C.3 is now oxidized to a diol motif. The all-*syn* configuration of the four contiguous stereogenic centers between C.23 and C.3 found in mandelalides C and D is noteworthy and was anticipated to pose a serious synthetic challenge. Remarkably, the mandelalides A (**124**) and B (**125**) differ in their sugar moiety, which is a 2-

methoxy L-rhamnosyl unit in **124**, whereas **125** contains the epimeric C.4' sugar unit derived from 6-dehydro L-talose.

In contrast, mandelalides C and D lack this glycosidic site and terminate in a free alcohol at C.7. Both compounds bear an additional stereogenic center at C.24 and differ only in the substitution pattern at this functional site. Moreover, **127** was found to degrad over the course of 12 months to deacylmandelalide D (**128**) by hydrolysis of the two butyrates.




*Scheme 3.2*: Degradation product of mandelalide D and related madeirolides A and B.

The structures of the mandelalide family are reminiscent of the equally scarce natural products madeirolides A (**129**) and B (**130**).[142] Surprisingly, these compounds were isolated from a lithistid *Leiodermatium* sponge but contain the enantiomeric northern THF fragment.[143] However, the similarities of the southern THP fragment and the diene moiety clearly link the structures of these two compound classes. The different origins suggest an underlying biosynthetic pathway, perhaps by a common microbial symbiont.

As the organic extract of the isolation showed promising cytotoxicity against three different cancer cell lines, mandelalides A and B were also tested. The pure compounds showed a half maximum inhibitory concentration ($IC_{50}$) in the two-digit nanomolar range with mandelalide A being twice as active as its counterpart mandelalide B.

Somewhat surprising, the related madeirolides exhibited no significant proliferative activity against pancreatic cancer cell lines, but are potent growth inhibitors against *Candida albicans*, thus displaying antifungal rather than antitumor properties.

*Table 3.1*: Cytotoxicity of mandelalide A and B as reported by the isolation team.

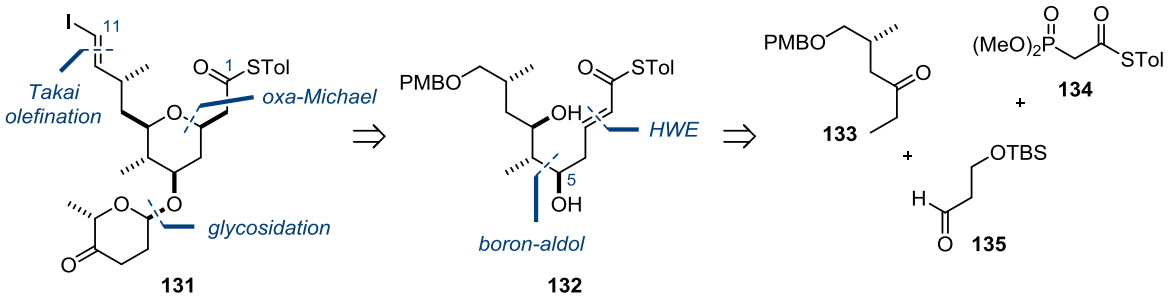
| | | $IC_{50}$ | | |
|---|---|---|---|---|
| **entry** | **cell line[1)]** | **organic extract** | **124** | **125** |
| 1 | NCI-H460 | 0.7 µg/mL | 12 nM | 29 nM |
| 2 | Neuro-2A | 5.6 µg/mL | 44 nM | 84 nM |
| 3 | MDA-MB-231 | 22.1 µg/mL | - | - |

1) NCI-H460: human lung cancer cells; Neuro-2A: mouse neuroblastoma cancer cells; MDA-MB-231:human breast carcinoma.

These preliminary results clearly demanded a more systematic investigation of the biological activity. The rare natural occurrence rendered a reliable and robust access by total synthesis indispensable. Moreover, the challenging structural features as outlined above made the mandelalide family an attractive target. Being the biologically most active family member, mandelalide A was chosen as the primary objective for our synthetic endeavor. The (*E*,*Z*)-diene scaffold within the macrocycle offered an excellent opportunity to implement RCAM followed by semihydrogenation of the enyne as the key sequence of the total synthesis.

## 3.2 Previous synthetic studies

At the outset of this study, neither a completed total synthesis nor any synthetic studies towards a member of the mandelalide family had been described. However, shortly after the initiation of the project, the group of Paterson described the synthesis of the C.1 to C.11 fragment of the related madeirolide A.[143] Their retrosynthetic strategy is outlined in scheme 3.3, which highlights the key reactions of the fragment synthesis.




*Scheme 3.3*: Retrosynthetic analysis of the C.1 to C.11 fragment of madeirolide A by Paterson.[143]

The macrocyclic framework was envisioned to be built up by a Yamaguchi macrolactonization, whereas the two fragments should be coupled by Stille cross-coupling. Vinyl iodide **131** was assembled by a Takai olefination and the cinerulose motif was attached by a glycosidation reaction. The all-*cis* configured THP ring was installed by an acid-mediated *oxa*-Michael addition on the α,β-unsatured thioester of **132**, which was constructed with a Horner-Wadsworth-Emmons olefination reaction using **134**. The stereogenic center at C.5 was introduced by a boron-mediated, asymmetric *syn*-aldol reaction of **133** and **135**. Although the obtained fragment **131** showed good spectral overlap with the reported data for the natural product and thus confirmed the assignment made for this region, the synthesis required 18 steps in the longest linear sequence. A significantly shorter route was thus desired and addressed for the synthesis of the southern mandelalide fragment during the course of this investigation.

Only after the total synthesis of the proposed structure of mandelalide A as a result of this thesis was published,[144] a total synthesis of the proposed aglycone of mandelalide A was

described by Ghosh and co-workers.[145] Furthermore, the group of Ye reported the successful synthesis and structure reassignment of mandelalide A[146] shortly after identical results had been disclosed in our group.[147] Consequently, these studies did not influence the retrosynthetic considerations nor any of the reactions carried out during the research outlined below and are therefore not discussed further. In contrast to our strategy, both approaches relied on a key cross-coupling between C.12 and C.13 and a Horner-Wadsworth-Emmons reaction to install the enoate motif at C.2 / C.3 (see Scheme 3.4 for numbering).

## 3.3 Objectives

Due to the seemingly promising biological profile, mandelalide A (**124**) was chosen as a target for total synthesis. The developed synthetic route was not only thought to confirm the structural assignment made by the isolation team, but also enable access to reasonable amounts of material to allow for a more detailed investigation of the biological properties. In view of these requirements, the overall strategy should be robust and scalable, and should rely on transition metal catalyzed reactions for C-C bond forming steps to establish an efficient pathway to the required material.

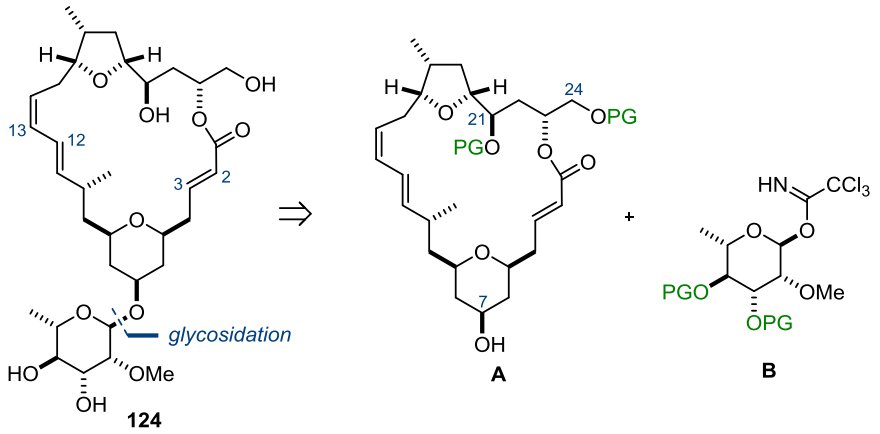
As in the leiodermatolide case, the synthetic sequence should depend on RCAM followed by semihydrogenation as the key operations for the selective formation of the macrocycle. In order to expand the limits of alkyne metathesis, the metathesis reaction envisioned for ring-closure was supposed to involve a terminal alkyne, a structural motif that was previously beyond reach due to significant polymerization on contact with a metal alkylidyne. Therefore, terminal acetylenes have never been metathesized in the context of a complex natural product synthesis.[148] The maturity of this recently developed method should therefore be challenged by the inevitable presence of a variety of polar functional groups in the mandelalide precursor.

The chosen strategy should further traverse an advanced intermediate that allows access to mandelalides B, C and D. Thus, the attachment of the sugar moiety should take place after the framework of the macrocycle is built up in order to clear the way for the synthesis of family members by deviation from the original route.

## 3.4 Retrosynthetic analysis

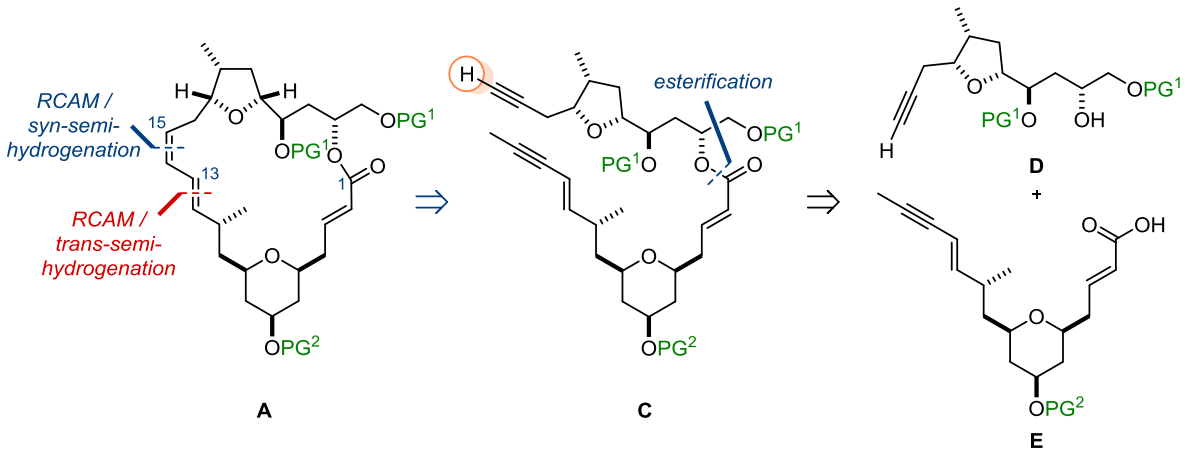
The first disconnection removes the mono-methylated rhamnosyl unit from the macrocycle. As outlined above, this late introduction of the sugar unit should allow the diversification of a common macrocyclic intermediate and could, if successful, give access to all mandelalide family members. This strategic consideration further dictated the choice of protecting groups.

Since the primary alcohol at C.24 might be easily differentiated from its sterically more shielded secondary relatives, the two secondary alcohols at C.7 and C.21 had to be adorned with orthogonally cleavable protecting groups. They were chosen in a way that selective deprotection of the alcoholic functionalities at either C.7 or C.24 could be achieved.




*Scheme 3.4*: Retrosynthetic analysis of mandelalide A: Late-stage introduction of the sugar moiety.

As previously outlined, the (*E*,*Z*)-diene scaffold of the macrocycle was envisioned to be the site of ring-closure for the synthesis of mandelalide A (**124**). Two possible disconnections of macrocycle **A** were thus analyzed: The retrosynthetic cut between C.12 and C.13 seemed attractive (red, scheme 3.5), since a direct *trans*-hydrogenation of alkynes was recently developed in the group.[149]




*Scheme 3.5*: Retrosynthetic analysis of the aglycone of mandelalide A.

However, enynes could not yet be successfully engaged in this transformation and suffer from low or no conversions. This direct transformation is unmet in terms of efficacy, yet substitutes are well established and include the hydrosilylation/protodesilylation sequence.[27, 150] Although this multistep alternative has already been fruitfully applied in natural product synthesis,[28, 95e] the cut between C.14 and C.15 seemed more viable since the direct (*Z*)-selective

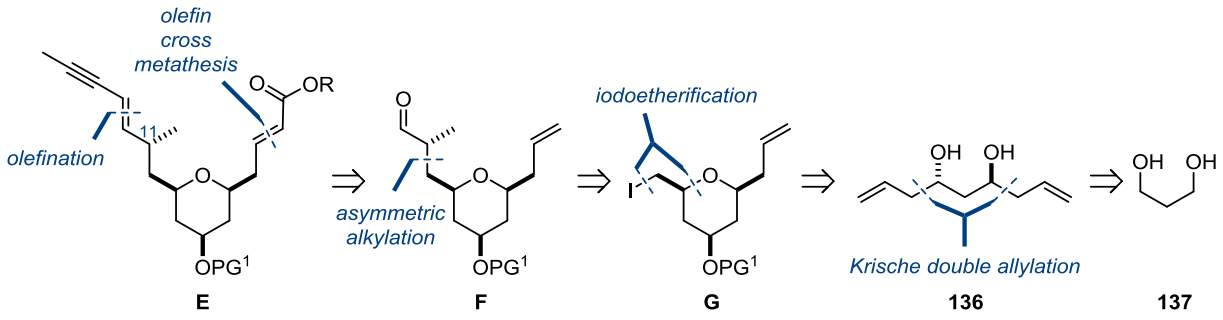
semihydrogenation of an (*E*)-cycloenyne would furnish the desired (*E*,*Z*)-dienyl motif without detours.

Thus, this approach was chosen and the macrocycle was retrosynthetically disconnected at the indicated site between C.14 and C.15 (blue, scheme 3.5). The key reaction sequence should involve the metathesis of the terminal acetylene subunit of **D** and would ultimately challenge the recently developed fusion of terminal and internal alkynes.[148h] In analogy to the leiodermatolide case, an esterification reaction should connect the northern alcohol fragment **D** with southern acid fragment **E**.

## 3.5 Synthesis of the southern acid fragment

Within the southern fragment **E**, the enyne lies next to a methyl-bearing stereogenic center in the allylic position, which is fused to an all-*cis* substituted THP ring via a methylene linker. The pseudo-symmetric nature of the THP ring with all substituents in equatorial positions further led to the decision to construct this moiety first and introduce the functionalities on the side chains later.

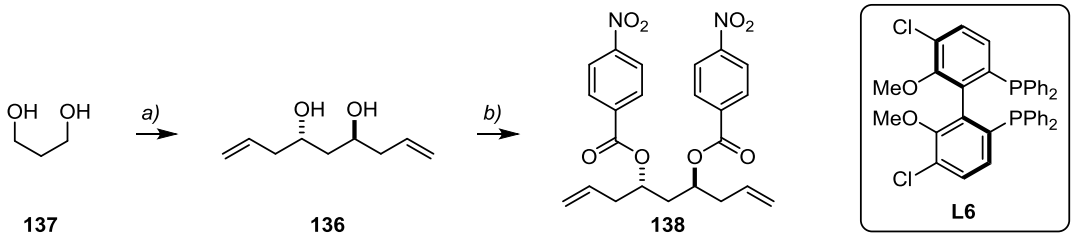
Thus, the enyne moiety was thought to be introduced by an (*E*)-selective olefination reaction, whereas the α,β-unsaturated ester was envisioned to derive from an alkene cross metathesis reaction. The stereogenic center at C.11 was supposed to originate from a diastereoselective alkylation reaction using a chiral auxiliary. This led back to the THP ring **G** decorated with a primary alkyl halide, which was to be built up by a halo-etherification reaction. This transformation could be carried out with the $C_2$-symmetric diol **136**, which is literature known and can be prepared conveniently in one step from commercial 1,3-propanediol (**137**) by bidirectional iridium-catalyzed allylation as reported by the group of Krische.[151]




*Scheme 3.6*: Retrosynthetic analysis of the southern acid fragment **E**.

In the forward direction, the procedure of Krische *et al.* was reproducible even on multigram-scale and afforded the desired diol **136** in good yield and diastereoselectivity.[152] In order to determine the enantiomeric excess, it had to be converted into bis-(4-nitrobenzoate) **138** to attach a UV chromophore for HPLC analysis on a chiral stationary phase, which revealed an

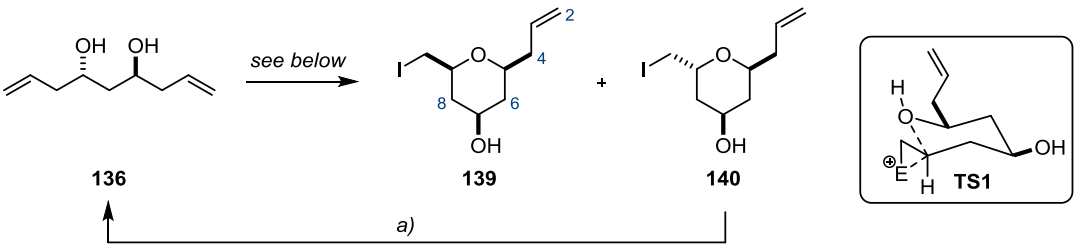
excellent enantiomeric enrichment of >99%. However, the high cost of the (*S*)-BIPHEP ligand **L6** might limit a further scale-up exercise. When cheaper (*S*)-BINAP was used as a substitute under otherwise identical conditions, similar levels of enantio- and diastereoselectivity were observed; unfortunately, the yield dropped to 37%. Additional experiments were carried out to reduce the catalyst loading or to recover the catalyst; yet, these efforts were not met with success and therefore abandoned.




*Scheme 3.7:* Bidirectional allylation of propanediol. Conditions: a) allyl acetate (10 eq.), $[Ir(cod)Cl]_2$ (5 mol%), **L1** (10 mol%), 3-nitro-4-chlorobenzoic acid (20 mol%), $Cs_2CO_3$, 1,4-dioxane, 90 °C, 71% (d.r. ≥ 29:1, 99% *ee*); b) 4-nitrobenzoyl chloride, DMAP (5 mol%), pyridine, $CH_2Cl_2$, rt, 94%.

With diol **136** in hand, the desymmetrizing iodo-etherification was investigated. From a mechanistic understanding, this reaction should proceed through a cyclic chair-like transition-state **TS1**, in which all substituents populate pseudo-equatorial positions. The all-*cis* isomer **139** should therefore be favored over the 9-*epi* isomer **140**.

*Table 3.2:* Selected results of the haloetherification. . Conditions: a) Zn, $I_2$ (cat.) DMA, 80 °C, 80%.




| entry | conditions | comb. yield, (pure **139**) [%] | **139**:**140**[1)] |
|---|---|---|---|
| 1 | $I_2$, $NaHCO_3$, MeCN, −20 °C | 65 | 4.3:1 |
| 2 | NIS, $CH_2Cl_2$, 0 °C | 44 | 3.8:1 |
| 3 | $(sym\text{-}collidine)_2I^+PF_6^-$, MeCN, 0 °C to rt | - | - |
| 4 | $Hg(OAc)_2$, toluene, 0 °C; then $I_2$ | - | - |
| 5 | $I_2$, KO*t*-Bu, THF, −78 °C to rt | - | - |
| 6 | $I_2$, MeCN, −35 °C | 48 | 3.5:1 |
| 7 | $I_2$, $NaHCO_3$, hexanes or $CH_2Cl_2$, −78 to 0 °C | < 10 | - |
| 8 | $I_2$, $NaHCO_3$, THF, −78 °C | 65 | 5:1 |
| 9 | $I_2$, $NaHCO_3$, MeCN, −40 °C | 81 (65) | 5:1 |

1) determined by integration of $^1H$ NMR signals.

This reaction had been previously described by Krische on a substrate bearing additional methyl groups at C.4, C.6 and C.8 and resulted in the formation of a single diastereomer.[152] For the present substrate however, identical reaction conditions led to a slight preference for

**139** of 4.3:1 (table 3.2, entry 1) with rather moderate yield. In order to improve this outcome, several electrophilic reagents known to induce such a cyclization were tested on diol **136** (entries 2-4), yet no improvement was reached.[153]

The use of molecular iodine was inevitable and the accompanying base as well as the solvent was next varied (entries 5-7).[154] Optimal results were obtained in THF at −78 °C (entry 8) or in MeCN at −40 °C (entry 9) with an acceptable diastereomeric ratio of 5:1 and good yields. The two diastereomeric compounds were fully separated after three consecutive chromatographic purifications.

The iodoetherification was further attempted with a mono-silylated variant of **136** to increase the steric bulk in the equatorial position at C.7, but a reduced diastereoselectivity of 2:1 in favor of the all-*cis* substituted product was observed.[155] To ensure recovery of the valuable material, especially in view of the high costs of the bis-allylation, the undesired diastereomer was converted back to diol **136** upon treatment with activated Zn in DMA at elevated temperature;[155, 156] the use of *t*-BuLi gave far inferior results.

Since different stereochemical outcomes of iodo-etherification reactions during THP syntheses had previously been reported,[157] the major product was carefully assigned by analysis of the NOESY spectrum after silylation (figure 3.1). Although no direct NOE signals were observed between the axial protons at C.5, C.7 and C.9 (which were detected on later intermediates), the other contacts around the six-membered ring clearly support the assignment. Additionally, the pseudo-symmetric nature of the signals is suggestive of an all-*cis* substituted THP ring. Further evidence was gained from the coupling constants recorded for **141** in deutero-benzene. The large $^{3}J$ of H.8$_{ax}$ (1.10 ppm, ddd, $J$ = 12.2, 11.1, 11.0 Hz) are indicative of one geminal and two axial vicinal couplings; whereas for H.8$_{eq}$ (1.74 ppm, dddd, $J$ = 12.3, 4.4, 2.3, 2.3 Hz) one geminal and two equatorial vicinal coupling constants were observed. The coupling constants of H.9 (2.93 ppm, dddd, $J$ = 11.2, 6.6, 4.6, 2.0 Hz) can be linked to H.8$_{ax}$ (11.2 Hz), H.10a (6.6 Hz), H.10b (4.6 Hz) and H.8$_{eq}$ (2.0 Hz) and are in full agreement with the stereochemical assignment.

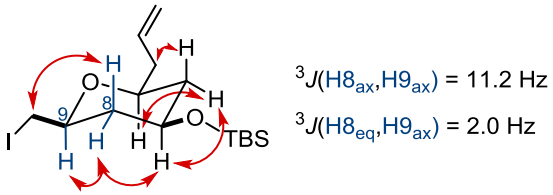
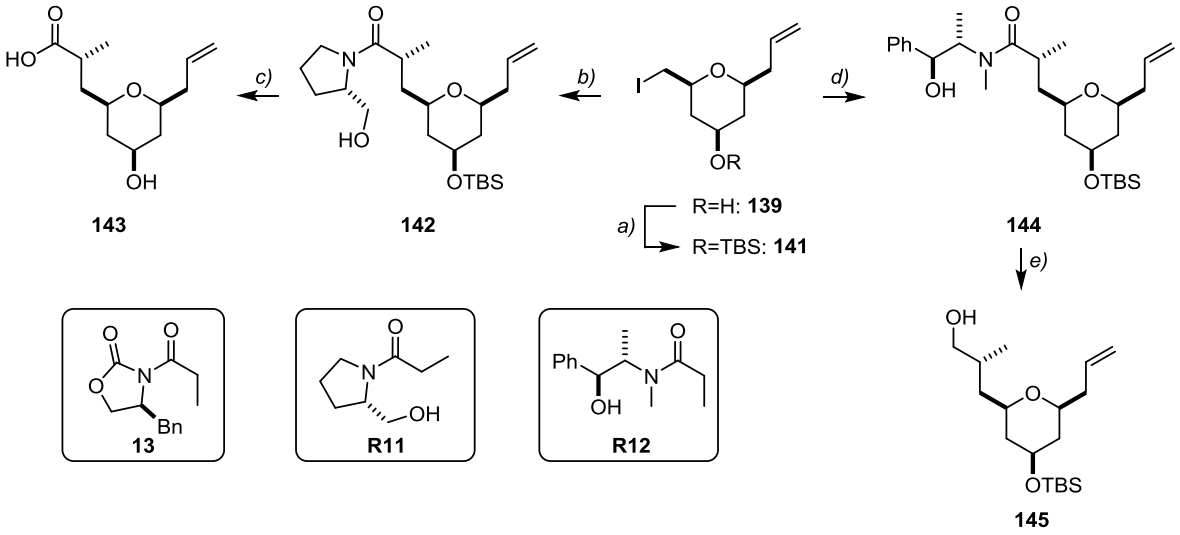



*Figure 3.1:* Observed NOE contacts for the major etherification isomer after silylation (**141**, $C_6D_6$, 400 MHz).

Next, the introduction of the stereogenic center at C.11 was addressed after converting the secondary alcohol into the corresponding TBS-ether **141**. Initial experiments had shown that

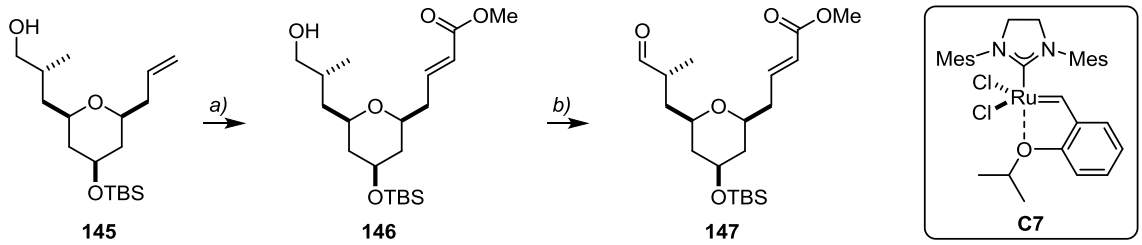
the enolate of the Evans oxazolidinone **13** failed to undergo the desired alkylation.[158] This is likely caused by the stereoelectronic bias of alkyl iodide **141**. The proximal oxygen lone pairs of the ether along with the steric demand imposed by the β-branched substitution pattern render **139** a particularly challenging electrophile.




*Scheme 3.8:* Asymmetric alkylation with alkyl iodide **141.** Conditions: a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 96%; b) **R11**, LDA, HMPA, THF, 0 °C; then **141**, 74%; c) 1N aq. HCl, 100 °C, 44%; d) **R12**, LDA, LiCl, THF; then **141**, 76%; e) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 96% (97:3 d.r.).

On this basis, the more reactive dianionic enolates of **R11** and **R12** were investigated. The prolinol-derived amide **R11**[159] was deprotonated with LDA and treated with alkyl iodide **141** in the presence of HMPA. The desired adduct **142** was formed and could be isolated in reasonable yields; however, the conditions for the cleavage of the auxiliary required 1N HCl at reflux temperature and simultaneously cleaved the silyl ether at C.7. The use of the Myers pseudoephedrine-derived amide **R12** was more promising:[160] Although somewhat forcing conditions (48 h at 45 °C) were needed to achieve reasonable rates and full conversion, the alkylated adduct **144** was isolated in 76% yield.[161] Even more importantly, the subsequent reduction was achieved under mild conditions using $LiNH_2{\cdot}BH_3$ and furnished the desired primary alcohol **145** with excellent yield and diastereoselectivity.[160]

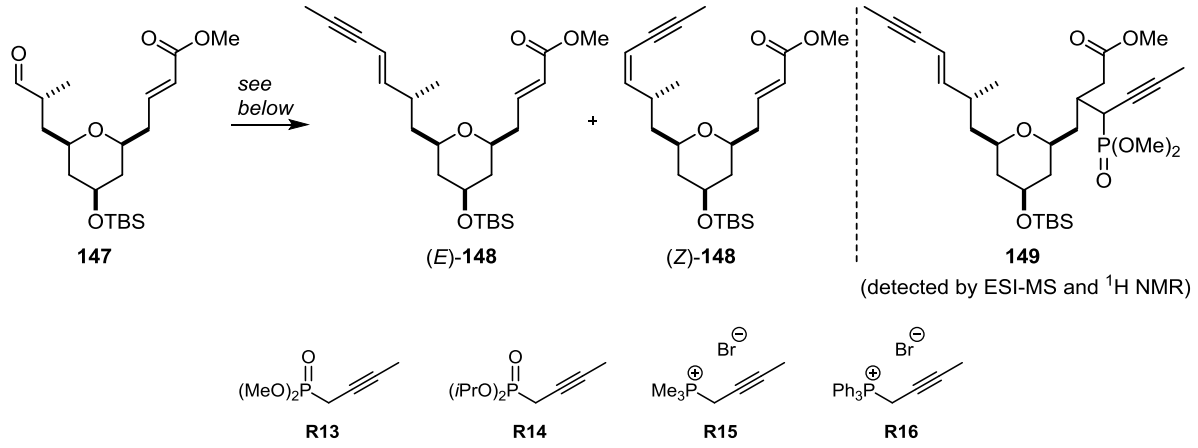
The stage was set for the envisioned alkene cross-metathesis reaction with methyl acrylate,[91] which proceeded at ambient temperature when catalyzed by the Hoveyda-Grubbs 2nd generation catalyst **C7**. The α,β-unsaturated ester **146** was formed in 83% yield after separation from minor amounts of the (*Z*)-isomer. The primary alcohol was then oxidized with Dess-Martin periodinane to give aldehyde **147** for the olefination reaction.




*Scheme 3.9:* Preparation of aldehyde **147.** Conditions: a) methyl acrylate (5 eq.), **C1** (3 mol%), $CH_2Cl_2$, rt, 83% (+7% *Z*-isomer); b) DMP, $CH_2Cl_2$, 0 °C to rt, 77%.

Exposure of aldehyde **147** to the lithium enolate of **R13** gave the desired product **148** as an inseparable mixture of (*E*)- and (*Z*)-isomers (table 3.3, entry 1). The yield was moderate, ranging between 41% and 54%, and could not be improved despite considerable experimentation. Change of the counterion (entry 2) or inversion of the addition protocol did not improve the outcome (entry 3). The detection of the water-soluble by-product **149** by ESI-MS and $^1$H NMR serves as an explanation for this disappointing result: after successful installation of the (*E*)-enyne, the enolate of the phosphonate reacts further with the α,β-unsaturated ester, thus diminishing the isolated yield.

*Table 3.3:* Selected conditions for the olefination of **147**.



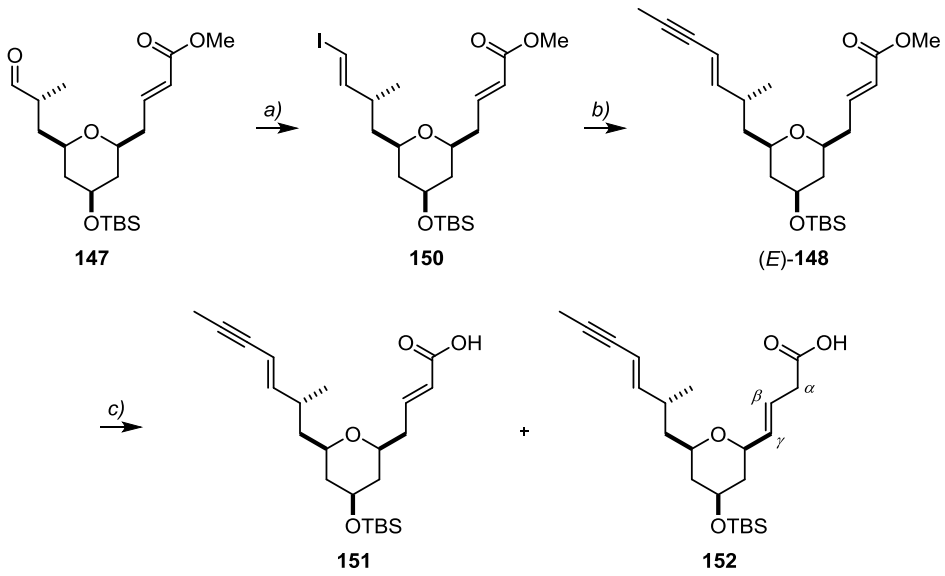

| entry | reagent | conditions | addition type | yield [%] | *E* / *Z* [1] |
|---|---|---|---|---|---|
| 1 | **R13** | LiHMDS, THF, −78 °C | Barbier[2] | 41-54 | 7 : 1 |
| 2 | **R13** | KO*t*-Bu, THF, −78 °C | Barbier[2] | 51 | 1 : 1 |
| 3 | **R13** | LiHMDS, THF, −78 °C | preformed enolate | 42 | 4 : 1 |
| 4 | **R14** | LiHMDS, THF, −78 °C | preformed enolate | 23 | 8 : 1 |
| 5 | **R15** | *n*-BuLi, THF, −78 °C | preformed enolate | 12 | 7 : 1 |
| 6 | **R16** | PhLi, KO*t*-Bu, *t*-BuOH, THF, 0 °C | preformed enolate | - | - |

1) determined by integration of olefinic $^1$H NMR signals. 2) Barbier: the base was added to a premixed solution of aldehyde and reagent at the indicated temperature.

In the following, the methyl groups of the phosphonate were replaced by more bulky isopropyl groups (**R14**, entry 4), but the yield remained disappointingly low. The use of lithiated trimethylpropargylphosphonium bromide (**R15**, entry 5) also furnished the desired product with

acceptable selectivity; yet, only trace amounts could be isolated. Use of the triphenylpropargylphosphonium bromide **R16** (entry 6) under Schlosser conditions resulted in the formation of a complex mixture, which was not further analyzed.

A more reliable, two-step alternative was developed, which commenced with an (*E*)-selective Takai olefination to give vinyl iodide **150**.[162] Initially, low yields were obtained due to problems associated with the removal of the chromium waste; however, this issue could be solved by quenching the reaction mixture with an aq. serine solution. Serine is thought to sequester the excess amount of chromium salts and its addition ensured an easy workup procedure.[163] Furthermore, the desired (*E*)-isomer **150** was easily separated from the undesired (*Z*)-isomer by column chromatography and subsequently subjected to a modified Suzuki propynylation protocol developed in the Fürstner group.[164] This protocol allowed the enyne to be obtained in 58% yield over two steps as a single olefin isomer.

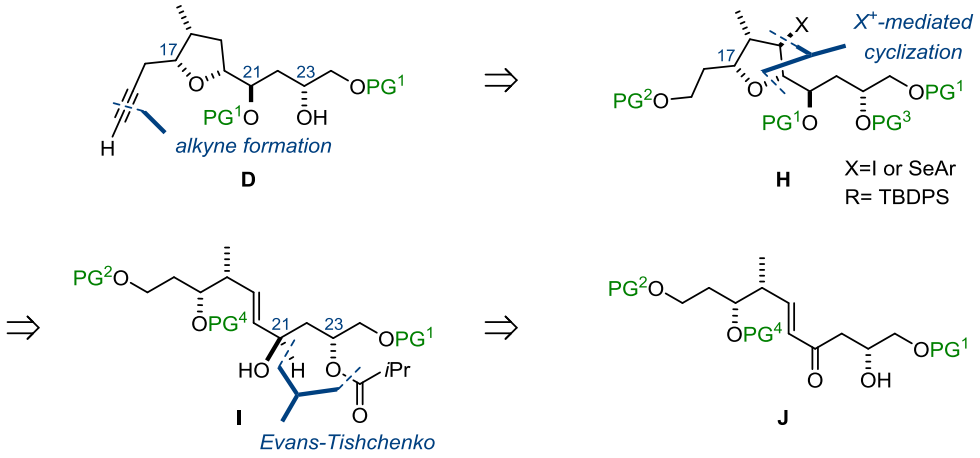



*Scheme 3.10:* Two-step alternative for the installation of the enyne**.** Conditions: a) $CHI_3$, $CrCl_2$·THF, THF, −8 °C, aq. serine workup, 72% (+8% (Z)-isomer); b) sodium propyne, $(MeO)_3B$, $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (10 mol%), THF, 70 °C, 81%; c) TMSOK, $Et_2O$, rt, **151**: 80% **152**: 7%.

Lastly, the ester was saponified with TMSOK at ambient temperature to give the desired acid **151** along with minute amounts of product **152**, in which the double bond isomerized out of conjugation. Both compounds could be separated by flash chromatography; as it turned out however, this deconjugation could not be avoided during the subsequent esterification step (see chapter 3.8). As a consequence, the two compounds were used as a mixture upon scale-up in order to simplify the purification process.

## 3.6 Synthesis of the northern alcohol fragment

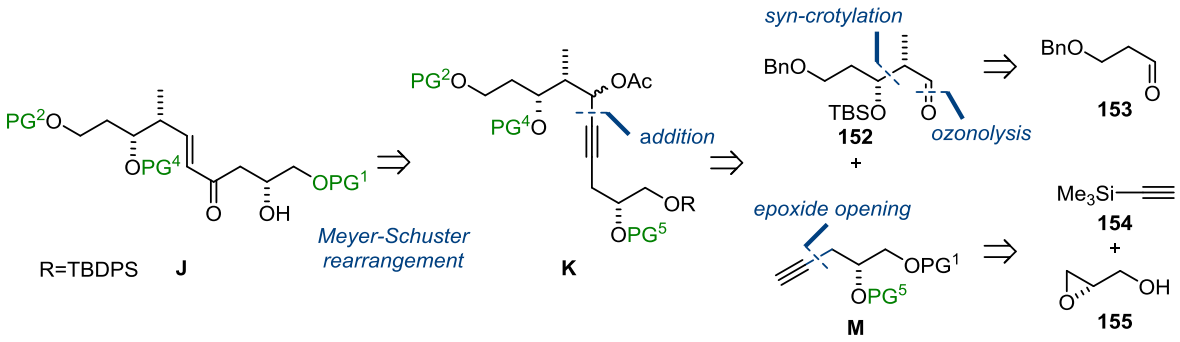
The northern alcohol fragment bears an all-*cis* substituted THF ring, the terminal alkyne for the envisioned ring-closure and three alcohol functionalities, two of which had to be protected to ensure a selective esterification of the secondary alcohol at C.23 with the southern fragment. TBDPS groups were chosen in order to allow the TBS group of the southern fragment to be selectively released under acidic conditions. The alkyne was thought to be assembled last during the fragment synthesis (scheme 3.11). The all-*cis* substituted five-membered ring of **H** was supposed to be built up by an electrophile-induced cyclization of an alcohol at C.17 onto an alkene in a formal 5-*endo* mode. The adjacent stereogenic center at C.21 was envisioned to derive from an Evans-Tishchenko reaction that would simultaneously differentiate the two secondary alcohols at C.21 and C.23. The β-hydroxy ketone **J** displayed a common intermediate of two different approaches that will be discussed separately in the following.




*Scheme 3.11*: Retrosynthetic analysis of the northern alcohol fragment **D** for the installation of the THF ring.

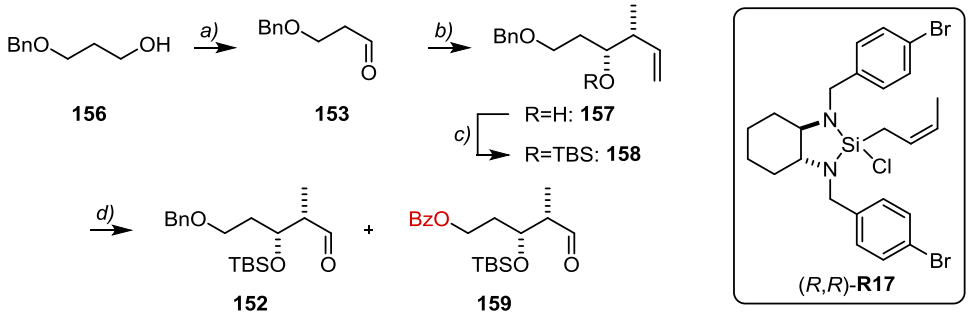
### 3.6.1 1st generation strategy: Meyer-Schuster rearrangement

Initially, enone **J** was meant to be constructed by a Meyer-Schuster rearrangement of the propargylic acetate **K** (scheme 3.12). This was designed to derive from addition of a lithiated alkyne **M** into aldehyde **152**. The terminal alkyne was further disassembled into epoxide **155**, which should be opened by TMS-acetylene **154**. Aldehyde **152** on the other hand could be derived from the corresponding alkene by ozonolysis, which in turn was deemed to be composed from aldehyde **153** by an asymmetric *syn*-crotylation reaction.




*Scheme 3.12:* Retrosynthetic strategy for enone **J**.

Aldehyde **153** was easily prepared by copper-catalyzed TEMPO/air oxidation of the commercially available mono-benzylated 1,3-propanediol (**156**) as reported by Stahl and co-workers,[58] which was significantly more convenient than the well-established Swern reaction. The subsequent *syn*-crotylation was first tested with the crotylboron reagent generated from (−)-Ipc$_2$BOMe and the potassium salt of *cis*-but-2-ene as reported by Brown;[165] however, the enantiomeric excess was unsatisfactory (84% *ee*) and the product isolation difficult (29% yield).

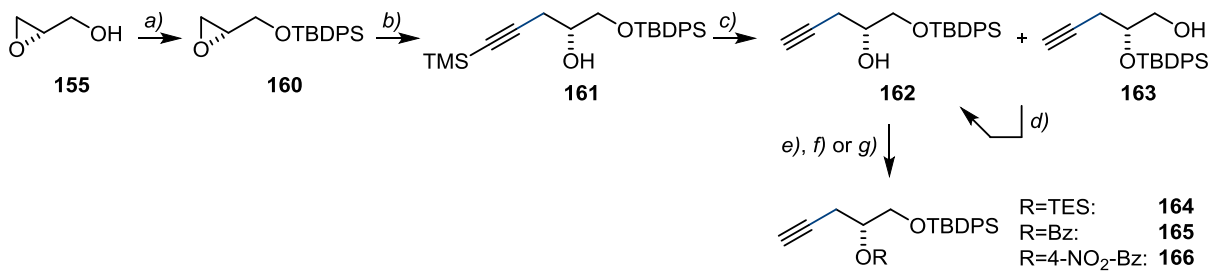



*Scheme 3.13:* Synthesis of aldehyde **152** using a *syn*-crotylation protocol**.** Conditions: a) [Cu(MeCN)$_4$]BF$_4$ (5 mol%), 2,2'-bipyridine (5 mol%), TEMPO (5 mol%), NMI (10 mol%), MeCN, air, 94%; b) (*R*,*R*)-**R17**, Sc(OTf)$_3$ (5 mol%), CH$_2$Cl$_2$, −78 to 0 °C, 82% (d.r. 98:2, 94% *ee*); c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 96%; d) O$_3$, CH$_2$Cl$_2$, −78 °C; then PPh$_3$, rt, **152**: 91%, **159**: 4%.

The chiral crotyl silane described by Leighton and co-workers proved to be more effective.[166] The synthesis of the chiral diamine ligand was straightforward and was carried out on a 40 g scale. The reagent **R17** failed to crystallize as described,[167] but was judged pure on the basis of NMR analysis and used as solution in the crotylation reaction. After slight modification of the protocol that involved the addition of Sc(OTf)$_3$ at −78 °C, a reproducible process was established, which afforded the crotylated product **157** in good yield and enantioselectivity (94% *ee*). After routine silylation of the secondary alcohol, ozonolysis furnished **152**, which was accompanied by over-oxidized aldehyde **159**. This side reaction could be almost completely suppressed by lowering the temperature to −78 °C allowing aldehyde **152** to be isolated in excellent yield after reductive workup.

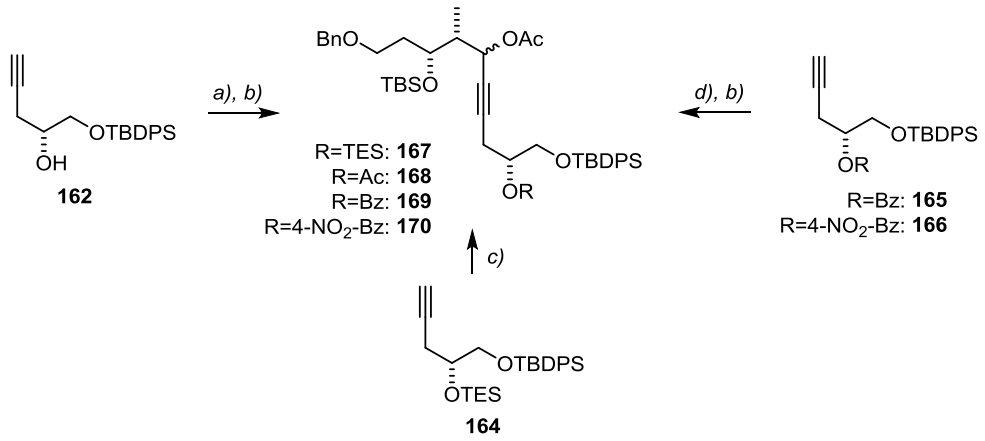
For the synthesis of the alkyne fragment, commercial (*S*)-glycidol (**155**) was converted into silyl ether **160**. The epoxide opening with lithiated trimethylsilylacetylene in the presence of $BF_3 \cdot Et_2O$ proceeded without incident and gave alcohol **161** in high yield on a 15 g scale. Although the subsequent silyl cleavage off the alkyne is literature known and reported to afford **162** in 99% yield,[168] the reaction suffered from 1,2-silyl migration and a mixture of the desired compound **162** and primary alcohol **163** was obtained.[169] Exposure of this mixture to classical silylation conditions at low temperature masked selectively the primary alcohol and allowed for the facile purification of **162**.

Compound **162** was then decorated with different protecting groups to allow for the systematic investigation of the Meyer-Schuster rearrangement. Thus, triethylsilyl ether **164**, benzoate **165**, and nitrobenzoate **166** were prepared.



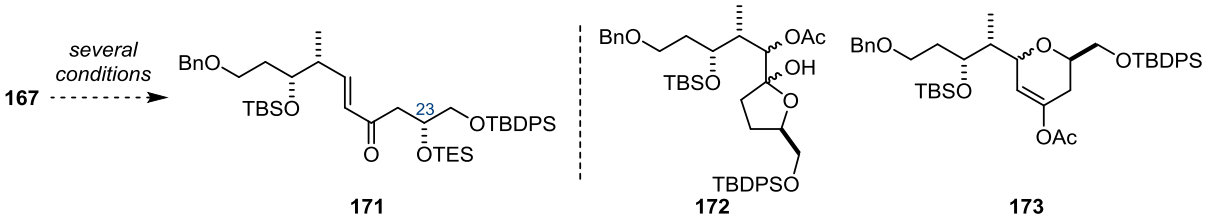

*Scheme 3.14:* Synthesis of several protected alkynes of type **M**. Conditions: a) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C to rt, 94%; b) **154**, *n*-BuLi, $BF_3 \cdot Et_2O$, THF, −78 °C, 91%; c) $K_2CO_3$, MeOH, 0 °C, 97% (**162**/**163** 8:1); d) TESCl (0.15 eq.), $NEt_3$, DMAP, $CH_2Cl_2$, −78 °C, 76%; e) TESCl, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C, **164**: 87%; f) benzoyl chloride, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C, **165**: 79%; g) 4-nitrobenzoyl chloride, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C, **166**: 87%.

The alkyne fragments were joined with aldehyde **152** en route to the propargylic acetate as the Meyer-Schuster precursor. The alkynyl lithium species was generated by treatment with either *n*-BuLi (for **162** and **164**) or LDA (for **165** and **166**), followed by the addition of aldehyde **152** at low temperature. In case of the triethylsilyl ether **164**, the reaction mixture was quenched with acetyl chloride to yield propargylic acetate **167** immediately, albeit in low yield. In all other cases, the propargylic alcohols were isolated in moderate yields and separately treated with acetic anhydride to yield a diverse set of substrates for the Au-catalyzed rearrangement.



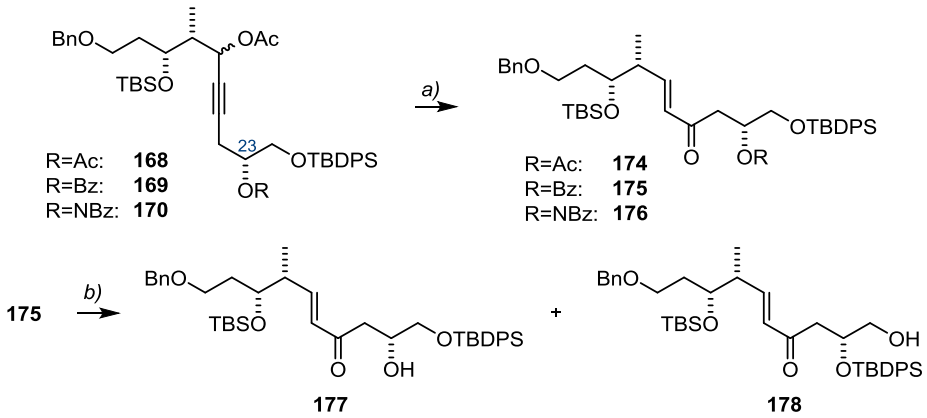

*Scheme 3.15:* Synthesis of rearrangement precursors **167**-**170**. Conditions: a) *n*-BuLi (2 eq.), THF, −78 °C; then **152**, 60%; b) $Ac_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C, **168**: 84%, **169**: 60%; **170**: 76%; c) *n*-BuLi, THF, −78 °C; then **152**, −78 to 0 °C; then AcCl, 0 °C to rt, 35%; d) LDA, THF, -78 °C; then **165** or **166**, −78 to 0 °C, R=Bz: 58%; R=4-$NO_2$-Bz: 40%.

Next, the envisioned gold-catalyzed Meyer-Schuster rearrangement was investigated. Regardless of the gold source, solvent or temperature,[170] the silyl ether **167** led to the formation of a complex mixture (scheme 3.18) and the desired compound **171** could never be isolated in pure form. Two major components were identified by $^1$H NMR analysis as well as mass spectrometry, to which structures **172** and **173** were assigned. This result indicated that the silyl ether interfered by attacking either the transitionally activated alkyne prior to rearrangement or the allene after rearrangement. From a mechanistic point of view, it cannot be ruled out that the silyl ether is first cleaved and the released secondary alcohol reacts with the activated alkyne.




*Scheme 3.16:* Attempted Meyer-Schuster rearrangement of **167** and observed by-products.

Although it remained unclear at which stage the triethylsilyl ether was cleaved,[171] it was speculated that the use of electron-withdrawing protecting groups like acetate or benzoate would diminish the nucleophilicity of the oxygen atom at C.23 and thus the formation of unwanted side-products. Indeed, this was the case with substrates **168**, **169** and **170**; the Meyer-Schuster rearrangement proceeded cleanly in the presence of cationic NHC-Au(I) complexes in wet THF.[172] As a consequence, the targeted enones **174**, **175** and **176** could be isolated in good yields and high purity after silica gel chromatography.

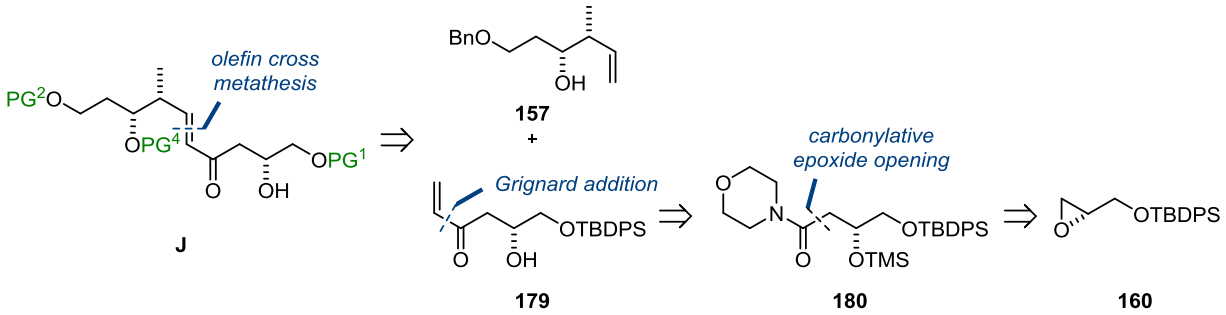



*Scheme 3.17:* Succesfull Meyer-Schuster rearrangements. Conditions: a) [(IPr)AuCl] (6 mol%), $AgSbF_6$ (6 mol%), THF/$H_2O$ 39:1, 60 °C, **174**: 79%; **175**: 73%; **176**: 73%; b) $K_2CO_3$, MeOH, 0 °C to rt, 84% (**177**/**178** 8:1).

Next, the ester protecting group had to be hydrolyzed. Even under mild conditions, scrambling of the silyl group occurred and a mixture of the desired secondary alcohol **177** and the primary alcohol **178** was obtained that could not be separated by chromatographic means.[169] Since reductive methods would also reduce the ketone, it became apparent that only an entirely different strategy would pave a reliable route to the key enone intermediate. Furthermore, the sequence described above was deemed too long to ensure reasonable material supply for the subsequent steps and the endgame. A shorter approach with fewer protecting group operations was thus drafted and developed as disclosed below.

### 3.6.2 Revised strategy: olefin cross metathesis

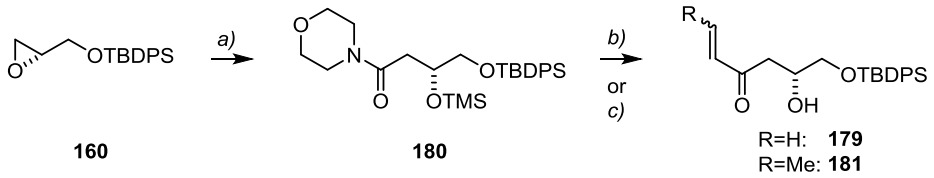
The revised retrosynthetic analysis is based on an olefin cross-metathesis reaction that should selectively built up the thermodynamically favored (*E*)-enone. This idea led to compound **157**, which had already been synthesized during the first generation approach, and enone **179**, which was accessible by addition of a vinyl magnesium species onto amide **180**. The latter compound was thought to derive from a carbonylative epoxide opening in the presence of a morpholine species that would trap the intermediate acyl metal species.




*Scheme 3.18:* Revised retrosynthetic analysis of enone **J**.

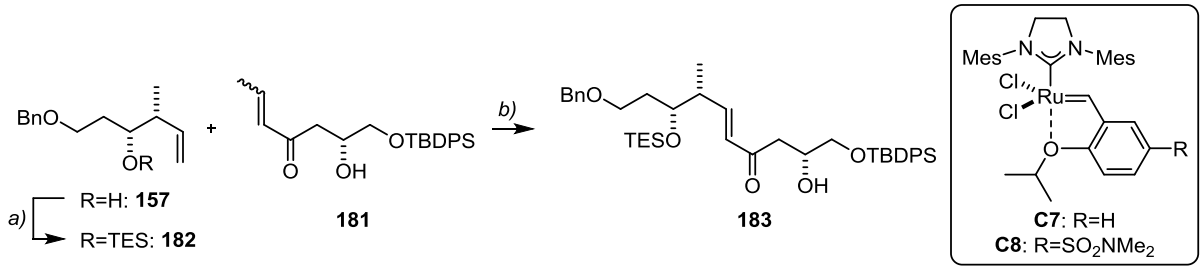
In the forward direction, epoxide **160** was subjected to carbon monoxide (1 atm), *N*-(trimethylsilyl)morpholine and catalytic amounts of dicobalt octacarbonyl as reported by the Jacobsen group.[173] This reaction mandates the solvent and the silylated morpholine to be rigorously dry; otherwise, a significant drop in yield was observed. Moreover, reproducible results were only obtained when the reaction mixture was concentrated and directly loaded onto silica gel without hydrolysis of the secondary TMS group, which was cleaved in the subsequent step anyway.

The addition of vinyl magnesium bromide was troublesome since the released morpholine underwent an *aza*-Michael addition to the produced enone **179** upon workup.[174] In order to reduce the electrophilicity of the 1,4-π-acceptor, a propenyl Grignard reagent was used instead. Moreover, the reaction mixture was cooled to −78 °C before being poured via canula into diluted hydrochloric acid, which ensured protonation of the amine and therefore inhibited the *aza*-Michael addition process. Enone **181** was obtained in high yield (83%) as an inconsequential mixture of (*E*/*Z*)-isomers in readiness for the envisioned cross metathesis.



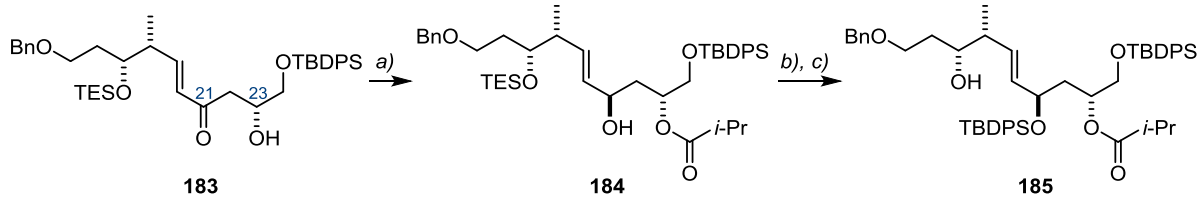

*Scheme 3.19:* Synthesis of enones **179** and **181**. Conditions: a) [$Co_2(CO)_8$] (8 mol%), *N*-(trimethylsilyl)morpholine, CO (1 atm), EtOAc, 74%; b) vinylmagnesium chloride, THF, −78 to 0 °C, **179**: 41%; c) propenylmagnesium bromide, THF, −25 °C; then −78 °C, 0.75 M HCl, **181**: 83% (*E*/*Z* = 2:1).

After routine silylation of alcohol **157**, the stage was set for the fragment coupling via cross metathesis. Intriguingly, the Hoveyda-Grubbs 2nd generation catalyst **C7** reacted only with the sterically more accessible (*Z*)-isomer of **181**, whereas (*E*)-**181** was reisolated. Resort to the slightly more active Zhan-1B catalyst **C8** allowed this problem to be solved and cleanly generated the desired enone with high (*E*)-selectivity (>19:1). To retain a high catalytic activity over the course of the reaction, the metal alkylidene was added in three portions. The key enone **183** was thus produced in only 4 steps in the longest linear sequence, which compares favorably to the first generation strategy (8 steps l.l.s.).




*Scheme 3.20:* Fragment coupling via cross metathesis. Conditions: a) TESCl, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C, 90%; b) **C7** (4+2+2 mol%), $CH_2Cl_2$, reflux, 79%.

The *anti*-configured 1,3-diol was subsequently introduced by an Evans-Tishchenko reaction with excess isobutanal.[52] To this end, $SmI_2$ was freshly synthesized from Sm and diiodoethane, since the reaction with commercial $SmI_2$ solution led to prolonged reaction times and substantial decomposition.[175] Not only was the stereogenic center of **184** formed with excellent stereoselectivity, but the alcohol at C.23 was simultaneously masked as an ester that provided the crucial discrimination of the two secondary alcohols. The alcohol at C.21 was elaborated into the corresponding TBDPS ether and the triethylsilyl group removed under moderately acidic conditions to give the secondary alcohol **185**.

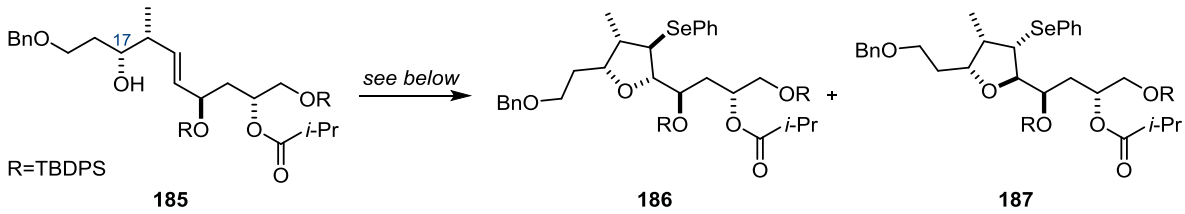



*Scheme 3.21:* Installation of the 1,3 *anti*-diol motif. Conditions: a) *i*-PrCHO, $SmI_2$ (35 mol%), THF, −50 °C, 78% (d.r. > 19:1); b) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C to rt, 87%; c) CSA (30 mol%), $CH_2Cl_2$/MeOH 2:1, 0 °C, 97%.

Inspired by the reports from Lipshutz[176] and Mihelich,[177] the homoallylic alcohol **185** was treated with phenylselenyl chloride (table 3.4, entry 1), which was expected to induce the highest selectivity. However, a disappointing 2:1 mixture of diastereoisomers was produced without reaching full consumption of the substrate. As alternatives, *N*-phenylselenophtalimide (*N*-PSP, entry 5) and phenylselenyl bromide (entry 2) were employed, causing an increase of

diastereoselectivity; yet, the reaction stopped at half conversion and several by-products began to form. It was speculated that the generated acid accounts for this observation and basic additives were therefore investigated. Surprisingly, the reactivity was completely shut down by addition of either homogeneous (entry 3) or heterogeneous bases (entry 4).[178] Iodine as an electrophilic mediator led to a stereorandom cyclization,[179] and the commitment of a C.17 OH-silylated cyclization precursor was also not fruitful.[180]

*Table 3.4:* Representative results of the cyclization of **185** for the construction of the THF ring.




**185** **186** **187**

| entry | reagent | conditions | conv.[1] (yield) [%] | 186 / 187[2] |
|---|---|---|---|---|
| 1 | **PhSeCl** | MeCN, −40 °C to rt | 30 | 2 : 1 |
| 2 | **PhSeBr** | MeCN, −40 °C to rt | 54 | 4.4 : 1 |
| 3 | " | 2,6-di(*t*-Bu)pyridine, MeCN, rt | - | - |
| 4 | " | $K_2CO_3$, MeCN, rt | - | - |
| 5 | ***N*-PSP** | PPTS, $CH_2Cl_2$, rt | 53 | 4.3 : 1 |
| 6 | " | TFA, $Ph_3P{=}S$, $CH_2Cl_2$, rt | 100 (76) | 7.4 : 1 |
| 7 | " | TFA, $Ph_3P{=}S$, $CH_2Cl_2$, −40 to −20 °C | 100 (84) | 14 : 1 |

1) determined by analysis of the crude $^1$H NMR; 2) determined by HPLC analysis of a crude sample.

Fortunately, activation of *N*-PSP with catalytic amounts of Lewis basic triphenylphosphinesulfide in the presence of a Brønsted acid, as reported by Denmark, resulted in the selective formation of **186**, provided that the transformation was carried out at low temperatures (entry 7).[181] Under optimized conditions, the crucial cyclization was successfully performed on a gram-scale.

The careful analysis of the NOESY spectra of both compounds allowed for a stereochemical assignment. As depicted in figure 3.2, the major isomer **186** showed NOE correlations of H.20 with H.17 and H.18, whereas these contacts were missing in the minor isomer **187**. Furthermore, the NOE contacts of the minor isomer implied spatial proximity of H.20 and the methyl group at C.18. Another indication for this assignment was gained by comparison of the chemical shifts of H.19 next to the selenyl moiety. In compound **186**, this proton has two *syn*-alkyl neighbors, which cause an upfield shift ($\delta$ = 2.93 ppm) as opposed to the very same proton of compound **187** flanked by only one *syn*-alkyl group ($\delta$ = 3.69 ppm). Comparison with literature values in similar systems are in full agreement with these conclusions.[177, 182]

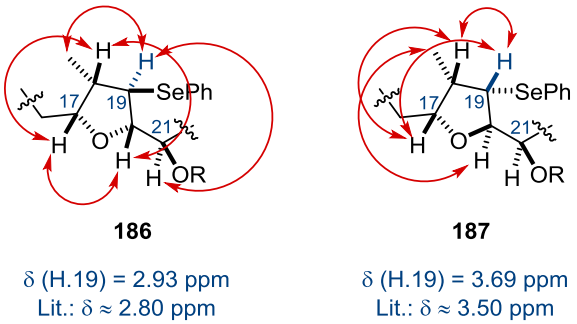
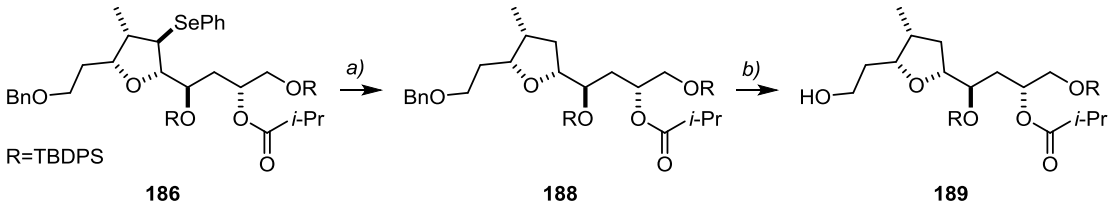


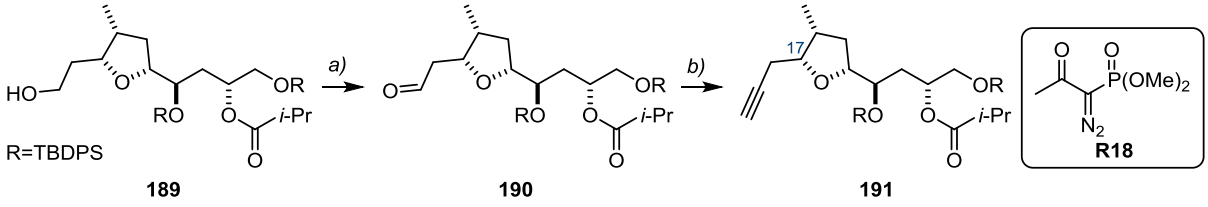

*Figure 3.2:* Key NOE contacts of the THF region of both isomers and chemical shifts of H.19 leading to the structure assignment ($CDCl_3$, 600 MHz).

Next, the simultaneous removal of the selenyl- and benzyl-moieties was investigated. However, when **186** was treated with Raney nickel under hydrogen atmosphere, the cleavage of both functionalities occurred, yet it was accompanied by reduction of one phenyl ring of the silyl protecting groups in varying amounts. As a consequence, the phenylselenyl entity was first removed under free-radical conditions using AIBN and tributyltin hydride followed by the reductive cleavage of the benzyl group over Pearlman's catalyst.



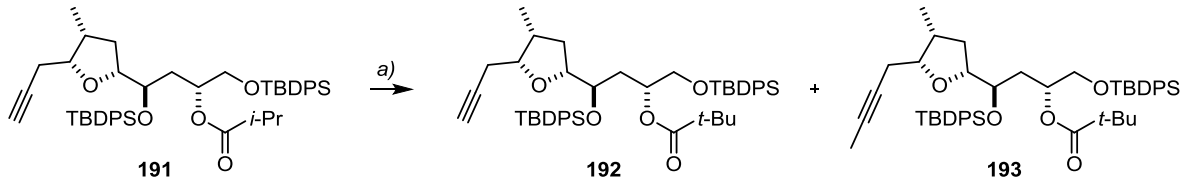

*Scheme 3.22:* Synthesis of primary alcohol **189**. Conditions: a) *n*-$Bu_3SnH$, AIBN, toluene, 80 °C, 93%; b) $Pd(OH)_2/C$ (cat.), $H_2$ (1 atm), EtOH/EtOAc (9:1), 88%.

Oxidation of the primary alcohol occurred readily upon contact with Dess-Martin periodinane. Treatment of aldehyde **190** with diazophosphonate **R18** under standard Ohira-Bestmann conditions ($K_2CO_3$, MeOH) resulted in the formation of the desired alkyne **191**;[183] however, the compound was obtained as a 2.3:1 diastereomeric mixture at C.17. This epimerization likely occurred via a retro-*oxa*-Michael/Michael process. This erosion of stereochemical information could be impeded by preforming the reactive anionic phosponate with stoichiometric amounts of NaOMe at −78 °C prior to addition of aldehyde **190**.[184] Once the reaction mixture was warmed to −55 °C, a heavy gas evolution indicated that the reaction took place. Under these conditions, the terminal alkyne **191** was isolated virtually as a single isomer.



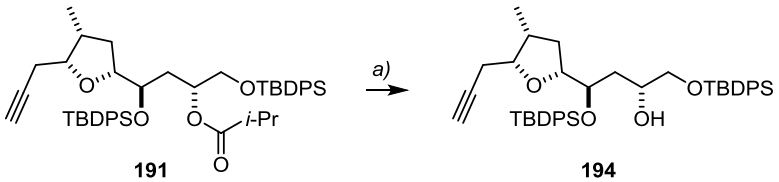

*Scheme 3.23:* Construction of terminal alkyne **191**. Conditions: a) DMP, $CH_2Cl_2$, 0 °C to rt, b) **R18**, NaOMe, THF, −78 °C; then **190**, −78 to −50 °C, 93% (d.r. ≥ 98:2).

At this stage, elaboration into the methyl-capped alkyne was investigated in case the alkyne metathesis with the terminal alkyne would fail. Therefore, the methylation of the alkyne was validated with compound **191**. After deprotonation with LDA and quenching with methyl iodide, only trace amounts of the alkylated product were observed by mass spectrometry. The addition of HMPA significantly increased the conversion and led to the isolation of a mixture of mono- and bis-methylated products. As evident from the $^1$H NMR spectrum, the majority of methylation occurred at the acidic α-position of the ester protecting group. The similar $pK_A$ values of the alkyne and the ester proton prohibited a selective deprotonation and rendered a selective mono-methylation impossible. The carcinogenic properties of HMPA encouraged the search for a less toxic alternative. The complete bis-methylation with excess base and methyl iodide was tried, but always gave mixtures of mono- and bis-methylated species **192** and **193**. It was therefore decided to skip further experiments regarding the methylation and first investigate the terminal alkyne metathesis, which seemed attractive in terms of stepcount and with respect to the novelty of the envisioned cyclization.




*Scheme 3.24:* Attempted methylation of **191**. Conditions: a) LDA, MeI, HMPA, THF, −78 to 0 °C.

To complete the northern alcohol fragment, the isobutylester of **191** was cleaved under reductive conditions (DIBAl-H) rather than by hydrolysis to avoid scrambling of the silyl groups as previously observed (scheme 3.16). The alcohol fragment **194** was thus synthesized in a longest linear sequence of 13 steps starting from commercial material.



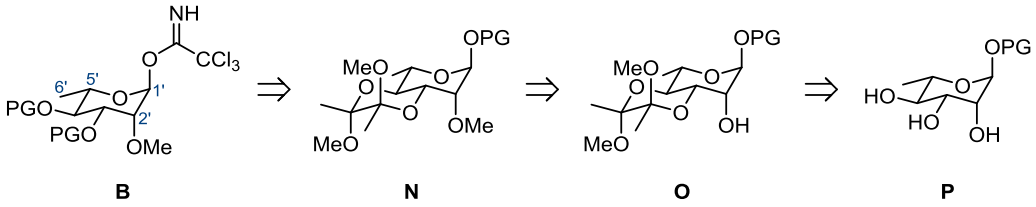

*Scheme 3.25:* Completion of the alcohol fragment. Conditions: a) DIBAl-H, toluene, −78 °C, 97%.

## 3.7 Synthesis of the sugar fragment

Two different strategies were explored in parallel and will be discussed successively. The results described in chapter 3.7.1 were obtained in collaboration with Ms. Katharina Holthusen during a six week research stay in our laboratory.

### 3.7.1 Selective bis-acetal approach

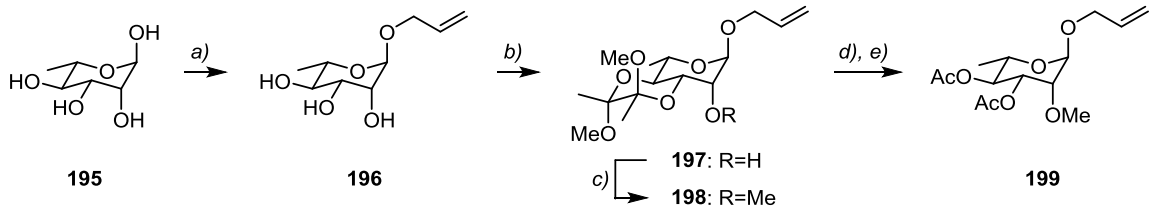
The presence of a methoxy group at the C.2' position required several protecting group manipulations on commercial rhamnose. The strategy followed in here was based on the selective formation of a bis-acetal engaging the two equatorial alcohols at C.3' and C.4' as originally developed by Ley and co-workers. This functionalization would allow for the selective methylation of the remaining alcohol at C.2'. The overall retrosynthetic strategy is outlined in scheme 3.26.




*Scheme 3.26*: Retrosynthetic analysis of the rhamnosyl donor **B**.

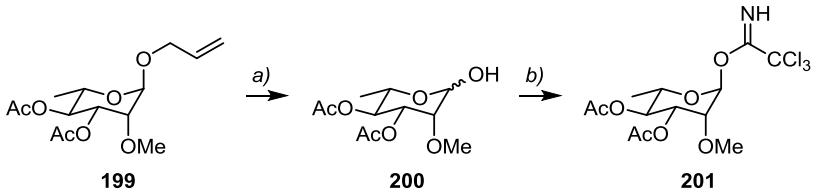
As an entry point, L-rhamnose (**195**) was treated with allyl alcohol in acidic media to install the allyl glycoside. Alternatively, a benzyl group was implemented, but slightly lower yields were obtained in the following steps.

The two equatorial alcohols were then transformed into the bis-acetal **197** upon treatment with butane-2,3-dione in acidic medium.[185] The alternative bis-acetal from 1,2-cyclohexadione gave inferior results and was not further heeded.[186] The subsequent methylation occurred without incident after deprotonation of the remaining alcohol with sodium hydride and furnished **198** in moderate yield. The bis-acetal was exchanged for more labile acetate groups in a two-step process to ensure mild deprotection conditions during the endgame of the mandelalide A synthesis.




*Scheme 3.27:* Selective introduction of the methyl group. Conditions: a) allyl alcohol, $H_2SO_4$ (cat.), reflux, 78%; b) butane-2,3-dione, $MeC(OMe)_3$, *p*TsOH·$H_2O$ (cat.), MeOH, reflux, 72%; c) NaH, MeI, DMF, 0 °C to rt, 64%; d) TFA/$H_2O$ 20:1; e) $Ac_2O$, DMAP, $NEt_3$, $CH_2Cl_2$, 0 °C to rt, 68% over 2 steps.

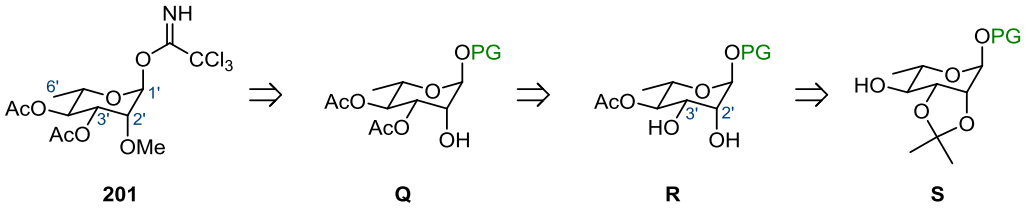
Suitable reaction conditions for the removal of the allyl group were found after a short screening. The best result was obtained with $SeO_2$,[187] which presumably causes an allylic oxidation; the generated hemiacetal spontaneously collapses to release the deprotected rhamnosyl donor as an inconsequential mixture of anomers. Finally, the trichloracetimidate moiety was introduced in the presence of trichloroacetonitrile in excellent yield and a single isomer of **201** was generated.




*Scheme 3.28:* Synthesis of the trichloroacetimidate **201**. Conditions: a) $SeO_2$, HOAc, 1,4-dioxane, reflux, 86%; b) $Cl_3CCN$, $Cs_2CO_3$, $CH_2Cl_2$, 98%.

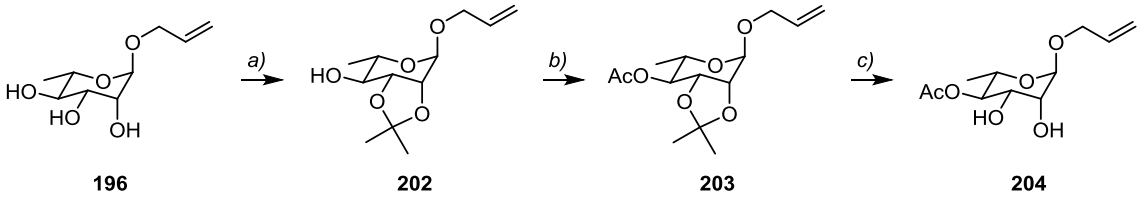
### 3.7.2 Selective acetylation approach

Simultaneously, a different strategy was explored that relied on the selective acetylation of the equatorial alcohol at C.3' in the presence of the neighboring alcohol at C.2'. The retrosynthetic scheme 3.32 shows that once two acetates are installed, the methylation of **Q** should give the appropriately functionalized rhamnosyl donor **201**. Compound **Q** was thought to be assembled from **R** by selective acetylation of the equatorial alcohol at C.3'. Diol **R** was further traced back to the acetal **S**, which should preferentially be formed with the two alcohols in *syn*-relationship at C.2'/C.3' as opposed to the *anti*-configured diol at C.3'/C.4'.




*Scheme 3.29*: Alternative retrosynthetic analysis of the sugar fragment.

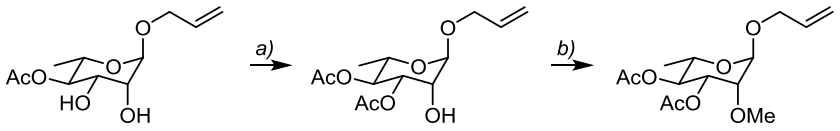
Again, the allyl group was selected as a suitable aglycone. Compound **196** was treated with 2,2-dimethoxypropane under acidic conditions to form the acetal moiety with the *syn*-diol. The crude mixture was subjected to the acetylation reaction to install the first acetate at C.4' in 73% yield over the two steps. Treatment of **203** with aqueous acetic acid at elevated temperatures cleaved the acetal and unmasked diol **204**.




*Scheme 3.30:* Synthesis of diol **204**. Conditions: a) 2,2-dimethoxypropane, *p*TsOH·$H_2O$, DMF, rt; b) AcCl, pyridine, DMF, 0 °C to rt, 73% over two steps; c) 90% aq. AcOH, 110 °C, 97%.

Although literature evidence suggested that the following acetylation might be selective for the C.3' position,[188] the experiment under standard conditions (AcCl, pyridine, DMAP) resulted in a rather moderate regioselectivity of 4:1, even when carried out at −78 °C. The application of preformed dialkylstannylene intermediates was inferior in terms of regioselectivity and yield.

However, with the recently developed method by Taylor and co-workers using the ethanolamine ester of diphenylborinic acid as catalyst,[189] a synthetically useful selectivity of 10:1 for the C.3' position was obtained. The separation of the two regioisomers proved to be difficult and was achieved only after several subsequent flash chromatographic purifications.




**204** **205** **199**

*Scheme 3.31:* Regioselective acetylation and methylation. Conditions: a) $Ph_2B(OCH_2CH_2NH_2)$, *i*-$Pr_2NEt$, AcCl, MeCN, rt, 97% (10:1 r.r.); b) $TMSCHN_2$ (24 eq.), aq. $HBF_4$, $CH_2Cl_2$, 0 °C, 71%.

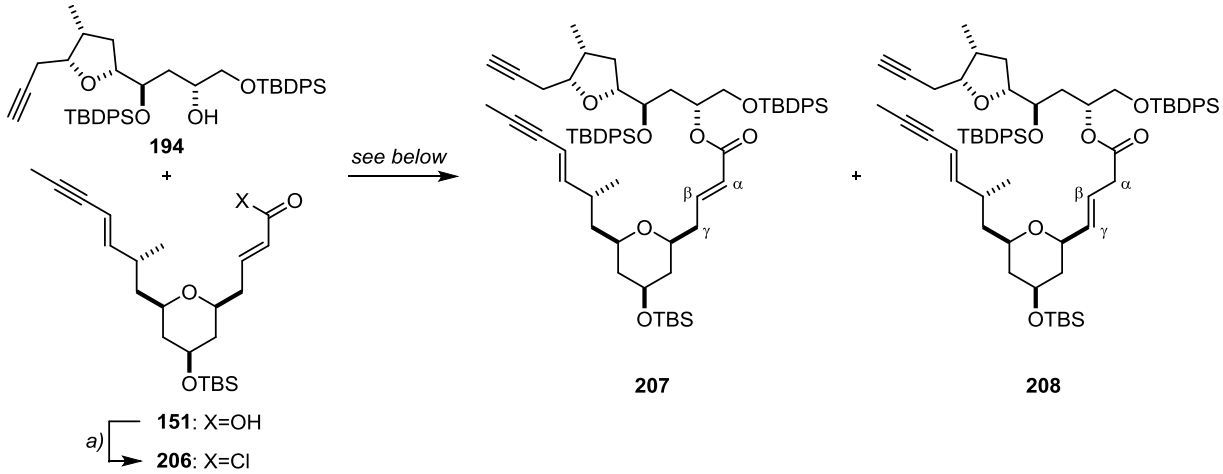
The methylation of the remaining alcohol at C.2' was plagued by 1,2-acyl shift under the basic conditions usually employed for methylation reactions (e.g. with NaH, MeI or $Ag_2O$, MeI). Fortunately, resort to trimethylsilyl diazomethane as methylating agent in the presence of aq. $HBF_4$ allowed this problem to be solved.[190] A large excess of the diazo compound was required to achieve full conversion, yet permitted the isolation of **199**, which intercepts the route described above.

Overall, the synthesis of the sugar fragment was achieved in seven (bis-acetal approach) or eight steps (selective acetylation approach) respectively. In practice, the bis-acetal route is not only one step shorter, but also more convenient in terms of product purification.

## 3.8 Fragment assembly, macrocyclization and endgame

With all required fragments in hand, the assembly stage began with the esterification of alcohol **194** with acid **151**. Despite the numerous methods available in the literature, this transformation turned out to be a fundamental challenge. As can be seen from table 3.5, application of the reaction conditions employed during the leiodermatolide synthesis (EDCI·HCl, DMAP) failed and led to full recovery of the starting alcohol (entry 1). With 2,4,6-trichlorobenzoyl chloride as the activator for acid **151** according to Yamaguchi,[191] the desired product was detected for the first time, although the yield remained disappointingly low (entry 2). Moreover, the product consisted of an inseparable mixture of α,β- and β,γ-isomers, both of which mostly as the (*E*)-isomer (>19:1). The more reactive 2-methyl-6-nitrobenzoic anhydride was evaluated (entry 3), but no improvement was achieved.[192] In these cases, the alcohol could be recovered, whereas the acid was fully consumed. Likewise, the use of a 2-chloropyridinium salt as described by Mukaiyama suffered from poor conversion (entry 4),[193] whereas the Lewis acidic conditions reported by Yamamoto caused decomposition (entry 5).[194]

*Table 3.5:* Optimization of the esterification of **151** and **194**. Conditions: a) $(COCl)_2$, DMF, $CH_2Cl_2$, quant.



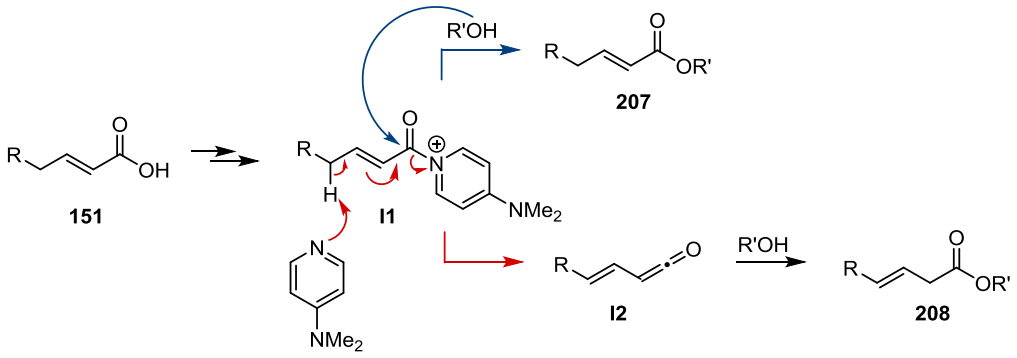

| entry | substrate | conditions | result | 207/208 [1)] |
|---|---|---|---|---|
| 1 | **151** | EDCI·HCl, DMAP, $CH_2Cl_2$ (0.1 M), rt to reflux | rec. **194** | - |
| 2 | " | 2,4,6-trichlorobenzoylchloride, $NEt_3$, DMAP, toluene, 100 °C | 33% | 1.5 : 1 |
| 3 | " | 2-methyl-6-nitro-benzoicanhydride $NEt_3$, DMAP, toluene, rt | 18% | 1.4 : 1 |
| 4 | " | 2-chloro-N-methylpyridinium iodide, $NEt_3$, $CH_2Cl_2$, rt | 9% | 0 : 1 |
| 5 | " | 4-$NO_2$-benzoicanhydride, $Sc(OTf)_3$ cat., MeCN, rt | decomp. | - |
| **6** | " | **DCC (2.2 eq), DMAP (5 eq), $CH_2Cl_2$(1.0 M), rt** | **64%** | **1.5 : 1** |
| 7 | **206** | $NEt_3$, $CH_2Cl_2$, rt | decomp. | - |
| 8 | " | **194**, *n*-BuLi; **206**, THF, −78 °C to rt | 8% | 1 : 0 |

1) determined by integration of olefinic signals in the crude $^1$H NMR.

Preactivation of the acid as acyl chloride was next investigated. Although the acyl chloride **206** could be readily synthesized in quantitative yield by treatment with oxalyl chloride, only decomposition occurred in the presence of $NEt_3$ (entry 7), whereas the lithium salt of **194** reacted sluggishly with acyl chloride **206** (entry 8). Fortunately, the use of excess DCC and DMAP at high concentration yielded the desired ester in 64% yield, although the isomerization of the double bond out of conjugation could not be suppressed (entry 6). Variations of the nucleophilic catalyst (NMI or $PBu_3$)[195] or addition of acidic proton sources (CSA or DMAP·HCl) under otherwise identical conditions gave inferior results.[196]

Control experiments with acid **151** and ester **207** implied that neither DMAP nor $NEt_3$ is able to isomerize the α,β-double bond out of conjugation. It seems likely that an activated intermediate of type **I1** with more acidic γ-protons can be deprotonated by a second molecule of DMAP to form a ketene **I2**, which is attacked by the alcohol and produces the isomeric product **208** (scheme 3.35, red pathway). The desired product **194** can be formed by attack of the alcohol on the active intermediate **I1** following the generally accepted mechanism of Steglich esterifications (blue). Model studies, in which **194** was replaced by menthol, resulted in

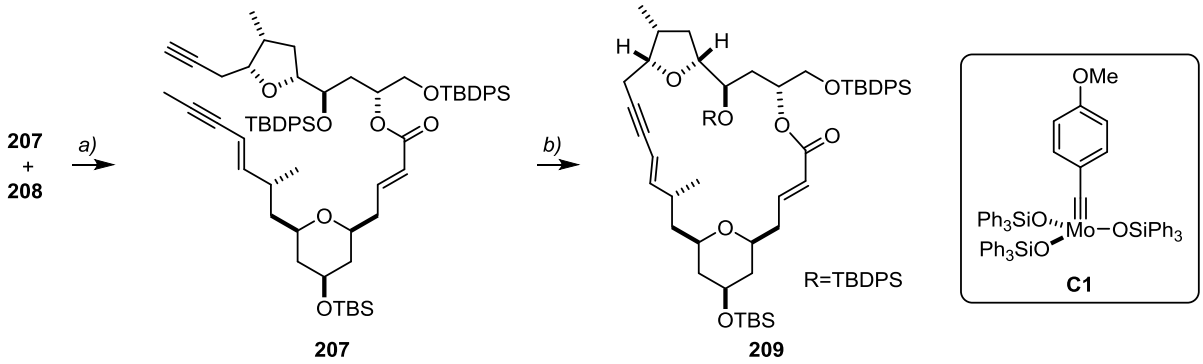
significantly reduced isomerization, indicating that the steric bulk around the secondary alcohol in **194** retards the reaction with **I1**.




*Scheme 3.32:* Mechanistic rationale for the observed isomerization during the esterification reaction.

Since this deconjugation process could not be avoided, the product mixture was treated with catalytic amounts of DBU in MeCN at elevated temperature, which initiated the migration of the double bond of **208** back into conjugation. Trace amounts of the generated (*Z*)-isomer (~3%) were separated by flash chromatography, affording the desired adduct **207** in 91% as a single isomer. The stage was set for the alkyne metathesis comprising an internal as well as a terminal alkyne within the substrate.

Upon exposure of diyne **207** to the undoubtedly most active and functional-group tolerant catalyst **C1**,[25] the desired macrocycle **209** formed readily even at ambient temperature. A catalyst loading of 10 mol% of the molybdenum alkylidyne was necessary to achieve full conversion and allowed the isolation of cycloalkyne **209** in 72% yield. The presence of 4 Å and 5 Å molecular sieves ensured that the reaction medium was rigorously dry and sequestered the released propyne. No dimeric or oligomeric species were detected by mass-spectrometric analysis when the reaction was carried out at high dilution (2 μM).

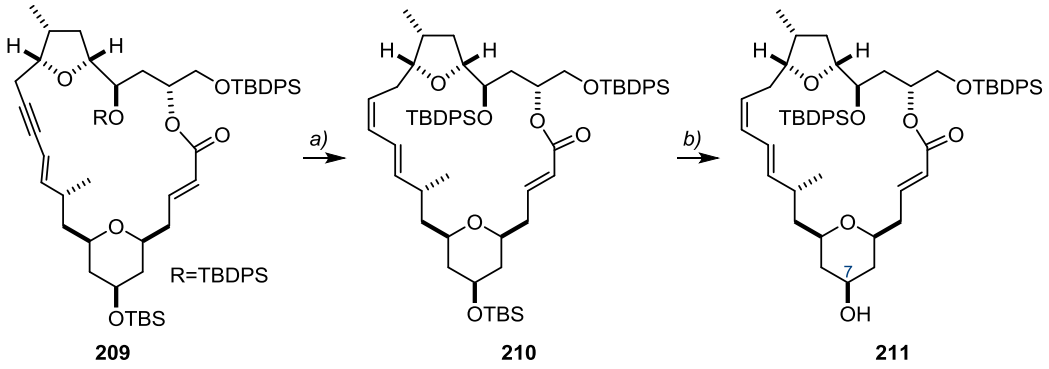



*Scheme 3.33:* Ring-closing alkyne metathesis of **207**. Conditions: a) DBU (25 mol%), MeCN, 50 °C, 91%; b) **C1** (10 mol%), 4 Å MS, 5 Å MS, toluene, 72%.

In light of the side reactions previously encountered with terminal acetylenes such as polymerization[148c-f] and catalyst deactivation,[148b, 148h] the result of this transformation is remarkable and enabling at the same time. Moreover, it represents the first successful example

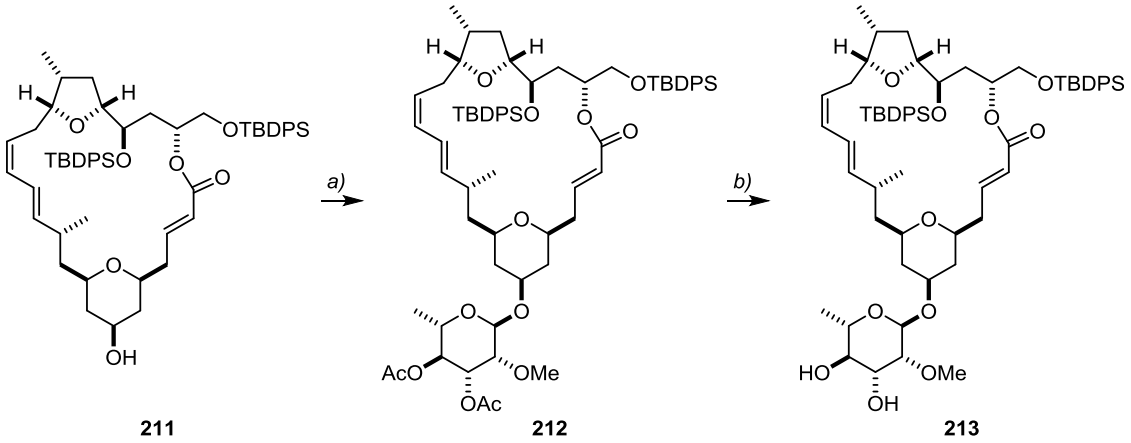
of a metathesized terminal alkyne in the context of natural product synthesis and likely encourages further applications in the future.[197]

The subsequent semihydrogenation was initially attempted with poisoned palladium catalysts under hydrogen atmosphere. These Lindlar reductions resulted in the formation of the desired cyclodiene **210** along with ~20% of an overreduced product that was not further characterized. Based on the experience gained during the total synthesis of leiodermatolide, it was found that an activated Zn(Cu/Ag) couple as the reducing agent enabled the clean formation of the desired (*E*,*Z*)-diene, which was the only isomer formed under these conditions.[96] Although some reactivity was noticed at ambient temperature, the reaction was carried out at 45 °C for the sake of reproducibility. With the diene installed, the TBS-ether was cleaved upon treatment with *p*-toluenesulfonic acid to unmask the alcohol functionality at C.7 without touching the more robust TBDPS groups within the northern fragment.




*Scheme 3.34:* Semihydrogenation and selective deprotection. Conditions: a) Zn(Cu/Ag), THF/MeOH/$H_2O$ 1:1:1, 45 °C, 88%; b) *p*TsOH·$H_2O$ (30 mol%), $CH_2Cl_2$/MeOH 2:1, 90%.

As expected, the glycosidation reaction of **211** with rhamnosyl donor **201** attached the sugar moiety to the parent macrocycle with high yield and high selectivity (d.r. > 16:1) even without neighboring group participation.[188] Of the tested Lewis acids, TESOTf produced compound **212** with the highest yield and allowed the temperature to be lowered to −50 °C, thus ensuring a clean reaction. The acetate groups of the rhamnosyl fragment were then carefully saponified under mild conditions ($K_2CO_3$, MeOH) without opening of the macrocyclic lactone.



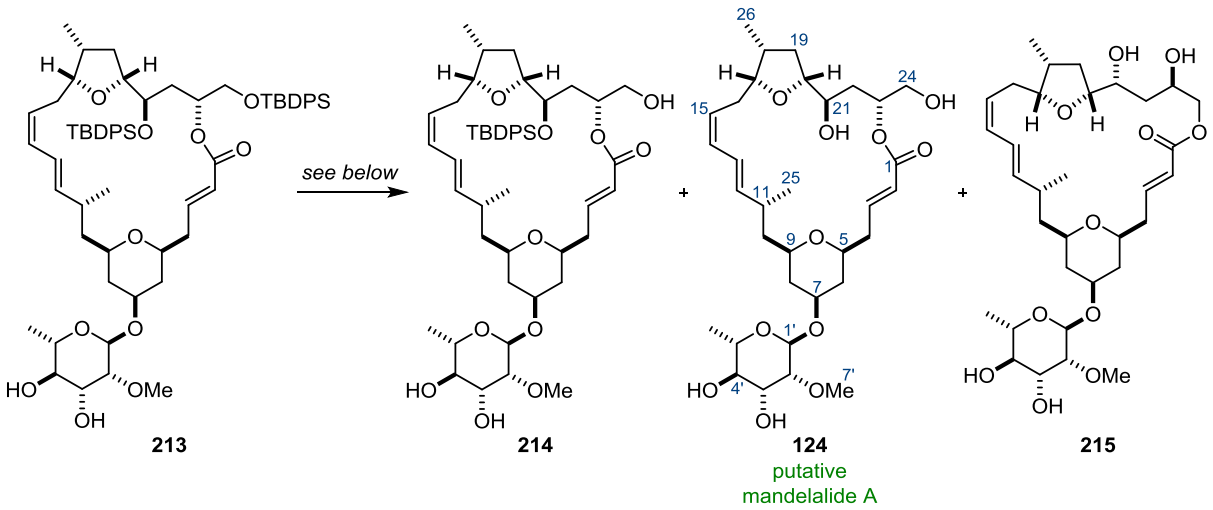

*Scheme 3.35:* Attachment of the rhamnosyl fragment. Conditions: a) **201**, TESOTf, $CH_2Cl_2$, 4 Å MS, −50 °C, 89%; b) $K_2CO_3$, MeOH, 0 °C, 80%.

For the final desilylation, compound **213** as the immediate precursor was subjected to typical conditions previously used for the global deprotection of macrocyclic compounds (table 3.6). Under almost all conditions tried, the primary TBDPS ether at C.24 was cleaved readily to give intermediate **214** with the secondary TBDPS-ether intact. The steric impediment around this site retarded the oxygen-silicon bond cleavage. The reaction was plagued by slow conversion and 1,2-acyl shift of the macrocyclic lactone, which led to the ring-expanded product **215**. This side reaction could easily occur under the basic conditions using fluoride sources, but could also be triggered by Brønsted acid catalysis. To bypass this undesired pathway, the deprotection was carried out under buffered conditions.

When TBAF was buffered with AcOH, the reaction stopped after deprotection of the primary alcohol (entry 1), whereas the use of TASF in different solvent mixtures failed to suppress the ring expansion (entries 2, 3). The use of mildly acidic aqueous hydrogen fluoride allowed the desired product to be isolated for the first time, however the reaction was rather messy and suffered from partial decomposition (entry 4). When the pyridine adduct of HF (Olah's reagent) was used, a slight improvement in yield was noticed; yet, the obtained reaction mixture contained several unidentified compounds (entry 5). Buffering the reaction mixture with excess pyridine slowed down the conversion and only traces of the desired product were detected (entry 6).

Finally, the combination of HF·pyridine and pyridine as the co-solvent allowed the reaction to proceed cleanly and allowed full conversion into **92** to be reached after 28 h (entry 7). Under these conditions, the globally deprotected compound **124** was isolated in 80% yield along with traces of its ring-expanded congener **215** (8%). This reaction was successfully performed with 42 mg of **213** as the single largest batch, allowing for the isolation of 19 mg of **124**.

*Table 3.6:* Optimization of the final deprotection.




| entry | conditions | 214 : 124 : 215 [1)] | yield of 124 [%] |
|---|---|---|---|
| 1 | TBAF, AcOH, rt | 90 : 7 : 3 | - |
| 2 | TASF, MeCN, DMF 2:1, rt | 8 : 20 : 72 | - |
| 3 | TASF, $H_2O$, THF, rt | 10 : 40 : 50 | - |
| 4 | aq. HF, MeCN, 0 °C to rt | 10 : 60 : 30 | 25 |
| 5 | HF·pyridine (50 eq), THF, rt | 3 : 73 : 24 | 41 |
| 6 | HF·pyridine (50 eq), pyridine (100 eq), THF, rt | 85 : 10 : 5 | - |
| **7** | **HF·pyridine, pyridine, THF (1:1:1), 0 °C to rt** | **0 : 91 : 9** | **80** |

1) determined by HPLC analysis of a crude sample.

Overall, more than 25 mg of **124** were prepared by the developed route, which, for the first time, opened a concise (21 steps l.l.s.) and flexible entry into the mandelalide family.

However, the $^{1}H$ as well as $^{13}C$ NMR spectra of both **124** and **215** did not comply with those reported for the natural product (for the full NMR spectra, see appendix). The $^{1}H$ NMR spectrum was clearly distinct from the one reported by the isolation team[141] and small deviations were observed throughout the relevant ppm range. As the concentration, at which the NMR spectrum was recorded by the isolation team, remained unknown, a concentration series was filed with the synthetic material. However, the spectral signature did not change for both the $^{1}H$ and $^{13}C$ nuclei and only the signals of two hydroxyl groups shifted observably.

On the other hand, the spectral data for synthetic **124** left no doubt about its constitution or stereochemistry. Thus, it was concluded that the structure of mandelalide A must have been misassigned by the isolation team and the putative structure of the natural product had been synthesized in the first instance.

## 3.9 Structure reassignment of mandelalide A

The direct comparison of the $^{13}C$ NMR data (figure 3.3) should help to identify a possible site of misassignment. The largest deviations were observed at the stereogenic center at C.11 ($\Delta\delta$ = +1.4 ppm) and the adjacent C.25 methyl group ($\Delta\delta$ = −1.8 ppm). Moreover the coupling constant recorded for H.11 and H.12 ($^3J_{11,12}$ = 7.6 Hz) did not match the one of the natural product ($^3J_{11,12}$ = 9.6 Hz). This stereogenic center had previously been assigned by analysis of the homo- and heteronuclear coupling constants.[141] Since a handheld model of the macrocycle was rather flexible, the NMR data likely reflects an average of more than a single conformation and hence renders the correct interpretation difficult, if not impossible. The observed differences were interpreted as an indication that the chiral center at C.11 might have previously been misassigned. A crafted ball-and-stick model with inverted C.11 stereochemistry suggested that this isomer might be able to adopt a confirmation which would be in agreement with the reported ROESY data and coupling constants.

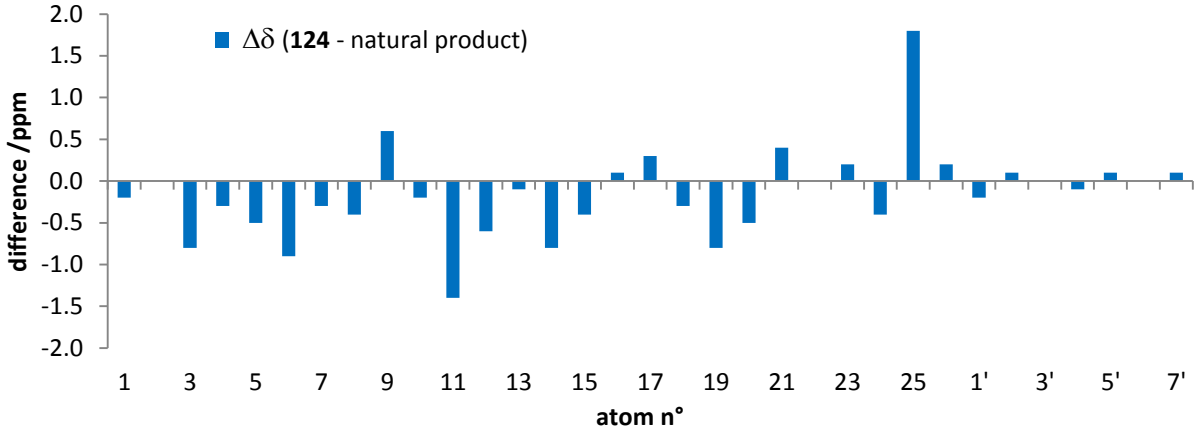
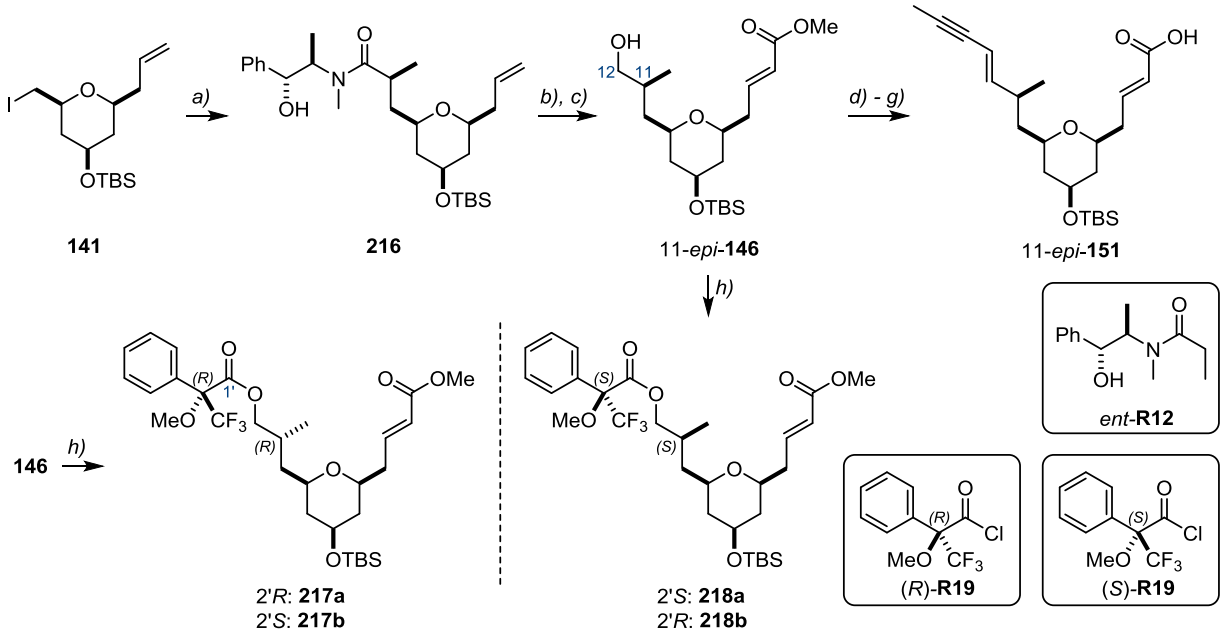



*Figure 3.3:* Observed $^{13}C$ NMR differences (in ppm) between synthetic **124** ($CDCl_3$, 600 MHz) and the natural product ($CDCl_3$, 700 MHz).

To corroborate this assumption, the epimer 11-*epi*-**1** was targeted. The modified synthesis is depicted in scheme 3.39 and starts with the alkylation of alkyl iodide **141** with the enantiomeric Myers auxiliary *ent*-**R12**. To exclude that the stereochemical information already contained in **141** overwrote that of the auxiliary **R12**, a detailed Mosher ester analysis was carried out after cross metathesis with methyl acrylate. The primary alcohols **146** and 11-*epi*-**146** were reacted with both (*R*)- and (*S*)-acylchloride **R19** and gave the Mosher esters **217a**, **217b**, **218a** and **218b**.[198]




*Scheme 3.36:* Synthesis of the epimeric southern fragment and Mosher esters **217** and **218**. Conditions: a) *ent*-**R12**, LDA, LiCl, THF, 0 °C to 45 °C, 84% (d.r. 98:2); b) LDA, $NH_3 \cdot BH_3$, THF, 0 °C to rt, 87%; c) methylacrylate, **C7** (3 mol%), $CH_2Cl_2$, rt, 91%; d) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 76%; e) $CHI_3$, $CrCl_2 \cdot THF$, THF, −8 °C; aq. serine workup, 61%; f) sodium propyne, $(MeO)_3B$, $[PdCl_2(dppf)] \cdot CH_2Cl_2$ (10 mol%), THF, 70 °C, 76%; g) KOTMS, $Et_2O$, rt, 88%; h) (*R*)- or (*S*)-**R19**, pyridine, $CH_2Cl_2$, 0 °C to rt, **217a**: 88%; **217b**: 91%, **218a**: 89%, **218b**: 93%.

Figure 3.4 displays the characteristic region of their $^1$H NMR spectra between 4.45 and 3.95 ppm, showing the two geminal protons at C.12. According to literature precedence,[199] the distance between the two inner lines of the two doublets of dublet is characteristic for each isomer. A large difference indicates either an (*R*,*R*)- or (*S*,*S*)-configuration.[200]

Indeed, the Δδ of the protons at C.12 is bigger for the (*R*)-Mosher Ester of the (11*R*)-isomer **217a**, whereas it increased in case of the (*S*)-Mosher Ester for the (11*S*)-isomer **218a**. Based on this evidence, the stereogenic center at C.11 is clearly controlled by the chiral Myers auxiliary employed in the reaction and not by the chiral alkyl iodide.

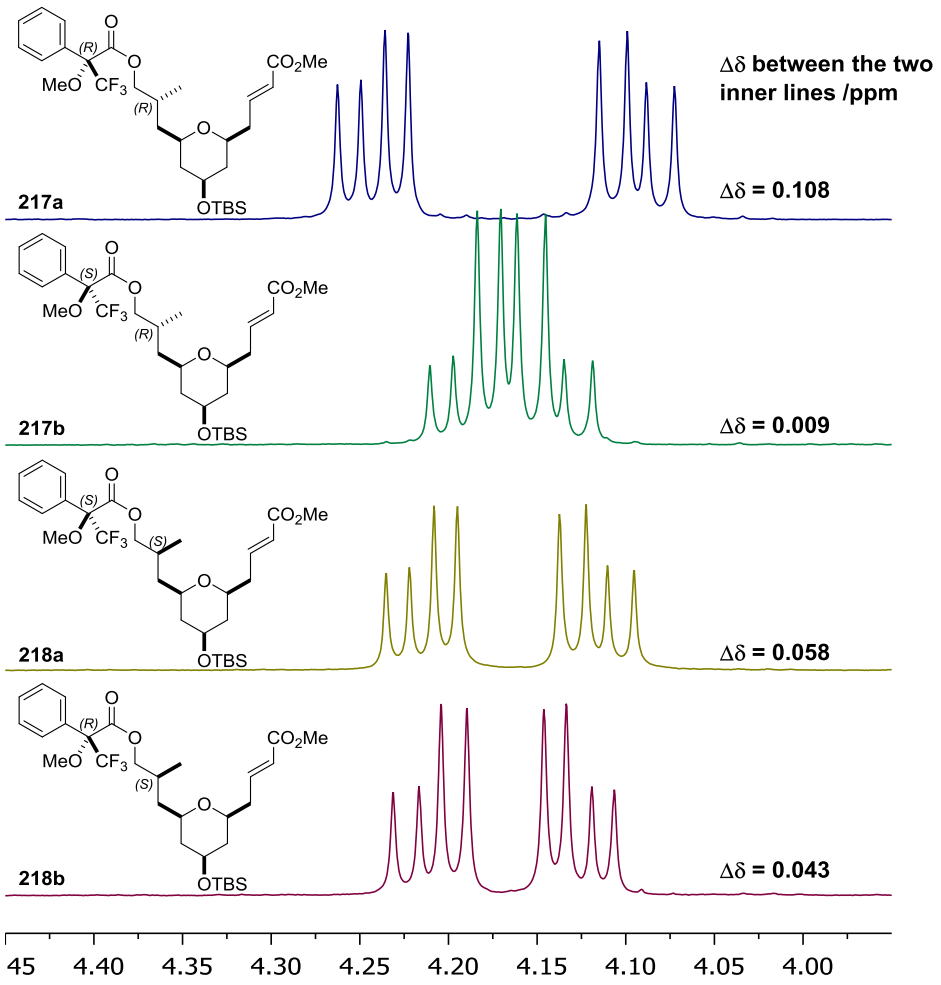
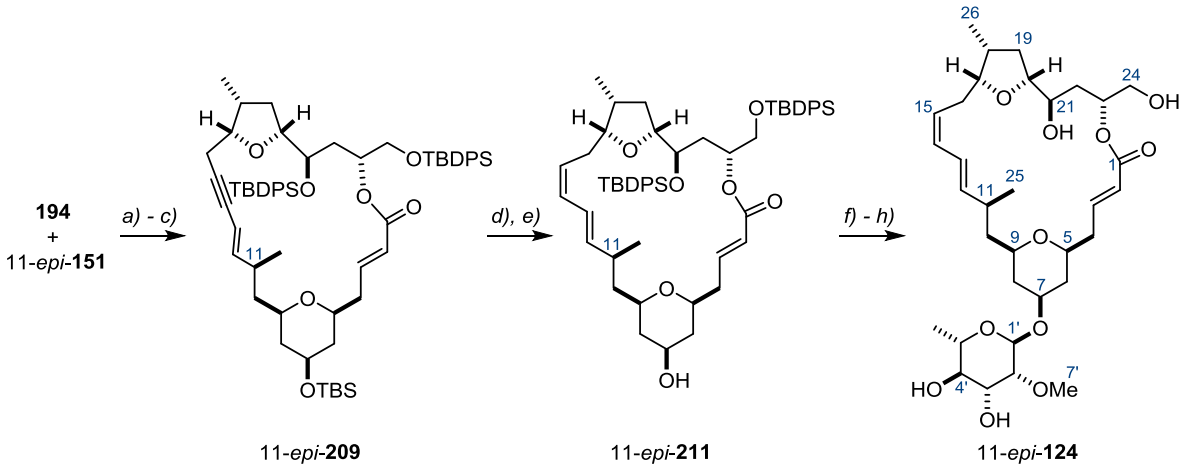



*Figure 3.4:* Mosher esters of compounds **146** and 11-*epi*-**146**. ($^1$H NMR, $CDCl_3$, 400 MHz, 4.45 – 3.95 ppm).

The remaining steps en route to the epimeric southern fragment are analogous to those of the original synthesis and afforded 11-*epi*-**151** after oxidation of the primary alcohol, Takai olefination, alkynylation and ester hydrolysis.

The endgame was similarly straightforward. After esterification, the macrocyclization proceeded readily upon contact with molybdenum alkylidyne **C1** and set the stage for the semihydrogenation, which afforded 11-*epi*-**211** cleanly. Selective removal of the TBS group, glycosidation, and global deprotection under previously optimized conditions afforded the targeted C.11 epimer. Remarkably, no ring-expanded isomer was detected during the deprotection in the 11-*epi* series.




*Scheme 3.37:* Synthesis of the C.11 epimer of putative mandelalide A. Conditions: a) DCC, DMAP, $CH_2Cl_2$, rt, 71% (α,β/β,γ = 1.5:1); b) DBU (25 mol%), MeCN, 50 °C, 92%; c) **C1** (10 mol%), toluene (0.002 M), rt, 64%; d) Zn(Cu/Ag), THF/MeOH/$H_2O$ 1:1:1, 45 °C, 86%; e) *p*TsOH·$H_2O$ (30 mol%), $CH_2Cl_2$/MeOH 2:1, rt, 89%; f) **201**, TESOTf (30 mol%), $CH_2Cl_2$, 4 Å MS, −40 °C, 87%; g) $K_2CO_3$, MeOH, 0 °C, 88%; h) HF·pyridine, pyridine, THF, 0 °C to rt, 85%.

Unfortunately, both $^{1}H$ and $^{13}C$ NMR spectra of 11-*epi*-**124** again showed significant differences when compared to the data of natural mandelalide A (see appendix for full spectra). Figure 3.5 reveals the deviations in the $^{13}C$ NMR with its peak being found at the methyl group of C.25 (Δδ = 3.7 ppm). Interestingly though, the coupling constant between the protons at C.11 and C.12 ($^{3}J_{11,12}$ = 9.7 Hz) is in agreement with the reported data.

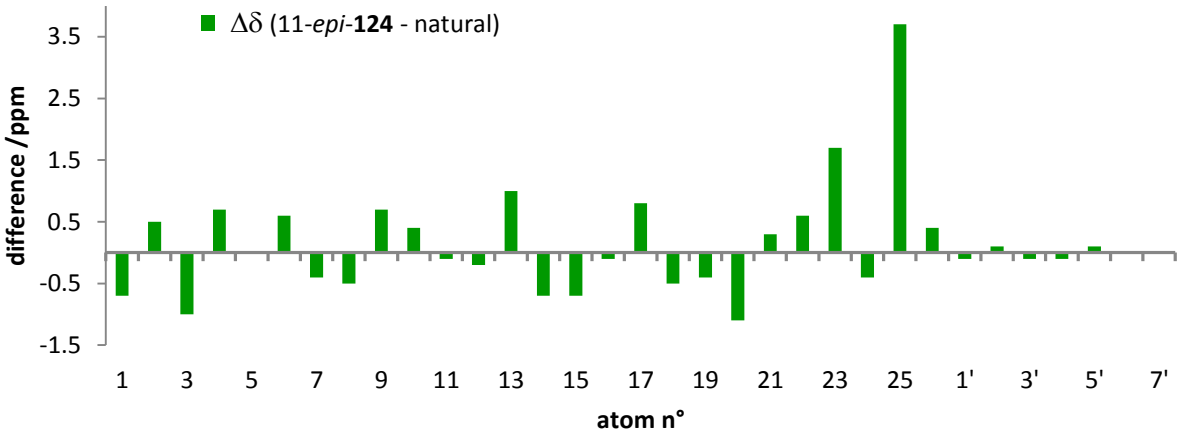



*Figure 3.5:* Observed $^{13}C$ NMR differences (in ppm) between synthetic 11-*epi*-**124** ($CDCl_3$, 600 MHz) and the natural product ($CDCl_3$, 700 MHz).

It was concluded that the error made during the assignment was more profound and may well be located in more than one position. Inspired by structural similarities with the madeirolides, likely candidates bore the enantiomeric northern fragment (see compounds **219** and 11-*epi*-**219**, figure 3.6). However, the presence of no less than nine stereogenic centers around the macrocyclic fragment led to the initiation of a cooperation with Ms. Berit Heggen from the group of Prof. Dr. Walter Thiel.[201] The calculations performed during this collaboration were

supposed to forecast the correct structure of mandelalide A with the aid of NMR prediction via the DP4 probability method developed by Goodman[202] and therefore minimize the number of isomers that had to be synthesized in order to find the correct structure of the natural product.
Over 20 diastereomers with configurational inversion of the whole northern fragment or alternatively at C.11, C.20 and C.21 were taken into account; for clarity aspects, only four diastereomers are discussed in the following (see figure 3.6). For all compounds, a conformer sampling using a molecular mechanics conformational search was performed with the CHARMM general force field (CGenFF). All gas-phase conformers at 298.15 K within a range of 10 kJ/mol were considered and subjected to either single-point DFT calculations or manual geometry optimizations to determine the calculated energies and the shielding constants in the gas phase. After averaging the shielding constants over the Boltzmann distribution, the NMR shifts relative to tetramethylsilane were calculated according to the GIAO method.[203] The calculated shifts were subsequently correlated to the experimental data and the DP4 probability was obtained, which indicates the probability that the computed structure matches the experimental data.[202] The advantage of this methodology is that it takes several conformers into account, weighs them according to their relative energies and should therefore be applicable to flexible macrocyclic compounds like in the present scenario.

*Table 3.8:* Conformer energies (in kcal/mol) of the diastereomers considered in the NMR prediction.[201]

| **entry** | **124** | 11-*epi*-**124** | **219** | 11-*epi*-**219** |
|---|---|---|---|---|
| 1 | 4.05 | 19.55 | 11.20 | 5.84 |
| 2 | 0.00 | 19.55 | 7.33 | 0.00 |
| 3 | 2.76 | 0.00 | 0.00 | |
| 4 | 11.56 | 6.98 | 0.95 | |
| 5 | 8.30 | 13.08 | 11.65 | |
| 6 | | 10.27 | 3.91 | |
| 7 | | 8.23 | | |
| 8 | | 16.52 | | |

The conformers, which correspond to the global energy minimum are depicted in figure 3.6 and reveal interesting structural features. Thus, compound **124** is the only isomer, in which the northern fragment is bent over the southern fragment and forms a U-shape with the methyl group of C.26 pointing into the semi-circle (figure 3.7a). This forces the (*E*,*Z*)-configured diene to adopt a conformation that is twisted with an angle of 38° around the C.13 and C.14 bond, which in turn decreases the efficacy of orbital overlap between the two π-systems (figure 3.7b). The proximity of the primary alcohol at C.24 and the neighboring carbonyl group at C.1 suggests a stabilizing hydrogen bond for **124** (figure 3.7c), which is clearly less pronounced for all other calculated structures that fail to adjust the alcohol and the carbonyl group in co-

planarity. Remarkably, the lowest lying energy conformers of all other structures adopt an ideal *s*-trans configuration of the diene and do not show the above mentioned bending.

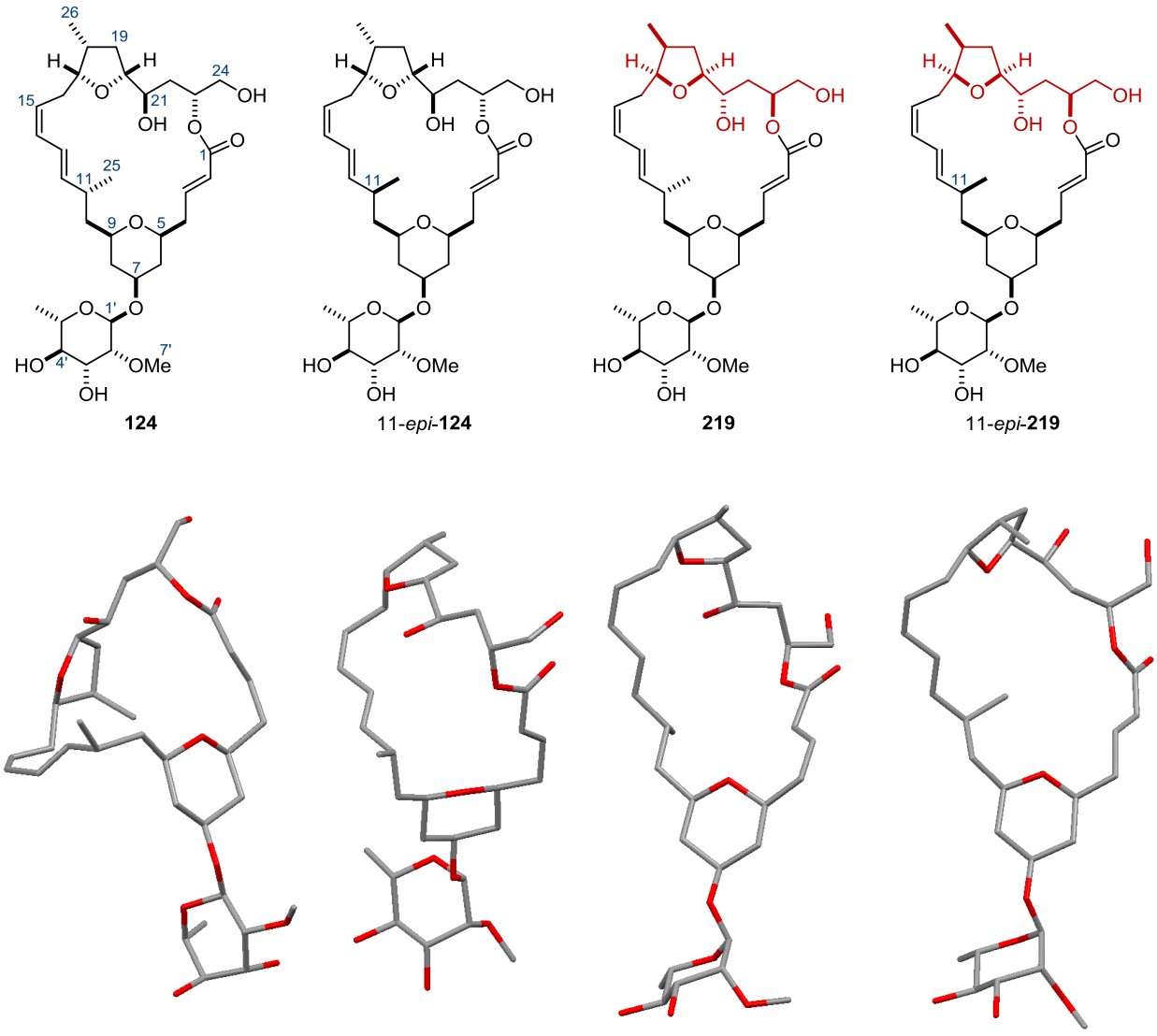



*Figure 3.6:* Lowest lying energy conformers calculated for the four most likely mandelalide isomers.[201]

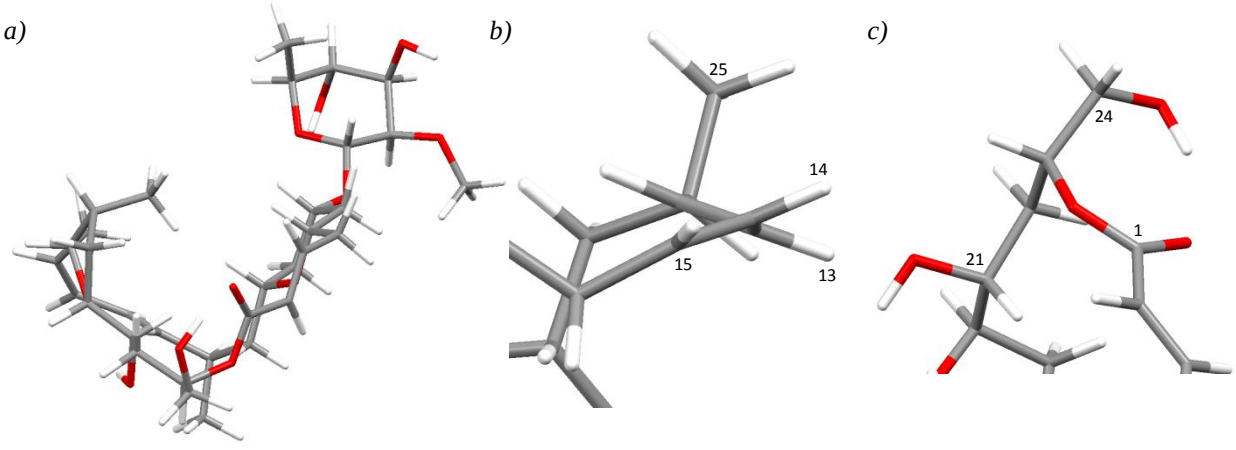



*Figure 3.7:* Lowest lying energy conformer of **124** from different perspectives: a) U-shape of the macrocycle; b) projection along the diene single bond between C.13 and C.14; c) postulated hydrogen bond.[201]

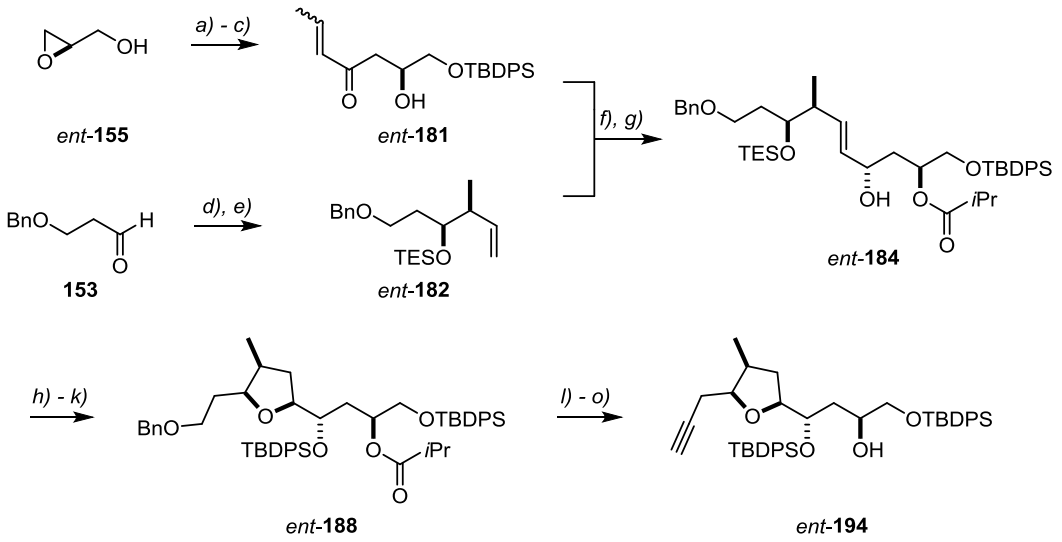
The calculated DP4 probabilities (table 3.9) however were contradictory in themselves and did not facilitate the search for actual mandelalide A. Of the calculated probabilities obtained for the four considered diastereomers, only structure **219** offers potential hits. Intriguingly, the DP4 probability for the calculated $^{13}C$ shifts of **219** shows a perfect match with all three available experimental datasets, whereas the predicted $^{1}H$ shifts cannot be assigned to any of the isomers. The different absolute overall values can be explained by the fact that they are not obtained from the $^{1}H$ and $^{13}C$ probability products displayed in the table, but are the result of an algorithm, which multiplies each probability value of a $^{1}H$ nuclei with the corresponding $^{13}C$ probality value.[201]

*Table 3.9:* Calculated DP4 probabilities of four calculated mandelalide A isomers.[201]

| | **NMR** | **124** (theor) | 11-*epi*-**124** (theor) | **219** (theor) | 11-*epi*-**219** (theor) |
|---|---|---|---|---|---|
| **natural** (experimental) | $^{13}C$ | 0 | 0 | 1.00 | 0 |
| | $^{1}H$ | 0 | 0 | 0 | 0 |
| | overall | 0 | 0 | 0.24 | 0 |
| **124** (experimental) | $^{13}C$ | 0 | 0 | 1.00 | 0 |
| | $^{1}H$ | 0 | 0 | 0 | 0 |
| | overall | 0 | 0 | 0.90 | 0 |
| 11-epi-**124** (experimental) | $^{13}C$ | 0 | 0 | 1.00 | 0 |
| | $^{1}H$ | 0 | 0 | 0 | 0 |
| | overall | 0 | 0 | 0 | 0 |

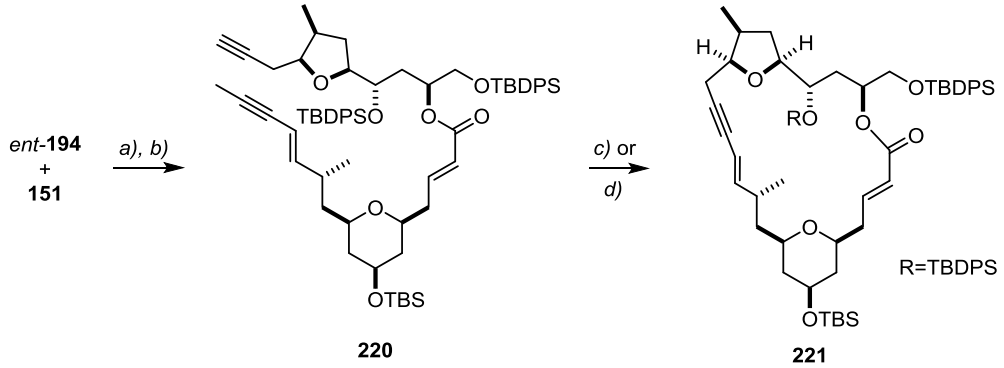
The best entire overlap was obtained for the calculated NMR shifts of **219** with the experimental data of compound **124**, which had already proven to be false by synthesis. Moreover, the expected matches of the calculated isomers **124** and 11-*epi*-**124** with the appropriate experimental data obtained during this study were not found and clearly indicated that this particular NMR prediction method had failed in the mandelalide case.

With this result, total synthesis remained the ultimate tool to shed light on the actual structure of mandelalide A. Based on biochemical reasoning and the similarity to the madeirolides, the most likely candidates consisted of compounds **219** and 11-*epi*-**219** with fully inverted stereochemistry within the northern fragment. As a consequence, these compounds were synthesized by using the corresponding enantiomeric building blocks. At the same time, this opportunity was used to scale up the synthesis of *ent*-**194** by a factor of three. The strategy and the synthetic operations were not changed and enabled reliable access to more than 700 mg of the required alcohol *ent*-**194** (scheme 3.38).




*Scheme 3.38:* Synthesis of the enantiomeric alcohol fragment. Conditions: a) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C to rt, 95%; b) $Co_2(CO)_8$ (8 mol%), *N*-TMS morpholine, CO (1 atm), EtOAc, rt, 74%; c) propenyl-magnesium bromide, THF, −25 °C; then −78 °C, aq. HCl workup, 79%; d) (*S*,*S*)-**R17**, $Sc(OTf)_3$ (5 mol%), $CH_2Cl_2$, −78 to 0 °C, 80% (94.6% ee); e) TESCl, $NEt_3$, DMAP, $CH_2Cl_2$, 0 °C to rt, 91%; f) **C8** (4+2+2 mol%), $CH_2Cl_2$, reflux, 73%; g) *i*-PrCHO (5 eq.), $SmI_2$ (35 mol%), THF, −50 °C, 74% (>19:1 d.r.); h) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C to rt, 82%; i) CSA (30 mol%), $CH_2Cl_2$/MeOH 2:1, 0 °C, 99%; j) *N*-PSP, TFA, $Ph_3P{=}S$ (12 mol%), $CH_2Cl_2$, −40 to −20 °C 82% (14:1 d.r.); k) *n*-$Bu_3SnH$, AIBN, toluene, 80 °C, 97%; l) $Pd(OH)_2$/C (cat.), $H_2$ (1 atm), EtOAc/EtOH 1:9, rt, 82%; m) DMP, $CH_2Cl_2$, 0 °C to rt, 94%; n) **R18**, NaOMe, THF, −78 °C; then *ent*-**190**, to −50 °C, 96%; o) DIBAl-H, toluene, −78 °C, 97%.

With the enantiomeric alcohol fragment in hand, the endgame was carried out with both previously synthesized acid fragments. Remarkably, the alkyne metathesis reaction to produce **221** under the previously employed conditions gave a diminished yield of only 45% (scheme 3.39).

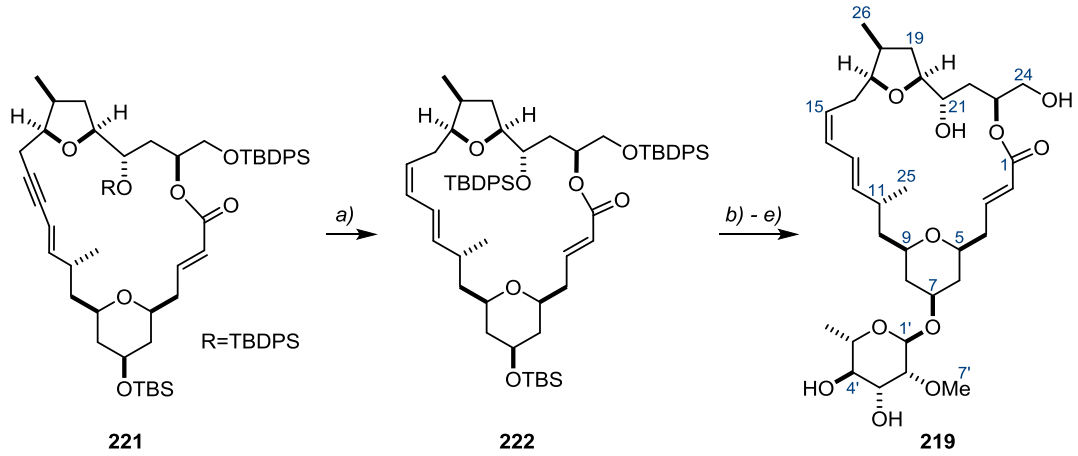



*Scheme 3.39:* Fragment assembly and RCAM with the enantiomeric northern fragment. Conditions: a) DCC, DMAP, $CH_2Cl_2$, rt, 52% (α,β/β,γ 1.5:1); b) DBU (25 mol%), MeCN, 50 °C, 85%; c) **C1** (10 mol%), toluene (0.002 M), 4 Å MS, 5 Å MS, rt, 45%; d) **C1** (10 mol%), toluene (0.002 M), 4 Å MS, 5 Å MS, 85 °C, 74%.

This problem could be overcome by increasing the reaction temperature to 85 °C, which significantly speeded up the reaction and allowed the desired cycloenyne **221** to be isolated in 74% yield. One may speculate that the diyne precursor adopts a conformation that does not

favor ring-closure and elevated temperatures are required to bring the two alkyne units in proximity. The reaction was significantly slower when carried out at ambient temperature and competing oligo- or polymerization pathways were believed to take over. To exclude an experimental error, several control reactions were performed in parallel at ambient and at elevated temperature with the same stock solution of catalyst and the same batch of substrate.

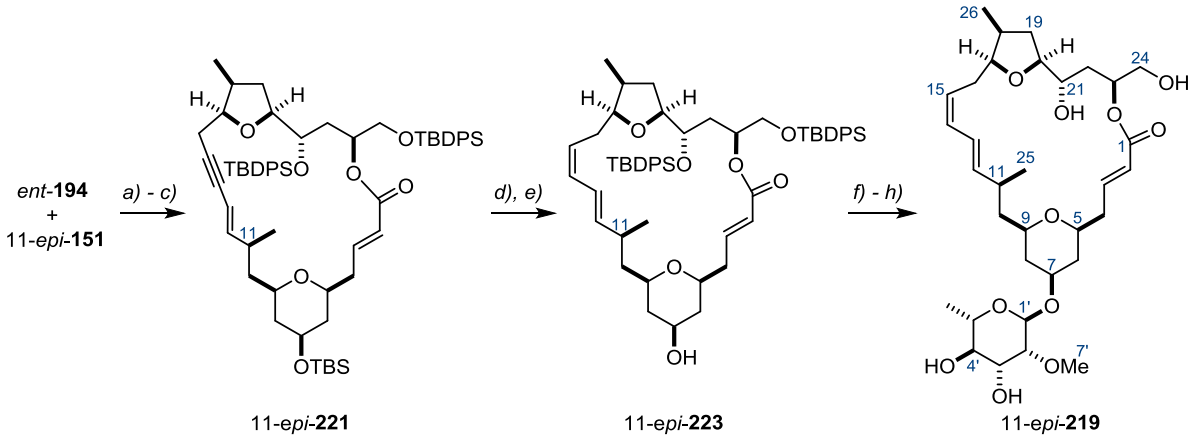
The remaining steps held no surprise and furnished the targeted compound **219** with good yields along the whole sequence (scheme 3.40).




*Scheme 3.40:* Completion of the synthesis of **219**. Conditions: a) Zn(Cu/Ag), THF/MeOH/$H_2O$ 1:1:1, 45 °C, 91%; b) *p*TsOH·$H_2O$ (30 mol%), $CH_2Cl_2$/MeOH 2:1, rt, 86%; c) **201**, TESOTf (30 mol%), $CH_2Cl_2$, 4 Å MS, −40 °C, 83%; d) $K_2CO_3$, MeOH, 0 °C, 96%; e) HF·pyridine, pyridine, THF, 0 °C to rt, 71%.

The epimeric compound 11-*epi*-**219** was prepared analogously. Notably, the RCAM to produce 11-*epi*-**221** proceeded readily at ambient temperature as previously observed and furnished the desired product in 83% isolated yield (scheme 3.44).

The C.11 stereogenic center seems to be, at least to a certain extent, responsible for retarding the ring-closure by dictating an unfavorable conformation. Again, the following steps worked reliably and produced the targeted compound 11-*epi*-**219** after semihydrogenation, glycosidation and global deprotection.




*Scheme 3.41:* Completion of the synthesis of 11-*epi*-**219**. Conditions: a) DCC, DMAP, $CH_2Cl_2$, rt, 53% (α,β/β,γ 1.5:1); b) DBU (25 mol%), MeCN, 50 °C, 93%; c) **C1** (10 mol%), toluene (0.002 M), 4 Å MS, 5 Å MS, rt, 83%; d) Zn(Cu/Ag), THF/MeOH/$H_2O$ 1:1:1, 45 °C, 83%; e) *p*TsOH·$H_2O$ (30 mol%), $CH_2Cl_2$/MeOH 2:1, rt, 90%; f) **201**, TESOTf (30 mol%), $CH_2Cl_2$, 4 Å MS, −40 °C, 80%; g) $K_2CO_3$, MeOH, 0 °C, 92%; h) HF·pyridine, pyridine, THF, 0 °C to rt, 68%.

The $^1$H and $^{13}$C NMR spectra of the two compounds **219** and 11-*epi*-**219** were again compared with those of the natural product. The recorded $^1$H and $^{13}$C spectra of **219** in $CDCl_3$ and $d^5$-pyridine show a perfect match and are identical in all respects, whereas those of 11-*epi*-**219** are clearly distinct (figure 3.8).

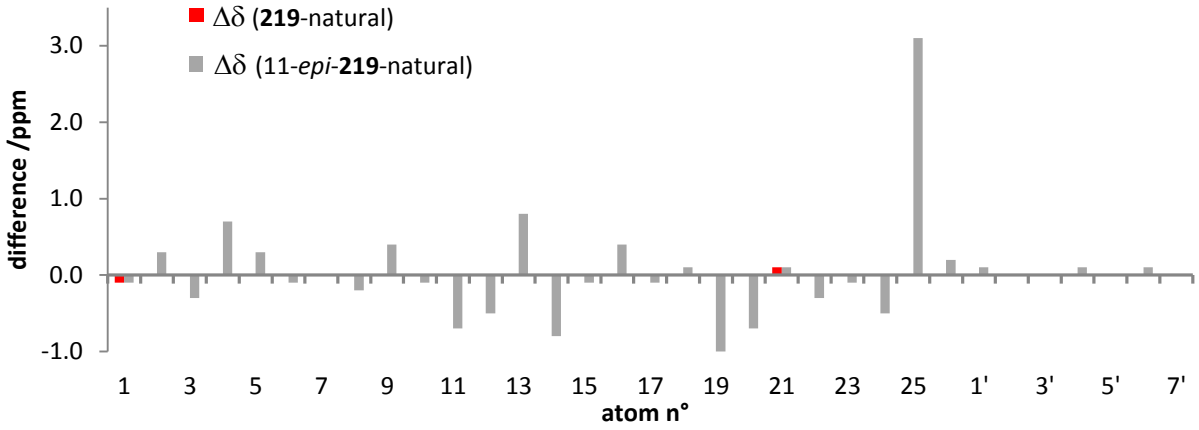



*Figure 3.8:* Observed $^{13}$C NMR differences (in ppm) between synthetic **219** (orange) and 11-*epi*-**219** (violet) (both: $CDCl_3$, 600 MHz) with the natural product ($CDCl_3$, 700 MHz).

In consequence, mandelalide A was reassigned and is correctly depicted by structure **219**. Thus, the stereogenic center at C.11 was properlyy assigned by the isolation team; however, the stereochemistry of the whole northern fragment is inverted.

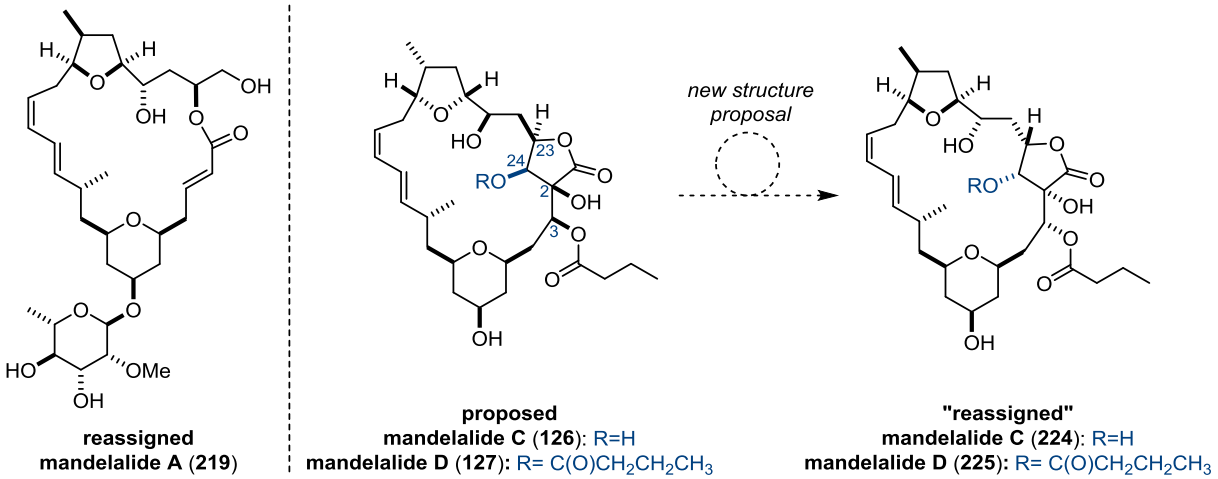
The recorded optical rotation of **219** ($[\propto]_D^{23}$ = –29 (c=0.25, MeOH)) is higher than the one reported for natural mandelalide A ($[\propto]_D^{23}$ = –9 (c=0.25, MeOH)) but its sign indicates the correct absolute configuration. It is unclear whether the differences are caused by an experimental error or by traces of highly optically active impurities in one of the samples. However, the group of Ye later reported an optical rotation for synthetic mandelalide A

($[\alpha]_D^{20}$ = –34.6 (c=0.25, MeOH)),[146] which is in reasonable agreement with the data found for the synthetic material in this study.

## 3.10 Studies towards the total synthesis of mandelalides C and D

### 3.10.1 Retrosynthetic analysis

Since the developed route was deemed robust and scalable, the project was extended to access other family members from a common macrocyclic intermediate. The mandelalides C (**126**) and D (**127**) were chosen as primary targets to evaluate this strategy, as these compounds lack the glycosidic unit and were believed to be more readily accessible. Since the stereochemistry of the northern fragment of mandelalide A had turned out to be misassigned, it was hypothesized that the northern stereocluster of **126** and **127** suffered from the very same structural incorrectness. Although the stereogenic centers were assigned by interpretation of the ROESY contacts and coupling constants,[141] it seemed likely that the stereogenic centers at C.2, C.3 and C.24 of **126** and **127** also needed to be inverted.

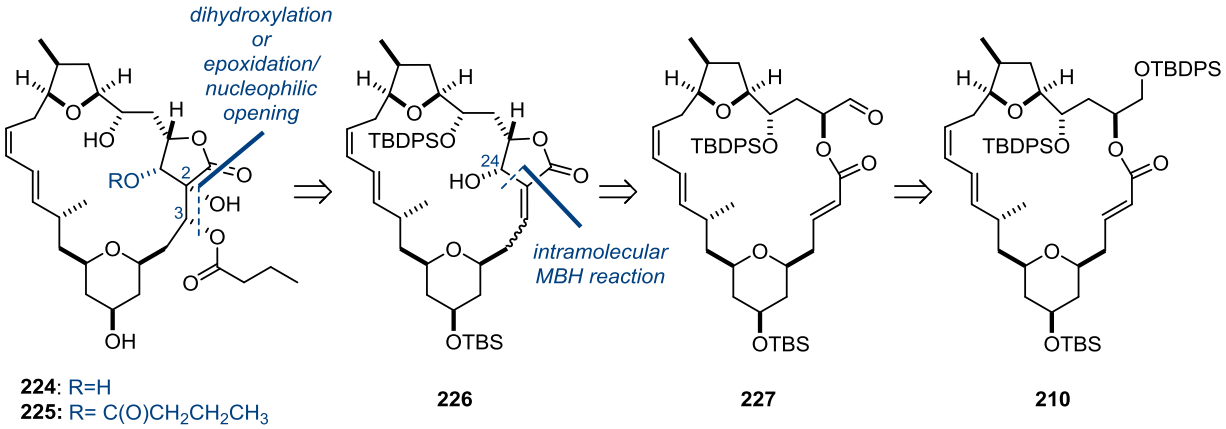



*Scheme 3.42:* Newly proposed structures for **126** and **127** based on the structural reassignment of mandelalide A.

This was based on the consideration that the stereogenic centers in question are in direct neighborhood to a previously fixed stereogenic center at C.23 from the northern fragment, whereas the assignment with regard to the southern fragment involved a rather flexible methylene unit at C.4, which renders a correlation difficult. As depicted in scheme 3.42, the targeted structures have all stereogenic centers of the northern and eastern part of the molecule inverted when compared to the originally proposed structures.[141]

The retrosynthetic analysis shown in scheme 3.43 highlights the key disconnection. The oxygen functionalities at C.2 and C.3 were supposed to be introduced via dihydroxylation directed by the alcohol at C.24 or via directed epoxidation reaction depending on the double bond configuration of the allylic alcohol precursor **226**. The carbon-carbon bond between C.24 and

C.2 distinguishes the macrocyclic core of the targeted compounds from mandelalide A and was thought to derive from an intramolecular Morita-Baylis-Hillman (MBH) reaction of aldehyde **227**. The just mentioned aldehyde was thought to be accessible by oxidation of the corresponding primary alcohol, which would be obtained after selective deprotection of the previously synthesized macrolactone **210**.




*Scheme 3.43:* Retrosynthetic analysis of mandelalides C and D leading back to previously synthesized **210**.

Since all four mandelalides were isolated from the same species, one might be tempted to speculate about the biomimetic pathway. The proposed synthesis via a late stage MBH reaction would indeed explain the occurrence of all four mandelalide species within the same ascidian. However, it was previously stated that "the MBH reaction does not occur in nature."[204] Simultaneously, the same authors have reported that certain carrier proteins were able to catalyze MBH reactions of simple model substrates; yet, these results were interpreted as unnatural enzymatic promiscuity.[204, 205] In this light, the alternative pathway involving classic aldol processes for the construction of the C.24/C.2 bond followed by redox and elimination processes seems more reasonable. Although it remains unknown whether this bond formation occurs before or after construction of the macrocycle, it was reasonable to assume that the macrocyclic framework exerts a certain degree of control over the forming stereogenic center at C.24.

The envisioned sequence with an intramolecular MBH reaction followed by directed oxidation seemed fascinating and synthetically challenging alike, and ensured motivation to pursue this approach. Before the synthetic endeavor with the macrocyclic system was initiated, the key MBH reaction was investigated on a simple model.

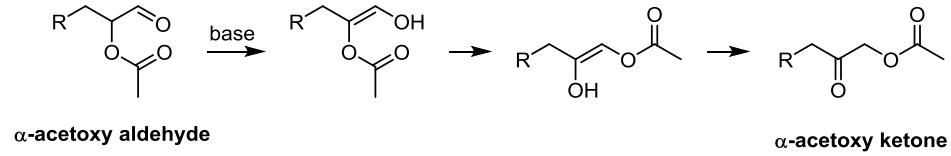
### 3.10.2 Model studies for the Morita-Baylis-Hillman reaction and directed dihydroxylation

A model compound was synthesized to explore the feasibility of the envisioned intramolecular MBH reaction. This transformation was deemed particularly challenging for three reasons:

i) β-substituted Michael acceptors are rarely employed in MBH reactions since they suffer from low reactivity towards the nucleophilic mediator due to steric shielding of the electrophilic 4-position of the Michael acceptor,[206]

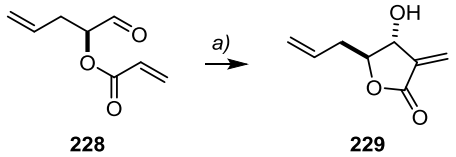
ii) the anticipated reaction formally displays a 5-(*enolendo*)-*exo*-trig cyclization, which is classified as "disfavored" by the Baldwin rules,[207] and

iii) the MBH precursor contains an α-acetoxy aldehyde motif, which is known to rearrange under basic conditions to the corresponding α-acetoxy ketone (scheme 3.47).[208] This transformation likely occurs through enolization, 1,2-acyl shift and keto-enol tautomerism.




*Scheme 3.44:* Base-catalyzed rearrangement of α-acetoxy aldehydes.

The presence of a single literature report of an intramolecular MBH reaction producing a five-membered ring emboldened the desire to find suitable conditions applicable to the mandelalide case.[209] However, the group of Krishna used a more reactive β-unsubstituted Michael acceptor **228** as can be seen in scheme 3.45.

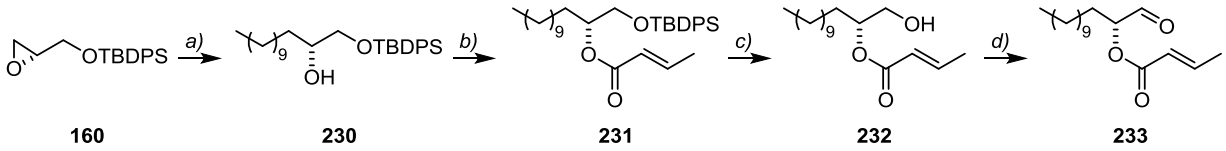



*Scheme 3.45:* Literature evidence for a 5-(*enolendo*)-*exo*-trig MBH cyclization. Conditions: a) DABCO (50 mol%), $CH_2Cl_2$, rt, 62%.[209]

Moreover, the produced γ-lactone **229** bears the hydroxyl and the alkyl substituent in an *anti*-relationship as opposed to the *syn*-motif in the mandelalide family. However, it was speculated that the conformation of the macrocycle as well as the chiral environment of the substrate could dictate the stereochemical outcome and override the inherent stereoselectivity of this reaction.

The synthesis of a suitable model substrate started with the copper-catalyzed epoxide opening of **160** with *n*-decyl Grignard, which was chosen to decrease the volatility of the subsequent products. The crude product **230** was engaged into the esterification reaction with *trans*-crotonic acid to furnish ester **231**. The silyl group on the masked primary alcohol was removed

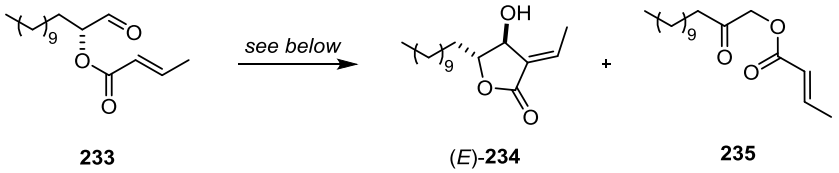
with TBAF in the presence of acetic acid to reduce the amount of 1,2-acyl shift. Oxidation of alcohol **232** with DMP under buffered conditions gave aldehyde **233** in acceptable yields and set the stage for the exploration of the MBH reaction.




*Scheme 3.46:* Synthesis of MBH model substrate **233**. Conditions: a) $C_{10}H_{21}MgBr$, CuCN (2 mol%), $Et_2O$/THF, −15 °C, 98%; b) (*E*)-crotonic acid, DCC, DMAP, $CH_2Cl_2$, rt, 81%; c) TBAF, AcOH, THF, 0 °C to rt, 89%; d) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 55%.

Aldehyde **233** was first subjected to the conditions reported by the group of Krishna, which employed DABCO to achieve the cyclization.[209] However, the additional methyl substituent shut down the reactivity of the Michael acceptor and no reaction was observed at ambient temperature, whereas clean conversion to the rearranged product **235** was detected at 50 °C (table 3.10, entry 1). Other amine-based nucleophiles were subsequently employed but none of these were able to promote the desired reaction; they either led to the formation of **235** (entries 2, 3)[210] or to rather complex mixtures (entry 4).[211]

*Table 3.10:* Selected attempts towards a MBH cyclization with model system **233**.




| entry | conditions[1)] | result[2)] |
|---|---|---|
| 1 | DABCO (50 mol%), $CH_2Cl_2$, rt to 50 °C | no reaction; then 95% **235** |
| 2 | Quinuclidine (1 eq.), MeOH (1.5 eq), rt | 97% **235** |
| 3 | DBU (50 mol%), MeCN, 0 °C to rt | 80% **235** |
| 4 | DMAP, DMAP·HCl, EtOH, reflux | complex mixture |
| 5 | NMI-oxide (5 eq.), neat, rt | s.m., trace **235** |
| 6 | $Ph_3P$=S, DMF, 90 °C | s.m. |
| 7 | $Et_3P$=O, DMF, 90 °C | s.m. |
| 8 | $Et_2AlI$, $CH_2Cl_2$/toluene, −78 to −20 °C | complex mixture |
| 9 | $PhSCH_2CH_2OH$ or $Me_2S$, $TiCl_4$, $CH_2Cl_2$, 0 °C | complex mixture |
| 10 | $N(CH_2CH_2NMe)_3P$=S, $TiCl_4$, $CH_2Cl_2$, 0 °C to rt | s.m.; complex mixture |
| 11 | $MgBr_2$, TMEDA, DMAP, MeOH | 20% **235**, complex mixture |
| 12 | *n*-BuSeLi, THF, −78 °C; $H_2O_2$ workup | trace **234**, complex mixture |
| 13 | PhSeMgBr, THF, −78 °C to rt | two unidentified products |
| 14 | *n*-BuTeLi, THF, 0 °C | complex mixture |

1) Unless stated otherwise, 1 eq. of MBH mediator was employed. 2) determined by $^1$H NMR.

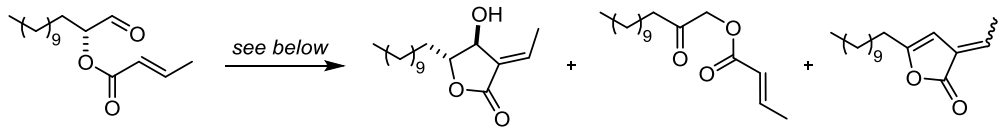
The use of other Lewis basic mediators like NMI-oxide,[212] phosphine sulfides or phosphine oxides failed and the starting material was recovered in these cases along with traces of the rearranged product **235** (entries 5 – 7). When Lewis acids combined with thiols, amines or

other Lewis bases were employed, complex mixtures caused by unknown decomposition pathways were obtained (entries 8 – 11).[210b, 213] The use of lithiated selenols or tellurols seemed more promising as they were reported to tolerate β-substition of the unsaturated ester in intermolecular settings, although the subsequent elimination might require an additional step.[214] However, application of these conditions to model substrate **233** led to the formation of several unidentified products that were difficult to purifiy (entries 12 - 14).

As a last resort, phosphines were thought to be appropriate catalysts for the MBH reaction.[215] Indeed, trimethylphosphine was able to cataylze the desired cyclization in $CH_2Cl_2$ when carried out at high dilution, but the dehydrated product **236** was isolated (table 3.11, entry 1). Nevertheless, the formation of the desired carbon-carbon bond was observed and encouraged a closer inspection of different phosphines.

As the more bulky tributylphosphine did not affect any cyclization, the reaction seems sensitive to both sterics and to the basicity of the phosphine. It was further hypothesized that a less basic, but slim phosphine might similarly induce the cyclization without triggering the elimination of the allylic hydroxyl group formed. Therefore, dimethylphenylphosphine was engaged in the reaction;[216] however the reaction in $CH_2Cl_2$ at ambient temperature afforded only reisolated starting material (entry 2). Increasing the solvent polarity (DMF) as well as the temperature allowed the cyclization to occur, yet it was again plagued by elimination of water (entry 3). Remarkably, the use of methyldiphenylphosphine as the catalyst enabled the isolation of the desired γ-lactone **234** after 2.5 days at 90 °C in 65% overall yield (entry 4).

*Table 3.11:* Phosphine-catalyzed MBH reaction.




**233** (*E*)-**234** **235** **236**

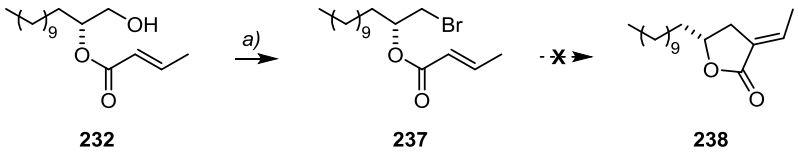
| **entry** | **conditions**[1)] | **result** (**234**:**235**:**236**)[2)] | **yield** of **234** (***E*/*Z***)[3)] |
|---|---|---|---|
| 1 | $PMe_3$, $CH_2Cl_2$, rt | (0 : 11 : 78) | - |
| 2 | $Me_2PPh$, $CH_2Cl_2$, rt | mainly s.m. | - |
| 3 | $Me_2PPh$, DMF, 90 °C | (4 : 9 : 73) | - |
| 4 | $MePPh_2$, DMF, 90 °C, 60 h | (70 : 6 : 8) | 65% (7:1) |
| **5** | **$MePPh_2$, DMF, 120 °C, 24 h** | **(72 : 3 : 12)** | **67% (5:1)** |
| 6 | $PPh_3$, DMF, 90 °C | no reaction | - |
| 7 | P(2-furyl)$_3$, DMF, 90 °C | no reaction | - |
| 8 | P(4-MeO-Ph)$_3$, DMF, 90 °C | no reaction | - |

1) Unless stated otherwise, 30 mol% of phosphine was employed. 2) determined by GC-MS analysis. Since several minor by-products were also formed, the products do not add up to 100. 3) determined by $^1$H NMR.

The careful analysis of the crude reaction mixture revealed that **234** was formed as the *trans*-isomer with high diastereoselectivity (> 18:1) as previously described, whereas the double bond was produced as an (*E*/*Z*)-mixture of 7:1. The *syn*/*trans* assignment was based on NOE contacts and coupling constants; moreover, the chemical shift of the protons at C.3 supported the NOE assignment of the double bond geometry: the proton at C.3 of (*E*)-**234** is shifted downfield as compared to the (*Z*)-isomer due to the magnetic anisotropy of the carbonyl group. The double bond isomers were separated by careful chromatography on silica gel.

The reaction time could be decreased to 24 h, when the reaction was performed at 120 °C in DMF, although the (*E*/*Z*)-ratio was slightly lower (entry 5). Electron neutral and rich triaryl phosphines were subsequently employed (entries 6-8);[217] however, they failed to mediate the MBH reaction and starting material could be recovered in all cases. Furthermore, variation of the solvent, catalyst loading, temperature, pressure and additives were explored in more than 25 additional experiments, but the original result with mere methyldiphenylphosphine could not be outperformed.

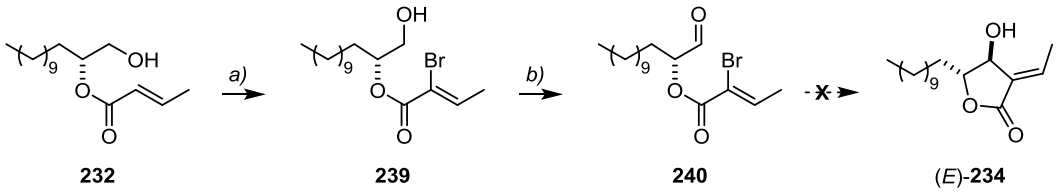
In parallel, two stepwise approaches to the γ-lactone were followed on model substrates. On the one hand, the primary alcohol **232** was converted into the corresponding primary alkyl bromide **237** and subjected to MBH alkylation reaction conditions. Neither phosphine-catalysis,[218] nor thioethanol in the presence of $Cs_2CO_3$[219] nor the use of strong organic bases like DBU promoted the transformation to **238**; rather, the starting material remained mainly untouched. As the following allylic oxidation was also expected to be troublesome, this sequence was quickly abandoned.




*Scheme 3.47:* Attempted MBH alkylation. Conditions: a) $PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C to rt, 62%.

On the other hand, the unsaturated ester in **232** was α-brominated by dibromination / elimination to produce **239**. After oxidation, aldehyde **240** was exposed to $SmI_2$, which was thought to induce a radical cyclization onto the carbonyl group. However, the desired product **234** was not detected; rather, the deacetylated aldehyde and alcohol were observed by mass spectrometry. Somewhat unexpectedly, the σ*-orbital of the carbon oxygen bond in α–position of the aldehyde seems to be a better electron acceptor than the one of the carbon bromine bond next to the double bond. Similarly, γ-lactone **234** was not formed when **240** was exposed to chromium(II) chloride in the presence of catalytic amounts of nickel(II) chloride. Finally, insertion of activated zinc into the carbon-bromine bond occurred, but debrominated and

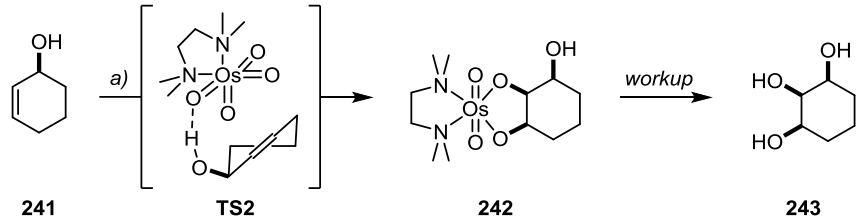
oligomeric species prevailed over the cyclized product, which was only detected in trace quantity.




*Scheme 3.48:* Attempted two-step alternative. Conditions: a) $Br_2$, $CH_2Cl_2$, 0 °C, then $NEt_3$, $Et_2O$, rt, 58%; b) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 51%.

Based on these results, the moderate yield of the phosphine-catalyzed MBH reaction remained the only hit. Next, the subsequent directed dihydroxylation reaction was modelled with (*E*)-**234**.

Despite the fact that several asymmetric variants are known, the directed dihydroxylation of allylic alcohols was only made possible by the research of the Donohoe group.[220] This transformation relies on the addition of TMEDA to stoichiometric amounts of osmium tetroxide. As exemplified for the dihydroxylation of cyclohexenol (**241**), the diamine is believed to coordinate to the rather electrophilic metal center and in consequence increases the electron density at osmium.



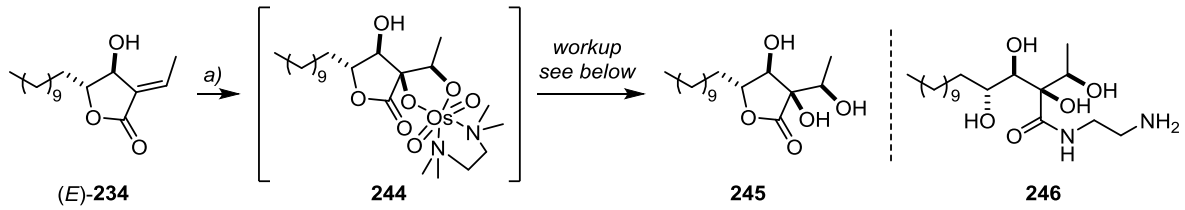

*Scheme 3.49:* Reported directed dihydroxylation and postulated mechanism. Conditions: a) TMEDA (1.10 eq.), $OsO_4$ (1.05 eq.), $CH_2Cl_2$, −78 °C; aq. $Na_2SO_3$ workup, 98% (6:1 *syn*/*anti*).[221]

At the same time, the back-bonding from the metal center to the oxo-ligands is increased and renders them potential hydrogen bond acceptors (**TS2**). Mechanistic studies have shown that the TMEDA ligand is chelated to the osmium center before and after the reaction with an alkene, indicating that the guidance occurs via hydrogen bonding with the oxo ligands rather than through interactions of the allylic alcohol with a free tertiary amine from a mono-coordinated ligand. The rather stable osmate ester **242** was then cleaved upon treatment with HCl, ethylenediamine or aq. $Na_2SO_3$ to release triol **243**.[221] If TMEDA was omitted, the reaction would produce the *anti*-product for both cyclic and acyclic allylic alcohols as first recognized by Kishi.[222]

When applied to the present model substrate **234**, a single diastereoisomer of the intermediate osmate ester **244** was produced, which was later assigned to be the expected *syn*-addition product. The reaction was surprisingly fast and reached full conversion, even at −78 °C,

immediately after complete addition of osmiumtetroxide to a solution of substrate and TMEDA.

*Table 3.12:* Selected attempts to cleave osmate ester **244**. Conditions: a) $OsO_4$, TMEDA, $CH_2Cl_2$, −78 °C.




(*E*)-**234** **244** **245** **246**

| entry | Workup | result |
|---|---|---|
| 1 | conc. HCl, MeOH, 0 °C | 41% (**245**); rather messy |
| 2 | ethylenediamine, $CH_2Cl_2$, −78 °C to rt | **246** (MS) |
| 3 | THF, aq. $Na_2SO_3$, 70 °C | no hydrolysis |
| 4 | Mannitol, AcOH, HFIP, rt to 50 °C | no hydrolysis |
| 5 | EDTA or $Na_2EDTA$, MeOH/HFIP, rt to 50 °C | no hydrolysis |
| 6 | THF, aq. $NaHSO_3$, 70 °C | 71% (**245**) |
| 7 | THF, aq. $NaHSO_3$, rt | 74% (**245**) |

However, the cleavage of the resulting osmate ester **244** proved to be less facile. The previously described conditions were initially investigated. Of those, only the rather harsh acidic conditions (table 3.12, entry 1) afforded the desired product in modest yield. However, application of these conditions to the macrocyclic system of mandelalide would most certainly be incompatible with the variety of functional groups and potentially acid labile protecting groups.[223]

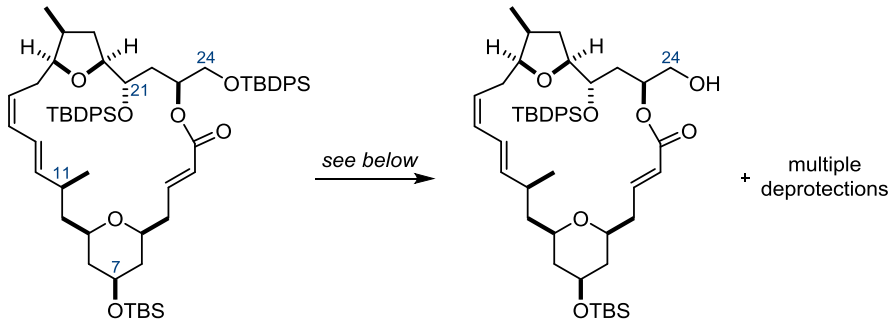
With ethylendiamine, the osmate ester was cleaved after 48 h reaction time. However, the product could neither be detected nor isolated; rather, ESI-MS analysis suggested that ethylenediamine simultaneously opened the γ-lactone to give amide **246**, which was not further characterized or purified due to the high polarity and good water solubility (entry 2). The seemingly mildest cleavage conditions were the treatment of the crude reaction mixture with an aqueous $Na_2SO_3$ solution.

Surprisingly though, no reaction occurred and the osmate ester **244** was recovered unchanged even after prolonged exposure at 70 °C (entry 3). Initial attempts to release the diol by treatment with chelating agents such as mannitol[224] or EDTA[225] were unsuccessful and quickly abandoned (entries 4, 5). An extensive literature survey suggested the use of sodium bisulfite as a reducing agent for the osmate ester.[226] In the event, the intermediate **244** could be cleanly elaborated into triol **245** with acceptable yields, regardless of the reaction temperature. These conditions were judged to be mild enough to be tried on the macrocyclic system during the envisaged synthesis of mandelalide C.

### 3.10.3 Application to the mandelalides: total synthesis of isomers of mandelalide C and deacylmandelalide D

With suitable conditions for both key reactions developed, their application on the macrocyclic system needed to be explored. To this end, the primary TBDPS group at C.24 had to be cleaved in the presence of the two secondary silyl ethers. The selectivity issue was addressed with the 11-*epi*-isomer of compound **210** as an appropriate model substrate. During the deprotection of mandelalide A, HF·pyridine cleanly deprotected the primary TBDPS first before touching the secondary silyl ether; however, these conditions could not be applied to 11-*epi*-**210** as the secondary TBS group at C.7 was cleaved at similar rates as the primary TBDPS group. Another promising literature report described the use of equimolar amounts of TBAF and AcOH to selectively remove TBDPS groups in the presence of TBS groups.[227] Unfortunately, in all circumstances and independent of the solvent or TBAF source, full conversion was not achieved and the secondary alcohol at C.21 was liberated along with the desired primary alcohol (entries 2, 3).

*Table 3.13:* Selected attempts to achieve the selective deprotection of macrocycle 11-*epi*-**210**.




11-*epi*-**210** 11-*epi*-**247**

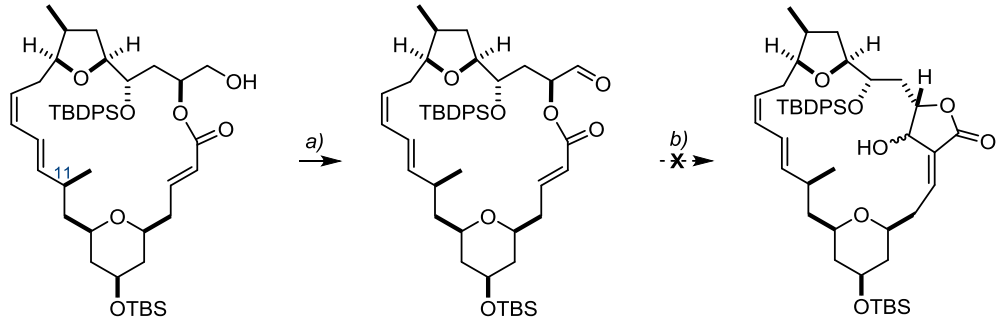
| entry | conditions | conv. [1] (yield) [%] | 11-*epi*-**247** / multiple deprot.[1,2] |
|---|---|---|---|
| 1 | HF·pyridine, pyridine, THF, 0 °C to rt | 100 | 1 : 16 (2° TBS cleaved) |
| 2 | TBAF (1.1 eq.), AcOH (1.1 eq.), DMF, rt | 70 | 1 : 1 (2° TBDPS cleaved) |
| 3 | TBAF·3$H_2O$ (1.1 eq), AcOH (1.1 eq.), THF, rt | 93 | 1 : 2 (mixture) |
| 4 | $Al_2O_3$, hexanes, rt | 0 | - |
| 5 | $NH_4F$ (1.5 eq.), MeOH, rt to 55 °C | 24 | 1 : 2 (2° TBS cleaved) |
| **6** | **$NH_4F$ (110 eq.), HFIP, 0 °C to rt** | **86 (67)** | **82 : 1 (2° TBDPS cleaved)** |

1) determined by HPLC analysis. 2) multiple deprot. = sum of multiple deprotection products. The major by-product is given in parenthesis.

The protocol with dried aluminum oxide in aprotic solvent also failed to induce any O-Si bond cleavage (entry 4).[228] Next, commercially available ammonium fluoride was employed: in methanol, a slight excess sufficed to induce accompanying cleavage of the TBS group at C.7 (entry 5),[229] whereas the use of hexafluoroisopropanol as solvent significantly improved the outcome of this reaction. Even when excess $NH_4F$ was utilized, the deprotection was selective

for the desired primary position and allowed the targeted primary alcohol 11-*epi*-**247** to be isolated in 67% yield after 60 h reaction time (entry 6).[230]

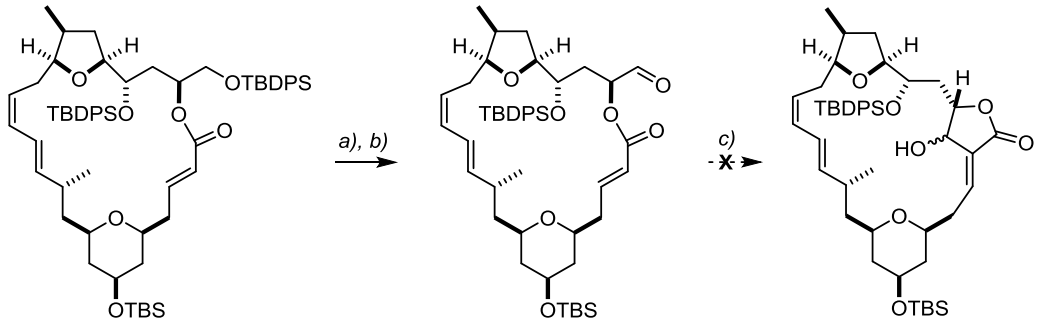
With suitable conditions for the crucial selective deprotection identified, Dess-Martin oxidation of the primary alcohol yielded aldehyde 11-*epi*-**227** as the immediate precursor for the envisioned MBH reaction. However, upon treatment with methyldiphenylphosphine in DMF at elevated temperature, no cyclization product was detected in the crude mixture. Rather, the NMR analysis pointed at the formation of the ring-expanded ketone; though, the small scale prohibited the isolation of the rearranged product.




11-*epi*-**247** 11-*epi*-**227** 11-*epi*-**226**

*Scheme 3.50:* Attempted MBH reaction with the mandelalide macrocycle. Conditions: a) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 52%; b) $MePPh_2$ (30 mol%), DMF, 90 to 120 °C, sealed tube.

To exclude that the epimeric stereogenic center at C.11 prohibited the population of a reactive conformation, the original diastereomer **227** was synthesized by applying the exact same conditions. The deprotection of **210** furnished the corresponding primary alcohol reliably, which was immediately oxidized to aldehyde **227**. Again, the envisioned MBH cyclization failed under the conditions previously developed, although the reasons remained unclear.




**210** **227** **226**

*Scheme 3.51:* Attempted MBH reaction with the mandelalide macrocycle. Conditions: a) $NH_4F$, HFIP, rt, 65%; b) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 84%; c) $MePPh_2$ (30 mol%), DMF, 90 to 120 °C, sealed tube.

It was speculated that the macrocyclic scaffold might prevent population of the required *s*-trans configuration of the indicated ester carbon-oxygen single bond (figure 3.9). Again, computational methods were used to evaluate whether the adoption of such a conformation was feasible.[201] To shorten the computing time, the silyl groups at C.7 and C.21 were omitted,

although the results might be influenced by these massive steric differences. After geometry optimization (Gaussian09 RevD.01, B3LYP/6-31G* level) of the truncated macrocycle **248**, energy minima for both *s*-cis and *s*-trans conformations were discovered. The displayed diagram shows that the *s*-trans configuration, which is approximately 11 kcal/mol higher in energy than the corresponding *s*-cis isomer, can be reached via a transition state amounting to 14 kcal/mol. As can be seen in the calculated structure of the *s*-trans isomer, the aldehyde and C.2 are closer and bond formation seems possible. Based on these encouraging results, which suggested that the adoption of a reactive conformation is not a mission impossible – at least for the truncated variant without protecting groups – further studies with the macrocyclic system were carried out.

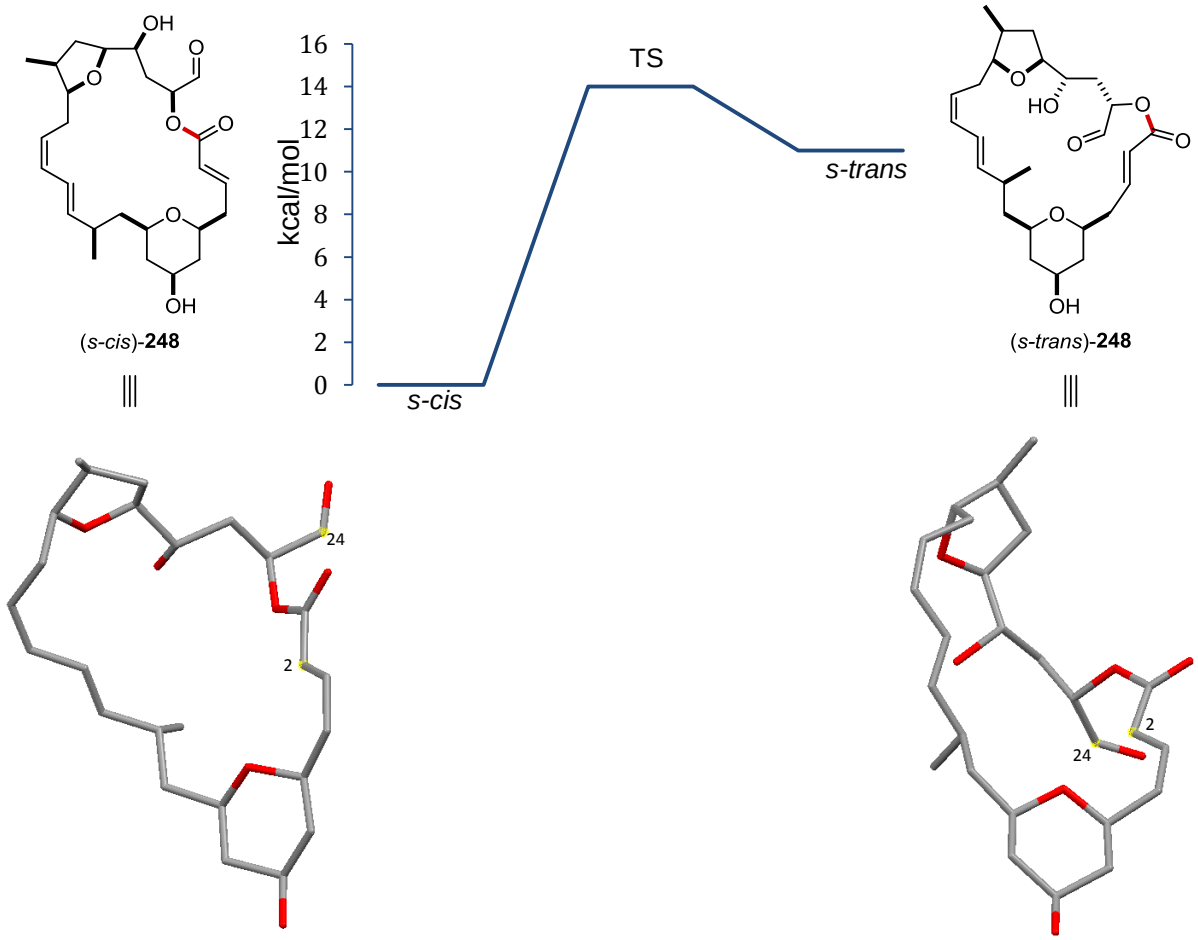
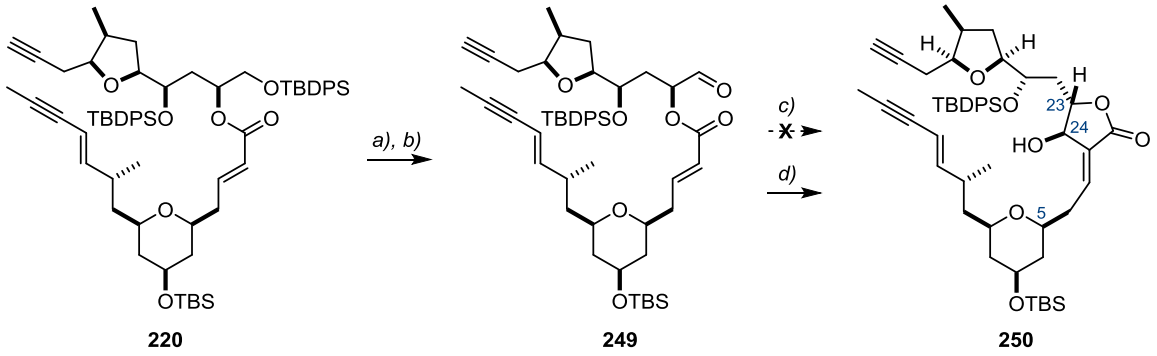



*Figure 3.9:* Calculated energy minima for s-cis and s-trans conformers of truncated macrocycle **248.**

In parallel, this hypothesis was tested on the open form, namely aldehyde **249**, which was obtained by selective desilylation of **220** and subsequent oxidation. Since compound **249** did not have any macrocyclic rigidity it was thought to better resemble model substrate **233**; it was expected to allow the translation of the developed conditions as it should be able to adopt the required *s*-trans configuration of the ester more readily. However, when exposed to catalytic amounts of methyldiphenylphosphine in DMF at 90 °C, only epimerization in the α-position of

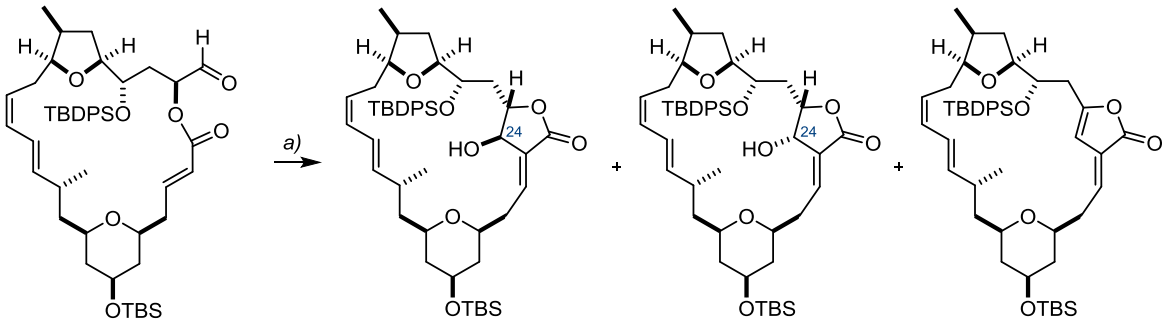
the aldehyde was observed. Further increase of the reaction temperature led to the formation of a complex mixture with several unidentified decomposition products. These results indicated that the constraints entailed by the macrocycle were not responsible for the failure of the envisioned cyclization.




*Scheme 3.52:* Attempted MBH reaction with a linear mandelalide precursor. Conditions: a) $NH_4F$, HFIP, rt, 70%; b) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 83%; c) $MePPh_2$ (30 mol%), DMF, 90 to 120 °C, sealed tube; d) $Me_2PPh$ (30 mol%), DMF, 90 to 120 °C, sealed tube, 38% (6:1 *E*/*Z*).

It was then speculated that the steric bulk imposed by the branching THP ring at C.5 might be accountable. Eventually, replacement of methyldiphenylphosphine by the sterically less bulky dimethylphenylphosphine enabled the crucial carbon-carbon bond formation and allowed the isolation of a 6:1 (*E*/*Z*)-mixture of **250** as a single diastereomer at C.24 comprising the γ-lactone along with minor amounts of the elimination product. Remarkably, the very same phosphine had given exclusively the dehydrated product with the model substrate. After detailed analysis of the NOESY spectrum and comparison of the coupling constants, the hydroxyl group of the newly formed stereogenic center at C.24 was found to be in an *anti*-relationship to the alkyl group at C.23. Therefore, the stereogenic center at C.24 was (*R*)-configured, whereas the reassigned natural products **224** and **225** bear the opposite (24*S*)-configuration.

As a consequence, aldehyde **227** was treated with dimethylphenylphosphine hoping to override the observed stereocontrol by the chiral environment of the macrocyclic scaffold. Although the complete inversion of stereochemistry was not achieved, γ-lactone **226** was produced as a 1.6 : 1 mixture of diastereomers in favor of the undesired (24*R*)-isomer. The two diastereomers and the dehydrated by-product **251** could be easily separated by column chromatography. The olefin geometry was assigned to be (*E*)-configured based on NOE contacts between the protons at C.4 and C.24; this assignment is consistent with the downfield shift of the proton at C.3, which experiences the anisotropic field of the ester carbonyl group. The corresponding (*Z*)-isomers were produced to only minor extents and were inadvertently removed during the purification process.




*Scheme 3.53:* MBH reaction with macrocyclic aldehyde **227**. Conditions: a) $Me_2PPh$ (30 mol%), DMF, 90 °C, sealed tube, (24*R*)-**226**: 34%, (24*S*)-**226**: 19%, **251**: 5%.

The stereogenic center at C.24 was assigned based on NOE contacts of the protons H.22, H.23 and H.24 as depicted in figure 3.10 and was supported by the measured coupling constants extracted from 1D-COSY experiments. The strong NOE contacts between the hydroxyl group at C.24 and H.23 for (24*R*)-**226**, as well as the strong NOE signal of the protons H.23 and H.24 for (24*S*)-**226** were deemed indicative. This original assignment was confirmed throughout the course of this investigation.

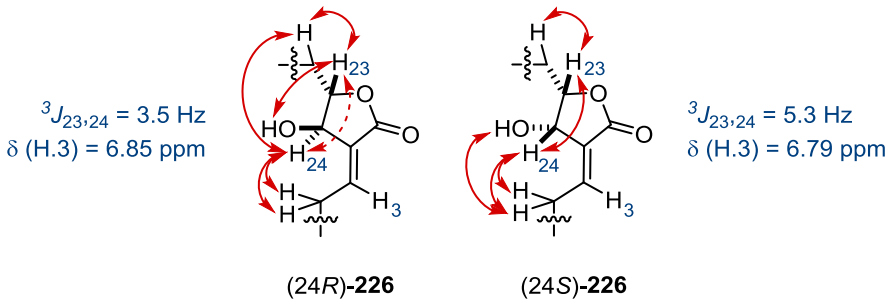
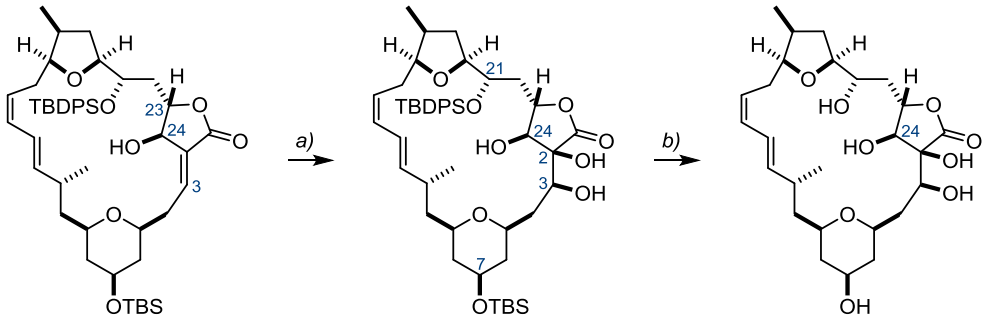



*Figure 3.10:* NOESY data and coupling constants for both diastereomeric γ-lactones of **226** ($CDCl_3$, 600 MHz).

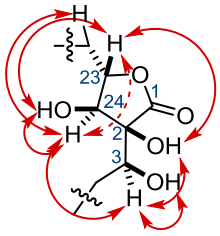
With both diastereomers in hand, the directed dihydroxylation was pursued. At first, the undesired isomer (24*R*)-**226** was dihydroxylated with osmium tetroxide in the presence of TMEDA. After reductive cleavage of the intermediate osmate ester with sodium bisulfite, the desired triol **252** was obtained as a single diastereomer in 65% yield. Intriguingly, the dihydroxylation was fully selective for the α,β-unsaturated double bond, although the diene offered potentially reactive sites. To prevent overoxidation, the reaction was performed with 1.01 eq. of osmium tetroxide and stopped once the addition was complete. The stereochemical outcome was assured by NOESY experiments, which clearly suggested that the delivery of the two hydroxyl groups occurred *syn* to the hydroxyl group at C.24 (figure 3.11) as expected. Indicative is the observed NOE contact between the hydroxyl group at C.2 with H.23.




(24*R*)-**226** **252** **253**

*Scheme 3.54:* Dihydroxylation and deprotection. Conditions: a) $OsO_4$ (1.01 eq.), TMEDA (1.15 eq.), $CH_2Cl_2$, −78 °C; then THF, aq. $NaHSO_3$, rt, 65%; b) HF·pyridine, pyridine, THF, 0 °C to rt, 72%.

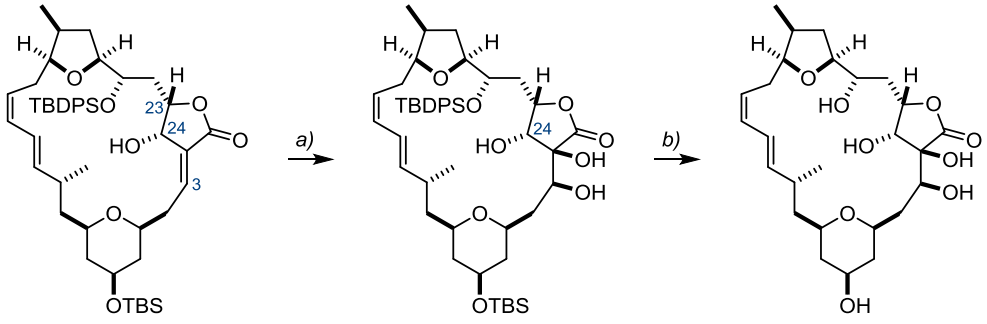
The two remaining silyl groups at C.21 and C.7 were removed upon treatment with buffered HF·pyridine and the expected pentaol **253** was isolated in good yield. As expected, the spectral signature of **253** showed small but distinct deviations from those of deacylmandelalide D as reported by the isolation team. Compound **253** possesses three inverted stereogenic centers when compared to the reassigned natural degradation product and represents most likely the 2,3,24-*epi*-isomer of deacylmandelalide D .



**252**

*Figure 3.11:* NOESY data for the γ-lactone region of **252** ($CDCl_3$, 600 MHz).

Likewise, (24*S*)-**226** was subjected to the conditions of directed dihydroxylation followed by reductive workup to give triol **254** as a single diastereomer in 78% yield.

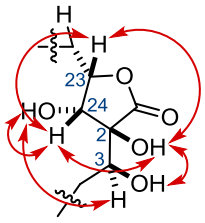



(24*S*)-**226** **254** **255**

*Scheme 3.55:* Dihydroxylation and deprotection. Conditions: a) $OsO_4$ (1.01 eq.), TMEDA (1.15 eq.), $CH_2Cl_2$, −78 °C; then THF, aq. $NaHSO_3$, rt, 78%; b) HF·pyridine, pyridine, THF, 0 °C to rt, 86%.

Surprisingly though, the observed NOE contacts suggested that the dihydroxylation was not directed by the allylic alcohol but rather delivered the two oxygen functionalities from the

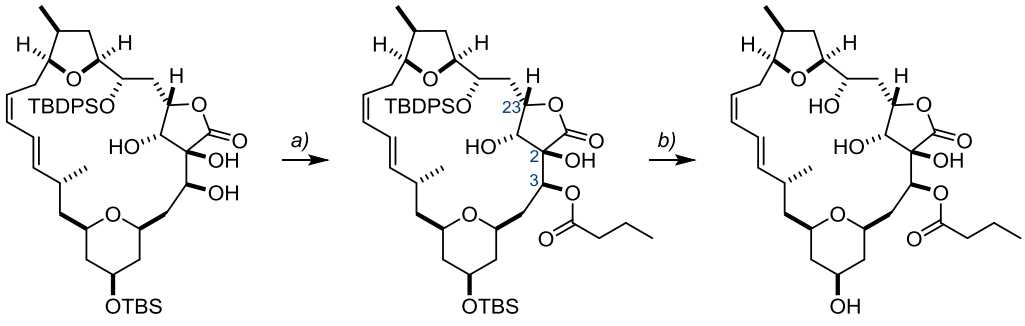
opposite site *anti* to the alcohol at C.24. As depicted in figure 3.12, the NOE contact of the OH group at C.2 with H.23 can only be explained by selective di-oxo delivery from the top face. Moreover, all other observed NOE contacts support this unexpected stereochemical outcome. This assignment was backed up by the fact that deprotection of **254** produced pentaol **255**, which clearly did not represent deacylmandelalide D. Again, both $^{1}H$ and $^{13}C$ spectra deviated significantly from those previously reported in the literature (see appendix for all spectra). According to this assignment, compound **255** represents the 2,3-*epi*-isomer of reassigned deacylmandelalide D.




**254**

*Figure 3.12:* NOESY data for the γ-lactone region of **254** ($CDCl_3$, 600 MHz).

The poor quality of the reported NMR spectra of deacylmandelalide D prohibited a detailed comparison with the synthetic material. To exclude any ambiguity, the butyrated variants mandelalide C and D were targeted. When triol **254** was subjected to the esterification reaction with 2.2 equivalents of butyric anhydride, the mono-butyrated compound **256** was selectively produced. Again, the NOESY data of **256** indicated the *syn*-relationship of the hydroxy group at C.2 and H.23 (figure 3.13) as was the case after deprotection with HF·pyridine, which enabled the isolation of **257** in good yield.




**254** **256** **257**

*Scheme 3.56:* Synthesis of a mandelalide C isomer. Conditions: a) butyric anhydride (2.2 eq.), pyridine, DMAP, $CH_2Cl_2$, 0 °C to rt, 69%; b) HF·pyridine, pyridine, THF, 0 °C to rt, 78%.

Again, the NMR spectra of the synthetic material were clearly distinct from those of the natural sample. Based on the assignment made above, the synthesized compound **257** likely equals the 2,3-*epi*-isomer of the putative reassigned structure of mandelalide C (**224**).

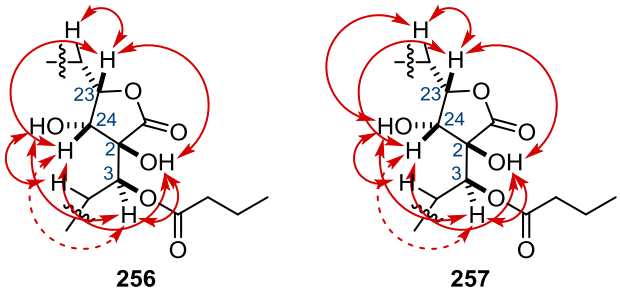



*Figure 3.13:* NOESY data for the γ-lactone region of **256** and **257** ($CDCl_3$, 600 MHz).

To evaluate why the allylic alcohol of (24*S*)-**226** was unable to direct the ligated osmium tetroxide, but still delivered a single diastereomer, an exhaustive conformational analysis was performed. The relevant NOESY cross-peaks are represented in figure 3.14 and served as a basis for a structural discussion. The observed NOE contact between the hydroxyl group at C.24 with H.11 for (24*S*)-**226** indicates that the hydroxyl group is likely pointing into the cavity of the macrocyclic ring and is therefore not available for hydrogen bonding with the incoming osmium complex. This is supported by the spatial proximity of protons H.3 and H.5 which have to align in a virtually parallel manner. The NOE contacts for (24*R*)-**226** were manifold and likely represent an average over more than a single conformation.

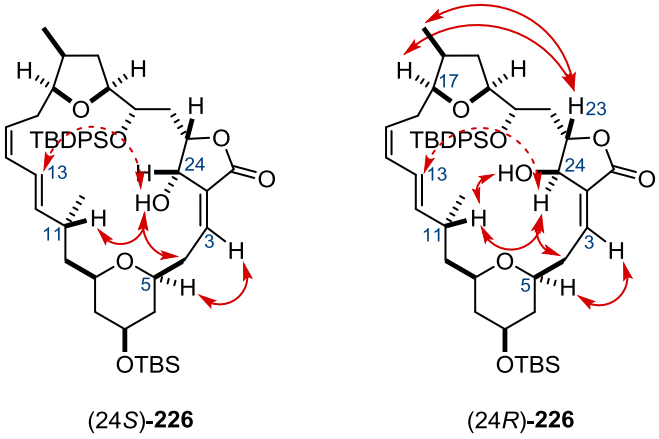



*Figure 3.14:* Selected NOESY contacts for allylic alcohols (24*S*)-**226** and (24*R*)-**226** ($CDCl_3$, 600 MHz).

In order to obtain a more detailed three-dimensional impression of the γ-lactones produced in the MBH reaction, the NOESY data of both diastereomers (24*S*)-**226** and (24*R*)-**226** were used as a basis for a computational energy optimization using Gaussian09 RevD.01 with the B3LYP/6-31G* method in the gasphase.[201] For simplification purposes, the silyl groups were replaced by *tert*-butyl groups, which are supposedly similar in size but easier to integrate in the calculation. The distance between each proton couple, for which a NOE contact was experimentally observed, was kept below 4 Å during the geometry optimization.

For the (24*S*)-isomer, an energy minimum (24*S*)-**258a** was quickly found, which was in agreement with all observed NOESY data (figure 3.15). The hydroxyl group at C.23 points

inside the macrocyclic ring and comes into close proximity to the THF oxygen atom suggesting the presence of a transannular hydrogen bond. This arrangement forces the alkene between C.2 and C.3 to be aligned orthogonally to the plane of the macrocycle, which in consequence shields the π-face of the olefin *syn* to the hydroxyl group at C.23. Both effects likely combine and contribute to the observed outcome of the dihydroxylation reaction: since the hydroxyl group is engaged in a hydrogen bonding, it cannot undergo a second interaction with the incoming osmium species, which then reacts with the more accessible site of the π-system that lies *anti* to the allylic alcohol. The second lowest energy conformation was significantly higher in energy (+4.0 kcal/mol) and did not align the protons H.3 andH.5 in parallel as expected from the observed NOE contacts. Nevertheless, the conformation (24*S*)-**258b** as depicted in figure 3.15 renders it unlikely that the allylic alcohol directs the bulky osmium species due to the flanking THP ring and the methyl group at C.11, which point towards the trajectory of an incoming reactant.

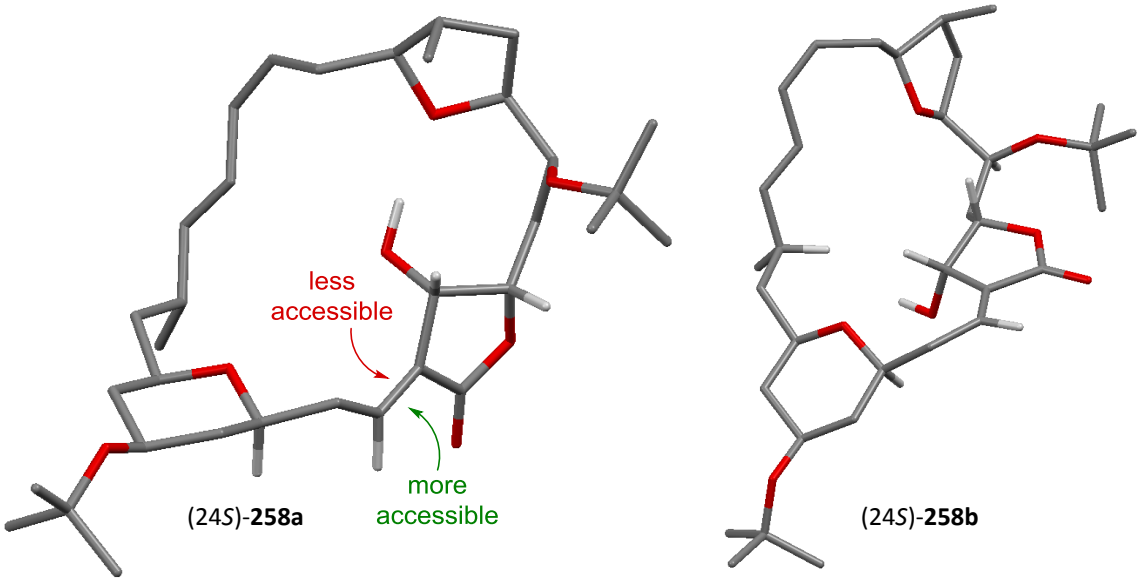



*Figure 3.15:* Computed energy minima of (24*S*)-**258**: **a** (±0 kcal/mol), **b** (+4.0 kcal/mol).

For the (24*R*)-isomer, all observed NOE contacts could not be mapped onto a single conformer. Rather, three different conformations within a range of 2.0 kcal/mol were found that collectively reflect the experimentally observed NOE correlations. The two conformers of lowest energies, (24*R*)-**258c** and (24*R*)-**258d** (figure 3.16), engage the C.23 hydroxyl group in a hydrogen bond with the oxygen atoms at C.5/9 or C.21, but do not allow for a clear distinction, which face of the olefin is more accessible. However, the third conformer (24*R*)-**258e** shows neither steric hindrance around the hydroxyl group nor around the top face of the alkene and could represent the most reactive conformer, which may well account for the observed directed dihydroxylation.

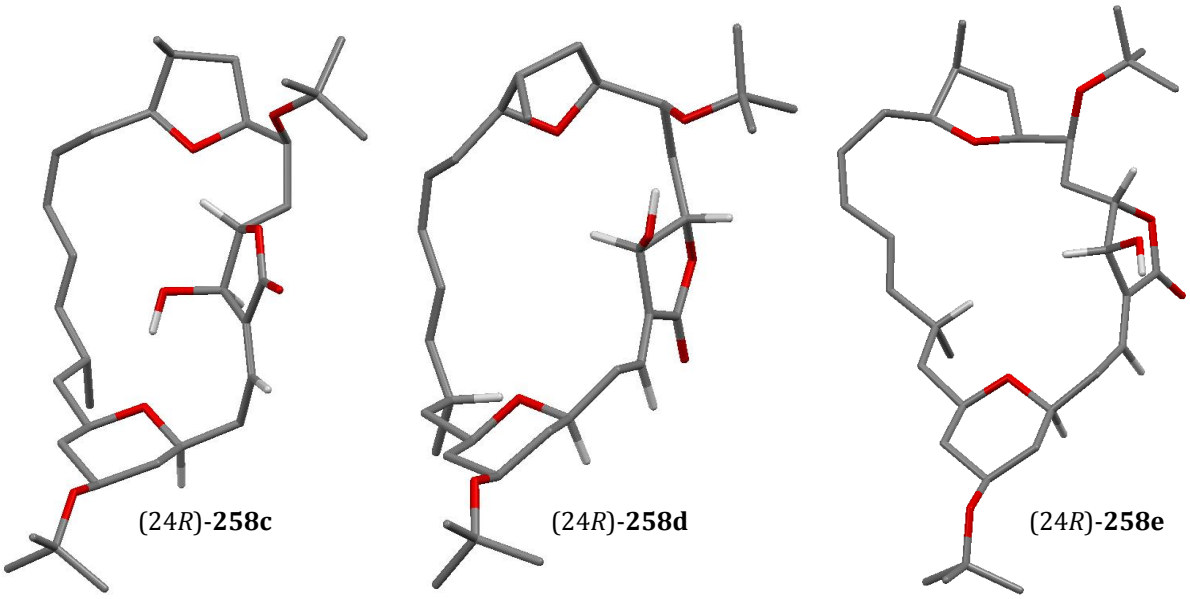


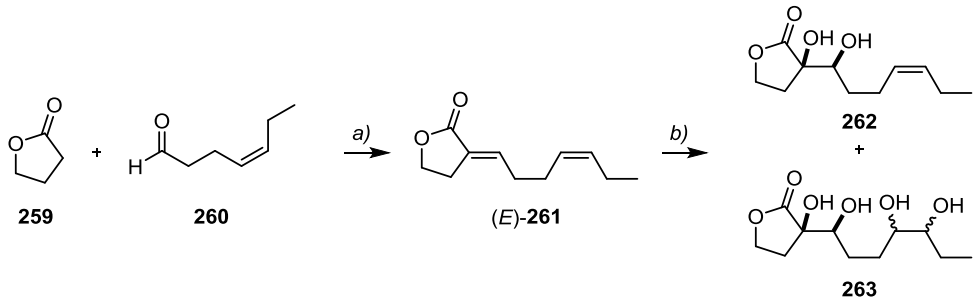

*Figure 3.16:* Computed energy minima of (24*R*)-**258**: **c** (−1.7 kcal/mol), **d** (−0.6 kcal/mol), **e** (+0.3 kcal/mol).

The regioselective attack of the osmium species on the electron deficient olefin of (24*S*)-**226** in the presence of the undoubtedly more electron rich dienyl motif was surprising and demanded closer inspection. It is generally accepted that osmium-based dihydroxylation reactions occur favorably with electron-rich double bonds unless they are sterically encumbered.[231] Indeed, a control experiment without TMEDA showed a decreased reaction rate and led to unselective dihydroxylation of the olefinic moieties of the diene. Since four isomers were possibly formed, product isolation was not attempted; however, the olefinic signal H.3 remained intact and integrated properly when compared to the integral of H.23.

Although in case of diamine ligands, improved reactivity towards electron-poor double bonds was reported,[232] the inversion of regioselectivity has never been reported for unbiased systems. However, several groups noted that the regiochemical outcome can be inversed, if the more electron rich double bond is sterically shielded.[233] In the present case, both olefins of the macrocyclic diene were thought to be sterically more accessible and more electron rich than the reactive site at C.2/C.3. Thus, this new type of reactivity is intriguing and was further explored on a simple model system.

In this regard, aldehyde **260** and γ-lactone **259** were fused by means of an aldol reaction and the generated alcohol in β-position was eliminated after transformation into the corresponding mesylate. This *in situ* protocol allowed the envisioned model system **261** to be accessed in only one step from commercial material. It possesses a trisubstituted α,β-unsaturated ester that has to compete with the isolated disubstituted olefin during the dihydroxylation reaction. When compared to the mandelalide case, it misses the allylic hydroxyl group within the γ-lactone scaffold. Osmium tetroxide was added to a solution of **261** in the presence of TMEDA at low

temperature until all starting material was consumed. The analysis of the crude mixture by $^1$H NMR indicated that two compounds were formed in a ratio of 8:1, which could be assigned to the mono-dihydroxylated compound **262** and the bis-dihydroxylated tetraol **263** after reductive workup. After column chromatography, the major component **262** was isolated in 72% yield.




*Scheme 3.57:* Model system for a regioselective dihydroxylation reaction. Conditions: a) LiHMDS, **259**, THF, −78 °C; then **260**; then MsCl, $NEt_3$, −78 °C to rt; then DBU, 0 °C to rt, (*E*)-**261**: 58%; (*Z*)-**261**: 9%; b) $OsO_4$ (1.01 eq.), TMEDA, $CH_2Cl_2$, −78 °C; then aq. $NaHSO_3$/THF, rt, crude: **262**/**263** = 8:1, **262**: 72%.

Together with the observations from the attempted mandelalide C synthesis, these results appear to be the first examples of selective dihydroxylation of the electron poor and sterically more hindered double bond in the presence of an electron rich, less hindered one. Two mechanistic scenarios may account for the observed selectivity:

(i) The TMEDA ligand increases the electron density at osmium, which leads to an increase of electron back-donation from the metal centers to the oxo-ligands. This electron enrichment might favor an inverse electron demand [3+2] cycloaddition with the electron poor double bond of the α,β-unsaturated ester. In unligated cases, the reaction likely proceeds via a 'normal' electron demand cycloaddition and therefore favors electron rich olefins.[234]

(ii) Due to the electron enriched oxo-ligands, the initial [3+2] cycloaddition occurs stepwise rather than concerted and starts with an *oxa*-Michael addition to the α,β-unsaturated ester. The generated enolate then attacks a second oxo-ligand completing the formal cycloaddition reaction or reacts with the osmium center under formation of a four-membered ring, which could rearrange to the five-membered metallacycle.[235]

At present, it remains unclear, which of the two mechanistic scenarios is responsible for the observed selectivity.[235]

Although the total synthesis of family members of mandelalide A was not achieved during the course of this investigation, the chosen strategy is unique and displays the immaturity of

seemingly well-established reactions. Thus, a novel intramolecular MBH reaction was developed involving a β-substituted Michael acceptor. However, the envisioned directed dihydroxylation reaction failed dependent on the configuration of the generated allylic alcohol. Nevertheless, an interesting reactivity pattern was observed for osmium-mediated dihydroxylations in the presence of diamines that merits further investigation. The current enterprise highlights the notion that total synthesis serves as a valuable platform for the design of new transformations and for the serendipitous discovery of novel reactivity.

## 3.11 Biological evaluation of mandelalide A and isomers of the mandelalide family

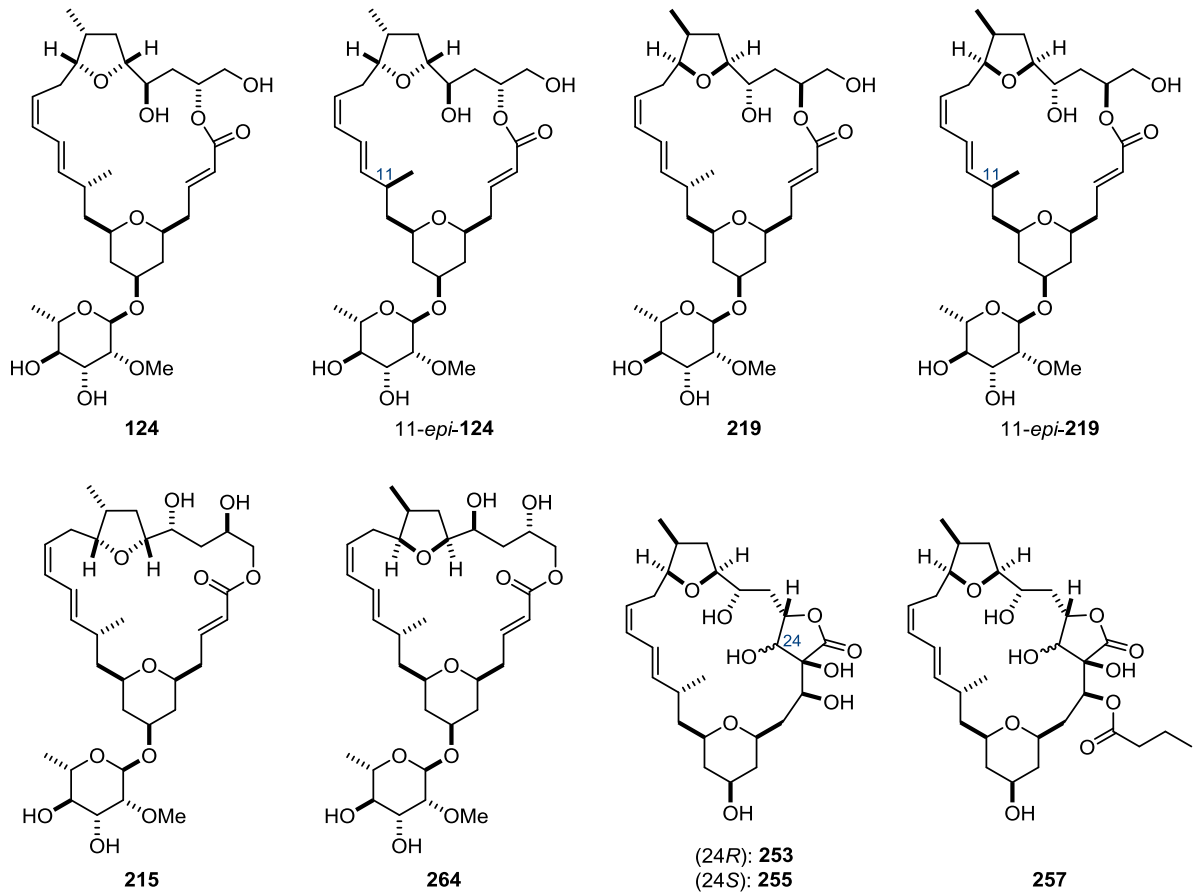
The promising biological profile as reported by the isolation team[141] demanded for a more detailed cytotoxicity investigation of the synthetic material. In cooperation with Pfizer Inc. under guidance of Dr. Andreas Maderna, synthetic mandelalide A (**219**) and all three synthesized isomers (**124**, 11-*epi*-**124**, 11-*epi*-**219**) were tested for their activity towards three representative cancer cell lines. Moreover, two ring-expanded by-products (**215**, **264**) formed in the final deprotection step were engaged in this initial screening (scheme 3.61).

Unexpectedly and contrary to the results from the isolation team, all compounds - including mandelalide A - were rather inactive and showed values in the three-digit nanomolar scale (table 3.14). Only the natural product reached a reasonable activity against one of the tested cancer cell lines, which was in the range of the $IC_{50}$ values reported by the isolation team. Simultaneously, the publication of Ye appeared online and independently validated these disappointing findings. In their hands, mandelalide A showed no appreciable activity ($IC_{50}$ < 1 μM) towards ten different cancer cell lines.[146]

*Table 3.14:* Cytotoxicity evaluation of mandelalide A and isomers ($GI_{50}$ are given in nM).

| entry | compound | N87[1)] | MDA-361[1)] | HT29[1)] |
|---|---|---|---|---|
| 1 | **219** | 206 | 41 | >1000 |
| 2 | **124** | 598 | >1000 | >1000 |
| 3 | 11-*epi*-**219** | 423 | 391 | >1000 |
| 4 | 11-*epi*-**124** | 962 | >1000 | >1000 |
| 5 | **215** | 873 | >1000 | >1000 |
| 6 | **263** | 722 | >1000 | >1000 |

1) N87: human stomach cancer cell line; MDA-MB-361-DYT2: human breast carcinoma cells; HT29: human colon cancer cells.



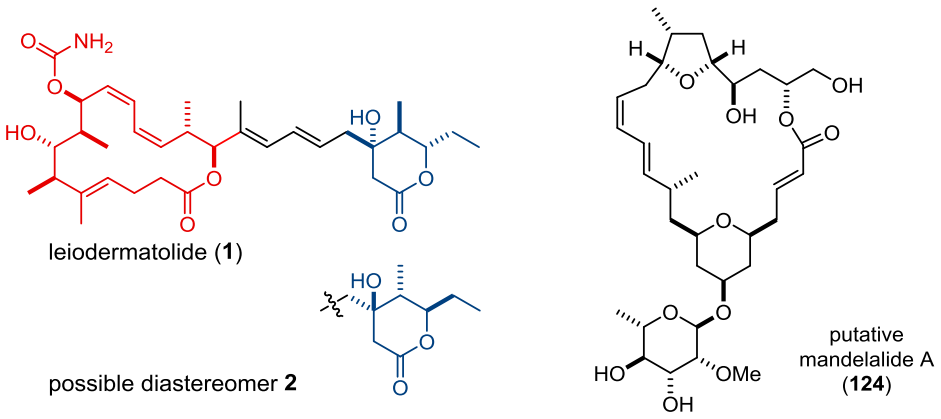

*Scheme 3.58:* Overview of compounds engaged in biological screenings.

All mandelalide A diastereomers as well as compounds **253**, **255**, and **257** were further engaged in a biological assessment to determine their antifungal activity inspired by the reported activity of related madeirolides. This investigation is still ongoing at present in the laboratories of Prof. Dr. Rolf Müller (Helmholtz-Institute for Pharmaceutical Research Saarland) and will be reported elsewhere.

# 4 Conclusion

During the course of this thesis, ring-closing enyne-yne metathesis reactions were investigated in combination with subsequent (*Z*)-selective semireduction in the context of the total syntheses of marine natural products bearing conjugated polyunsaturated systems. To date, the selective assembly of 1,3-diene motifs via ring-closing alkene metathesis is far from mature and cannot be used as a reliable tool in complex settings.[17] It is shown that the use of alkyne metathesis allows this problem to be fixed and enables the access to such scaffolds that are otherwise difficult to prepare.

As a demanding setting for the recently developed generation of alkyne metathesis catalysts,[25] the total syntheses of leiodermatolide and mandelalide A were addressed. Isolated in 2008 from Wright *et al.* from a deep-water marine sponge, leiodermatolide (**1**) comprises not only intriguingly challenging structural features such as an unusually substituted δ-lactone and a highly unsaturated macrocycle, but also displayed a fascinating biological profile.[30] It showed antimitotic activity at single-digit nanomaler concentrations against a select panel of human cancer cell lines without interacting with purified tubulin.[31] This stands in sharp contrast to other well-established anticancer agents, like the vinca alkaloids, the taxanes, the epothilones or discodermolide to name only the most prominent ones. However, the structure of leiodermatolide could not be fully assigned by the isolation team, which led us to consider two possible diastereomers as the correct structure of the natural product (**1** and **2**). The unprecendented mode of action, the challenging structural features and the low natural abundance prompted us to engage in a total synthesis program.

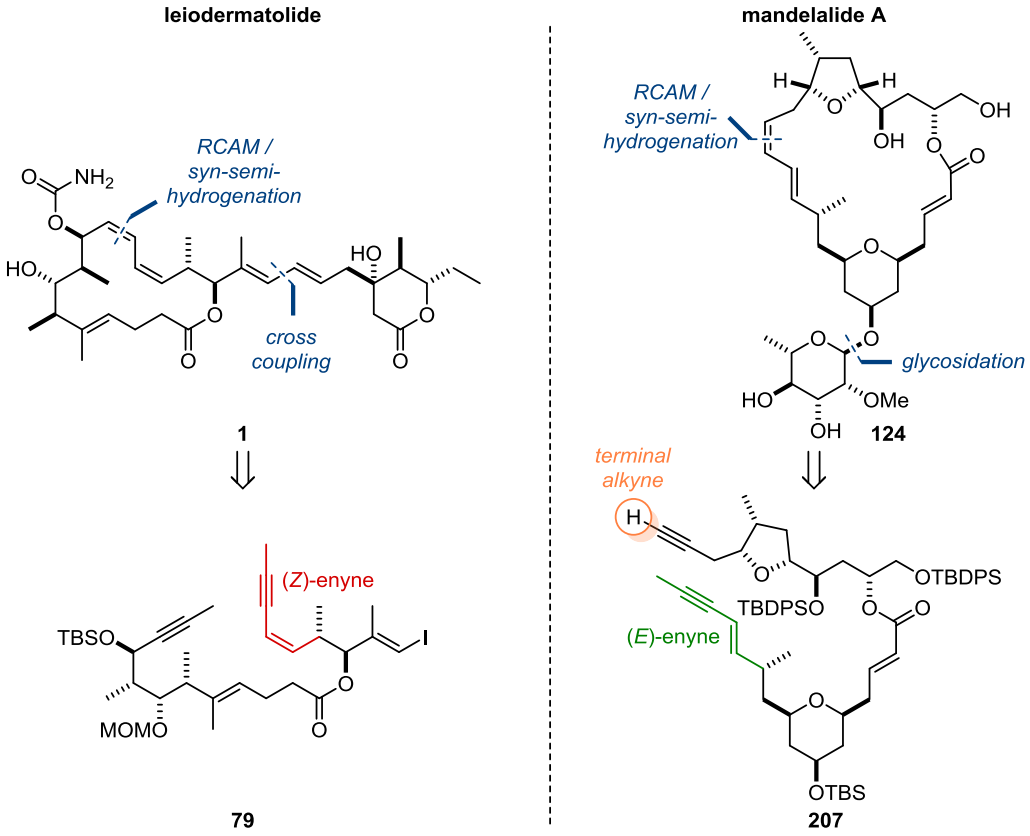



*Scheme 4.1:* Two possible stereostructures of leiodermatolide and putative mandelalide A.

Mandelalide A, isolated in 2012 from a new ascidian *Lissoclinum* species, presented an even more complex architecture along with a purported high activity in a first cytotoxicity assay.[141] Again, the low natural abundance prohibited further investigation of the biological

profile and a more sustainable and reliable supply to this glycosylated polyketidic natural product by total synthesis was desirable.

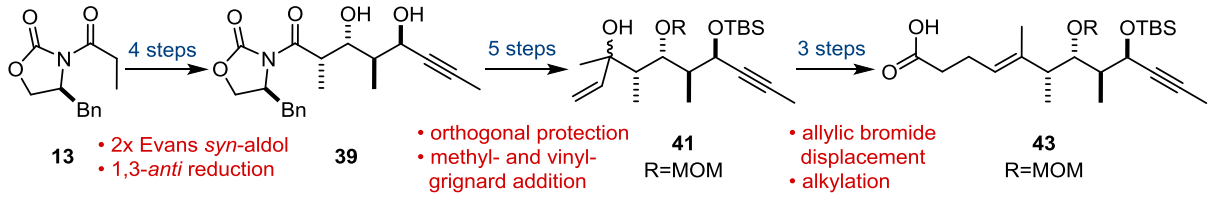
The retrosynthetic strategies to both molecules are depicted in scheme 4.1; they rely on the use of a sequence of ring-closing alkyne metathesis (RCAM) and semihydrogenation for the selective assembly of the dienyl motifs within the macrocyclic frameworks. Both retrosynthetic disconnections offer novel challenges for the alkyne metathesis catalyst. In the leiodermatolide case, the challenge arises collectively from the steric impediment of the propargylic silyl ether, the electronic deactivation of both alkynes and by the ring strain of the highly unsaturated macrocycle. In the mandelalide series, a terminal alkyne was to be engaged in the alkyne metathesis reaction, a structural motif that has not been amenable for a long time to synthetic applications due to its tendency to polymerize upon contact with metal alkylidynes.




*Scheme 4.2:* Common strategy for the selective assembly of leiodermatolide and mandelalide A.

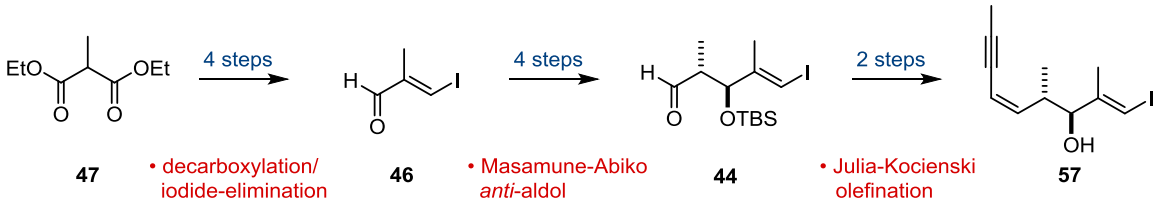
A first generation synthesis of leiodermatolide was developed in cooperation with Dr. Nina Kausch-Bausies and started with the synthesis of the required acid and alcohol fragments, which were designed to be of similar size for maximal convergence. This strategy should eventually allow for the synthesis of both possible diastereomers of the natural product (**1** and **2**).

The synthesis of acid fragment **43** started with the literature-known *syn*-aldol reaction of **13** and subsequent Parikh-Doering oxidation, followed by a second aldol reaction and 1,3-*anti* reduction to install the stereotetrad. After the crucial orthogonal protection of the two secondary alcohols, the site of the auxiliary was further elaborated into the tertiary allylic alcohol **41**. This moiety was transformed into the γ,δ-unsaturated acid to complete the 12-step synthesis of this fragment with an overall yield of 17%.



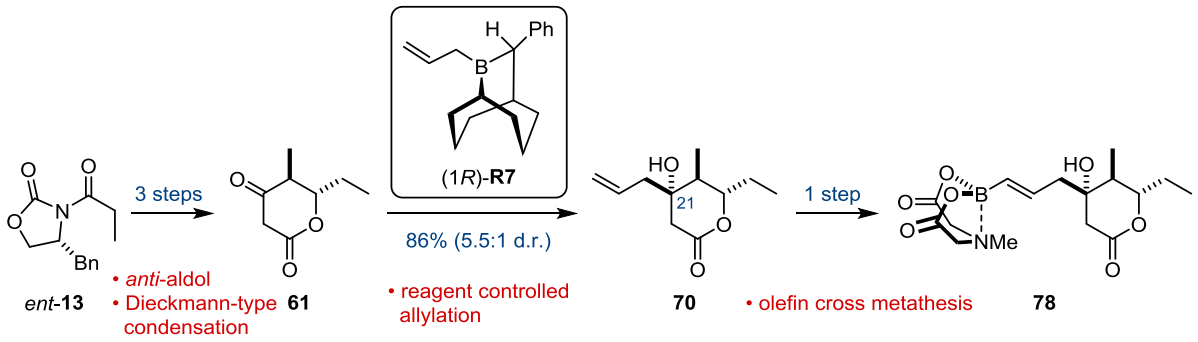

*Scheme 4.3:* Synthesis of acid fragment **43**.

The enyne fragment **57** was synthesized from the literature-known iodo-aldehyde **46**, which can be prepared in 4 steps from commercial malonate **47**.[56] A Masamune-Abiko *anti*-aldol reaction set the two contiguous stereogenic centers.[60] After TBS-protection, the auxiliary was reductively removed and the generated alcohol oxidized to aldehyde **44**, which was immediately employed in the Julia-Kocienski olefination reaction with sulfone **R1**. Lastly, silyl group removal with TBAF furnished alcohol **57**, which was obtained after 10 steps with an overall yield of 12%.



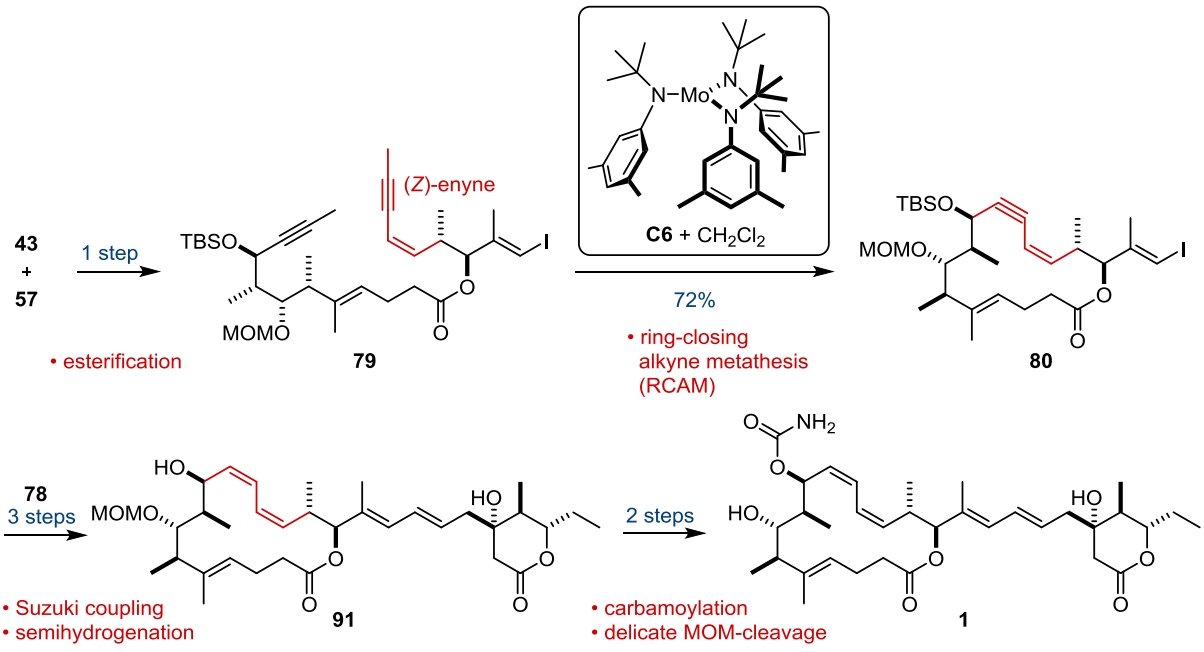

*Scheme 4.4:* Synthesis of enyne fragment **57**.

The successful strategy for the synthesis of the δ-lactone fragment **78** started with an *anti*-aldol reaction of *ent*-**13** with propanal. The resulting alcohol was acetylated and the product engaged in a Dieckmann-type condensation reaction to give literature-known **61**.[65] After extensive screening of suitable reaction conditions, the reagent controlled allylation of the highly enolizable β-keto lactone **61** was achieved with the chiral allyl boron reagent **R7** allowing the side chain to be attached in the unusual pseudo-axial position.[84] Further functionalization of the terminal alkene was achieved via olefin cross metathesis and furnished access to vinyl MIDA boronate **78**. This strategy allowed for the synthesis of the δ-lactone fragment in only 5 steps from commercial material with 30% overall yield and compares favorably with other approaches to this fragment.[32, 40]




*Scheme 4.5:* First generation synthesis of the δ-lactone fragment **78**.

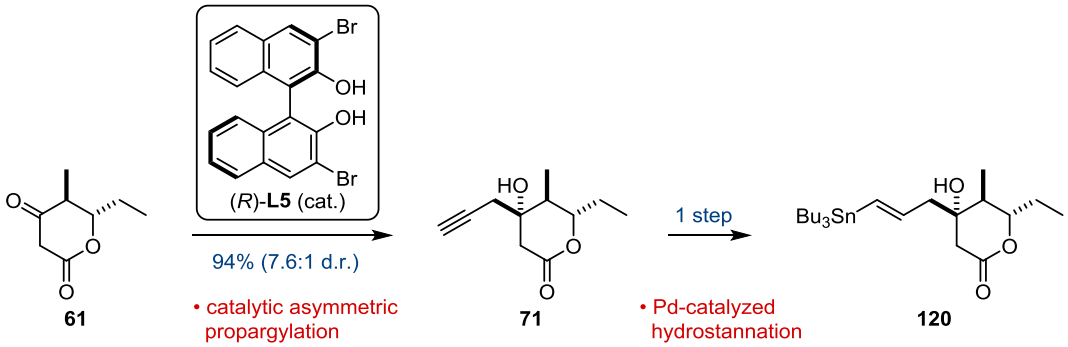
The fragment coupling was realized by esterification of **43** and **57** under mediation of EDCI and DMAP. Notably, the key RCAM failed when catalyzed by molybdenum alkylidyne **C1** endowed with silyloxy-based ligands, producing instead an open dimeric species.[25] However, the use of the Cummins precatalyst **C6** in combination with $CH_2Cl_2$ allowed the ring-closure to proceed and afforded macrocyclic enyne **80** in 72% yield.[94] Compound **80** was next engaged in a Suzuki-coupling with δ-lactone fragment **78**, which mandated the use of a thallium base. After acidic workup, the cross-coupled adduct was reliably isolated in up to 56% yield.




*Scheme 4.6:* Completion of the first generation synthesis of leiodermatolide (**1**).

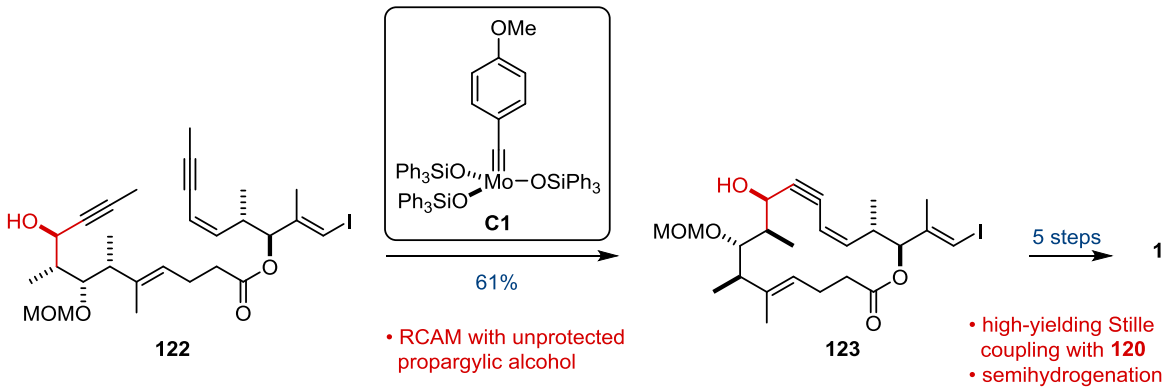
The propargylic alcohol had to be unmasked prior to semihydrogenation with Zn(Cu/Ag) to install the isomerization-prone (*Z*,*Z*)-diene motif as a single isomer. Selective carbamoylation was readily achieved at low temperatures, whereas the cleavage of the MOM group required careful optimization of the reaction conditions. Finally, it was discovered that treatment with dimethylboron bromide allowed the targeted natural product to be isolated with a longest linear sequence of 19 steps and an average yield of 82% per step. The very same sequence

was carried out with the enantiomeric δ-lactone to yield the isomeric compound **2**. The natural product was assigned based on subtle differences in the NMR spectra and recorded optical rotations, which are fully matched by compound **1**.[39] This assignment was independently confirmed by the biological activity of synthetic **1**, which is approximately two orders of magnitude higher than that of **2**.




*Scheme 4.7:* Second generation synthesis of δ-lactone fragment **120**.

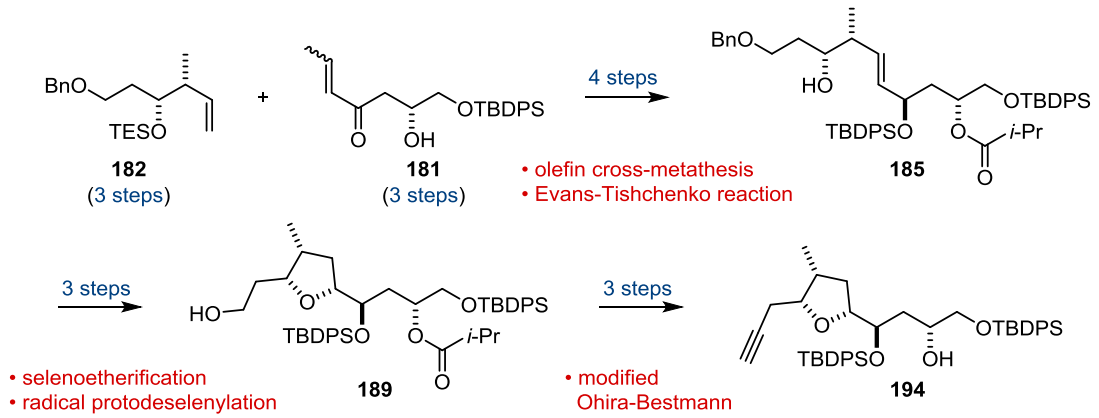
Because of the promising biology, a second generation synthesis was developed in collaboration with Dr. Damien Mailhol to obliterate the remaining synthetic bottlenecks.[113] In detail, the stoichiometric allylboration of β-keto ester **61** was replaced by a catalytic version that relied on a commercial binol-derived ligand allowing the practicability, yield and diastereoselectivity of this transformation to be largely improved.[118] The corresponding propargylation further enabled the replacement of the rather low-yielding Suzuki coupling for a high-yielding Stille coupling (93%). Inspired by observations during the first generation synthesis, the alkyne metathesis was carried out with the free propargylic alcohol. This adjustment enabled the use of the undoubtedly more user-friendly molybdenum alkylidyne **C1**, which catalyzed the reaction with significantly reduced loading even at ambient temperature.[25] This result is remarkable in light of the potential side reactions of propargylic alcohols and represents one of the earliest examples, in which a free alcohol is tolerated during an alkyne metathesis reaction.[122a, 122b]




*Scheme 4.8:* Revised alkyne metathesis and second generation synthesis of **1**.

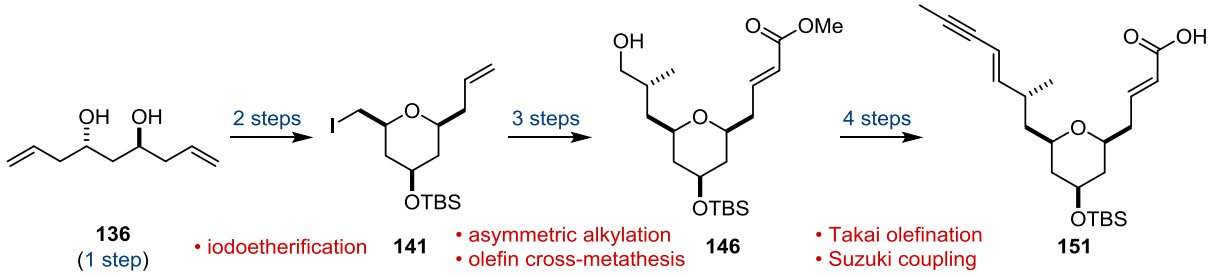
In summary, all throughput-limiting steps of the first generation synthesis were replaced by more convenient and more robust protocols to establish a reliable supply of appreciable amounts of this otherwise scarce natural product.
Moreover, the sequence described herein enabled the synthesis of a first set of analogues, which was used to record structure activity relationships and shed light on the pharmacophore of leiodermatolide. Whereas the δ-lactone scaffold seems to be required for the remarkable potency of **1**, the carbamate is an extraneous site and can be replaced by an acetate moiety without significant loss of biological activity. This result might enable the use of leiodermatolide as a payload for an antibody drug conjugate and deserves closer investigation.[126] Furthermore, the biochemical mechanism of leiodermatolide was investigated in some detail. All acquired data, including cell cycle analysis, micronuclei formation, centrosome amplification and immunofluorescence imaging, point to centrosome declustering as the likely mode of action.[113] If confirmed in further studies, this result is promising due to the fact that healthy cells generally do not suffer from amplified centrosomes and are significantly less susceptible towards centrosome declustering agents than tumor cells.

An even more challenging enyne-yne metathesis/semihydrogenation tactic was employed for the total synthesis of mandelalide A (**124**). The northern alcohol fragment was assembled with a strategic olefin cross-metathesis reaction that fused the readily accessible building blocks **181** and **182**. Subsequently, a $SmI_2$-catalyzed Evans-Tishchenko reaction installed the 1,3-*anti* diol motif and simultaneously allowed the differentiation of the two secondary alcohols. The all-*cis* substituted THF ring was constructed via cyclization of an alcohol onto the double bond, which was activated with an electrophilic selenyl species generated from *N*-PSP and catalytic amounts of a Lewis base.[181b] Finally, the alkyne was introduced and the secondary alcohol at C.23 released to give the northern fragment **194** after 13 steps in the longest linear sequence with an overall yield of 17%.



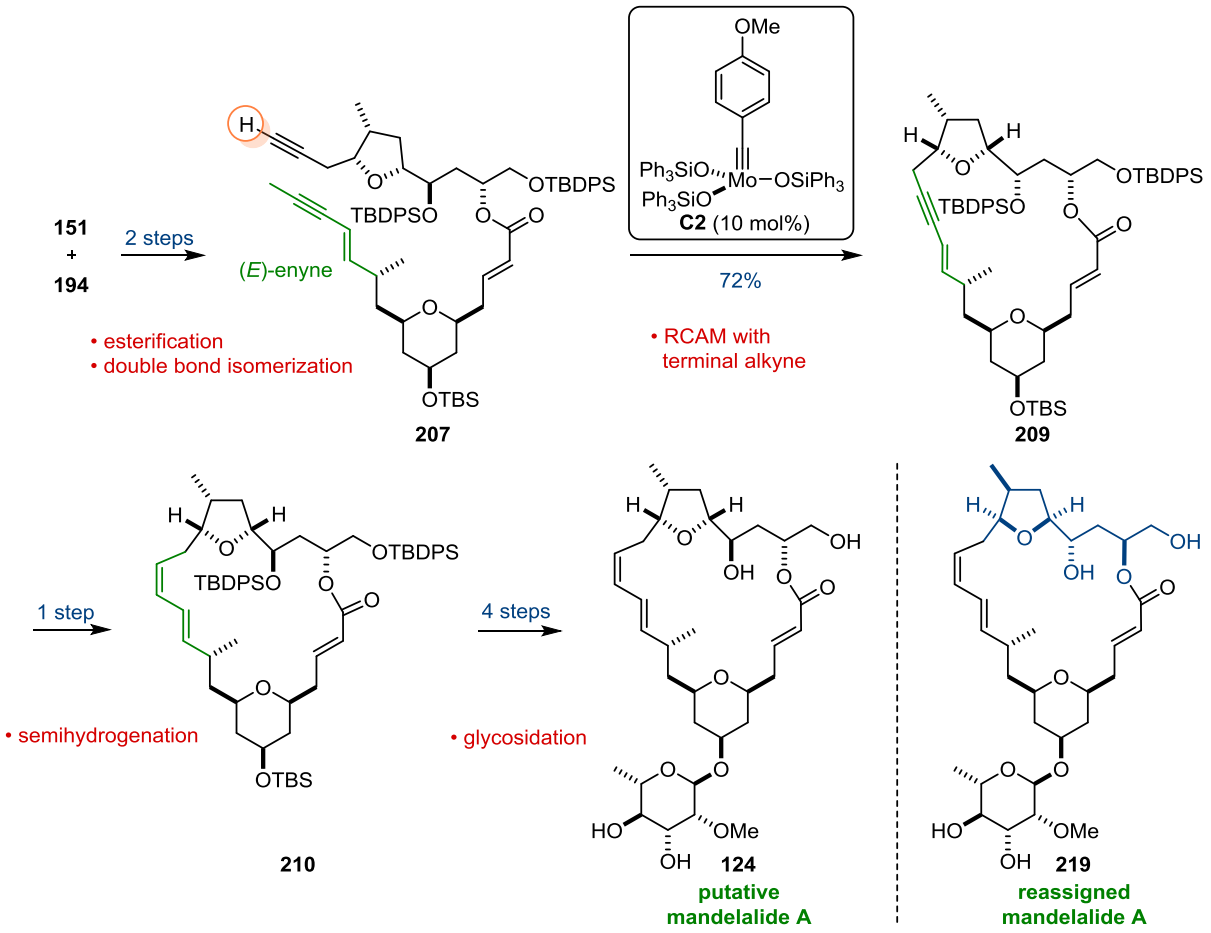

*Scheme 4.9:* Synthesis of alcohol fragment **194** via olefin cross-metathesis.

The synthesis of the southern fragment started with a bidirectional allylation of 1,3-propanediol to give the literature-known C2-symmetric diol **136** that was desymmetrized upon iodo-etherification.[151] The stereogenic center at C.11 was next introduced by an asymmetric alkylation reaction with the pseudoephedrine-derived auxiliary **R12**, which was reductively cleaved prior to installing the enoate moiety via cross-metathesis. The (*E*)-enyne was introduced in a multi-step sequence consisting of oxidation, Takai olefination and Suzuki coupling. Saponification of the ester completed the synthesis of the acid fragment, which was achieved with an overall yield of 11% over ten steps.




*Scheme 4.10:* Synthesis of acid **151** fragment containing the (*E*)-enyne.

The two fragments were combined in an esterification reaction setting the stage for the projected enyne-yne metathesis. The formation of the macrocycle via RCAM worked exceptionally well in the presence of molybdenum catalyst **C1** and proceeded at ambient temperature. This reaction represents the first application of terminal acetylene metathesis in the context of complex natural product synthesis and will certainly encourage further applications of this emerging strategy in the future.[148h, 236] The following semihydrogenation with Zn(Cu/Ag) produced the desired diene with full control over the double bond geometry.[96] Protecting group manipulations and glycosidation with the trichloroacetimidate **201**, which could be prepared via two independent routes, completed the synthesis of putative mandelalide A (**124**). A largely catalysis-based route was thus developed that required 21 steps along the longest linear sequence with an overall yield of 4% (average yield: 83%).[144]



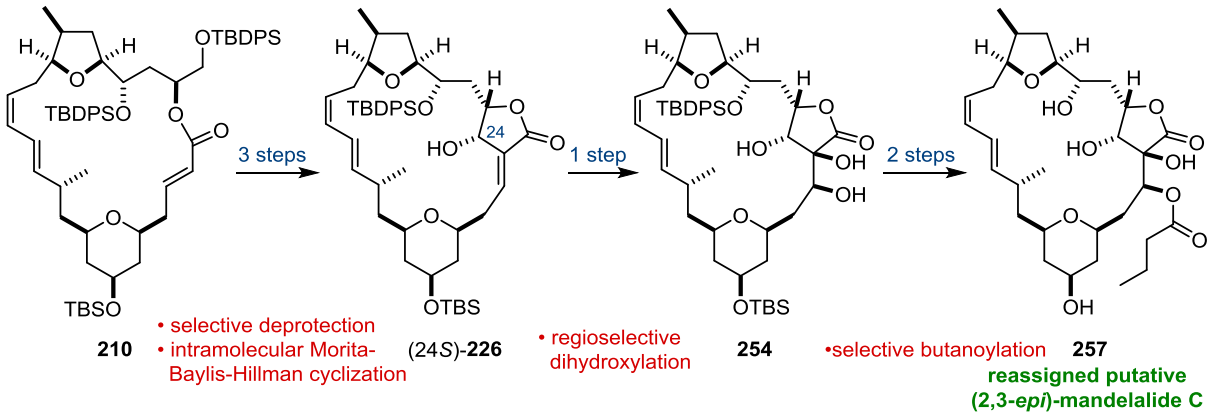

*Scheme 4.11:* Completion of the total synthesis of mandelalide A enabled the structural reassignment.

However, the recorded NMR spectra were not in agreement with those reported for the natural product. Thus, mandelalide A had been missasigned by the isolation team. During the course of this investigation, four stereoisomers that might constitute the true natural product were prepared following the same synthetic logic and allowed for a structural reassignment of mandelalide A, which is correctly represented by structure **219**. This compound has all five stereogenic centers of the northern fragment inverted, which is reminiscent of the madeirorolides, a related family of polyketidic natural products. Unfortunately, the promising biological profile as suggested by the isolation team could not be confirmed with the synthetic material obtained in this study or by others.[146]

Equipped with a robust scalable route and the correct structure, it was hypothesized that access to other members of the mandelalide family could be gained from subjecting a common intermediate to a modified endgame. For this purpose, a novel intramolecular Morita-Baylis-Hillman cyclization was developed that could eventually be performed on the macrocyclic system.

The choice of phosphine was crucial and only dimethylphenylphospine allowed the unprecedented formation of the desired γ-lactone within the macrocyclic scaffold. The

generated allylic alcohol was intended to serve as a directing group for the consecutive dihydroxylation;[220a, 221] however, this reaction occurred from the opposite face *anti* to the alcohol at C.24. The careful analysis of NOESY data in combination with computational geometry optimizations indicated that (24*S*)-**226** likely adopts a conformation in which the allylic alcohol points into the cavity of the macrocycle and can no longer steer the incoming osmium tetroxide reagent. Moreover, one face of the alkene is shielded by the surrounding macrocycle, leaving only the π-face *anti* to the hydroxyl group open to attack by the dihydroxylating agent. Intriguingly, the regioselectivity was unprecedented and could be generalized by translation to a simple model substrate. These results seem to represent the first examples of selective dihydroxylation of electron poor olefins in the presence of less hindered and more electron rich alkenes and deserve further investigation. Selective butanoylation and deprotection of the remaining silyl groups allowed the isolation of tetraol **257**, which most likely comprises the (2,3)-epimer of reassigned putative mandelalide C.




*Scheme 4.12:* Attempted synthesis of "reassigned" mandelalide C.

Although the challenging carbon framework of the mandelalide family could be prepared via the chosen strategy, the introduction of the oxygen functionalities via directed dihydroxylation failed to follow the expected stereochemical course. Future studies should therefore consider to carry out the dihydroxylation at an earlier stage of the synthesis or to redesign the synthesis of this fragment.

In conclusion, the results obtained herein highlight the maturity of ring-closing alkyne metathesis, which can be reliably performed in the presence of various proximal, Lewis basic functional groups even within the challenging context of natural product synthesis. The synthetic applications clearly expanded the frontiers of alkyne metathesis with two inherently challenging substrates and proved that RCAM is an indispensable tool, even in cases where olefin metathesis is likely to find its limits. The combination with subsequent (*Z*)-selective semireduction allowed the stereoselective assembly of (*Z*,*Z*)- and (*E*,*Z*)-dienes within

macrocyclic frameworks as exemplified by the stereoselective total syntheses of leiodermatolide and mandelalide A.

Both successful endeavors further highlight that total synthesis remains the ultimate tool for structure assignments, especially when dealing with segregated stereoclusters, which are difficult or impossible to assign via spectroscopic means. In the course of this thesis, the synthesis of two leiodermatolide isomers enabled the assignment of the previously unknown stereostructure of the natural compound. Furthermore, mandelalide A was originally misassigned by the isolation team and required four possible diastereomers to be synthesized, as an attempted computational prediction failed. Fortunately, one of the synthesized isomers correctly resembles the natural product and allowed the structure to be established. This encouraged us to pursue a close relative, mandelalide C, of which only a diastereomer could be accessed; yet, the unprecedented discoveries made during this specific synthetic approach are deemed intriguing.

The results of this thesis, in particular the total synthesis and structure assignment of leiodermatolide along with the biological evaluation of the natural product and analogues thereof, as well as the total synthesis and structure reassignment of mandelalide A together with the methodology spin-off towards mandelalide C, demonstrate the importance of synthetic organic chemistry.

# 5. Experimental section

## 5.1 General

All reactions were carried out under Ar in flame-dried glassware unless $H_2O$ was used as a solvent or otherwise noted. The following solvents and organic bases were purified by distillation over the drying agents indicated and were transferred under Ar: THF, $Et_2O$ (Mg/anthracene); hexane, toluene (Na/K), DBU, diisopropylamine, DMSO, $CH_2Cl_2$, DMA, HMPA ($CaH_2$); MeOH (Mg, stored over 3 Å MS), EtOH (3 Å MS), EtOAc ($P_2O_5$, filter through dry $Al_2O_3$, store over 4 Å MS). 1,4-Dioxane, DMF, MeCN , $NEt_3$ and pyridine were dried by an adsorbtion solvent purification system based on molecular sieves. DBU ($CaH_2$), diisopropylamine ($CaH_2$), ($n$-Bu)$_2$BOTf, allyl acetate, trimethylborate, acetyl chloride, acetic anhydride, *N*-trimethylsilyl morpholine, and isobutyraldehyde were distilled under Ar prior to use. All other commercially available compounds (Alfa Aesar, Aldrich, Fluka, Lancaster) were used as received. The following compounds were prepared according to the cited protocol by myself or within the department of Prof. Fürstner: **C1**,[25a] **C2**,[25a] **C4**,[25b] **C5**,[92] **C6**,[93a] Soderquist reagent **R7**,[84] $Pd(PPh_3)_4$,[237] $Me_2BBr$,[238] **R10**,[117b] **R11**,[159a] **R12**,[160] $SmI_2$,[175] Leighton reagent **R17**,[167] TBDPSCl,[239] Ohira-Bestmann reagent **R18**.[183b]

Compounds **13**, *ent*-**13**, **21**, **38**, **39**, **40**, **41**, **42**, **43** and their precursors were originally prepared by Dr. Nina Kausch-Busies; compounds **195**, **196**, **197**, **198**, **199**, **200**, and **201** were prepared by M. Sc. Katharina Holthusen. The procedures described herein are taken from their reports with only minor modifications.

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 either acidic *p*-anisaldehyde or basic $KMnO_4$ solution.

Flash chromatography was performed with Merck silica gel 60 (40-63 µm) using predistilled or HPLC grade solvents. In some cases, fine silica gel (15-40 µm pore size) had to be used and is indicated within the experimental procedure.

Spectra were recorded on Bruker DPX 300, AMX 300, AV 400, AV 500 or AVIII 600 spectrometer in the solvents indicated; chemical shifts ($\delta$) 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 ($CDCl_3$: $\delta_H \equiv 7.24$ ppm, $\delta_C \equiv 77.0$ ppm; $C_6D_6$: $\delta_H \equiv 7.16$ ppm, $\delta_C \equiv 128.0$ ppm; $CD_2Cl_2$: $\delta_H \equiv 5.32$ ppm, $\delta_C \equiv 53.8$ ppm; [$D_6$]-DMSO: $\delta_H \equiv 2.50$ ppm, $\delta_C \equiv 39.52$ ppm; pyridine-$d^5$: $\delta_H \equiv 8.74$ ppm; $\delta_C \equiv 150.35$ ppm). Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet; hept: heptet, m: multiplet. The abbreviation "br" indicates a broad signal. $^{13}C$ NMR spectra were recorded [$^1H$]-decoupled and the values of chemical shifts are rounded to one position after decimal point. All spectra from the 500 MHz and 600 MHz spectrometers were acquired by the NMR department under guidance of Dr. Christophe Farès at the Max-Planck-Institut für Kohlenforschung.

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

Mass spectrometric samples were measured by the department for mass spectrometry at the Max-Planck-Institut für Kohlenforschung. The following equipment was used: MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Bruker ESQ3000, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). All values are given in

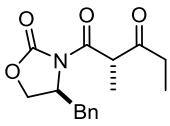
Optical rotations were measured with a Perkin-Elmer Model 343 polarimeter at a wavelength of 589 nm. They are given as specific optical rotation with exact temperature, concentration ($c$ /(10 mg/mL)) and solvent.

## 5.2 Total synthesis of leiodermatolide

### 5.2.1 Synthesis of acid 43.

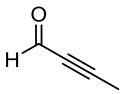
**(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one (20).** (*n*-Bu)$_2$BOTf (1 M in $CH_2Cl_2$, 49 mL, 49 mmol) was slowly added to a solution of oxazolidinone **13** (9.7 g, 41.6 mmol) in $CH_2Cl_2$ (92 mL) at 0 °C. $NEt_3$ (7.6 mL, 55 mmol) was then added at such a rate as to keep the internal temperature below 2 °C. Once the addition was complete, the mixture was cooled to −78 °C before freshly distilled propionaldehyde (4.4 mL, 46.4 mmol) was introduced. The mixture was stirred for 30 min at –78 °C before the $CO_2$/acetone bath was replaced by an ice bath. Stirring was continued for 1 h and the reaction quenched with aq. phosphate buffer (46 mL, pH 7) and MeOH (138 mL) (T < −6 °C). Next, a 1:2 mixture of MeOH and 30% aqueous $H_2O_2$ (138 mL) was carefully added such that the internal temperature never rose above 10 °C. The mixture was stirred for 1 h once the addition was complete. After concentration, $Et_2O$ (50 mL) was added to the slurry and the aqueous phase extracted with $Et_2O$ (3 x 50 mL). The combined extracts were washed with aq. sat. $NaHCO_3$ (12 mL) and brine (12 mL) before being dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (hexanes/EtOAc, 3:1) of the residue, followed by recrystallization of the product from $Et_2O$/hexanes afforded the title compound as a white solid (11.71 g, 97%). $[\alpha]_D^{20}$ = + 20.8 ($c$ = 1.38, $CHCl_3$), $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.36 – 7.25 (m, 3H), 7.22 – 7.16 (m, 2H), 4.68 (ddq, $J$ = 13.7, 6.9, 3.4 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.89 – 3.80 (m, 1H), 3.80 – 3.70 (m, 1H), 3.24 (dd, $J$ = 13.4, 3.3 Hz, 1H), 2.76 (dd, $J$ = 13.4, 9.5 Hz, 1H), 1.88 (br s, 1H), 1.66 – 1.32 (m, 2H), 1.23 (d, $J$ = 7.0 Hz, 3H), 0.96 (t, $J$ = 7.4 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 177.6, 153.0, 135.0, 129.4, 129.0, 127.4, 73.0, 66.2, 55.1, 41.7, 37.8, 26.7, 10.4, 10.2 ppm; IR (film): $\tilde{\nu}$ = 3466, 2969, 1778, 1696, 1455, 1385, 1210, 1113, 1030, 969, 762, 749, 702 $cm^{-1}$; MS (EI) *m/z* (%): 292 (7), 291 (30), 273 (9), 244 (46), 233 (30), 178 (42), 158 (100), 142 (12), 134 (63), 133 (20), 117 (38), 116 (23), 115 (49), 97 (26), 91 (56), 86 (80), 77 (7), 69 (34), 57 (45), 42 (15); HRMS (ESIpos): *m/z*: calcd for $C_{16}H_{21}NO_4Na$: 314.1363, found 314.1364. The analytical and spectroscopic data are in agreement with those reported in the literature.[240]

**(*S*)-1-((*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methylpentane-1,3-dione (21).** The aldol product



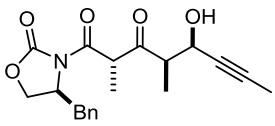
obtained in the previous step (5.70 g, 19.6 mmol) was dissolved in $CH_2Cl_2$ (92 mL) and DMSO (92 mL) and the solution cooled to −15 °C. $NEt_3$ (8.20 ml, 58.8 mmol) was introduced, followed by slow addition of a solution of $SO_3$·pyridine (9.40 g, 58.8 mmol) in DMSO (92 mL) and the resulting mixture was stirred for 3 h. For workup, $Et_2O$ (400 mL) was added and the organic phase washed with aq. $KHSO_4$ (1 M, 400 mL), sat. aq. $NaHCO_3$ (400 mL) and brine (400 mL). After drying of the organic layer over $MgSO_4$ and concentration *in vacuo*, the residue was purified by flash chromatography (hexanes/EtOAc, 6:1 to 3:1) to give product **21** as a white solid (4.96 g, 88%). m.p. = 71-72 °C (hexanes); $[\alpha]_D^{20}$= +137.4 (*c* = 0.91, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.39 – 7.29 (m, 3H), 7.27 – 7.18 (m, 2H), 4.82 – 4.70 (m, 1H), 4.62 (q, *J* = 7.3 Hz, 1H), 4.31 – 4.09 (m, 2H), 3.33 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.85 – 2.57 (m, 3H), 1.46 (d, *J* = 7.3 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 208.2, 170.3, 153.8, 135.1, 129.4, 129.0, 127.3, 66.5, 55.3, 52.7, 38.0, 34.0, 12.9, 7.5 ppm; IR (film): $\tilde{\nu}$ = 2985, 1760, 1718, 1702, 1455, 1390, 1360, 1250, 1213, 1125, 1082, 1082, 1051, 1010, 974, 763, 748, 703 cm$^{-1}$; MS (EI) *m/z* (%): 289 (15) [$M^+$], 260 (15), 233 (15), 178 (10), 142 (25), 117 (40), 91 (25), 65 (5), 57 (100), 42 (5); HRMS (ESIpos): *m/z*: calcd for $C_{16}H_{19}NO_4Na$: 312.1206, found 312.1204. The analytical and spectroscopic data are in agreement with those reported in the literature.[241]

**But-2-ynal (38).** But-2-ynol (5.0 mL, 66 mmol) was added to a vigorously stirred suspension of $MnO_2$



(activated, 65 g, 748 mmol) in $Et_2O$ (7 mL). Additional $Et_2O$ (17 mL) was then added and the mixture was stirred at ambient temperature overnight. After filtration through a pad of Celite® and careful evaporation of the filtrate at ≤ 40 °C bath temperature, the residue was distilled (b.p. 75-80 °C) under Ar to give but-2-ynal as a pale yellow liquid (1.99 g, 44%), which must be stored at low temperature and used readily. $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.13 (dd, *J* = 1.8, 0.9 Hz, 1H), 2.05 (d, *J* = 1.0 Hz, 3H) ppm. The analytical and spectroscopic data are in agreement with those reported in the literature.[242]

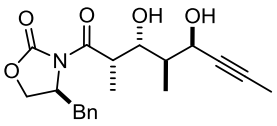
**(2*S*,4*R*,5*R*)-1-((*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-5-hydroxy-2,4-dimethyloct-6-yne-1,3-dione.**



$NEt_3$ (0.78 mL, 5.66 mmol) was added dropwise to a solution of $Sn(OTf)_2$ (2.36 g, 5.66 mmol) in $CH_2Cl_2$ (27 mL). After cooling to −30 °C, a solution of **21** (1.56 g, 13.07 mmol) in $CH_2Cl_2$ (9 mL) was slowly introduced and the mixture was stirred for 1 h at this temperature before it was cooled to −78 °C and but-2-ynal (**38**) (1.8 ml, 29 mmol) was added dropwise. After an additional 45 min, the mixture was diluted with $CH_2Cl_2$ (30 mL) and added to a vigorously stirred aq. solution of $NaHSO_4$ (1 M, 80 mL) at 0 °C. This slurry was stirred for 10 min before the aqueous phase was extracted with $CH_2Cl_2$ (4 x 80 mL). The combined extracts were washed with aq. sat. $NaHCO_3$ (120 mL), dried over $Na_2SO_4$ and concentrated. Flash chromatography of the residue afforded the title compound as a white solid (1.05 g, 55%, 88%

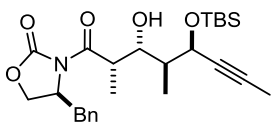
brsm). $[\alpha]_D^{20}$= + 101.1 (*c* = 0.55, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 3H), 7.23 – 7.14 (m, 2H), 4.90 (q, *J* = 7.3 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.60 (s, 1H), 4.31 – 4.21 (m, 1H), 4.17 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.02 – 2.88 (m, 1H), 2.76 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.40 (s, 1H), 1.82 (d, *J* = 1.8 Hz, 3H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.36 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 209.3, 170.5, 153.7, 135.0, 129.3, 129.0, 127.4, 82.5, 78.0, 66.4, 63.3, 55.2, 51.8, 50.3, 37.9, 12.7, 12.0, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3511, 2940, 1775, 1716, 1690, 1454, 1357, 1212, 1117, 998, 913, 762, 735, 703 cm$^{-1}$; MS (EI) *m/z* (%): 357 (2), 339 (2), 311 (2), 289 (40), 260 (17), 233 (30), 204 (1), 178 (29), 159 (3), 156 (5), 142 (19), 134 (38), 125 (33), 117 (78), 112 (100), 107 (26), 101 (16), 97 (3), 91 (74), 86 (73), 83 (25), 79 (24), 77 (13), 69 (32), 65 (19), 57 (89), 42 (30), 39 (28), 29 (26); HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{23}NO_5Na$: 380.1468, found 380.1470.

**(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethyloct-6-ynoyl)oxazolidin-2-one (39).**

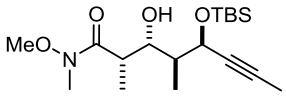



$Me_4NBH(OAc)_3$ (3.72 g, 14.2 mmol) was dissolved in MeCN (260 mL) and HOAc (160 mL) and the resulting mixture cooled to −50 °C. A solution of the ketone described above (1.01 g, 2.83 mmol) in MeCN (34 mL) was added and the mixture warmed to +10 °C overnight. The mixture was then poured into a pre-cooled (0 °C) mixture of sat. aq. solution of Rochelle salt (140 mL) and *tert*-butyl methyl ether (140 mL). Under vigorous stirring, sat. $NaHCO_3$-solution and solid $NaHCO_3$ were added in small portions until no further gas evolution could be observed. The phases were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4 x 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated to obtain the desired diol (1.00 g, 98%) as a mixture of diastereomers (2:92:4:1:0.5 as determined by HPLC: 50 mm Ultra HAT Pro 18, 120 A, 2 μm, ∅ 3.0 mm, MeOH/$H_2O$ = 60:40, 0.5 mL/min, 308 K, 27.4 MPa). $[\alpha]_D^{20}$= + 36.0 (*c* =1.1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 3H), 7.21 – 7.15 (m, 2H), 4.75 – 4.66 (m, 1H), 4.45 (s, 1H), 4.27 – 4.15 (m, 3H), 4.14 – 4.01 (m, 1H), 3.89 – 3.76 (m, 2H), 3.22 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.06 – 1.93 (m, 1H), 1.84 (t, *J* = 3.6 Hz, 3H), 1.24 (dd, *J* = 13.8, 7.0 Hz, 3H), 0.91 – 0.83 (m, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.1, 152.7, 134.9, 129.4, 129.0, 127.5, 81.9, 78.3, 73.7, 67.3, 66.2, 54.9, 39.7, 39.1, 37.8, 12.9, 9.7, 3.6 ppm; IR (film): $\tilde{\nu}$ = 3417, 2974, 2921, 1778, 1698, 1455, 1388, 1287, 978, 762, 702 cm$^{-1}$; MS (EI) *m/z* (%): 359 (1), 341 (3), 308 (1), 273 (68), 262 (7), 244 (3), 233 (38), 183 (3), 178 (50), 165 (14), 159 (4), 149 (4), 142 (12), 136 (11), 134 (29), 126 (13), 117 (57), 109 (34), 103 (8), 96 (100), 91 (71), 86 (74), 80 (44), 77 (11), 69 (35), 67 (11), 65 (17), 57 (51), 41 (32), 39 (18), 29 (23), 27 (9); HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{25}NO_5Na$: 382.1625, found 382.1620.

**(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4-dimethyloct-6-ynoyl)oxazolidin-2-one.** $NEt_3$ (0.97 mL, 4.2 mmol) and TBSOTf (0.78 mL, 5.6 mmol) were successively added to a solution of the above diol (1.00 g, 2.78 mmol) in $CH_2Cl_2$ (15 mL) at −78 °C. After stirring for 3 h, the reaction was quenched with sat. aq. $NaHCO_3$ and the resulting mixture warmed to ambient temperature. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL), and the combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1 to 7:1) to obtain the title compound as a colorless oil (1.17 g, 89%). $[\propto]_D^{20}$ = + 36.8 (*c* =1.64, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 4.73 – 4.62 (m, 2H), 4.26 – 4.05 (m, 3H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.85 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.31 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.74 (dt, *J* = 16.7, 8.4 Hz, 1H), 1.86 – 1.73 (m, 4H), 1.26 – 1.18 (m, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.5, 153.0, 135.4, 129.4, 128.9, 127.3, 82.1, 78.5, 72.6, 66.4, 66.1, 55.6, 41.8, 40.3, 37.8, 25.8, 18.1, 11.7, 9.1, 3.5, −4.5, −5.4 ppm; IR (film): $\tilde{\nu}$ = 3509, 2928, 1782, 1702, 1680, 1455, 1387, 1360, 1285, 1242, 1209, 1104, 1050, 1019, 984, 938, 836, 777, 702, 678 cm$^{-1}$; MS (EI) *m/z* (%): 473 (M+, 6), 416 (21), 398 (3), 348 (4), 341 (3), 337 (7), 336 (32), 324 (329, 318 (10), 306 (14), 290 (5), 273 (8), 262 (4), 252 (44), 239 (14), 233 (14), 183 (100), 178 (41), 165 (5), 159 (42), 147 (85), 143 (53), 136 (5), 133 (6), 127 (9), 119 (14), 117 (32), 115 (25), 109 (20), 97 (14), 91 (27), 81 (8), 77 (6), 75 (72), 73 (49), 57 (11), 29 (5); HRMS (ESIpos): *m/z*: calcd for $C_{26}H_{39}NO_3SiNa$: 496.2490, found 496.2491.

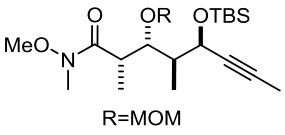



**(2*S*,3*R*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethyloct-6-yn amide (40).** $AlMe_3$ (2 M in heptane, 4.2 mL, 8.31 mmol) was carefully added (exothermic reaction) to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.811 g, 8.31 mmol) in THF (7 mL) at 0 °C and the resulting suspension was stirred for 15 min at this temperature and for 75 min at room temperature. The mixture was then cooled to −70 °C before a solution of the above mentioned silyl ether (1.05 g, 2.22 mmol) in THF (10 mL) was slowly added. The mixture was warmed to −10 °C over 8 h before it was poured into a chilled (0 °C) sat. aq. Rochelle salt solution (300 mL). The resulting suspension was stirred for 45 min and then repeatedly extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 6:1) to afford the title compound as a colorless oil that solidified in the fridge (715 mg, 90%). $[\propto]_D^{20}$ = +46.5 (*c* = 0.79, $CHCl_3$); mp ≈ 13 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.86 – 4.82 (m, 1H), 4.05 (s, 1H), 3.75 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 3.06 – 2.92 (m, 1H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.73 – 1.63 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.3, 80.5, 80.3, 71.7, 63.1, 61.4, 42.2, 36.0, 32.0, 25.8, 18.1, 10.4, 9.5, 3.4, −4.6, −5.3 ppm; IR (film): $\tilde{\nu}$ = 3458, 2956, 2932, 2857, 1639, 1462, 1416, 1388,

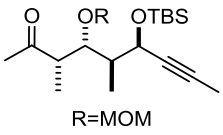


1361, 1292, 1251, 1178, 1146, 1113, 1056, 1016, 998, 863, 833, 776, 684 $cm^{-1}$; MS (EI) *m/z* (%): 357 (1), 326 (2), 302 (3), 300 (47), 297 (13), 241 (9), 232 (3), 225 (6), 220 (34), 217 (24), 208 (27), 183 (100), 174 (7), 164 (16), 159 (8), 153 (16), 143 (24), 138 (7), 127 (7), 117 (30), 115 (42), 109 (17), 97 (19), 87 (9), 85 (11), 81 (12), 75 (90), 73 (64), 62 (8), 61 (12), 59 (12), 45 (7), 41 (8), 29 (14); HRMS (ESIpos): *m/z*: calcd for $C_{18}H_{35}NO_4SiNa$: 380.2228, found 380.2228.

**(2*S*,3*R*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-3-(methoxymethoxy)-*N*,2,4-trimethyl oct-6-ynamide.** *i*-$Pr_2NEt$ (3.01 mL, 18.2 mmol) and MOMCl (0.691 mL, 9.10 mmol) were added to a solution of **16** (650 mg, 1.82 mmol) in DMF (5 mL) and the resulting slightly fuming mixture was stirred at 50 °C for 18 h. After cooling, *tert*-butyl methyl ether (20 mL) and brine (30 mL) were introduced and the aqueous phase was extracted with *tert*-butyl methyl ether (3 x 15 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 29:1 to 8:1) to furnish product **17** as a colorless oil (651 mg, 89%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.64 – 4.43 (m, 3H), 3.97 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.65 (s, 3H), 3.31 (s, 3H), 3.15 (s, 3H), 2.96 (qd, *J* = 6.9, 2.7 Hz, 1H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.78 – 1.68 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.08 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.2, 98.1, 96.0, 80.9, 79.6, 62.7, 61.0, 56.3, 44.2, 38.1, 25.8, 18.2, 14.2, 10.9, 9.7, 3.5, −3.9, −5.0 ppm; IR (film): $\tilde{\nu}$ = 2931, 2890, 2857, 1672, 1463, 1408, 1377, 1250, 1168, 1143, 1031, 1002, 940, 920, 834, 776, 673 $cm^{-1}$; MS (EI) *m/z* (%): 370 (5), 357 (3), 356 (12), 344 (51), 341 (10), 312 (6), 300 (5), 282(11), 274 (16), 271 (34), 260 (8), 253 (7), 239 (10), 234 (14), 227 (15), 223 (18), 208 (32), 183 (62), 179 (25), 157 (19), 149 (12), 127 (12), 119 (15), 115 (28), 105 (16), 97 (28), 89 (73), 73 (84), 59 (179, 45 (100), 29 (6) ; HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{39}NO_5SiNa$: 424.2490, found 424.2489.

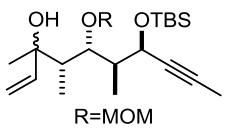



**(3*S*,4*R*,5*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-4-(methoxymethoxy)-3,5-dimethylnon-7-yn-2-one.** MeMgCl (2.76 M in THF, 1.76 mL, 4.86 mmol) was added dropwise to a solution of compound **17** (650 mg, 1.62 mmol) in $Et_2O$ (15.0 mL) at 0 °C and the resulting mixture was stirred for 2 h. The reaction was quenched with brine (15 mL) and the aqueous phase was extracted with $Et_2O$ (3 x 10 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated to give the desired ketone as a colorless oil which was used as such in the next step (562 mg, 97%, > 98% pure). An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc, 29:1 to 8:1). $[\alpha]_D^{20}$ = +64.1 (*c* = 0.88, hexanes); $^1$H NMR (300 MHz, $CDCl_3$): δ = 4.65 – 4.43 (m, 3H), 4.03 (dd, *J* = 9.2, 1.9 Hz, 1H), 3.21 (s, 3H), 2.58 (qd, *J* = 6.9, 1.8 Hz, 1H), 2.19 (s, 3H), 1.81 (d, *J* = 2.2 Hz, 3H), 1.79 – 1.70 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 210.0, 97.9, 81.4, 80.5, 79.9, 62.7, 55.9, 49.5, 44.1, 28.1, 25.9, 18.2, 11.0, 8.2, 3.5, −3.8, −4.5 ppm; IR (film): $\tilde{\nu}$ =

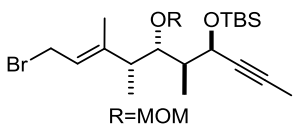


2931, 2857, 1716, 1462, 1360, 1251, 1188, 1142, 1090, 1058, 1032, 918, 834, 777, 677 $cm^{-1}$; MS (EI) *m/z* (%): 311 (1), 299 (1), 293 (3), 255 (4), 239 (12), 237 (99, 229 (59, 227 (9), 225 (4), 197 (27), 183 (86), 163 (46), 159 (27), 157 (15), 153 (15), 119 (19), 115 (18), 97 (21), 89 (57), 75 (55), 74 (6), 59 (17), 45 (100), 43 (46), 41 (8); HRMS (ESIpos): *m/z*: calcd for $C_{19}H_{36}O_5SiNa$: 379.2275, found 379.2273.

**(4*S*,5*R*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-3,4,6-trimethyldec-1-en-8-yn-3-ol (41).** Vinylmagnesium bromide (1.0 M in THF, 3.15 mL, 3.15 mmol) was slowly added at –78 °C to a solution of the ketone obtained in the previous step (562 mg, 1.58 mmol) in THF (15 mL). The mixture was slowly warmed to ambient temperature (2 h) and stirred for an additional 2 h. Sat. aq. $NH_4Cl$ (25 mL) was then introduced and the aqueous phase was extracted with $Et_2O$ (3 x 12 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 8:1) to provide alcohol **18** as an incosequential mixture of isomers (2:1, $^1$H NMR) (530 mg, 87%). $[\alpha]_D^{20}$ = + 47.4 (*c* = 0.69, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$, data given for the major isomer): δ = 5.92 – 5.68 (m, 1H), 5.39 – 5.16 (m, 1H), 5.12 – 4.95 (m, 1H), 4.79 – 4.59 (m, 2H), 4.56 – 4.44 (m, 1H), 4.05 – 3.78 (m, 2H), 3.37 (s, 3H), 1.89 – 1.76 (m, 3H), 1.76 – 1.52 (m, 3H), 1.31 (s, 1H), 1.18 (d, *J* = 0.7 Hz, 2H), 1.03 – 1.01 (m, 2H), 0.95 – 0.90 (m, 3H), 0.89 – 0.83 (m, 9H), 0.16 – 0.05 (m, 6H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$, data given for the major isomer): δ = 146.7, 111.5, 99.5, 82.7, 81.4, 80.4, 75.9, 63.1, 55.8, 44.5, 41.9, 27.3, 25.9, 18.1, 11.2, 7.1, 3.5, −3.6, −5.0; IR (film): $\tilde{\nu}$ = 3483, 2931, 2857, 1462, 1380, 1361, 1250, 1209, 1143, 1032, 920, 833, 814, 776, 678 $cm^{-1}$; MS (EI) *m/z* (%): 384, 339, 253 (1), 215 (4), 185 (11), 183 (100), 157 (9), 143 (10), 127 (7), 119 (7), 115 (9), 97 (11), 89 (22), 75 (24), 73 (37), 59 (6), 45 (34) ; HRMS (ESIpos): *m/z*: calcd for $C_{21}H_{40}O_4SiNa$: 407.2588, found 407.2592.

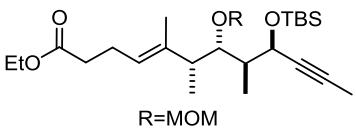



**(5*S*,6*S*,7*R*)-5-((*R*,*E*)-5-Bromo-3-methylpent-3-en-2-yl)-6,9,9,10,10-pentamethyl-7-(prop-1-ynyl)-2,4,8-trioxa-9-silaundecane.** Pyridine (0.32 mL, 3.92 mmol) was added at 0 °C to a solution of alcohol **18** (502 mg, 1.31 mmol) in $Et_2O$ (6.1 mL), followed by dropwise addition of $PBr_3$ (1.0 M in toluene, 3.13 mL, 3.13 mmol) over 10 min. The resulting mixture was stirred for 3 h at 0 °C before it was diluted with $Et_2O$ (20 mL). The reaction was carefully quenched with sat. aq. $NaHCO_3$ (100 mL) and the aqueous phase was extracted with $Et_2O$ (3 x 20 mL). The combined extracts were dried over $Na_2SO_4$, filtered through a short pad of $SiO_2$ and evaporated. The sensitive residue was immediately used in the next reaction (556 mg, 95%). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.49 – 5.42 (m, 1H), 4.95 (ddd, *J* = 4.8, 2.3, 2.3 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 3.75 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.66 (dd, *J* = 8.4, 2.1 Hz, 2H), 3.17 (s, 3H), 2.16 (dq, *J* = 6.8, 1.1 Hz, 1H), 2.04 – 1.96 (m, 1H), 1.55 (d, *J* = 1.0 Hz,



3H), 1.50 (d, *J* = 2.2 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.36 (s, 3H), 0.28 (s, 3H) ppm; HRMS (ESIpos): *m/z*: calcd for $C_{21}H_{39}BrO_3SiNa$: 469.1744, found 469.1749.

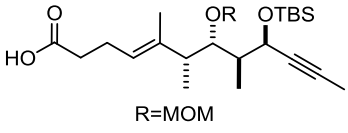
**(6*R*,7*S*,8*S*,9*R*,*E*)-Ethyl 9-(*tert*-butyldimethylsilyloxy)-7-(methoxymethoxy)-5,6,8-tri-methyldodec-4-en-10-ynoate (42).** *n*-BuLi (1.6 M in hexanes, 14.6 mL, 23.4 mmol) was added to a solution of




diisopropylamine (3.47 mL, 24.7 mmol) in THF (20 mL) at 0 °C and the resulting mixture stirred for 1 h.

In parallel, CuI (8.9 g, 46.8 mmol) was suspended in THF (40 mL) and the suspension cooled to −110 °C (cooling bath: $Et_2O/CO_2/N_2$). EtOAc (2.43 mL, 24.7 mmol) was added via syringe followed by dropwise addition of the freshly prepared LDA-solution via canula. The mixture was warmed over 3 h to −30 °C, causing a color change of the slurry from grey to yellow-brown. A solution of allyl bromide **19** (580 mg, 1.30 mmol) in THF (5 mL) was then slowly introduced and the mixture stirred for 2.5 h. The suspension was cooled to −60 °C before the reaction was quenched with aq. $NH_4Cl/NH_4OH$ (9:1; 63 g $NH_4Cl$, 17.5 mL 30% aqueous $NH_4OH$, filled up to 350 mL with $H_2O$). The aqueous phase was repeatedly extracted with *tert*-butyl methyl ether (5 x 150 mL), the combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. Flash chromatography of the residue (hexanes/EtOAc, 100:0 to 19:1) afforded the title compound as a pale yellow oil (369 mg, 62%). $[\alpha]_D^{20}$ = + 16.0 (*c* = 0.24, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.17 (t, *J* = 6.3 Hz, 1H), 4.56 (ddd, *J* = 5.6, 2.1, 2.0 Hz, 1H), 4.52 (dd, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 6.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.61 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.32 (s, 3H), 2.31 (m, 4H), 2.26 – 2.17 (m, 1H), 1.80 (d, *J* = 2.1 Hz, 3H), 1.78 – 1.71 (m, 1H), 1.64 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 6.9, 4.7 Hz, 6H), 0.88 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 173.3, 138.98, 123.1, 98.0, 81.2, 80.6, 80.6, 63.2, 60.2, 55.9, 44.3, 42.8, 34.2, 25.8, 23.6, 18.2, 15.8, 14.2, 12.5, 11.1, 3.4, −4.1, −5.1 ppm; IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1727, 1462, 1374, 1249, 1143, 1116, 1093, 1033, 919, 835, 814, 777, 676 cm$^{-1}$; MS (EI) *m/z* (%): 439, 397 (1), 365 (1), 329 (4), 283 (13), 253 (3), 211 (6), 183 (100), 169 (11), 157 (17), 115 (9), 95 (17), 89 (17), 73 (29), 45 (31); HRMS (ESIpos): *m/z*: calcd for $C_{25}H_{46}O_5SiNa$: 477.3007, found 477.3009.

**(6*R*,7*S*,8*S*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-7-(methoxymethoxy)-5,6,8-trimethyl-dodec-4-en-10-ynoic acid (43).** TMSOK (521 mg, 4.06 mmol) was added to a solution of the ethyl ester described

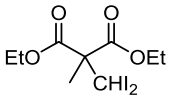



above (369 mg, 0.812 mmol) in $Et_2O$ (48 mL). The suspension was stirred for 48 h before being carefully neutralized with solid $CO_2$ and sat. aq. $NH_4Cl$ solution (50 mL) containing 5 drops of 1 M HCl. The aqueous phase was extracted with EtOAc (5 x 25 mL) and the combined extracts were washed with brine (40 mL), dried over $Na_2SO_4$ and concentrated. The crude acid **20**, obtained as a pale yellow oil, was judged pure and therefore used without further purification in the next step (347 mg, quant.).

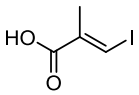
$[\propto]_D^{20}$= +44.7 (*c* = 0.75, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 11.5 – 9.5 (br s, 1H), 5.16 (t, *J* = 6.1 Hz, 1H), 4.56 – 4.53 (m, 1H), 4.52 (d, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 6.3 Hz, 1H), 3.60 (dd, *J* = 7.8, 3.5 Hz, 1H), 3.32 (s, 3H), 2.42 – 2.29 (m, 4H), 2.28 – 2.20 (m, 1H), 1.80 (d, *J* = 2.7 Hz, 3H), 1.78 – 1.71 (m, 1H), 1.64 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 6H), 0.89 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.7 139.3, 122.8, 98.0, 81.2, 80.7, 80.6, 63.2, 55.9, 44.3, 42.8, 33.8, 25.9, 23.4, 18.2, 15.8, 12.5, 11.1, 3.5, −4.1, −5.0 ppm; IR (film): $\tilde{\nu}$ = 3095, 2929, 2857, 2333, 2171, 1712, 1463, 1377, 1250, 1143, 1033, 923, 834, 777, 676 $cm^{-1}$; MS (EI) *m/z* (%): 411, 337 (1), 307 (3), 283 (12), 227 (6), 183 (100), 173 (8), 157 (16), 154 (14), 115 (9), 97 (8), 89 (14), 75 (16), 73 (30), 45 (48); HRMS (ESIpos): *m/z*: calcd for $C_{23}H_{42}O_5SiNa$: 449.2694, found 449.2695.

### 5.2.2 Synthesis of alcohol 57.

**Diethyl 2-(diiodomethyl)-2-methylmalonate (48).** A solution of diethyl methylmalonate (**47**) (9.81 mL, 57.0 mmol) in $Et_2O$ (20 mL) was added over 30 min to a suspension of NaH (1.65 g, 69.0 mmol) in $Et_2O$ (100 mL), causing the mixture to reach reflux temperature while vigorously evolving $H_2$. Once the addition was complete, the mixture was stirred at reflux temperature for 1.5 h before solid $CHI_3$ (22.6 g, 57.0 mmol) was added. Stirring was continued at reflux temperature for 12 h before the mixture was cooled to 0 °C and excess NaH was carefully quenched with aq. HCl (1 M, 100 mL). After stirring for 20 min, the layers were separated and the aqueous phase was extracted with $Et_2O$ (3 x 65 mL). The combined organic extracts were washed with brine (80 mL), dried over $Na_2SO_4$ and concentrated to give the title compound as a pale brown oil, which was used in the next without further purification (24.9 g, 99%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.73 (br s, 1H), 4.18 (dq, *J* = 7.1 Hz, 1.4 Hz, 4H), 1.75 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.0, 62.6, 62.1, 20.3, 13.9, −26.0 ppm; IR (film): $\tilde{\nu}$ = 1731, 1447, 1380, 1366, 1261, 1207, 1162, 1093, 1074, 1015, 859 $cm^{-1}$; MS (EI) *m/z* (%): 440 (12), 313 (9), 241 (22), 213 (27), 195 (17), 167 (12), 113 (7), 85 (12), 41 (16), 39 (23), 29 (100), 27 (15); HRMS (ESI): *m/z*: calcd for $C_9H_{14}O_2I_2Na$: 462.8874, found 462.8871. The analytical and spectroscopic data are in agreement with those reported in the literature.[56]




**(*E*)-3-Iodo-2-methylacrylic acid (49).** KOH (15.9 g, 283 mmol) and water (60 mL) were added to a solution of crude malonate **48** (24.8 g, 56.3 mmol) in EtOH (180 mL), and the resulting red solution was stirred at reflux temperature for 4 h. After cooling and evaporation of all volatile materials, the residue was dissolved in aq. $K_2CO_3$ (10%, 150 mL), which was then carefully acidified with conc. HCl at 0 °C. Extraction with $CH_2Cl_2$ (8 x 50 mL) was followed by drying of the combined organic layers over $Na_2SO_4$ and evaporation of the solvent. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1 + 0.5% HOAc) to yield the title compound as a pale yellow solid (8.58 g, 72%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 12.28 (br s, 1H), 8.00 (q, *J* = 1.2 Hz, 1H), 2.03 (d, *J* = 1.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl3): δ = 169.3, 139.0, 102.1, 19.8 ppm;



IR (film): $\tilde{\nu}$ = 3079, 2966, 2596, 1682, 1593, 1409, 1379, 1296, 1235, 1108, 991, 915, 838, 727, 685 $cm^{-1}$; MS (EI) *m/z* (%): 212 (56), 167 (6), 127 (6), 85 (75), 57 (12), 45 (14), 43 (11), 41 (28), 40 (16), 39 (100), 38 (18), 37 (9), 29 (18); HRMS (EI): *m/z*: calcd for $C_4H_5O_2I$: 211.9334, found 211.9336. The analytical and spectroscopic data are in agreement with those reported in the literature.[62]

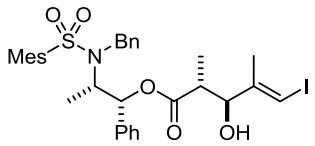
**(*E*)-3-Iodo-2-methylprop-2-en-1-ol.** A solution of acid **5** (8.4 g, 39.6 mmol) in $Et_2O$ (25 mL) was added over 20 min to a suspension of $LiAlH_4$ (1.65 g, 43.6 mmol) in $E_2O$ (60 mL) at 0 °C. After additional 30 min at this temperature, the ice bath was removed and the mixture stirred at ambient temperature for 2.5 h. The excess $LiAlH_4$ was carefully quenched with sat. aq. $Na_2SO_4$ (130 mL) and the mixture diluted with $H_2SO_4$ (2 M, 60 mL) and $Et_2O$. The aqueous layer was extracted with $Et_2O$ (3 x 40 mL), the combined organic phases were washed with aq. $K_2CO_3$ (10%, 50 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification of the remaining oil by flash chromatography (pentane/$Et_2O$, 4:1) gave the title compound as a colorless oil (3.6 g, 49%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.25 (m, 1H), 4.09 (d, *J* = 5.4 Hz, 2H), 1.85 – 1.81 (m, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 147.2, 77.3, 67.1, 21.3 ppm; IR (film): $\tilde{\nu}$ = 3295, 2912, 2851, 1620, 1433, 1376, 1274, 1252, 1145, 1066, 1008, 942, 829, 771, 665 $cm^{-1}$; MS (EI) *m/z* (%): 198 (75), 183 (5), 127 (9), 71 (100), 53 (28), 43 (59), 31 (57), 39 (61), 38 (12), 31(34), 29(14), 27(26); HRMS (EI): *m/z*: calcd for $C_4H_7IO$: 197.9542, found 197.9541. The analytical and spectroscopic data are in agreement with those reported in the literature.[56]

**(*E*)-3-Iodo-2-methylacrylaldehyde (46).** $MnO_2$ (11.1 g, 127 mmol) was added in three portions to a vigorously stirred solution of (*E*)-3-iodo-2-methylprop-2-en-1-ol (2.52 g, 12.7 mmol) in $CH_2Cl_2$ (35 mL), causing a slightly exothermic reaction. After 3.5 h, the mixture was filtered through a pad of flame-dried Celite®, which was rinsed with $CH_2Cl_2$ (2 x 10 mL). The combined filtrates were evaporated and the residue was briefly dried in high vacuum to give the title compound as a pink oil (2.46 g, 98%). Due to the unstable nature of this compound, it was dissolved in $CH_2Cl_2$ (10 mL) containing 4 Å MS and immediately used in the next step. $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.8 (q, *J* = 1.2 Hz, 1H), 1.92 (d, *J* = 1.2 Hz, 3H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 189.4, 150.8, 109.4, 16.4 ppm; IR (film): $\tilde{\nu}$ = 2921, 2842, 1691, 1591, 1294, 1099, 1027, 1015, 798, 679 $cm^{-1}$; MS (EI) *m/z* (%): 196 (99), 167 (14), 127 (8), 69 (86), 41 (59), 30 (11), 39 (100), 38 (13), 29 (8); HRMS (EI): *m/z*: calcd for $C_4H_5IO$: 195.9385, found 195.9384.

**Masamune *anti*-aldol bromide 53.** $NEt_3$ (59.6 µl; 0.430 mmol) and (1*R*,2*S*)-2-(*N*-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl propionate (**52**)[243] (82.0 mg, 0.170 mmol) were dissolved in $CH_2Cl_2$ (2.4 mL) and the solution cooled to −78 °C. A solution of dicyclohexylboryl triflate (1.0 M in $CH_2Cl_2$, 0.43 mL, 0.43 mmol) was then added over 12 min to give a yellow suspension, which was

kept at this temperature for 5 h. A solution of freshly prepared aldehyde **46** (56.6 mg, 0.375 mmol) in $CH_2Cl_2$ (1 mL) was then added and stirring was continued for 1.5 h before the cooling bath was removed and the mixture allowed to reach room temperature. After 3 h, the reaction was quenched with pH 7 buffer (3 mL) and the mixture treated with MeOH (2 mL) and aq. $H_2O_2$ (35% *w/w*, 1.5 mL) overnight. The solvent was removed in vacuo, the residue was dissolved in $CH_2Cl_2$ (5 mL), and the organic phase was washed with $H_2O$ (6 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 5 mL), the combined organic layers were dried over $Na_2SO_4$ and evaporated. $^1$H NMR analysis of the crude product showed a diastereomeric ratio of 13:1. Purification of the residue by flash chromatography (hexanes/EtOAc 9:1 to 6:1) yielded the title compound as a pale yellow oil (62.0 mg, 58%, 13:1 d.r.). $[\alpha]_D^{20}$ = +38.3 (c = 0.87, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.20 (m, 8H), 6.93 (s, 2H), 6.92- 6.88 (m, 2H), 6.28 (d, *J* = 1.0 Hz, 1H), 5.90 (d, *J* = 3.8 Hz, 1H), 4.82 (d, *J* = 16.6 Hz, 1H), 4.64 (d, *J* = 16.7 Hz, 1H), 4.24 (dd, *J* = 9.2, 3.7 Hz, 1H), 4.09 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.00 (d, J = 4.0 Hz, 1H), 2.68 (dq, *J* = 9.0, 7.3 Hz, 1H), 2.56 (s, 6H), 2.33 (s, 3H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.1, 142.5, 140.8, 140.2, 138.7, 138.0, 133.2, 132.0, 128.3, 128.2, 127.9, 127.5, 127.0, 125.7, 107.4, 78.5, 77.4, 56.8, 48.1, 43.2, 35.5, 22.9, 20.8, 17.2, 14.0, 13.5 ppm; IR (film): $\tilde{\nu}$ = 3482, 1743, 1606, 1498, 1381, 1321, 1211, 1152, 1117, 1010, 931, 859, 750, 731, 698 cm$^{-1}$; MS (EI) *m/z* (%): 406 (2), 317 (20), 316 (100), 183 (6), 149 (2), 119 (18), 91 (61). HRMS (ESIpos): *m/z*: calcd for $C_{32}H_{38}NO_5Br_1S_1Na$: 650.1546, found 650.1540.

**(2*R*,3*S*,*E*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 3-hydroxy-5-iodo-2,4-dimethylpent-4-enoate (54).** $NEt_3$ (0.904 mL, 6.52 mmol) and (1*R*,2*S*)-2-(*N*-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl propionate (**52**)[243] (2.61 g, 5.43 mmol) were dissolved in $CH_2Cl_2$ (45 mL) and the solution cooled to −78 °C. A solution of dicyclohexylboryl triflate (2.13 g, 6.52 mmol) in pentane (12 mL) was then added over 12 min to give a yellow suspension, which was kept at this temperature for 5 h. A solution of freshly prepared aldehyde **6** (2.45 g, 12.5 mmol) in $CH_2Cl_2$ (10 mL) was then added and stirring continued for 1.5 h before the cooling bath was removed and the mixture allowed to reach room temperature. After 3 h, the reaction was quenched with pH 7 buffer (30 mL) and the mixture treated with MeOH (100 mL) and aq. $H_2O_2$ (35% *w/w*, 15 mL) overnight. The solvent was removed in vacuo, the residue was dissolved in $CH_2Cl_2$ (150 mL), and the organic phase was washed with $H_2O$ (60 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL), the combined organic layers were dried over $Na_2SO_4$ and evaporated. $^1$H NMR analysis of the crude product showed a diastereomeric ratio of 13:1. Purification of the residue by flash chromatography yielded the title compound as a white solid (2.79 g, 76%, single isomer). $[\alpha]_D^{20}$ = +45.0 (c = 0.95, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.13 (m, 8H), 6.87 (s, 2H), 6.86- 6.82 (m, 2H), 6.28 (s, 1H), 5.83 (d, *J* = 4.0 Hz, 1H), 4.73 (d, *J* = 16.7 Hz, 1H), 4.54 (d, *J* = 16.7 Hz, 1H), 4.23 (dd, *J* = 8.9, 3.8 Hz, 1H), 4.09



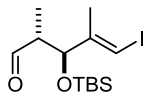
(dq, *J* = 4.0, 7.0 Hz, 1H), 2.73 (d, *J* = 4.1 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.48 (s, 6H), 2.26 (s, 3H), 1.80 (d, *J* = 1.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.0, 146.9, 142.6, 140.3, 138.5, 138.1, 133.4, 132.1, 128.5, 128.3, 128.0, 127.6, 127.2, 125.9, 81.2, 78.6, 78.5, 56.8, 48.2, 43.3, 22.9, 20.9, 18.8, 14.1, 13.3 ppm; IR (film): $\tilde{\nu}$ = 3496, 1741, 1604, 1496, 1455, 1379, 1317, 1151, 1117, 1031, 1011, 929, 858, 752, 730, 698, 659 cm$^{-1}$; MS (EI) *m/z* (%): 406 (1), 317 (20), 316 (100), 183 (5), 119 (17), 91 (60), 57 (3), 41 (3); HRMS (ESIpos): *m/z*: calcd for $C_{32}H_{38}NO_5ISNa$: 698.1408, found 698.1411. The analytical and spectroscopic data are in agreement with those reported in the literature.[62]

**(2*R*,3*S*,*E*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 3-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-enoate (55).** 2,6-Lutidine (0.863 mL, 7.43 mmol) was added via syringe to a stirred solution of alcohol **54** (2.51 g, 3.71 mmol). The mixture was cooled to 0 °C before TBSOTf (1.28 mL, 5.57 mmol) was slowly added. After stirring for 2 h at 0 °C, the reaction was quenched with sat. aq. $NH_4Cl$ and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated to give a white solid, which was used in the next step without further purification (2.89 g, 95%). An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc, 9:1). $[\alpha]_D^{20}$ = +36.3 (c = 0.85, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.3 Hz, 2H), 7.30 – 7.22 (m, 3H), 7.19 – 7.13 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.85 (s, 2H), 6.7 (d, *J* = 7.3 Hz, 2H), 6.18 (s, 1H), 5.67 (d, *J* = 6.0 Hz, 1H), 4.85 (d, *J* = 16.1 Hz, 1H), 4.37 (d, *J* = 16.1 Hz, 1H), 4,29 (d, *J* = 9.3 Hz, 1H), 4.04 (dq, *J* = 6.6, 6.6 Hz, 1H), 2.61 (dq, *J* = 9.1, 7.3 Hz, 1H), 2.39 (s, 6H), 2.29 (s, 3H), 1.73 (d, *J* = 0.8 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.80 (s, 9H), 0.74 (d, *J* = 7.2 Hz, 3H), −0.03 (s, 3H), −0.05 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.9, 147.5, 142.4, 140.4, 138.5, 138.0, 132.9, 132.1, 128.4, 128.4, 128.2, 127.9, 127.4, 126.4, 80.6, 79.2, 77.7, 56.6, 48.1, 44.7, 25.7, 22.8, 20.9, 18.6, 18.1, 14.9, 13.8, −5.1, −5.1 ppm; IR (film): $\tilde{\nu}$ = 2956, 2935, 2857, 1743, 1605, 1455, 1379, 1325, 1254, 1154, 1072, 1030, 1011, 929, 857, 836, 777, 729, 698, 659. cm$^{-1}$; MS (EI) *m/z* (%): 406 (23), 317 (21), 316 (100), 183 (6), 132 (7), 119 (20), 91 (62), 73 (11); HRMS (ESIpos): *m/z*: calcd for $C_{38}H_{52}NO_5ISSiNa$: 812.2272, found 812.2280.

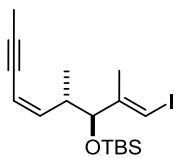
**(2*S*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-en-1-ol.** DIBAl-H (1 M in toluene, 9.38 mL, 9.38 mmol) was added over a period of 12 min to a solution of the above silyl ether (2.89 g, 95% pure, 3.48 mmol) in toluene (25 mL) at −78 °C. After stirring 2 h at this temperature, the excess DIBAl-H was carefully quenched with MeOH (2 mL). The mixture was diluted with *tert*-butyl methyl ether (20 mL) and aq. sat. Rochelle salt solution (30 mL). The resulting mixture was stirred overnight at ambient temperature before the aqueous layer was extracted with *tert*-butyl methyl ether (3 x 30 mL). The combined extracts were washed with brine

(25 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to give the title compound as a colorless oil (1.07 g, 83% over two steps). $[\alpha]_D^{20}$ = −32.3 (c = 1.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1H), 4.00 (d, *J* = 8.0 Hz, 1H), 3.61 (dd, *J* = 4.5, 0.7 Hz, 1H), 3.60 (d, *J* = 4.8 Hz, 1H), 2.44 (t, *J* = 5.68 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.76 (d, *J* = 1.0 Hz, 3H), 0.88 (s, 9H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 3H), −0.02 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 148.8, 82.8, 79.3, 66.2, 38.7, 25.8, 19.5, 18.1, 14.0, −4.8, −5.3 ppm; IR (film): $\tilde{\nu}$ = 339, 2956, 2928, 2884, 2857, 1615, 1471, 1462, 1376, 1361, 1252, 1140, 1064, 1037, 1004, 982, 938, 834, 774, 672 cm$^{-1}$; MS (EI) *m/z* (%): 313 (46), 311 (23), 271 (18), 185 (52), 171 (16), 115 (6), 111 (9), 75 (100), 73 (44), 53 (6), 45 (5), 43 (5), 41 (6); HRMS (ESIpos): *m/z*: calcd for $C_{13}H_{27}O_2ISiNa$: 393.0717, found 393.0715.

**(2*R*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-enal (44).** A solution of the above primary alcohol (600 mg, 1.62 mmol) in $CH_2Cl_2$ (6 mL) was added to a suspension of Dess-Martin periodinane (756 mg, 1.78 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C. After stirring for 15 min, the mixture was allowed to warm to room temperature and stirring continued for 2 h. The reaction was quenched with sat. $Na_2S_2O_3$/$Na_2CO_3$ (1:1, 10 mL) and the aqueous phase extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and evaporated. The residue was suspended in hexane/EtOAc (9:1) and the resulting suspension filtered through a short pad of $SiO_2$. Concentration of the filtrate under reduced pressure gave the rather unstable aldehyde, which was immediately used in the next step (586 mg, 98%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 9.73 (d, *J* = 2.7 Hz, 1H), 6.28 (s, 1H), 4.27 (d, *J* = 8.4 Hz, 1H), 2.59 (dqd, *J* = 8.4, 7.1, 2.5 Hz, 1H), 1.79 (d, *J* = 1.0 Hz, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 203.8, 147.6, 80.1, 79.0, 50.1, 25.6, 19.0, 18.0, 10.8, −4.8, −5.4 ppm.




***tert*-Butyl-((1*E*,3*S*,4*S*,5*Z*)-1-iodo-2,4-dimethylnona-1,5-dien-7-yn-3-yloxy)dimethylsilane (56).** A precooled (−78 °C) solution of KHMDS (0.729 g, 3.66 mmol) in THF (6 mL) was added to a solution of sulfone **R1** (1.00 g, 3.98 mmol) in THF (6 mL) at –55 °C, causing a color change to dark-red. After stirring for 30 min at this temperature, a precooled (−78 °C) solution of aldehyde **44** (586 mg, 1.59 mmol) in THF (3 mL) was added dropwise and the resulting mixture stirred for 13 h at −55 °C before it was poured into brine (15 mL) and warmed to ambient temperature. MTBE (20 mL) and $H_2O$ (5 mL) were added and the aqueous phase was extracted with MTBE (2 x 20 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography yielded the title compound as a colorless oil (364 mg, 56%). $[\alpha]_D^{20}$ = +100.1 (c = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.09 (m, 1H), 5.61 (dd, *J* = 10.3, 10.0 Hz, 1H), 5.39 (dq, *J* = 10.8, 2.3 Hz, 1H), 3.98 (d, *J* = 5.4 Hz, 1H), 2.92 (ddq, *J* = 9.3, 6.5, 6.4 Hz, 1H), 1.94 (d, *J* = 2.4 Hz, 3H), 1.76 (d, *J* = 0.9 Hz, 3H),



0.91 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), −0.06 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 149.2, 143.7, 109.8, 89.4, 80.8, 78.0, 76.6, 39.5, 25.7, 20.6, 18.2, 17.1, 4.4, −4.9, −5.2 ppm; IR (film): $\tilde{\nu}$ = 2956, 2928, 2885, 2856, 2332, 2330, 2324, 1615, 1471, 1462, 1361, 1252, 1081, 1019, 1005, 938, 862, 833, 773, 749, 673 cm$^{-1}$; MS (EI) *m/z* (%): 347 (6), 312 (16), 311 (100), 146 (7), 127 (8), 115 (12), 91 (6), 75 (13), 73 (70), 59 (9), 53 (7); HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{29}OISiNa$: 427.0925, found 427.0926.

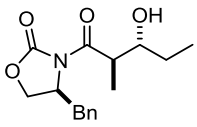
**(1*E*,3*S*,4*S*,5*Z*)-1-Iodo-2,4-dimethylnona-1,5-dien-7-yn-3-ol (57).** TBAF (1 M in THF, 1.42 mL, 1.42 mmol) was added to a solution of silyl ether **56** (230 mg, 0.568 mmol) in THF (5 mL) at 0 °C and the mixture stirred at this temperature for 3.5 h before the reaction was quenched with water (5 mL), sat. $NH_4Cl$ solution (2 mL) and *tert*-butyl methyl ether (10 mL). The aqueous phase was extracted with MTBE (3 x 10 mL), and the combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to yield alcohol **57** as a colorless oil (163 mg, 99%). $[\propto]_D^{20}$ = +24.0 (c = 0.50, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.24 (s, 1H), 5.64 (dd, *J* = 10.3 Hz, 10.1 Hz, 1H), 5.55 (dq, *J* = 10.7 Hz, 2.1 Hz, 1H), 3.91 (dd, *J* = 8.0 Hz, 3.1 Hz, 1H), 2.97 (dqd, *J* = 9.2, 7.2, 7.1 Hz, 1H), 1.97 (d, *J* = 2.2 Hz, 3H), 1.88 (d, *J* = 3.3 Hz, 1H), 1.83 (d, *J* = 0.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 148.2, 142.9, 111.8, 90.8, 80.7, 79.6, 76.0, 38.8, 19.4, 16.8, 4.4 ppm; IR (film): $\tilde{\nu}$ = 3535, 3419, 2962, 2916, 2873, 2853, 1615, 1454, 1399, 1377, 1271, 1143, 1117, 1072, 1005, 933, 753, 671 cm$^{-1}$; MS (EI) *m/z* (%): 290 (1), 197 (59), 163 (10), 95 (9), 94, (100), 93 (16), 91(26)79 (89), 77 (40), 60 (5), 65 (9), 53 (10), 51 (7), 43 (12), 4 1 (6), 39 (25), 29 (5); HRMS (EI): *m/z*: calcd for $C_{11}H_{15}OI$: 290.0168, found 290.0166.

### 5.2.3 Synthesis of δ-lactone fragment 57.

**(*S*)-4-Benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one.** According to the protocol of Heathcock,[244] *i*-$Pr_2NEt$ (3.35 mL, 19.7 mmol) was added to a cooled (0 °C) solution of *ent*-**13** (4.00 g, 17.1 mmol) and freshly destilled (*n*-$Bu)_2BOTf$ (7.38 mL, 34.2 mmol) in $Et_2O$ (40 mL). After stirring for 45 min at 0 °C, the yellow suspension was cooled to −78 °C before a precooled (−78 °C) solution of freshly destilled propionaldehyde (**14**) (1.62 mL, 22.2 mL) in $Et_2O$ (10 mL) was slowly introduced. After an additional 30 min, the reaction was quenched by addition of solid tartaric acid (13 g) and the mixture stirred at ambient temperature for 2 h. The reaction was partitioned between ether and $H_2O$, and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution (2 x 40 mL). A mixture of MeOH/30% $H_2O_2$ (3:1, 50 mL) was added under vigorous stirring at 0 °C and the resulting mixture stirred for 1 h at room temperature before the aqueous phase was extracted with $Et_2O$ (2 x 30 mL). The combined organic extracts were washed with sat. $NaHCO_3$ solution and brine (30 mL each), dried over $Na_2SO_4$ and concentrated. The crude material was purified by flash chromatography (hexanes/EtOAc, 3:1) to

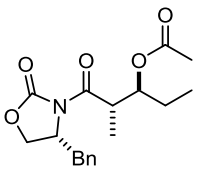
give the title compound as an off-white solid (3.69 g, 74%, 11:1 dr.), along with additional 350 mg of mixed fractions. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 4.67 (ddd, *J* = 13.0, 6.8, 3.2 Hz, 1H), 4.21 – 4.12 (m, 2H), 3.90 (dq, *J* = 6.9, 6.9 Hz, 1H), 3.65 (dddd, *J* = 8.3, 8.3, 7.4, 3.5 Hz, 1H), 3.31 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.56 – 2.52 (m, 1H), 1.73 – 1.63 (m, 1H), 1.54 – 1.41 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.9, 153.6, 135.2, 129.4, 129.0, 127.3, 76.0, 66.0, 55.6, 42.9, 37.9, 27.8, 14.6, 9.8 ppm; IR (film): $\tilde{\nu}$ = 3516, 2967, 2936, 2879, 1775, 1695, 1455, 1385, 1351, 1291, 1209, 1111, 1051, 1015, 969, 762, 749, 702 cm$^{-1}$; MS (EI) *m/z* (%): 291 (10), 244 (28), 233 (18), 178 (32), 158 (15), 142 (13), 134 (24), 133 (16), 118 (14), 117 (51), 116 (25), 115 (42), 97 (27), 96 (11), 92 (39), 91 (100), 86 (87), 85 (25), 77 (11), 70 (13), 69 (37), 65 (29), 59 (57), 58 (19), 57 (89), 56 (24), 45 (27), 43 (22), 42 (33), 41 (38), 39 (18), 31 (42), 30 (15), 29 (73), 28 (22), 27 (33); HRMS (EI): *m/z*: calcd for $C_{16}H_{21}NO_4Na$: 314.1363, found 314.1357.

**(*R*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one.** This enantiomer was



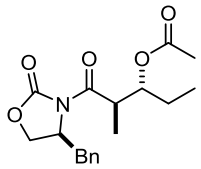

obtained analogously from **13** (4.00 g, 17.1 mmol) as a white solid (3.50 g, 71%).

**(2*R*,3*R*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-1-oxopentan-3-yl acetate (62).** $NEt_3$



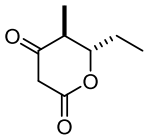

(2.20 mL, 15.8 mmol) and freshly distilled acetic anhydride (1.40 mL, 14.6 mmol) were successively added to a solution of the above alcohol (3.55 g, 12.1 mmol) in $CH_2Cl_2$ (36 mL). The mixture was cooled to 0 °C and DMAP (296 mg, 2.40 mmol) was introduced. After 30 min, the ice bath was removed and stirring was continued for 90 min before the reaction was quenched with sat. $NH_4Cl$ solution (20 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 x 25 mL), the combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1 to 3:1) to give the title compound as a white solid (single d.r., 3.26 g, 82%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.22 – 7.18 (m, 2H), 5.23 (ddd, *J* = 8.1, 8.0, 3.6 Hz, 1H), 4.70 – 4.63 (m, 1H), 4.20 – 4.10 (m, 3H), 3.25 (dd, *J* = 13.1, 3.3 Hz, 1H), 2.68 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.00 (s, 3H), 1.88 – 1.78 (m, 1H), 1.63 – 1.52 (m, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.6, 170.1, 153.0, 135.1, 129.4, 129.0, 127.4, 75.7, 65.8, 55.3, 40.8, 37.8, 24.1, 21.0, 14.0, 8.8 ppm; IR (film): $\tilde{\nu}$ = 3029, 2978, 2944, 2883, 1782, 1737, 1699, 1491, 1455, 1378, 1349, 1291, 1208, 1111, 1098, 1049, 1016, 962, 884, 840, 762, 741, 726, 698 cm$^{-1}$; MS (EI) *m/z* (%): 273 (14), 244 (27), 178 (11), 157 (14), 117 (19), 97 (86), 96 (18), 91 (32), 69 (23), 57 (10), 43 (100), 41 (16), 29 (13); HRMS (EI): *m/z*: calcd for $C_{18}H_{23}NO_5Na$: 356.1468, found 356.1469.

**(2*S*,3*S*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-1-oxopentan-3-yl acetate (*ent*-62).** This



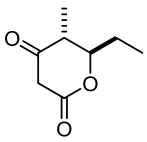
enantiomer was obtained analogously from (*R*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one (3.50 g, 12.1 mmol) as a white solid (3.00 g, 75%).

**(5*S*,6*S*)-6-Ethyl-5-methyldihydro-2H-pyran-2,4(3*H*)-dione (61).** A pre-cooled solution (−78 °C) of



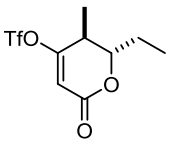
LiHMDS (4.5 g, 27.0 mmol) in THF (50 mL) was added via canula to a solution of acetate **62** (3.00 g, 9.01 mmol) in THF (50 mL) at −78 °C. After 1 h, the mixture was poured into sat. $NH_4Cl/H_2O$/MeOH (1:1:1, 250 mL) and diluted with EtOAc (150 mL). The organic phase containing the chiral auxiliary was separated, which could be recovered by flash chromatography (hexanes/EtOAc, 1:1). The aqueous phase was acidified with HCl (1 M) to pH 2 and then extracted with $CH_2Cl_2$ (3 x 60 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 3:1 to 1:1) to yield the desired ß-keto ester as a white solid (1.17 g, 83%). $[\propto]_D^{20}$ = +14.4 (c = 0.55, $Et_2O$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 4.25 (ddd, *J* = 10.5, 7.6, 3.0 Hz, 1H), 3.53 (d, *J* = 19.1 Hz, 1H), 3.41 (d, *J* = 19.2 Hz, 1H), 2.40 (dq, *J* = 10.4, 7.1 Hz, 1H), 1.93 (tdd, *J* = 14.8, 7.3, 3.0 Hz, 1H), 1.69 (qdd, *J* = 14.7, 7.4, 7.3 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.08 (t, 3H, *J* = 7.3 Hz) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 202.7, 167.2, 81.2, 46.3, 45.8, 25.4, 10.7, 8.5 ppm; IR (neat): $\tilde{\nu}$ = 3205, 2969, 2928, 2763, 2346, 1652, 1587, 1450, 1395, 1376, 1323, 1275, 1260, 1220, 1152, 1127, 1084, 1055, 1039, 991, 964, 903, 872, 850, 823, 750, 697 cm$^{-1}$; MS (EI) *m/z* (%): 156 (12), 127 (20), 98 (70), 97 (14), 85 (58), 70 (29), 69 (16), 57 (35), 56 (100), 55 (34), 43 (12), 42 (41), 31 (18), 39 (13), 29 (35), 28 (25), 27 (20); HRMS (EI): *m/z*: calcd for $C_8H_{12}O_3$: 156.0787, found 156.0787.

**(5*R*,6*R*)-6-Ethyl-5-methyldihydro-2H-pyran-2,4(3H)-dione (*ent*-61).** This enantiomer was obtained



analogously from *ent*-**62** (2.90 g, 8.78 mmol) as a white solid (1.23 g, 79%).

**Vinyl triflate 67.** A solution of β-keto lactone **61** (300 mg, 1.921 mmol) in $CH_2Cl_2$ (12 mL) was



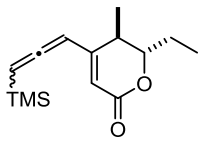
cooled to −78 °C, before triethylamine (293 µL, 2.11 mmol) and triflic anhydride (348 µL, 2.08 mmol) were added dropwise via syringe. The reaction mixture was stirred at this temperature for 1 h before the reaction was quenched with water (10 mL). After warming to ambient temperature, the aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 6:1) to give the desired product as a colorless oil (505 mg, 91%). $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.03 (d, *J* = 1.1 Hz, 1H), 4.17 (dt, *J* = 6.3, 6.2 Hz,

1H), 2.74 (dqd, *J* = 7.0, 6.9, 1.0 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 165.1, 162.3, 109.0, 83.5, 35.8, 26.0, 14.4, 9.4 ppm; IR (film): $\tilde{\nu}$ = 2979, 2944, 2886, 1729, 1656, 1459, 1427, 1378, 1348, 1315, 1246, 1207, 1133, 1074, 1041, 1008, 903, 874, 833, 799, 761, 732 cm$^{-1}$; MS (EI) *m/z* (%): 289 (1), 259 (47), 231 (8), 230 (100), 109 (15), 81 (26), 69 (67), 53 (25), 41 (16), 29 (13); HRMS (EI): *m/z*: calcd for $C_9H_{11}F_3O_5S_1Na$: 311.0172, found 311.0175.

**Pinacolborolane R5.** Trimethyl(prop-1yn-1-yl)silane (**R4**) (1.15 mL, 7.7 mmol) was dissolved in THF (10 mL) and the resulting solution cooled to −78 °C. A solution of *n*-BuLi (1.6 M in hexanes, 4.7 mL, 7.5 mmol) was then added via syringe and the resulting yellow solution stirred for 1 h. The mixture was then transferred via canula into a solution of triisopropyl pinacolborate (1.5 mL, 7.2 mmol) and $MgCl_2$ (0.68 g, 7.2 mmol) in THF (10 mL) at −40 °C. The yellow solution was stirred for 2 h before being carefully quenched with aq. HCl (1 M, 20 mL). The aqueous phase was extracted with $Et_2O$ (3 x 20 mL) and the combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The yellow residue was dried under high-vacuum and was judged pure on the basis of NMR and GC-MS analysis (1.43 g, 83%). $^1$H NMR (500 MHz, $CDCl_3$) δ = 1.85 (s, 2H), 1.14 (s, 12H), 0.00 (s, 9H) ppm; $^{13}$C NMR (100 MHz, $C_6D_6$) δ = 103.2, 84.0, 83.2, 24.7, 0.2 ppm; MS (EI) *m/z* (%): 238 (1), 223 (52), 167 (24), 138 (29), 123 (47), 107 (35), 96 (21), 83 (100), 73 (33), 69 (11), 55 (22); HRMS (EI): *m/z*: calcd for $C_{12}H_{23}BO_2Si_1Na$: 261.1458, found 261.1455.

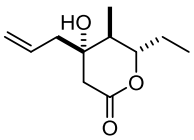
**Alkyne 68.** Vinyl triflate **67** (20.0 mg, 69.4 µmol) and borolane **R5** (18.2 mg, 76.3 µmol) were dissolved in a degassed mixture of THF and water (10:1, 0.77 mL). $Cs_2CO_3$ (67.7 mg, 20.8 µmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (5.1 mg, 6.3 µmol) were added at ambient temperature and the resulting orange solution placed in a pre-heated oil bath at 80 °C and strirred for 17 h. After cooling to ambient temperature, the reaction was quenched by addition of aq. HCl (1 M, 5 mL) and the aqueous phase extracted with MTBE (3 x 6 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 19:1 to 9:1) to give a white solid (4.2 mg, 33%). $^1$H NMR (400 MHz, $CD_2Cl_2$): δ = 5.99 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.03 (td, *J* = 7.7, 4.2 Hz, 1H), 2.41 (qd, *J* = 7.2, 1.8 Hz, 1H), 2.07 (s, 3H), 1.78 – 1.67 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ = 164.1, 145.5, 122.5, 99.5, 84.5, 77.3, 36.5, 26.6, 16.2, 9.6, 5.1 ppm; IR (film): $\tilde{\nu}$ = 2970, 2933, 2880, 2222, 1712, 1602, 1456, 1376, 1348, 1311, 1283, 1255, 1237, 1221, 1135, 1111, 1059, 1024, 1008, 990, 971, 846 cm$^{-1}$; MS (EI) *m/z* (%): 178 (11), 149 (42), 120 (100), 91 (54), 77 (23), 65 (14), 51 (8). HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{14}O_2Na$: 178.0994, found 178.0991.

**Allene 69.** Vinyl triflate **67** (80.0 mg, 0.284 mmol) and borolane **R5** (169 mg, 0.709 mmol) were



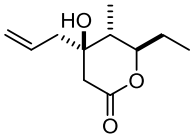

dissolved in a degassed mixture of THF and water (10:1, 2.8 mL). $Cs_2CO_3$ (277 mg, 0.851 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (20.8 mg, 25.5 µmol) were added at ambient temperature and the resulting orange solution stirred for 15 h. The reaction was quenched by addition of water (5 mL) and extracted with $Et_2O$ (3 x 6 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9:1) to give a white solid (56.7 mg, 18:1 d.r., 60%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.76 (t, *J* = 1.1 Hz, 1H), 4.76 (d, *J* = 1.2 Hz, 2H), 4.18 (ddd, *J* = 8.2, 6.1, 1.2 Hz, 1H), 2.60 (qd, *J* = 7.0, 1.2 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.58 – 1.46 (m, 1H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.21 (s, 9H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 213.3, 163.8, 157.7, 114.5, 98.6, 84.7, 72.4, 34.8, 26.7, 19.4, 10.3, −0.6 ppm; IR (film): $\tilde{\nu}$ = 2980, 2945, 2867, 1712, 1461, 1441, 1382, 1323, 1262, 1210, 1118, 1101, 1008, 987, 915, 705 cm$^{-1}$; MS (EI) *m/z* (%): 250 (38), 160 (11), 145 (12), 117 (14), 73 (100), 45 (12). HRMS (ESIpos): *m/z*: calcd. for $C_{14}H_{22}O_2Si_1Na$ [$M^+$+Na]: 273.1281, found 273.1279.

**(4*S*,5*S*,6*S*)-4-Allyl-6-ethyl-4-hydroxy-5-methyltetrahydro-2*H*-pyran-2-one (70).** A precooled



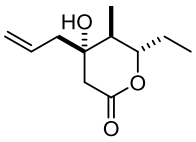

(0 °C) solution of the freshly prepared Soderquist reagent (1*R*)-**R7** (150 mg, 0.596 mmol) in THF (2 mL + 0.5 mL rinse) was slowly added to a cold (0 °C) solution of ß-keto ester **22** (84.6 mg, 0.542 mmol) in THF (3.5 mL) via syringe. After stirring at 0 °C for 4 h, the mixture was diluted with hexanes (15 mL) and *N*,*N*-dimethylethanolamine (53.0 mg, 0.596 mmol) was introduced. The resulting cloudy solution was stirred overnight under reflux. After cooling to ambient temperature, sat. $NH_4Cl$ solution (35 mL) was introduced and the aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (silica gel 60 (15 x 40 µm), hexanes/EtOAc, 2.5:1 to 2:1) to yield the desired isomer (77.3 mg, 72%) as white needles. $[\alpha]_D^{20} = -1.8$ (c = 0.56, $CHCl_3$); $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.70 (dddd, *J* = 17.1, 10.1, 7.5, 7.1 Hz, 1H), 5.02 (dddd, *J* = 10.1, 1.9, 0.9, 0.8 Hz, 1H), 4.95 (ddd, *J* = 17.1, 3.3, 1.4 Hz, 1H), 3.44 (ddd, *J* = 10.2, 7.4, 2.9 Hz, 1H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.18 (dd, *J* = 16.5, 1.1 Hz, 1H), 1.98 (ddq, *J* = 13.9, 6.8, 1.1 Hz, 1H), 1.90 (br s, 1H), 1.78 – 1.71 (m, 1H), 1.55 (dq, *J* = 10.1, 6.9 Hz, 1H), 1.51 – 1.41 (m, 1H), 1.32 – 1.21 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.57 (d, *J* = 6.9 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 168.4, 132.2, 120.2, 82.5, 71.0, 43.1, 42.9, 38.9, 27.0, 10.7, 9.1 ppm; IR (neat): $\tilde{\nu}$ = 3434, 3078, 2974, 2939, 1721, 1640, 1463, 1377, 1247, 1163, 1085, 1042, 1006, 919, 838, 796 cm$^{-1}$; MS (EI) *m/z* (%): 157 (25), 127 (9), 111 (9), 99 (45), 98 (11), 95 (37), 71 (100), 67 (14), 57 (37), 55 (35), 53 (29), 43 (60), 42 (43), 41 (96), 40 (13), 39 (44), 29 (73), 27 (42); HRMS (EI): *m/z*: calcd for $C_{11}H_{18}O_3Na$: 221.1148, found 221.1146.

**(4*R*,5*R*,6*R*)-4-Allyl-6-ethyl-4-hydroxy-5-methyltetrahydro-2*H*-pyran-2-one (*ent*-70).** This



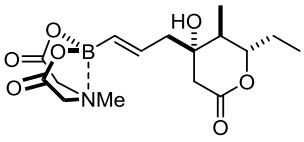
enantiomer was obtained analogously from *ent*-**61** (40.5 mg, 0.161 mmol) as a white solid (22.3 mg, 70%). A crystal suitable for X-ray analysis was obtained by slowly cooling a concentrated solution of the compound in hexanes/$CH_2Cl_2$ (92:8) to −40 °C.

**(4*S*,5*R*,6*R*)-4-Allyl-6-ethyl-4-hydroxy-5-methyltetrahydro-2*H*-pyran-2-one (*epi*-70).** Prepared



analogously from β-keto ester **61** (40.8 mg, 0.262 mmol) and (1*S*)-**R7** as a white solid (45.6.3 mg, 88%). $^1$H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 7.5:1 in favor of *epi*-**70**. A crystal suitable for X-ray analysis was obtained by slowly cooling a concentrated solution of the compound in hexanes/$CH_2Cl_2$ (92:8) to –40 °C. $^1$H NMR (500 MHz, $C_6D_6$): δ = 5.45 (dddd, *J* = 17.1, 9.9, 7.3, 7.3 Hz, 1H), 4.94 (dddd, *J* = 10.1, 1.7, 0.7, 0.7 Hz, 1H), 4.88 (ddd, *J* = 17.0, 3.2, 1.3 Hz, 1H), 4.21 (ddd, *J* = 10.5, 7.7, 2.8 Hz, 1H), 2.48 (d, *J* = 17.3 Hz, 1H), 2.38 (br s, 1H), 2.21 (d, *J* = 17.3 Hz, 1H), 2.00 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.90 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.59 – 1.50 (m, 1H), 1.19 – 1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.8, 131.6, 120.6, 82.3, 71.1, 44.4, 42.3, 38.9, 25.8, 9.6, 8.6 ppm; IR (film): $\tilde{\nu}$ = 3429, 2978, 2935, 1710, 1460, 1442, 1385, 1326, 1261, 1107, 1008, 987, 919, 702 cm$^{-1}$; MS (EI) *m/z* (%): 157 (26), 127 (9), 111 (9), 99 (45), 98 (12), 95 (37), 71 (100), 67 (16), 57 (37), 55 (30), 53 (29), 43 (60), 42 (43), 41 (96), 40 (13), 39 (44), 29 (73), 27 (43); HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{18}O_3Na$: 221.1148, found 221.1146.

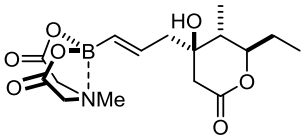
**(−)-MIDA ester 78.** A flame-dried Schlenk flask was charged with the ruthenium carbene complex



**C3** (25.8 mg, 30.4 µmol) and the vinylboronic acid derivative **R8** (116.6 mg, 0.637 mmol), evacuated and backfilled with Ar (3 cycles). A solution of the homoallylic alcohol **70** (120.4 mg, 0.607 mmol) in $CH_2Cl_2$ (6 mL) was then introduced and the flask fitted with a reflux condenser and an Argon bubbler, allowing the generated ethane to evaporate. The reaction mixture was heated to 40 °C for 16 h. After cooling to room temperature, DMSO (300 µL) was added and the mixture stirred for 8 h. It was then concentrated under reduced pressure and the resulting residue purified by flash chromatography (*tert*-butyl methyl ether/MeCN, 3:1) to yield the title compound as a white solid (174 mg, 81%). $[\alpha]_D^{20}$ = −4.4 (c = 0.88, MeCN); $^1$H NMR (400 MHz, [D$_6$]-DMSO): δ = 6.05 (ddd, *J* = 17.7, 8.1, 5.6 Hz, 1H), 5.44 (d, *J* = 17.7 Hz, 1H), 4.91 (s, 1H), 4.22 (d, *J* = 7.3 Hz, 1H), 4.17 (d, *J* = 7.4 Hz, 1H), 3.99 – 3.90 (m, 3H), 2.75 (s, 3H), 2.61 (d, *J* = 16.3 Hz, 1H), 2.33 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.25 (d, *J* =16.4 Hz, 1H), 2.08 (dd, *J* = 13.9, 8.4 Hz, 1H), 1.81 – 1.69 (m, 2H), 1.57 – 1.47 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, [D$_6$]-DMSO): δ = 170.3, 169.2, 169.1, 139.3, 130.4 (br), 82.8, 70.7, 61.3, 61.2, 46.7, 43.0, 42.4, 41.0, 26.2, 11.0, 9.0 ppm; IR (film): $\tilde{\nu}$ = 3504,

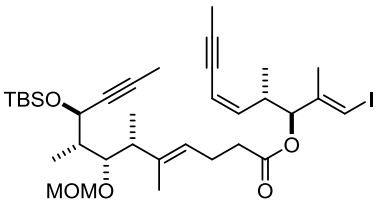
2953, 1745, 1716, 1639, 1464, 1375, 1286, 1247, 1223, 1118, 1029, 1001, 987, 958, 893, 859, 841, 779, 723 $cm^{-1}$; MS (ESI) *m/z 376.2* [$M^+$+Na]; HRMS (ESIpos): *m/z*: calcd for $C_{16}H_{24}BNO_7Na$: 376.1552, found 376.1543.

**(+)-MIDA ester** *ent*-**78**. This enantiomer was obtained analogously from *ent*-**70** (15 mg, 75.6 µmol) as a white solid (22.4 mg, 84%).




### 5.2.4 Fragment assembly and endgame.

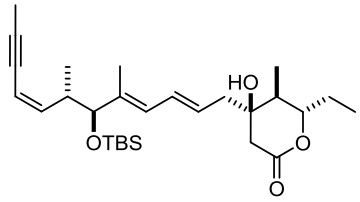
**(6*R*,7*S*,8*S*,9*R*,*E*)-((1*E*,3*S*,4*S*,5*Z*)-1-Iodo-2,4-dimethylnona-1,5-dien-7-yn-3-yl) 9-(*tert*-butyl-dimethylsilyloxy)-7-(methoxymethoxy)-5,6,8-trimethyldodec-4-en-10-ynoate (79).** EDCI·HCl (83.1 mg, 0.433 mmol) was added to a solution of alcohol **57** (114 mg, 0.393 mmol) in $CH_2Cl_2$ (2.8 mL) and the resulting mixture cooled to 0 °C. Next, DMAP (52.9 mg, 0.433 mmol) was introduced in three portions and the mixture stirred for 10 min before a solution of acid **43** (185 mg, 0.433 mmol) in $CH_2Cl_2$ (2.5 mL) was slowly added. Stirring was continued for 30 min at 0 °C before the ice bath was removed. After 5 h at ambient temperature, the mixture was poured into brine (10 mL) and diluted with $CH_2Cl_2$ (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 8 mL), the combined organic phases were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 29:1 to 19:1) to give the title compound as a colorless oil (244 mg, 89%). $[\alpha]_D^{20}$ = +80.9 (c = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.26 (s, 1H), 5.56 (dd, *J* = 10.1, 10.0 Hz, 1H), 5.43 (dq, *J* = 10.7, 2.2 Hz, 1H), 5.19 (d, *J* = 7.4 Hz, 1H), 5.16 – 5.10 (br t, 1H), 4.56 – 4.52 (m, 1H), 4.51 (d, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 6.2 Hz, 1H), 3.60 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.32 (s, 3H), 3.12 (ddq, *J* = 9.3, 7.1, 7.1 Hz, 1H), 2.37 – 2.27 (m, 4H), 2.27 – 2.19 (m, 1H), 1.96 (d, *J* = 2.2 Hz, 3H), 1.83 (d, *J* = 0.8 Hz, 3H), 1.80 (d, *J* = 2.1 Hz, 3H), 1.79 – 1.73 (m, 1H), 1.63 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.2, 144.6, 142.1, 139.0, 123.0, 111.0, 98.0, 90.3, 81.2, 80.8, 80.7, 80.4, 80.1, 76.1, 63.3, 56.0, 44.4, 42.8, 37.1, 34.3, 25.9, 23.7, 20.5, 18.2, 16.8, 15.8, 12.5, 11.1, 4.4, 3.5, −4.0, −5.0 ppm; IR (film): $\tilde{\nu}$ = 2955, 2928, 2856, 1738, 1618, 1461, 1376, 1248, 1142, 1117, 1091, 1075, 1061, 1031, 938, 920, 833, 775, 675 $cm^{-1}$; MS (EI) *m/z* (%): 458 (5), 283 (28), 185 (16), 184 (16), 183 (100), 174 (5), 169 (26), 163 (5), 159 (6), 157 (15), 153 (12), 146 (40), 145 (17), 137 (11), 131(29), 115 (7), 97 (6), 93 (8), 91 (8), 89 (16), 82 (8), 73 (29), 45 (39); HRMS (EI): *m/z*: calcd for $C_{34}H_{55}IO_5SiNa$: 721.2756, found 721.2755.



**Cycloenyne 80.** *All glassware used for the ring closing alkyne metathesis reaction was flame-dried under vacuum and backfilled with Argon after cooling to room temperature (3 cycles). All employed solvents were freshly distilled (toluene from Na/K, $CH_2Cl_2$ from $CaH_2$), stored over 4 Å MS and degassed by 4 freeze-pump-thaw cycles prior to use.* A stock solution of activated catalyst was prepared as follows: $CH_2Cl_2$ (205 µL, 3.26 mmol) was added to a solution of complex **C6** (80.0 mg, 0.128 mmol) in toluene (6.4 mL). The resulting brown solution was stirred for 30 min to give a 0.194 M stock solution of the active catalyst.

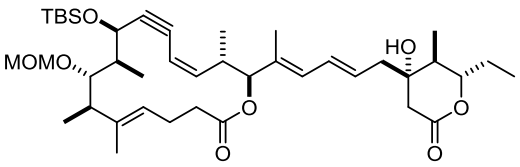
Diyne **79** (350 mg, 0.501 mmol) was azeotropically dried with toluene (3 x 3 mL). It was then transferred as a toluene solution to a two-necked round-bottom flask equipped with a reflux condenser and septum. Additional toluene was added to reach a total volume of 350 mL. The solution was heated to 100 °C and an aliquot of the activated catalyst solution (0.773 mL, 0.150 mmol) was introduced via syringe. The reaction was stirred at 100 °C for 7 h before a second aliquot of the catalyst solution (0.258 mL, 50.1 µmol) was added. Stirring was continued at 100 °C for further 12 h. After reaching ambient temperature, the mixture was diluted with $Et_2O$ (300 mL) to slowly form a brown precipitate, which was filtered off through a short pad of $SiO_2$, eluting with $Et_2O$ (350 mL). The pale brown filtrate was evaporated and the residue purified by flash chromatography (hexanes/EtOAc, 39:1 to 19:1) to provide a mixture of *N-tert*-butyl-3,5-dimethylaniline and the desired product. The amine was removed at 60 °C under high vacuum overnight to leave the desired compound **80** as a pale yellow oil (232.6 mg, 72%). $[\alpha]_D^{20}$ = +83.0 (c = 0.57, hexanes); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 1.0 Hz, 1H), 5.63 (dd, *J* = 10.6, 9.6 Hz, 1H), 5.54 (dd, *J* = 10.6, 1.6 Hz, 1H), 5.36 – 5.30 (m, 1H), 5.24 (d, *J* = 9.6 Hz, 1H); 4.73 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.37 (dd, *J* = 9.1, 1.1 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.39 (s, 3H), 3.17 (dddd, *J* = 16.5, 9.7, 6.9, 6.8 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.45 – 2.36 (m, 1H), 2.35 – 2.19 (m, 3H), 2.07 (dddd, *J* = 15.5, 7.2, 7.2, 0.6 Hz, 1H), 1.83 (d, *J* = 1.0 Hz, 3H), 1.48 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.9, 144.6, 144.3, 137.4, 126.4, 110.3, 98.9, 96.9, 87.0, 82.5, 82.0, 80.6, 63.9, 56.0, 46.0, 42.0, 37.7, 34.6, 25.8, 22.5, 19.5, 18.2, 17.4, 16.6, 16.3, 12.1, −4.5, −5.1 ppm; IR (film): $\tilde{\nu}$ = 2957, 2929, 2856, 1732, 1617, 1462, 1377, 1361, 1257, 1143, 1058, 1031, 990, 932, 858, 835, 801, 775, 753, 672 cm$^{-1}$; MS (ESIpos) *m/z* (%): 683 (M+K, 30), 667 (M+Na, 100); HRMS (EI): *m/z*: calcd for $C_{30}H_{49}IO_5SiNa$: 667.2286, found 667.2290.

**Suzuki coupling model compound 84.** A flame-dried Schlenck flask was charged with solutions of




MIDA-boronate *epi*-**78** (5.0 mg, 14.2 µmol) and vinyl iodide **56** (4.8 mg, 11.9 µmol) in $CH_2Cl_2$. The solvent was evaporated by application of an Ar flow and the flask subjected to high-vacuum/Ar cycles (3x). A degassed mixture of THF and water (3:1, 0.12 mL) was then introduced and the mixture stirred until all substrates were completely dissolved. [$Pd(PPh_3)_4$] (2.8 mg, 2.4 µmol) was then added as a solid, followed by Tl(OEt) (4.8 µL, 6.0 µmol) via syringe causing the precipitation of a yellow solid. After 105 min, the reaction was judged complete by TLC analysis and was quenched with aqueous HCl (0.5 M, 2 mL). The mixture was transferred to a round-bottom flask (10 mL), rinsed with MTBE (2 mL) and stirred vigorously overnight. It was then diluted with $H_2O$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9:1 to 4:1) to give the desired product as a pale-brown oil (4.6 mg, 81%). $^1$H-NMR (400 MHz, $CD_2Cl_2$) δ = 6.39 (ddt, *J* = 15.0, 10.9, 1.3 Hz, 1H), 5.95 (d, *J* = 10.9 Hz, 1H), 5.71 (t, *J* = 10.2 Hz, 1H), 5.56 (dt, *J* = 15.2, 7.7 Hz, 1H), 5.38 (dq, *J* = 10.6, 2.4 Hz, 1H), 4.26 (ddd, *J* = 10.3, 7.3, 2.9 Hz, 1H), 3.87 (d, *J* = 5.8 Hz, 1H), 2.94 (dq, *J* = 8.9, 6.6 Hz, 1H), 2.53 (s, 2H), 2.36 (d, *J* = 7.7 Hz, 2H), 1.93 (d, *J* = 2.3 Hz, 3H), 1.86 (dqd, *J* = 14.9, 7.4, 3.0 Hz, 1H), 1.74 – 1.71 (m, 4H), 1.68 (dd, *J* = 6.8, 3.7 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.04 – 0.95 (m, 6H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), −0.04 (s, 3H) ppm; $^{13}$C-NMR (100 MHz, $CD_2Cl_2$) δ = 170.6, 145.6, 140.1, 132.2, 125.8, 125.7, 109.7, 89.7, 82.9, 82.0, 77.2, 72.5, 44.1, 43.1, 40.2, 39.6, 26.6, 26.2, 18.7, 17.7, 13.3, 10.2, 9.1, 4.6, −4.3, −4.8 ppm; IR (film): $\tilde{\nu}$ = 3425, 2956, 2929, 2856, 1714, 1471, 1461, 1387, 1323, 1250, 1119, 1071, 1007, 986, 971, 937, 889, 859, 836, 775, 680 cm$^{-1}$; MS (ESIpos) *m/z* (%): 497.3 (100); HRMS (EI): *m/z*: calcd. for $C_{28}H_{46}O_4Si_1Na$: 497.3058, found 497.3059.

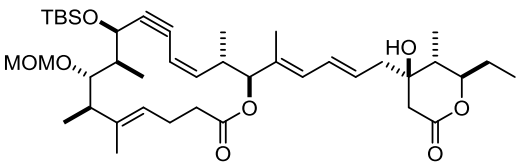
**Compound 86**. A solution of compound **80** (129 mg, 0.200 mmol) in THF/$H_2O$ (3:1, 2.4 mL,




degassed by three freeze-pump-thaw cycles) was added to a degassed solution of MIDA ester (−)-*ent*-**28** (85.2 mg, 0.241 mmol) and $Pd(PPh_3)_4$ (46.5 mg, 40.2 µmol) in degassed THF/$H_2O$ (3:1 1.0 mL). Thallium ethoxide (85.0 µL, 1.21 mmol) was added via syringe to the yellow mixture causing a yellow solid to precipitate from the reaction mixture, which was stirred for 2.5 h at room temperature. It was next diluted with *tert*-butyl methyl ether (10 mL) and transferred to a round-bottom flask equipped with a stirbar. Aqueous HCl (0.5 M, 11 mL) was introduced (pH ~ 2) and the mixture stirred for 2.5 h. $H_2O$ (10 mL) was added and the aqueous phase was extracted with *tert*-butyl methyl ether (4 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over $Na_2SO_4$ and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 2.5:1 to 2:1) to give the title compound as a white solid (79 mg, 55%). $[\alpha]_D^{20}$= +117.3 (c = 0.88, $CHCl_3$); $^1$H NMR (500

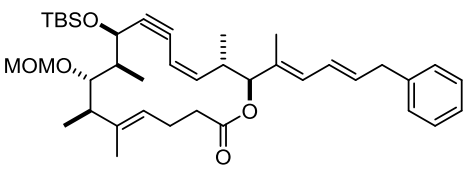
MHz, $CDCl_3$): δ = 6.31 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.01 (d, *J* = 11.0 Hz, 1H), 5.70 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 5.65 (dd, *J* = 10.3, 10.2 Hz, 1H), 5.52 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.37 – 5.32 (m, 1H), 5.07 (d, *J* = 9.8 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 3.92 (ddd, *J* = 10.0, 7.3, 2.9 Hz, 1H), 3.41 (br d, *J* = 7.6 Hz, 1H), 3.38 (s, 3H), 3.24 – 3.13 (m, 1H), 3.00 – 2.80 (br s, 1H), 2.77 (d, *J* = 16.7 Hz, 1H), 2.45 – 2.37 (m, 2H), 2.35 (d, *J* = 16.7 Hz, 1H), 2.33 – 2.24 (m, 2H), 2.23 – 2.12 (m, 2H), 2.08 (ddd, *J* = 15.4, 7.6, 7.5 Hz, 1H), 1.90 (ddd, *J* = 16.8, 6.9, 6.9 Hz, 1H), 1.83 (ddq, *J* = 14.7, 7.3, 2.8 Hz, 1H), 1.73 (s, 3H), 1.60 (ddq, , *J* = 14.7 Hz, 7.3, 7.3 Hz, 1H), 1.45 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.02 – 0.97 (m, 9H), 0.87 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 172.2, 170.2, 145.1, 137.0, 134.0, 131.4, 128.9, 127.4, 126.7, 109.8, 98.9, 96.5, 87.2, 83.6, 82.5, 82.2, 71.5, 63.9, 56.0, 46.1, 42.7, 42.6, 41.8, 37.8, 37.6, 34.6, 26.8, 25.7, 22.4, 18.1, 17.4, 16.8, 16.5, 12.1, 11.9, 11.2, 8.9, −4.5, −5.2 ppm; IR (film): $\tilde{\nu}$ = 3448, 2961, 2930, 2857, 1724, 1462, 1377, 1248, 1144, 1058, 1032, 1004, 983, 919, 858, 835, 750, 667 $cm^{-1}$; MS (EI) *m/z* (%): 714 (5), 696 (4), 657 (4), 425 (5), 381 (13), 357 (8), 325 (7), 299 (9), 267 (12), 249 (27), 222 (72), 173 (11), 171 (14), 169 (68), 159 (11), 157 (16), 145 (13), 143 (11), 137 (18), 133 (18), 119 (17), 107 (16), 95 (25), 89 (36), 81 (20), 75 (41), 73 (100), 72 (24); HRMS (EI): *m/z*: calcd for $C_{41}H_{66}O_8SiNa$: 737.4412, found 737.4419.

**Isomeric cross-coupling adduct 103.** This diastereomer was obtained analogously from vinyl iodide

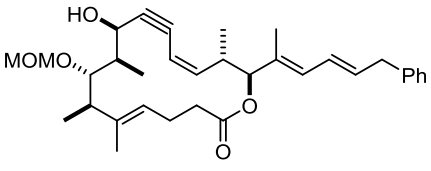



**80** (54 mg, 83.8 µmol) as an off-white solid (30.3 mg, 56%) using MIDA ester (+)-**28.** $[\alpha]_D^{20}$ = +206.5 (c = 0.94, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): 6.35 (dd, *J* = 15.1, 10.8 Hz, 1H), 6.04 (dd, *J* = 10.8, 0.8 Hz, 1H), 5.70 (ddd, *J* = 15.4, 7.7, 7.7 Hz, 1H), 5.66 (dd, *J* = 10.5, 10.4, 1H), 5.53 (dd, *J* = 10.6, 1.5 Hz, 1H), 5.37 (dd, *J* = 6.6, 3.9 Hz, 1H), 5.09 (d, *J* = 9.7 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.36 (dd, *J* = 9.3, 1.1 Hz, 1H), 3.93 (ddd, *J* = 10.2, 7.3, 3.0, 1H), 3.42 (br d, *J* = 7.8 Hz, 1H), 3.39 (s, 3H), 3.20 (ddq, *J* = 10.1, 10.1, 6.8 Hz, 1H), 2.96 (br s, 1H), 2.78 (d, *J* = 16.8 Hz, 1H), 2.41 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.37 (d, *J* = 16.8 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.22 – 2.16 (m, 2H), 2.13 – 2.05 (m, 1H), 1.95 (br s, 1H), 1.92 (dq, *J* = 10.3, 6.9 Hz, 1H), 1.83 (ddq, *J* = 14.7, 7.3, 3.0 Hz, 1H), 1.61 (ddq, *J* = 14.6, 7.3, 7.3 Hz, 1H), 1.46 (s, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.05 – 0.98 (m, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.01 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): 172.2, 170.1, 145.1, 137.2, 134.3, 131.7, 128.8, 127.1, 126.7, 109.9, 99.0, 96.6, 87.2, 83.5, 82.6, 82.2, 71.5, 63.9, 56.0, 46.1, 42.8, 42.5, 41.9, 37.8, 37.6, 34.7, 26.8, 25.8, 22.5, 18.2, 17.4, 16.8, 16.6, 12.1, 12.0, 11.1, 8.9, −4.5, −5.1 ppm; IR (film): $\tilde{\nu}$ = 3465, 2960, 2930, 2857, 1727, 1463, 1389, 1332, 1250, 1144, 1060, 1035, 1005, 985, 918, 859, 837, 776, 755, 733, 669 $cm^{-1}$; MS (ESIpos) *m/z* (%): 737.5 (M+Na, 100); HRMS (EI): *m/z*: calcd for $C_{41}H_{66}O_8SiNa$: 737.4412, found 737.4423.

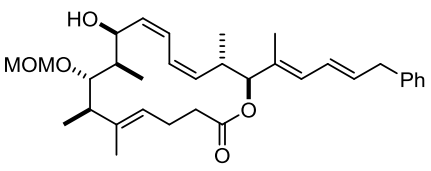
**Analogous cross-coupling product 87.** A schlenck-flask was charged with *trans*-3-phenyl-1-propen-1-ylboronic acid (**R9**) (2.4 mg, 15 µmol) and $Pd(PPh_3)_4$ (1.7 mg, 1.5 µmol), sealed, evacuated and backfilled with Argon (3 cycles). A solution of macrocyclic vinyl iodide **80** (3.8 mg, 5.9 µmol,) in THF/$H_2O$ (9:1, 0.2 mL, degassed by bubbling Ar through the solvent for 15 min) was added to the reaction mixture, followed by the addition of thallium ethoxide (2.1 µL, 29 µmol) via syringe. The resulting yellow suspension was stirred for 1 hour at room temperature before being diluted with EtOAc (2 mL). The mixture was filtered through Celite® and concentrated. The red residue was purified by flash chromatography (Hex/$Et_2O$=9:1) to give the title compound as a white solid (2.1 mg, 56% yield). $^1$H NMR (400 MHz, $C_6D_6$): δ = 7.13 – 7.09 (m, 2H), 7.08 – 7.02 (m, 3H), 6.26 (ddt, *J* = 14.9, 10.9, 1.3 Hz, 1H), 6.12 (d, *J* = 11.0 Hz, 1H), 5.72 (ddd, *J* = 14.7, 7.3, 7.2 Hz, 1H), 5.66 – 5.61 (m, 1H), 5.58 (dd, *J* = 10.4, 10.3 Hz, 1H), 5.42 – 5.38 (m, 2H), 4.69 (d, *J* = 8.6 Hz, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 3.56 – 3.47 (m, 1H), 3.45 – 3.34 (m, 1H), 3.25 – 3.22 (m, 2H), 3.22 (s, 3H), 2.39 – 2.30 (m, 1H), 2.25 – 2.10 (m, 5H), 1.82 (s, 3H), 1.43 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.28 (s, 3H), 0.19 (s, 3H) ppm.




**Propargylic alcohol 88.** To a 0 °C solution of silylether **87** (1.4 mg, 2.2 µmol) was added a solution of TBAF (1.0 M in THF, 4.8 µL, 4.8 µmol) at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C befored being quenched with sat. $NH_4Cl/H_2O$ (1:1, 3 mL), extracted with MTBE (3 x 4 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (Hex/EtOAc=4:1) to give the title compound as a white solid (1.1 mg, 96% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.25 (m, 3H), 7.20 – 7.15 (m, 2H), 6.26 (ddt, *J* = 14.9, 10.9, 1.3 Hz, 1H), 5.92 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.79 (ddd, *J* = 14.8, 7.3, 7.2 Hz, 1H), 5.65 (dd, *J* = 10.2, 9.5 Hz, 1H), 5.53 (d, *J* = 10.9 Hz, 1H), 5.33 (dd, *J* = 6.5, 5.6 Hz, 1H), 5.11 (d, *J* = 5.8 Hz, 1H), 4.95 – 4.91 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 3.47 – 3.41 (m, 3H), 3.41 (s, 3H), 3.11 (d, J = 2.7 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.56 (ddd, *J* = 15.9, 7.3, 7.2 Hz, 1H), 2.43 – 2.17 (m, 4H), 2.00 – 1.92 (m, 1H), 1.70 (s, 3H), 1.54 (s, 3H), 1.18 (d, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H) ppm.



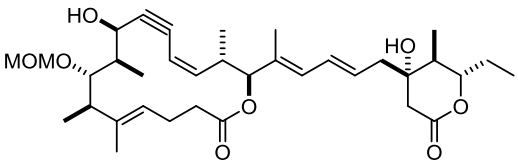

**Allylic alcohol 89.** *Method A:* A solution of propargylic alcohol **88** (0.60 mg, 1.2 µmol) in MeOH/$H_2O$ (1:1, 0.4 mL) was added to freshly prepared Zn(Cu/Ag)[96] (150 mg) via syringe and the resulting grey suspension was heated to 50 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc



(4 mL) and filtered through a short pad of $SiO_2$. The filtrate was dried over $Na_2SO_4$ and concentrated to afforde the title compound as a white solid (0.54 mg, 91%).

*Method B:* A solution of propargylic alcohol **88** (0.49 mg, 0.95µmol) in MeOH/$H_2O$ (1:2, 0.5 mL) was added to a refluxing solution of Rieke zinc[97a] (16.7 mg, 0.256 mmol) in THF (0.3 mL) via syringe and the reaction mixture was stirred at reflux temperature for 14 h. After being cooled to room temperature, the mixture was diluted with EtOAc (4 mL) and filtered through a short pad of silica gel. The filtrate was washed with sat. $NH_4Cl$ solution, sat. $NaHCO_3$ solution and brine (3 mL each), dried over $Na_2SO_4$ and concentrated to give the title compound as a white solid (yield 0.42 mg, 85% yield). $^1$H-NMR (600 MHz, $C_6D_6$) δ = 7.16 – 7.12 (m, 2H), 7.08 – 7.04 (m, 3H), 6.63 (dd, *J* = 11.0 Hz, 1H), 6.33 (dd, *J* = 11.3, 11.3 Hz, 1H), 6.25 (ddt, *J* = 14.9, 10.9, 1.5 Hz, 1H), 6.10 (d, *J* = 10.7 Hz, 1H), 5.86 (dd, *J* = 10.3, 10.0 Hz, 1H), 5.70 (ddd, *J* = 14.7, 7.3, 7.2 Hz, 1H), 5.41 (d, *J* = 10.3 Hz, 1H), 5.41 – 5.31 (m, 3H), 4.36 (d, *J* = 6.6 Hz, 1H), 4.32 (d, *J* = 6.6 Hz, 1H), 3.25 – 3.22 (m, 2H), 3.09 (s, 3H), 3.09 – 3.07 (m, 1H), 2.98 – 2.91 (m, 1H), 2.65 – 2.58 (m, 1H), 2.44 (dd, *J* = 14.1, 13.7 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.96 – 1.83 (m, 2H), 1.69 (s, 3H), 1.36 – 1.26 (m, 1H), 1.24 (d, *J* = 7.3 Hz, 3H), 1.15 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H) ppm; $^{13}$C-NMR (150 MHz, $C_6D_6$) δ = 171.6, 140.2, 136.0, 135.0, 133.2, 132.4, 130.6, 128.9 (2C), 128.7 (2C), 128.4, 127.6, 126.8, 126.4, 124.8, 124.0, 99.5, 82.9, 65.2, 56.0, 48.0, 39.6, 39.3, 35.2, 33.6, 25.6, 22.3, 16.6, 16.5, 12.5, 11.9, 11.2 ppm; MS (ESI) *m/z*: 545.3 ($M^+$+Na). HRMS (ESIpos): *m/z*: calcd for $C_{33}H_{46}O_5Na$: 522.3345, found 522.3347.

**Propargylic alcohol 90.** TBAF (1 M in THF, 0.259 mL, 0.259 mmol) was slowly added to a




suspension of silyl ether **86** (74.2 mg, 0.104 mmol) and activated 4 Å molecular sieves in THF (1.5 mL) at 0 °C. After 1 h, the reaction was quenched with $H_2O$/brine (2:1, 10 mL) and diluted with EtOAc (6 mL). The aqueous layer was extracted with EtOAc (3 x 7 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was quickly purified by flash chromatography (Florisil®, hexanes/EtOAc, 2:1 to 1:2), keeping the contact time with the Florisil® as short as possible. The white solid (53.2 mg, 85%) thus obtained was immediately used in the next step as it was prone to decomposition upon storage. $^1$H NMR (400 MHz, $C_6D_6$): δ = 6.36 (dd, *J* = 14.9, 10.8 Hz, 1H), 6.15 (d, *J* = 10.8 Hz, 1H), 5.73 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.53 – 5.46 (m, 3H), 5.41 – 5.35 (m, 1H), 5.08 (br t, *J* = 2.7 Hz, 1H), 4.41 (s, 2H), 3.52 (ddd, *J* = 10.0, 7.4, 2.8 Hz, 1H), 3.42 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.36 – 3.26 (m, 1H), 3.12 (s, 3H), 3.12 – 3.10 (m, 1H), 2.65 (d, *J* = 16.4 Hz, 1H), 2.56 (dq, *J* = 7.4, 7.3 Hz, 1H), 2.30 – 2.15 (m, 6H), 2.14 – 2.02 (m, 2H), 1.93 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.74 (s, 3H), 1.61 (dd, *J* = 15.9, 9.1, 6.9, 2.2 Hz, 1H), 1.50 (ddq, *J* = 14.6, 7.2, 3.1 Hz, 1H), 1.41 (s, 3H), 1.33 – 1.23 (m, 1H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H) ppm; IR (film): $\tilde{\nu}$ = 3454, 2972, 2932, 1727, 1462, 1379, 1246,

1193, 1151, 1090, 1029, 1022, 986, 844, 759 $cm^{-1}$; HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{52}O_8Na$: 623.3554, found 623.3551.

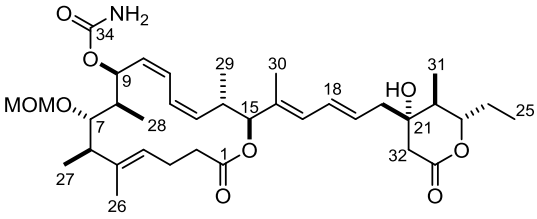
**Isomeric propargylic alcohol 104**. This diastereomer was obtained analogously from **103** (26.5 mg, 37.1 µmol) as a white solid (17.2 mg, 76%). $^1H$ NMR (400 MHz, $C_6D_6$): δ = 6.31 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.13 (d, *J* = 10.9 Hz, 1H), 5.58 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.53 – 5.46 (m, 3H), 5.41 – 5.36 (m, 1H), 5.10 (br t, *J* = 2.5 Hz, 1H), 4.39 (s, 2H), 3.44 (ddd, *J* = 10.2, 7.5, 2.9 Hz, 1H), 3.41 (dd, *J* = 8.7, 2.7 Hz, 1H), 3.37 – 3.27 (m, 1H), 3.10 (s, 3H), 2.95 (d, *J* = 2.9°Hz, 1H), 2.61 – 2.52 (m, 1H), 2.56 (d, *J* = 16.3 Hz, 1H), 2.29 – 2.15 (m, 3H), 2.15 – 2.09 (m, 1H), 2.05 (d, *J* = 16.2 Hz, 1H), 2.09 – 2.00 (m, 2H), 1.84 (dd, *J* = 14.1, 7.6 Hz, 1H), 1.71 (s, 3H), 1.51 – 1.41 (m, 2H), 1.40 (s, 3H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.24 (ddq, *J* = 14.5, 7.3, 7.2 Hz, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (t, 3H, *J* = 7.3 Hz), 0.58 ppm (d, 3H, *J* = 6.8 Hz); IR (film): $\tilde{\nu}$ = 3457, 2970, 2934, 1728, 1455, 1377, 1246, 1189, 1149, 1091, 1022, 987, 843, 755 $cm^{-1}$; HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{52}O_8Na$: 623.3554, found 623.3553.

**Cyclodiene 91.** A solution of propargyl alcohol **90** (48.2 mg, 80.2 µmol) in THF (0.6 mL) was added to a suspension of freshly prepared Zn(Cu/Ag)[245] (1.8 g) in degassed MeOH/$H_2O$ (1:1, 1.6 mL) and the resulting mixture was stirred for 18 h at 50 °C. After cooling to room temperature, the mixture was diluted with EtOAc (8 mL) and filtered through a short pad of Celite®, which was carefully rinsed with EtOAc (180 mL) and EtOH (20 mL). The combined filtrates were concentrated under reduced pressure to ca. 1/10 of the original volume and then washed with brine/$H_2O$ (1:1, 15 mL). The aqueous phase was extracted with EtOAc (2 x 15 mL), the combined organic layers were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 2:1 to 1:1) to give the title compound as a white solid (43.1 mg, 89%). $[\alpha]_D^{20}$ = −72.0 (c = 0.66, $CH_2Cl_2$); $^1H$ NMR (600 MHz, $CD_2Cl_2$): see Table 5.1; $^{13}C$ NMR (150 MHz, $CD_2Cl_2$): see Table 5.1; IR (film): $\tilde{\nu}$ = 3447, 2966, 2932, 1729, 1456, 1415, 1368, 1243, 1206, 1147, 1089, 1020, 985, 918, 863, 783, 748, 736, 700 $cm^{-1}$; HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{54}O_8Na$: 625.3711, found 625.3709.

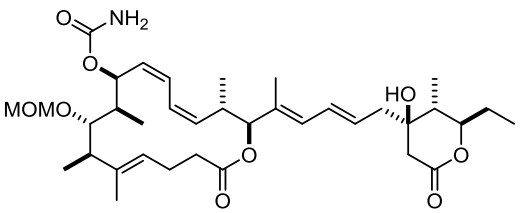
**Isomeric bis-diene 105**. This diastereomer was obtained analogously from **104** (14.0 mg, 24.1 µmol) as a white solid (11.7 mg, 81%). $[\alpha]_D^{20}$ = −40.1 (c = 0.76, $CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$): δ = 6.45 (dd, 1H, *J* = 11.3, 11.2 Hz), 6.40 (dd, 1H, *J* = 15.0, 10.9 Hz), 6.29 (dd, 1H, *J* = 11.3, 11.3 Hz), 6.10 (d, 1H,

*J* = 11.0 Hz), 5.76 (ddd, 1H, *J* = 15.1, 7.6, 7.6 Hz), 5.57 (dd, 1H, *J* = 10.6, 10.3 Hz), 5.29 (d, 1H, *J* = 10.7, 10.5 Hz), 5.15 – 5.10 (m, 1H), 5.09 (d, 1H, *J* = 10.4 Hz), 5.04 (d, 1H, *J* = 10.1 Hz), 4.73 (d, 1H, *J* = 6.3 Hz), 4.64 (d, 1H, *J* = 6.3 Hz), 3.91 (ddd, 1H, *J* = 10.0, 7.3, 2.9 Hz), 3.41 (s, 3H), 3.35 (d, 1H, *J* = 10.4 Hz), 3.04 – 2.94 (m, 1H), 2.90 – 2.80 (br s, 1H), 2.73 (d, 1H, *J* = 16.6 Hz), 2.62 – 2.54 (m, 1H), 2.40 (d, 1H, *J* = 14.2, 7.9 Hz), 2.36 (d, 1H, *J* = 16.6 Hz), 2.35 – 2.30 (m, 3H), 2.27 – 2.18 (m, 3H), 2.06-2.02 (m, 1H), 1.92 (s, 1H), 1.93 – 1.87 (m, 1H), 1.84 (ddq, *J* = 7.4, 7.4, 2.8 Hz, 1H), 1.80 (s, 3H), 1.64 (ddq, *J* = 14.4, 7.2, 7.1 Hz, 1H), 1.44 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.3 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 0.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.4, 170.2, 137.1, 136.4, 134.1, 132.4, 131.6, 129.7, 128.3, 126.4, 124.5, 124.3, 100.0, 89.4, 83.9, 82.9, 72.1, 65.0, 56.6, 48.1, 43.3, 43.0, 39.1, 38.7, 35.3, 33.8, 27.2, 26.4, 22.4, 16.7, 16.5, 12.1, 11.6, 11.4, 9.2 ppm; IR (film): $\tilde{\nu}$ = 3457, 2966, 2934, 1729, 1455, 1367, 1244, 1147, 1089, 1019, 985, 949, 918, 863, 736 cm$^{-1}$; HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{54}O_8Na$: 625.3711, found 625.3716.

**Allylic carbamate 92.** A solution of trichloroacetyl isocyanate (9.15 µL, 77.2 µmol) was added to a precooled solution (−78 °C) of allylic alcohol **91** (42.3 mg, 70.2 µmol) in $CH_2Cl_2$ (3.0 mL). The mixture was stirred at −78 °C for 2 h, before excess isocyanate was quenched with MeOH (0.3 mL) at this temperature. After warming to ambient temperature and concentration under reduced pressure, the residue was dissolved in $CH_2Cl_2$ (2 mL) and the solution soaked on basic $Al_2O_3$. After 1.5 h, the alumina was loaded onto a short pad of Celite®, which was eluted with EtOAc/EtOH (9:1, 12 mL). The solvent was evaporated and the residue purified by flash chromatography (Florisil®, hexanes/EtOAc, 1:1 to 1:2 to 1:4) to furnish the title compound as a white foam (38.2 mg, 84%). $[\alpha]_D^{20}$ = −66.4 (c = 0.94, $CD_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): see Table 5.2; $^{13}$C NMR (150 MHz, $CD_2Cl_2$): see Table 5.2; IR (film): $\tilde{\nu}$ = 3452, 3365, 2965, 2931, 1723, 1602, 1455, 1376, 1312, 1259, 1209, 1146, 1092, 1058, 1033, 954, 916, 863, 801, 748, 710, 679 cm$^{-1}$; HRMS (ESIpos): *m/z*: calcd for $C_{36}H_{55}NO_9Na$: 668.3780, found 668.3774.




**Isomeric Carbamate 106**. This diastereomer was obtained analogously from **105** (9.0 mg, 15 µmol) as a white foam (6.1 mg, 63%). $[\alpha]_D^{20}$ = −43.7 (c = 0.31, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CD_2Cl_2$): δ = 6.69 (dd, *J* = 10.8, 10.6 Hz, 1H), 6.40 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.32 (dd, *J* = 10.8, 10.6 Hz, 1H), 6.10 (d, *J* = 10.8 Hz, 1H), 5.92 (d, *J* = 9.2 Hz, 1H), 5.76 (ddd, *J* = 15.1, 7.6, 7.6 Hz, 1H), 5.50 (dd, *J* = 5.5 Hz, 1H), 5.36 – 5.33 (m, 1H), 5.11 – 5.08 (m, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.56 – 4.44 (br s, 2H), 3.90 (ddd, *J* = 10.1, 7.4,



2.9 Hz, 1H), 3.38 (s, 3H), 3.30 (d, *J* = 9.8 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.73 (d, *J* = 16.5 Hz, 1H), 2.54 – 2.46 (br s, 1H), 2.40 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.36 (d, *J* = 16.5 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.26 – 2.15 (m, 3H), 2.05 – 1.94 (m, 2H), 1.93 – 1.91 (m, 1H), 1.89 (dq, *J* = 10.5, 7.1 Hz, 1H), 1.84 (ddq, *J* = 7.4, 7.3, 3.1 Hz, 1H), 1.79 (s, 3H), 1.62 (ddq, *J* = 14.7, 7.4, 7.3 Hz, 1H), 1.26 (s, 3H), 1.13 (d, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, $CD_2Cl_2$): δ = 172.3, 170.2, 156.2, 137.3, 136.8, 134.1, 131.7, 129.7, 129.2, 128.1, 126.1, 125.1, 124.9, 98.8, 85.9, 83.7, 82.7, 72.1, 67.3, 56.2, 48.2, 43.1, 42.9, 38.6, 38.6, 34.9, 33.8, 27.1, 22.3, 16.7, 16.7, 13.7, 12.0, 11.6, 11.3, 9.2 ppm; IR (film): $\tilde{\nu}$ = 3441, 3368, 2969, 2931,1729, 1603, 1376, 1208, 1147, 1059, 1035, 917, 747 cm$^{-1}$; MS (ESI) *m/z* (%): 684.4 (100); HRMS (ESIpos): *m/z*: calcd for $C_{36}H_{55}NO_9K$: 684.3508, found 625.3514.

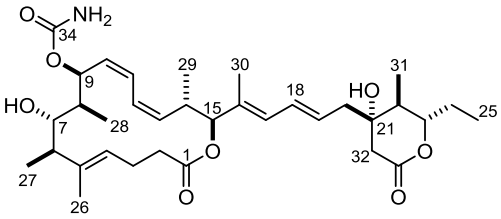
*Table 5.1:* Assignment of $^{1}H$ and $^{13}C$ NMR data of cyclodiene **91**.

| atom n° | $^{1}H$ NMR ($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | integral | m | COSY | *J* (Hz) | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 172.4 | 2, 15 |
| 2a | 2.34 | 1H | m | 2b, 3a | - | 33.7 | 1, 3, 5, 26 |
| 2b | 1.94 | 1H | m | 2a, 3b | - | | |
| 3 | 2.19 | 2H | m | 2a, 2b, 4 | - | 22.2 | 1, 2, 4, 26 |
| 4 | 5.12 | 1H | m | 3a, 3b, 26 | - | 126.3 | 2, 3, 6, 26 |
| 5 | - | - | - | - | - | 137.01 | 3, 6, 7, 26, 27 |
| 6 | 2.59 | 1H | m | 7, 27 | - | 47.9 | 4, 5, 7, 26, 27 |
| 7 | 3.35 | 1H | d | 6 | 10.6 | 89.3 | 6, 9, 27, 28, 28 |
| 8 | 1.66 | 1H | m | 28 | - | 38.9 | 7, 9, 10, 28 |
| 9 | 5.04 | 1H | d | 10 | 9.8 | 65.0 | 7, 8, 11, OH1, 28 |
| 10 | 5.57 | 1H | dd | 9, 11 | 10.8, 9.9 | 132.2 | 8, 9, 12, OH1 |
| 11 | 6.29 | 1H | dd | 10, 12 | 11.4, 10.9 | 124.3 | 9, 12, 13, 14 |
| 12 | 6.45 | 1H | dd | 11, 13 | 11.4, 10.7 | 124.4 | 10, 13, 14, 29 |
| 13 | 5.28 | 1H | dd | 12, 14 | 10.7, 10.4 | 136.3 | 11, 14, 15, 29 |
| 14 | 3.01 | 1H | m | 13, 15, 29 | - | 35.1 | 12, 13, 15, 29 |
| 15 | 5.09 | 1H | d | 14 | 10.4 | 82.9 | 13, 14, 16, 17, 29, 30 |
| 16 | - | - | - | - | - | 133.8 | 14, 15, 17, 18 |
| 17 | 6.09 | 1H | d | 18 | 10.9 | 129.7 | 15, 16, 18, 19, 30 |
| 18 | 6.38 | 1H | dd | 17, 19 | 11.0, 15.0 | 131.4 | 17, 20, 30 |
| 19 | 5.77 | 1H | ddd | 20a, 20b | 15.0, 7.5, 7.5 | 128.5 | 17, 18, 20, 21 |
| 20a | 2.41 | 1H | dd | 19, 20b | 14.0, 7.2 | 38.5 | 18, 19, 21, 22, 32 |
| 20b | 2.19 | 1H | m | 19, 20a | - | | |
| 21 | - | - | - | - | - | 72.0 | 19, 20a, 20b, 22, 32 |
| 22 | 1.88 | 1H | dq | 23, 33 | 10.0, 6.9 | 43.2 | 20, 31, 32, |
| 23 | 3.91 | 1H | ddd | 22, 24a, 24b | 10.0, 7.4, 2.8 | 83.8 | 22, 24, 25 |
| 24a | 1.83 | 1H | ddq | 23, 24b, 25 | 7.4, 7.3, 3.0 | 27.1 | 23, 25 |
| 24b | 1.60 | 1H | ddq | 23, 24b, 25 | 7.4, 7.3, 7.3 | | |
| 25 | 1.00 | 3H | t | 24a, 24b | 7.3 | 9.2 | 24 |
| 26 | 1.43 | 3H | s | 4 | - | 11.3 | 4, 5, 6 |
| 27 | 1.09 | 3H | d | 6 | 6.8 | 16.4 | 5, 7, 28 |
| MOM-$CH_2$ | 4.72 | 1H | d | $CH_2$b | 6.5 | 99.8 | 7, MOM-$CH_3$ |
| | 4.63 | 1H | d | $CH_2$a | 6.5 | | |
| MOM-$CH_3$ | 3.40 | 3H | s | - | - | 56.6 | MOM-$CH_2$ |
| 28 | 1.06 | 3H | d | 8 | 7.3 | 12.0 | 5, 9 |
| 29 | 0.86 | 3H | d | 14 | 6.7 | 16.6 | 13, 14, 15 |
| 30 | 1.79 | 3H | s | 17 | - | 12.0 | 15, 17 |
| 31 | 1.01 | 3H | d | 22 | 6.9 | 11.5 | 21, 22 |
| 32a | 2.72 | 1H | d | 32b | 16.5 | 42.8 | 21, 35 |
| 32b | 2.34 | 1H | d | 32a | 16.6 | | |
| 33 | - | - | - | - | - | 170.3 | 32a, 32b |
| OHa | 2.91 | 1H | br s | | | | |
| OHb | 2.23 | 1H | br s | | | | |

*Table 5.2:* Assignment of $^{1}H$ and $^{13}C$ NMR data of the allylic carbamate **92**.

| atom n° | $^{1}H$ NMR($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | integral | m | COSY | *J* (Hz) | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 172.3 | 2, 15 |
| 2a | 2.27 - 2.33 | 1H | m | 2b, 3a | - | 33.8 | 1, 4, 5, 26 |
| 2b | 1.93 - 2.02 | 1H | m | 2a, 3b | - | | |
| 3 | 2.18 - 2.23 | 2H | m | 2a, 2b, 4 | - | 22.3 | 1 |
| 4 | 5.05 - 5.11 | 1H | m | 3a, 3b, 26 | - | 126.1 | 6 |
| 5 | - | - | - | - | - | 137.3 | 3, 26, 27 |
| 6 | 2.45 - 2.55 | 1H | m | 7, 27 | - | 48.2 | 6, 26, 27 |
| 7 | 3.30 | 1H | d | 6 | 9.9 | 85.9 | 9, 27, 28 |
| 8 | 1.72 - 1.79 | 1H | br m | 30 | - | 38.6 | 30 |
| 9 | 5.92 | 1H | br d | 10 | 9.3 | 67.3 | 7, 11, 12, 28 |
| 10 | 5.50 | 1H | br dd | 9, 11 | 9.3, 10.0 | 129.2 | 12 |
| 11 | 6.32 | 1H | br dd | 10, 12 | 10.1, 11.1 | 125.1 | 9, 13, 15 |
| 12 | 6.68 | 1H | br dd | 11, 13 | 10.7, 11.0 | 124.9 | 10, 14 |
| 13 | 5.29 - 5.36 | 1H | m | 12, 14 | - | 136.8 | 11, 14, 15, 29 |
| 14 | 2.95 - 3.03 | 1H | m | 13, 15, 32 | - | 34.9 | 12, 13, 15, 29 |
| 15 | 5.08 | 1H | d | 14 | 10.3 | 82.7 | 13, 14, 16, 17, 29, 30 |
| 16 | - | - | - | - | - | 133.9 | 14, 15, 17, 18, 19, 30 |
| 17 | 6.10 | 1H | d | 18 | 10.9 | 129.8 | 15, 16, 17, 18, 19, 30 |
| 18 | 6.39 | 1H | dd | 17, 19 | 15.1,10.9 | 131.5 | 17, 20, 30 |
| 19 | 5.77 | 1H | ddd | 18, 20a, 20b | 15.1, 7.6, 7.6 | 128.3 | 17, 20, 21, 30 |
| 20a | 2.41 | 1H | dd | 19, 20b | 14.0, 7.3 | 38.6 | 18, 19, 21, 22, 32 |
| 20b | 2.19 - 2.22 | 1H | m | 19, 20a | - | | |
| 21 | - | - | - | - | - | 72.1 | 19, 20, 22, 314, 32 |
| 22 | 1.89 | 1H | dq | 23, 34 | 9.9, 6.8 | 43.1 | 20, 34, 32 |
| 23 | 3.91 | 1H | ddd | 22, 24a, 24b | 10.1, 7.4, 2.9 | 83.8 | 22, 24, 25, 31 |
| 24a | 1.84 | 1H | ddq | 23, 24b, 25 | 7.4, 7.3, 2.8 | 27.1 | 23, 25 |
| 24b | 1.62 | 1H | ddq | 23, 24b, 25 | 7.4, 7.3, 7.3 | | |
| 25 | 1.00 | 3H | t | 24a, 24b | 7.4 | 9.2 | 24 |
| 26 | 1.43 | 3H | br s | - | - | 11.3 | 2, 6, 7 |
| 27 | 1.08 | 3H | d | 6 | 6.6 | 16.7 | 5, 6, 7 |
| MOM-$CH_2$ | 4.70 | 1H | d | 28b | 6.7 | 98.8 | MOM-$CH_3$ |
| | 4.58 | 1H | d | 28a | 6.7 | | |
| MOM-$CH_3$ | 3.38 | 3H | s | - | - | 56.2 | MOM-$CH_2$ |
| 28 | 1.13 | 3H | d | 8 | 7.1 | 13.7 | 8, 27 |
| 29 | 0.86 | 3H | d | 14 | 6.6 | 16.6 | 13, 14, 15 |
| 30 | 1.79 | 3H | d | 17 | 0.7 | 12.0 | 15, 16, 17, 19 |
| 31 | 1.01 | 3H | d | 22 | 7.1 | 11.6 | 21, 22 |
| 32a | 2.73 | 1H | d | 32b | 16.5 | 42.8 | 21, 33 |
| 32b | 2.35 | 1H | dd | 32a | 16.6, 0.3 | | |
| 33 | - | - | - | - | - | 170.3 | 32a, 32b |
| 34 | - | - | - | - | - | 156.3 | 9 |
| $NH_2$ | 4.51 - 4.66 | 2H | br s | - | - | - | - |
| OH | 1.66 - 1.69 | 1H | br s | - | - | - | - |

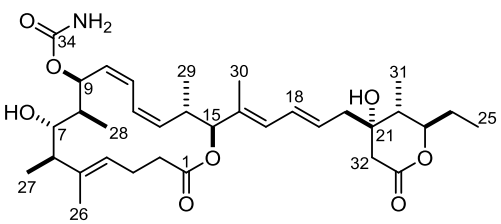
**Leiodermatolide (1).** A solution of compound **33** (9.0 mg, 13.9 µmol) in $CH_2Cl_2$ (1.6 mL) was cooled



to −90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared $Me_2BBr$[238] (0.5 M in $CH_2Cl_2$, 30.6 µL, 15.3 µmol) was carefully added via the cold wall of the flask. The mixture was allowed to reach −78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of $Me_2BBr$ (0.5 M, 30.6 µL, 15.3 µmol) was introduced. After additional 1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 10 mL) and the flask was rinsed with THF (2 x 0.7 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 1:2.5) to give the title compound as a white solid (5.1 mg, 61%). $[\alpha]_D^{24}$ = –74.3 (c = 0.41, MeOH); $^1$H NMR (600 MHz, $CD_2Cl_2$, 4.8 mg in 0.3 mL $CD_2Cl_2$): δ = 6.53 (dd, *J* = 11.7, 11.3 Hz, 1H), 6.39 (dd, *J* = 15.3, 10.7 Hz, 1H), 6.37 (dd, *J* = 11.3, 11.2, 1H), 6.10 (d, *J* = 10.9 Hz, 1H), 5.89 (d, *J* = 10.1 Hz, 1H), 5.77 (ddd, *J* = 15.1, 7.6, 7.6 Hz, 1H), 5.53 (dd, *J* = 10.4, 10.4 Hz, 1H), 5.35 (dd, *J* = 10.5, 10.4°Hz, 1H), 5.09 (m, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.84 – 4.63 (br s, 2H), 3.91 (ddd, *J* = 10.1, 7.4, 2.9 Hz, 1H), 3.26 (br t, 1H), 2.97 (ddq, *J* = 10.1, 10.1, 6.7 Hz, 1H), 2.73 (d, *J* = 16.5 Hz, 1H), 2.46 (dq, *J* = 11.2, 5.8 Hz, 1H), 2.42 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.35 (dd, *J* = 16.6, 0.9 Hz, 1H), 2.31 (ddd, *J* = 16.7, 5.8, 3.0 Hz, 1H), 2.21 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.27 – 2.17 (m, 3H), 2.13 – 2.06 (br s, 1H), 1.99 (ddd, *J* = 16.7, 10.6, 3.6 Hz, 1H), 1.89 (dq, *J* = 10.3, 7.0 Hz, 1H), 1.83 (ddq, *J* = 7.4, 7.3, 3.1 Hz, 1H), 1.79 (d, *J* = 0.9 Hz, 3H), 1.74 (q, *J* = 7.2 Hz, 1H), 1.62 (ddq, *J* = 14.7, 7.4, 7.3 Hz, 1H), 1.42 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = .6.8 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, $CD_2Cl_2$, 4.8 mg in 0.3 mL): δ = 172.2, 170.3, 157.4, 137.6, 137.2, 133.8, 131.5, 129.8, 128.5, 128.4, 126.2, 125.6, 124.1, 83.8, 82.5, 78.2, 72.1, 67.6, 48.5, 43.1, 42.8, 39.3, 38.6, 35.0, 33.7, 27.1, 22.2, 16.6, 16.5, 12.5, 12.0, 11.6, 11.3, 9.2 ppm; IR (film): $\tilde{\nu}$ = 3360, 2963, 2924, 1708, 1605, 1455, 1375, 1312, 1246, 1207, 1148, 1082, 1056, 1040, 986, 949, 915, 778, 745 cm$^{-1}$; MS (ESI) *m/z* (%): 624.4 (100); HRMS (ESIpos): *m/z*: calcd for $C_{34}H_{51}NO_8Na$: 624.3507, found 624.3513.

For an assignment of $^1$H and $^{13}$C NMR data, see table 5.3.

**Leiodermatolide isomer 2.** Prepared analogously from compound **106** (3.6 mg, 5.6 µmol) as a white



solid (0.6 mg). $[\alpha]_D^{24}$= –58 (c = 0.09, MeOH); $^1$H NMR (600 MHz, $CD_2Cl_2$): δ = see table 5.4; $^{13}$C NMR (150 MHz, $CD_2Cl_2$): δ = see table 5.4; MS (ESI) *m/z* (%): 624.4 (100); HRMS (ESIpos): *m/z*: calcd. for $C_{34}H_{51}NO_8Na$ [$M^+$+Na]: 624.35069, found 624.35155.

*Table 5.3:* Assignment of $^{1}H$ and $^{13}C$ NMR data of leiodermatolide (**1**), recorded with 0.8 mg in 0.3 mL $CD_2Cl_2$.

| atom n° | $^{1}H$ NMR ($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | Integral | m | COSY | *J* (Hz) | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 172.2 | 2, 3, 15 |
| 2a | 2.31 | 1H | ddd | 2b, 3 | 16.7, n.d. | 33.7 | 3, 4, 26 |
| 2b | 1.99 | 1H | ddd | 2a, 3 | 16.7, n.d. | | |
| 3 | 2.20 | 2H | m | 2, 4, 26 | - | 22.2 | 2, 4, 5, 26 |
| 4 | 5.09 | 1H | ddq | 3, 26 | 9.9, 5.5, 1.6 | 125.6 | 2, 3, 5, 6, 26 |
| 5 | - | - | - | - | - | 137.2 | 3, 4, 6, 26, 27 |
| 6 | 2.46 | 1H | dq | 7, 27 | 10.5, 6.7 | 48.5 | 4, 7, 25, 26, 27 |
| 7 | 3.26 | 1H | br t | OH, 6, 8 | 9.9 | 78.2 | 6, 8, 9, 28 |
| 8 | 1.74 | 1H | qt | 7, 27, 28 | 7.4, n.d. | 39.3 | 7, 10, 28 |
| 9 | 5.89 | 1H | d | 10 | 10.0 | 67.6 | 7, 28, 11 |
| 10 | 5.53 | 1H | ddt | 9, 11 | 10.7, 10.0, 1.4 | 128.5 | 9, 11, 12, 13 |
| 11 | 6.38 | 1H | ddt | 10, 12 | 12.0, 10.9 | 126.2 | 9, 10, 12, 13 |
| 12 | 6.53 | 1H | ddt | 11, 13 | 11.8, 11.0, 1.0 | 124.4 | 10, 11, 13, 14 |
| 13 | 5.35 | 1H | ddt | 12, 14 | 10.8, 10.2, 1.4 | 137.6 | 11, 12, 14, 15, 29 |
| 14 | 2.98 | 1H | tq | 13, 15, 29 | 10.2, 6.7 | 35.0 | 12, 13, 15, 29, 30 |
| 15 | 5.07 | 1H | d | 14 | 10.3 | 82.5 | 12, 13, 14, 17, 29, 30 |
| 16 | - | - | - | - | - | 134.0 | 14, 15, 17, 18, 30 |
| 17 | 6.10 | 1H | dq | 18, 30 | 10.9, 1.4 | 129.7 | 15, 16, 18, 19, 30 |
| 18 | 6.40 | 1H | ddt | 17,19, 20 | 15.1, 10.9, 1.3 | 131.7 | 16, 17, 20, 30 |
| 19 | 5.76 | 1H | dt | 18, 20 | 15.0, 7.6 | 128.2 | 17, 20, 30 |
| 20a | 2.41 | 1H | dd | 19, 20b | 14.0, 7.5 | 38.6 | 18, 19, 32 |
| 20b | 2.22 | 1H | dd | 19, 20a | 13.8, 7.9 | | |
| 21 | | | | | | 72.1 | 18, 19, 20, 22, 31, 32 |
| 22 | 1.89 | 1H | dq | 23, 31 | 10.5, 6.7 | 43.1 | 20, 21, 23, 24, 31, 32 |
| 23 | 3.91 | 1H | ddd | 22, 24 | 10.0, 7.6, 3.1 | 83.8 | 22, 24, 25, 31 |
| 24a | 1.85 | 1H | ddq | 23, 24b, 25 | 14.5, 7.4, 3.1 | 27.1 | 22, 23, 25 |
| 24b | 1.62 | 1H | dq | 23, 24a, 25 | 14.6, 7.4 | | |
| 25 | 1.01 | 3H | t | 24 | 7.3 | 9.2 | 23, 24 |
| 26 | 1.42. | 3H | s | 3, 4 | - | 11.3 | 3, 4, 5, 6 |
| 27 | 1.12 | 3H | d | 6 | 6.7 | 16.5 | 5, 6 |
| 28 | 1.08 | 3H | d | 8 | 7.3 | 12.5 | 7, 8, 9 |
| 29 | 0.87 | 3H | d | 14 | 6.7 | 16.6 | 13, 14, 15 |
| 30 | 1.79 | 3H | d | 17 | 1.0 | 12.0 | 14, 15, 16, 17, 18, 19 |
| 31 | 1.02 | 3H | d | 22 | 6.8 | 11.6 | 21, 22, 23, 32 |
| 32a | 2.72 | 1H | d | 32b | 16.4 | 42.8 | 21, 22, 31, 33 |
| 32b | 2.35 | 1H | dd | 32a | 16.5, 1.0 | | |
| 33 | - | - | - | - | - | 170.2 | 32 |
| 34 | - | - | - | - | - | 157.3 | 9 |
| $NH_2$ | 4.66 | 2H | br s | - | - | - | - |
| C.7-OH | 2.16 | 1H | d | 7 | 7.9 | - | - |
| C.21-OH | 1.91 | 1H | s | - | - | - | - |

*Table 5.4:* Assignment of $^{1}H$ and $^{13}C$ NMR data of leiodermatolide isomer **2**; recorded with 0.6 mg in 0.3 mL $CD_2Cl_2$.

| atom n° | $^{1}H$ NMR ($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | Integral | m | *J* (Hz) | COSY | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 172.2 | 2, 3, 15 |
| 2a | 2.29 | 1H | ddd | 16.6, n.d. | 2b, 3 | 33.7 | 3, 4, 26 |
| 2b | 1.99 | 1H | ddd | 16.7, n.d. | 2a, 3 | | |
| 3 | 2.20 | 2H | m | - | 2, 4, 26 | 22.2 | 2, 4, 5, 26 |
| 4 | 5.09 | 1H | ddq | 8.4, 5.2, 1.4 | 3, 26 | 125.6 | 2, 3, 5, 6, 26 |
| 5 | - | - | - | - | - | 137.3 | 3, 4, 6, 26, 27 |
| 6 | 2.47 | 1H | dq | 10.5, 6.7 | 7, 27 | 48.5 | 4, 7, 25, 26, 27 |
| 7 | 3.26 | 1H | br m | - | OH, 6, 8 | 78.1 | 6, 8, 9, 28 |
| 8 | 1.74 | 1H | qt | 7.3, n.d. | 7, 27, 28 | 39.3 | 7, 10, 28 |
| 9 | 5.89 | 1H | d | 10.0 | 10 | 67.6 | 7, 28, 11 |
| 10 | 5.53 | 1H | ddt | 10.7, 10.0, 1.3 | 9, 11 | 128.5 | 9, 11, 12, 13 |
| 11 | 6.38 | 1H | t | 11.3 | 10, 12 | 126.2 | 9, 10, 12, 13 |
| 12 | 6.53 | 1H | t | 11.5 | 11, 13 | 124.4 | 10, 11, 13, 14 |
| 13 | 5.35 | 1H | ddt | 10.8, 10.2, 1.4 | 12, 14 | 137.6 | 11, 12, 14, 15, 29 |
| 14 | 2.98 | 1H | tq | 10.2, 6.7 | 13, 15, 29 | 35.0 | 12, 13, 15, 29, 30 |
| 15 | 5.07 | 1H | d | 10.3 | 14 | 82.5 | 12, 13, 14, 17, 29, 30 |
| 16 | - | - | - | - | - | 134.0 | 14, 15, 17, 18, 30 |
| 17 | 6.10 | 1H | dq | 10.9, 1.4 | 18, 30 | 129.7 | 15, 16, 18, 19, 30 |
| 18 | 6.40 | 1H | ddt | 15.0, 10.9, 1.3 | 17,19, 20 | 131.7 | 16, 17, 20, 30 |
| 19 | 5.76 | 1H | dt | 15.1, 7.6 | 18, 20 | 128.2 | 17, 20, 30 |
| 20a | 2.40 | 1H | dd | 14.1, 7.8 | 19, 20b | 38.6 | 18, 19, 32 |
| 20b | 2.23 | 1H | dd | 14.2, 7.5 | 19, 20a | | |
| 21 | | | | | | 72.1 | 18, 19, 20, 22, 31, 32 |
| 22 | 1.89 | 1H | dq | 10.0, 6.8 | 23, 31 | 43.1 | 20, 21, 23, 24, 31, 32 |
| 23 | 3.91 | 1H | ddd | 10.0, 7.6, 3.1 | 22, 24 | 83.8 | 22, 24, 25, 31 |
| 24a | 1.85 | 1H | ddq | 14.5, 7.4, 3.1 | 23, 24b, 25 | 27.1 | 22, 23, 25 |
| 24b | 1.62 | 1H | dq | 14.6, 7.4 | 23, 24a, 25 | | |
| 25 | 1.01 | 3H | t | 7.4 | 24 | 9.2 | 23, 24 |
| 26 | 1.42. | 3H | s | - | 3, 4 | 11.3 | 3, 4, 5, 6 |
| 27 | 1.12 | 3H | d | 6.7 | 6 | 16.5 | 5, 6 |
| 28 | 1.08 | 3H | d | 7.3 | 8 | 12.5 | 7, 8, 9 |
| 29 | 0.87 | 3H | d | 6.7 | 14 | 16.6 | 13, 14, 15 |
| 30 | 1.79 | 3H | d | 0.7 | 17 | 12.0 | 14, 15, 16, 17, 18, 19 |
| 31 | 1.02 | 3H | d | 6.9 | 22 | 11.6 | 21, 22, 23, 32 |
| 32a | 2.73 | 1H | d | 16.5 | 32b | 42.9 | 21, 22, 31, 33 |
| 32b | 2.36 | 1H | d | 16.6 | 32a | | |
| 33 | - | - | - | - | - | 170.2 | 32 |
| 34 | - | - | - | - | - | 157.3 | 9 |
| $NH_2$ | 4.67 | 2H | br s | - | - | - | - |
| C.7-OH | 2.17 | 1H | br s | - | 7 | - | - |
| C.21-OH | 1.91 | 1H | s | - | - | - | - |

### 5.2.5 Syntheses of analogues.

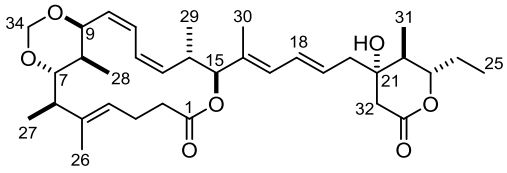
Analogues **107**, **108** and **109** were prepare by Dr. Damien Mailhol. The procedures can be found in the Supporting Information of the leiodermatolide full paper.[113]

**Allylic acetate 118.** Acetic anhydride (2.3 µL, 25 µmol), triethylamine (4.6 µL, 33 µmol) and DMAP (0.2 mg, 1.7 µmol) were added successively to a –78 °C solution of alcohol **91** (10.0 mg, 16.6 µmol) in $CH_2Cl_2$, which was stirred for 1 h. The reaction mixture was then allowed to warm to 0 °C and stirred for further 18 h before the reaction was quenched with a mixture of brine and $H_2O$ (1:1, 4 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 4 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 3:1 to 2:1) to yield the desired mono-acetylated product **118** as a white solid (5.8 mg, 54% yield, ~95% purity) along with the bis-acetylated compound as an off-white foam (3.1 mg, 27% yield). $[\alpha]_D^{20}$ = –65.7 (c = 0.48, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CD_2Cl_2$): δ = 6.65 (br t, *J* = 12.2 Hz, 1H), 6.38 (ddt, *J* = 15.0, 10.7, 1.2 Hz, 1H), 6.31 (br t, *J* = 10.3 Hz, 1H), 6.09 (dd, *J* = 10.8, 1.7 Hz, 1H), 6.03 (d, *J* = 10.8 Hz, 1H), 5.75 (dt, *J* = 15.2, 7.6 Hz, 1H), 5.47 (br t, J = 10.0 Hz, 1H), 5.36 – 5.30 (m, 1H), 5.09 – 5.04 (m, 2H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.90 (ddd, *J* = 10.3, 7.5, 3.2 Hz, 1H), 3.36 (s, 3H), 3.27 (br s, 1H), 2.97 (ddq, *J* = 10.3, 6.7, 6.6 Hz, 1H), 2.72 (d, *J* = 16.5 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.41 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.34 (d, J = 16.5, 0.9 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.24 – 2.17 (m, 4H), 2.00 – 1.95 (m, 2H), 1.94 (s, 3H), 1.88 (dq, *J* = 9.8, 7.1 Hz, 1H), 1.84 (ddd, *J* = 14.7, 7.3, 3.2 Hz, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.77 – 1.74 (m, 1H), 1.68 – 1.54 (m, 3H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 – 0.99 (m, 6H), 0.86 (d, *J* = 6.6 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CD_2Cl_2$): δ = 172.5, 170.4, 170.3, 137.6, 137.2, 135.6, 134.3, 131.9, 129.9, 129.2, 128.5, 126.4, 125.0, 99.1, 86.1, 84.1, 83.0, 72.4, 66.8, 56.5, 48.4, 43.4, 43.1, 42.3, 34.0, 27.4, 22.6, 21.6, 16.9, 16.7, 13.8, 12.3, 11.8, 11.6, 9.4 ppm; IR (film): $\tilde{\nu}$ = 3480, 2967, 2930, 1732, 1457, 1369, 1243, 1208, 1148, 1091, 1036, 949, 748 cm$^{-1}$; MS (ESI) *m/z* (%): 667.5 (100); HRMS (ESIpos): *m/z*: calcd for $C_{37}H_{56}O_9Na$: 667.3817, found 667.3817.

**Analogue 110.** A solution of allylic acetate **118** (4.8 mg, 7.4 µmol) in $CH_2Cl_2$ (0.8 mL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared $Me_2BBr$ (0.5 M in $CH_2Cl_2$, 16.4 µL, 8.2 µmol) was carefully added via the cold wall of the flask. The mixture was allowed to reach –78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of $Me_2BBr$ (0.5 M, 16.4 µL, 8.2 µmol) was introduced. The reaction mixture was stirred for 1.5 h, when a third aliquot of $Me_2BBr$ (0.5 M, 16.4 µL, 8.2 µmol) was introduced. After an additional

1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 7 mL) and the flask was rinsed with THF (2 x 0.5 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 1:1) to yield the title compound as an off-white solid (2.4 mg, 54% yield). $^1$H NMR (600 MHz, $CD_2Cl_2$): see table 5.5; $^{13}$C NMR (150 MHz, $CD_2Cl_2$): see table 5.5; IR (film): $\tilde{\nu}$ = 3472, 2956, 2924, 2854, 1733, 1459, 1371, 1259, 1246, 1207, 1149, 1100, 1015, 979 cm$^{-1}$. MS (ESI) *m/z* (%): 593.4 (100); HRMS (ESIpos): *m/z*: calcd. for $C_{34}H_{50}O_7Na$ [$M^+$+Na]: 593.3449, found 593.3455.

**Dioxane Analogue 119.** A solution of alcohol **91** (4.0 mg, 6.66 µmol) in $CH_2Cl_2$ (0.71 mL) was




cooled to −90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared $Me_2BBr$ (0.5 M in $CH_2Cl_2$, 30.6 µL, 15.3 µmol) was carefully added along the cold wall of the flask. The mixture was allowed to reach −78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of $Me_2BBr$ (0.5 M, 14.6 µL, 15.3 µmol) was introduced. This was repeated after another 1.5 h. After an additional 1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 7 mL) and the flask was rinsed with THF (2 x 0.5 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 3:2) to give the title compound as an off-white solid (1.1 mg, ~75% purity, 20% yield). $^1$H NMR (600 MHz, $CD_2Cl_2$): see table 5.6; $^{13}$C NMR (150 MHz, $CD_2Cl_2$): see table 5.6; IR (film): $\tilde{\nu}$ = 3469, 2963, 2924, 2855, 1732, 1458, 1376, 1249, 1206, 1146, 1080, 1042, 1006, 898, 800, 739 cm$^{-1}$. MS (ESI) *m/z* (%): 593.4 (100); HRMS (ESIpos): *m/z*: calcd for $C_{34}H_{50}O_7Na$: 593.3449, found 593.3455.

*Table 5.5:* Assignment of $^{1}H$ and $^{13}C$ NMR data of leiodermatolide analogue **110**.

| atom n° | $^{1}H$ NMR ($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ (ppm) | Integral | Splitting | COSY | *J* (Hz) | δ (ppm) | HMBC |
| 1 | – | – | – | – | – | 172.4 | 2ab, 3, 15 |
| 2a | 2.31 | 1 | ddd | 2b, 3 | 16.7, 6.2, 2.8 | 34.0 | 3, 4, (26) |
| 2b | 1.99 | 1 | ddd | 2a, 3 | 16.7, 11.0, 3.2 | | |
| 3 | 2.23 | 2 | m | 2ab, 4 | – | 22.5 | 2a(b), 4 |
| 4 | 5.11 | 1 | ddd | 3ab, 26 | 9.4, 5.1, 1.2 | 126.1 | 2ab, 3, 6, 26 |
| 5 | – | – | – | – | – | 137.4 | 3, 6, 26, 27 |
| 6 | 2.44 | 1 | dq | 7, 27 | 9.0, 6.6 | 48.5 | 4, (8), 26, 27 |
| 7 | 3.31 | 1 | br d | 6, OH | 8.7 | 78.6 | 6, (8), 9, 27, 28 |
| 8 | 1.77 | 1 | q | 28 | 7.3 | 39.4 | (9), (10), 28 |
| 9 | 6.02 | 1 | d | 10 | 10.3 | 67.0 | (8), 11, 28, 35 |
| 10 | 5.52 | 1 | ddt | 9, 11, 13 | 10.6, 10.3, 1.2 | 128.6 | (8), 9, 12 |
| 11 | 6.36 | 1 | dd | 10, 13 | 11.6, 10.8 | 126.3 | 9, 12, 13 |
| 12 | 6.56 | 1 | dd | 11, 13 | 11.5, 11.3 | 124.8 | 10, 11, 14 |
| 13 | 5.35 | 1 | ddt | 10, 12, 14 | 11.2, 10.1, 1.2 | 137.8 | 11, (13), 14, 15, 29 |
| 14 | 2.98 | 1 | ddq | 13, 15, 29 | 10.1, 7.9, 6.6 | 35.3 | 12, 13, 15, 29 |
| 15 | 5.08 | 1 | d | 14 | 10.3 | 82.8 | (12), 14, 17, 29, 30 |
| 16 | – | – | – | – | – | 134.2 | 14, 15, (17), 18, 30 |
| 17 | 6.10 | 1 | dq | 18, 30 | 10.8, 1.1 | 129.9 | 15, 18, 19, 30 |
| 18 | 6.40 | 1 | ddt | 17, 19, 20 | 14.9, 10.6, 0.8 | 131.9 | 17, 20ab, 30 |
| 19 | 5.76 | 1 | ddd | 18, 20ab | 15.0, 7.6, 7.5 | 128.4 | 17, 20ab, (30) |
| 20a | 2.22 | 1 | m | 19, 20b | – | 38.9 | 18, 19, 22, 32ab |
| 20b | 2.41 | 1 | dd | 19, 20a | 13.6, 7.4 | | |
| 21 | – | – | – | – | – | 72.4 | 19, 20ab, 22, 32ab, 31 |
| 22 | 1.89 | 1 | dq | 23, 31 | 10.0, 6.8 | 43.4 | (23), 24ab, 31, 32ab |
| 23 | 3.91 | 1 | ddd | 22, 24a, 24b | 10.1, 7.3, 3.0 | 84.1 | 22, 24ab, 25, 31 |
| 24a | 1.85 | 1 | dqd | 23, 24b, 25 | 14.7, 7.3, 3.2 | 27.4 | 22, (23), 25, 31 |
| 24b | 1.63 | 1 | dqd | 23, 24a, 25 | 14.6, 7.4, 7.3 | | |
| 25 | 1.02 | 3 | t | 24ab | 7.4 | 9.42 | 23, 24ab, (31) |
| 26 | 1.43 | 3 | s | 4 | – | 11.6 | 4, 6 |
| 27 | 1.11 | 3 | d | 6 | 6.7 | 16.6 | 6 |
| 28 | 1.10 | 3 | d | 8 | 7.3 | 12.9 | 8, 9 |
| 29 | 0.87 | 3 | d | 14 | 6.7 | 16.9 | 13, 14, 15 |
| 30 | 1.80 | 3 | d | 17 | 1.2 | 12.3 | 15, 17 |
| 31 | 1.02 | 3 | d | 22 | 6.5 | 11.9 | 22, (23) |
| 32a | 2.73 | 1 | d | 32b | 16.4 | 43.1 | 20ab, 22 |
| 32b | 2.35 | 1 | dd | 32a | 16.4, 1.0 | | |
| 33 | – | – | – | – | – | 170.3 | 32ab |
| 34 | – | – | – | – | – | 171.5 | 9, 35 |
| 35 | 1.98 | 3 | s | – | – | 21.7 | – |
| C7-OH | 1.64 | 1 | br s | 7 | – | – | – |
| C21-OH | 1.90 | 1 | br s | – | – | – | – |

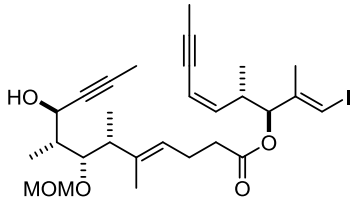
*Table 5.6:* Assignment of $^{1}H$ and $^{13}C$ NMR data of leiodermatolide analogue **119**.

| atom n° | $^{1}H$ NMR ($CD_2Cl_2$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_2Cl_2$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ (ppm) | Integral | Splitting | COSY | *J* (Hz) | δ (ppm) | HMBC |
| 1 | - | - | - | - | - | 172.4 | 2, 15 |
| 2a | 2.31 - 2.38 | 1H | m | 2b, 3a, 3b | - | 33.8 | 1, 3, 5, 26 |
| 2b | 1.88 - 1.96 | 1H | m | 2a, 3a, 3b | - | | |
| 3 | 2.18 - 2.30 | 2H | m | 2a, 2b, 4 | - | 22.1 | 1, 2, 4, 26 |
| 4 | 5.12 | 1H | dd | 3a, 3b, (26) | 10.2, 4.5 | 126.1 | 2, 3, 6, 26 |
| 5 | - | - | - | - | - | 137.0 | 3, 6, 7, 26, 27 |
| 6 | 2.49 | 1H | dq | 7, 27 | 10.9, 6.6 | 48.3 | 4, 5, 7, 26, 27 |
| 7 | 3.44 | 1H | d | 6 | 11.0 | 80.4 | 6, 9, 27, 28, 34 |
| 8 | 1.60-1.66 | 1H | m | 7, 9, 28 | - | 38.4 | 7, 9, 10, 28 |
| 9 | 5.07 | 1H | d | 10 | 10.1 | 65.2 | 7, 8, 11, OH1, 28 |
| 10 | 5.56 – 5.60 | 1H | m | 9, 11 | - | 131.7 | 8, 9, 12, OH1 |
| 11 | 6.31 – 6.38 | 1H | m | 10, 12 | - | 123.7 | 9, 12, 13, 14 |
| 12 | 6.46 | 1H | dd | 11, 13 | 11.4, 10.3 | 126.7 | 10, 13, 14, 29 |
| 13 | 5.28 | 1H | dd | 12, 14 | 10.3, 10.2, 0.7 | 137.7 | 11, 14, 15, 29 |
| 14 | 2.96 - 3.02 | 1H | m | 13, 15, 30 | - | 35.3 | 12, 13, 15, 29 |
| 15 | 5.09 | 1H | d | 14 | 10.3 | 83.1 | 13, 14, 16, 17, 29, 30 |
| 16 | - | - | - | - | - | 134.0 | 14, 15, 17, 18 |
| 17 | 6.05 | 1H | d | 18 | 10.8 | 129.7 | 15, 16, 18, 19, 30 |
| 18 | 6.38 – 6.42 | 1H | m | 17, 19 | - | 131.7 | 17, 20, 30 |
| 19 | 5.77 | 1H | ddd | 20a, 20b | 15.1, 7.5, 7.5 | 128.3 | 17, 18, 20, 21 |
| 20a | 2.41 | 1H | dd | 19, 20b | 14.3, 7.9 | 38.7 | 18, 19, 21, 22, 32 |
| 20b | 2.22 | 1H | dd | 19, 20a | 14.2, 7.6 | | |
| 21 | - | - | - | - | - | 72.1 | 19, 20a, 20b, 22, 32 |
| 22 | 1.89 | 1H | dq | 23, 31 | 10.1, 7.1 | 43.2 | 20, 32, 33 |
| 23 | 3.91 | 1H | ddd | 22, 24a, 24b | 10.1, 7.4, 2.9 | 83.9 | 22, 24, 25 |
| 24a | 1.86 – 1.90 | 1H | m | 23, 24b, 25 | - | 27.2 | 23, 25 |
| 24b | 1.63 | 1H | ddq | 23, 24b, 25 | 7.3, 7.3, 7.4 | | |
| 25 | 1.02 | 3H | t | 24a, 24b | 7.2 | 9.2 | 24 |
| 26 | 1.44 | 3H | s | 4 | - | 11.3 | 4, 5, 6 |
| 27 | 1.11 | 3H | d | 6 | 6.9 | 16.1 | 5, 7 |
| 28 | 1.07 | 3H | d | 8 | 7.2 | 12.1 | 6, 9, (27) |
| 29 | 0.87 | 3H | d | 14 | 6.8 | 16.6 | 13, 14, 15 |
| 30 | 1.79 | 3H | d | 17 | 0.6 | 12.2 | 15, 17 |
| 31 | 0.98 | 3H | d | 22 | 6.9 | 11.7 | 21, 22 |
| 32a | 2.73 | 1H | d | 32b | 16.5 | 42.9 | 21, 33 |
| 32b | 2.35 | 1H | d | 32a | 16.6 | | |
| 33 | - | - | - | - | - | 170.1 | 32a, 32b |
| 34a | 5.00 | 1H | d | 34b | 6.2 | 88.7 | 7, 9 |
| 34b | 4.80 | 1H | d | 34a | 6.3 | | |
| OH | 2.17 - 2.26 | 1H | br s | - | - | - | - |

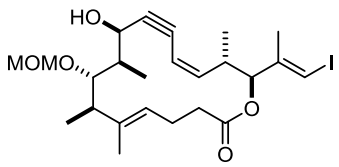
### 5.2.6 2nd generation synthesis of leiodermatolide.

The catalytic allylation/propargylation of **61** as well as the Stille couplings were carried out by Dr. Damien Mailhol. The corresponding procedures can be found in the leiodermatolide full paper.[113]

**(1*E*,3*S*,4*S*,5*Z*)-1-Iodo-2,4-dimethylnona-1,5-dien-7-yn-3-yl (6*R*,7*S*,8*R*,9*R*,*E*)-9-hydroxy-7-(methoxymethoxy)-5,6,8-trimethyldodec-4-en-10-ynoate (122).** A schlenck tube was charged with a solution of silyl ether **79** (60.0 mg, 85.9 µmol) in THF (0.6 mL) and the solution cooled to 0 °C. A solution of TBAF (1.0 M in THF, 0.258 mL, 258 µmol) was added dropwise via syringe. The reaction mixture was allowed to warm to ambient temperature and was stirred for 3 h before being quenched with brine (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over $Na_2SO_4$ before being concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 6:1 to 5:1) to give a colorless oil (44.2 mg, 88% yield). $[\alpha]_D^{20}$ = +97.0 (c = 1.15, $CH_2Cl_2$). $^1$H NMR (500 MHz, $C_6D_6$): δ = 6.22 (s, 1H), 5.54 – 4.46 (m, 2H), 5.29 (d, *J* = 7.6 Hz, 1H), 5.09 (dd, *J* = 7.1, 6.7 Hz, 1H), 5.05 (br s, 1H), 4.36 (s, 2H), 3.54 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.33 (br s, 1H), 3.28 – 3.19 (m, 1H), 3.05 (s, 3H), 2.25 – 2.18 (m, 3H), 2.15 (dd, *J* = 7.8, 6.7 Hz, 1H), 2.12 – 2.05 (m, 1H), 2.02 – 1.95 (m, 1H), 1.80 (s, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.55 (*d*, *J* = 2.2 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, $C_6D_6$): δ = 171.6, 145.1, 142.6, 138.7, 124.0, 111.5, 99.4, 90.8, 84.1, 81.5, 81.2, 80.3, 80.1, 76.7, 63.2, 56.2, 44.0, 42.3, 37.6, 34.3, 23.8, 20.6, 16.8, 15.5, 13.1, 12.1, 4.2, 3.4 ppm; IR (film): $\tilde{\nu}$ = 3480, 2967, 2918, 2864, 1736, 1454, 1376, 1243, 1213, 1142, 1088, 1023, 980, 927, 757, 674 cm$^{-1}$; MS (ESI) *m*/*z* (%): 607.2 (100); HRMS (ESIpos): *m*/*z*: calcd for $C_{28}H_{41}O_5I_1Na$: 607.1891, found 607.1893.




**(5*E*,7*R*,8*S*,9*R*,10*R*,13*Z*,15*S*,16*S*)-10-hydroxy-16-((*E*)-1-iodoprop-1-en-2-yl)-8-methoxymethoxy)-6,7,9,15-tetramethyloxacyclohexadeca-5,13-dien-11-yn-2-one (123).**




*Care should be taken to exclude moisture during the ring closing alkyne metathesis step.*

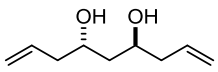
A flame-dried Schlenck tube was charged with 5 Å MS (1.2 g), sealed and flame-dried until a stable vacuum was obtained. Toluene (45 mL) and a solution of diyne **122** (45.0 mg, 77.0 µmol) in toluene (1 mL + 0.5 mL rinse) were added via syringe and the resulting suspension stirred for 30 min at room temperature. A solution of catalyst **C1** (12.0 mg, 11.5 µmol) in toluene (1.2 mL) was added and the reaction mixture stirred for 13 h at ambient temperature. After complete consumption of starting material (HPLC:50 mm Zorbax Eclipse Plus C18, 1.8 µm, 3mm Ø, MeOH/$H_2O$ = 90:10, 0.5 mL/min 224 bar: $R_t$ (product) = 1.09 min; $R_t$ (starting material) = 1.49 min; $R_t$ (dimer) = 3.57 min), the reaction mixture was filtered through a pad of Celite® and rinsed with $Et_2O$ (150 mL). After concentration under reduced pressure, the residue was purified by flash column chromatography (hexanes/EtOAc 6:1 to 5:1 to 4:1) to give a pale yellow oil

(24.8 mg, 61% yield). $[\propto]_D^{20}$ = +86.7 (c = 0.83, $CH_2Cl_2$). $^1$H NMR (400 MHz, ): δ = 6.16 (dq, *J* = 1.2, 1.0 Hz, 1H), 5.64 (dd, *J* = 10.5, 8.5 Hz, 1H), 5.58 (dd, *J* = 10.7, 0.9 Hz), 5.34 (td, *J* = 6.7, 1.0 Hz, 1H), 5.27 (d, *J* = 5.1 Hz, 1H), 4.97 (s, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 3.46 (dd, *J* = 9.4, 2.4 Hz, 1H), 3.42 (s, 3H), 3.27 (d, *J* = 2.1 Hz, 1H), 2.56 (dq, *J* = 9.2, 6.9 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.37 – 2.30 (m, 1H), 2.28 – 2.22 (m, 1H), 1.91 (qt, *J* = 7.2, 2.5 Hz, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.54 (d, *J* = 0.8 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H) ppm; $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 144.1, 138.2, 125.5, 111.3, 99.2, 96.1, 87.7, 80.8, 79.8, 79.6, 63.2, 56.7, 46.7, 40.6, 38.7, 34.3, 22.7, 22.2, 17.0, 14.8, 13.3, 12.9 ppm; IR (film): $\tilde{\nu}$ = 3481, 2962, 2928, 2869, 1737, 1456, 1378, 1261, 1185, 1146, 1091, 1025, 929, 754 $cm^{-1}$; MS (ESI) *m*/*z* (%): 553.1 (100); HRMS (ESIpos): *m*/*z*: calcd for $C_{24}H_{35}O_5I_1Na$: 553.1421, found 553.1420.

## 5.3 Total synthesis of mandelalide A

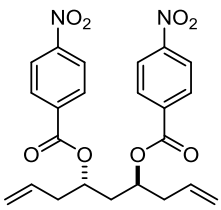
### 5.3.1 Synthesis of acid 151.

**(4*S*,6*S*)-Nona-1,8-diene-4,6-diol (136).** According to the procedure from Krische et. al.,[151] a flame-




dried Young tube was charged with $[Ir(cod)Cl]_2$ (974 mg, 1.45 mmol), (*S*)-Cl,MeO-BIPHEP (1.89 g, 2.90 mmol), $Cs_2CO_3$ (3.78 g, 11.6 mmol) and 4-chloro-3-nitrobenzoic acid (1.17 g, 5.80 mmol). 1,4-Dioxane (65 mL) and distilled allyl acetate (31.3 mL, 290 mmol) were added, the flask was sealed, and the suspension heated to 90 °C for 30 min and cooled back to room temperature. A solution of 1,3-propanediol (**137**) (2.10 mL, 29.0 mmol) in 1,4-dioxane (65 mL) was introduced, the flask sealed and stirring continued at 90 °C for 72 h. After cooling to ambient temperature, the mixture was filtered through a pad of Celite® (eluent: EtOAc) and the filtrate was concentrated. The brown residue was purified by flash chromatography (hexanes/EtOAc 3:1) to give the desired diol as a pale yellow oil (3.22 g, 71% yield, >99% ee, >29:1 d.r.). $[\propto]_D^{20}$ = +24.5 (c = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.85 – 5.72 (m, 2H), 5.13 – 5.09 (m, 2H), 5.09 – 5.07 (m, 2H), 4.01 – 3.91 (br s, 2H), 2.72 – 2.57 (br s, 2H), 2.27 – 2.21 (m, 4H), 1.60 (tr, J = 5.8 Hz, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 134.6, 118.0, 68.1, 42.0, 41.5 ppm. IR (film): $\tilde{\nu}$ = 3340, 3077, 2979, 2936, 1723, 1641, 1434, 1327, 1232, 1133, 1047, 994, 912, 871, 830 $cm^{-1}$. MS (EI) *m/z* (%) = 115 (10), 97 (74), 79 (38), 73 (19), 71 (89), 69 (52), 67 (49), 55 (19), 45 (39), 41 (100), 39 (29), 29 (13), 27 (28). HRMS (ESIpos): *m/z*: calcd for $C_9H_{16}O_2H$: 157.1228; found: 157.1229.

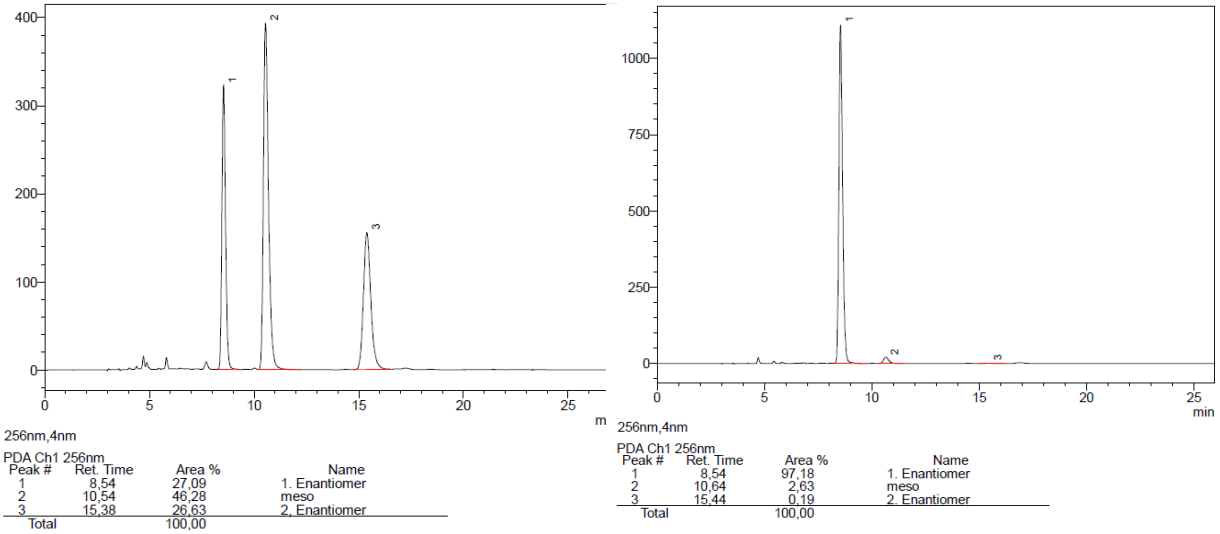
**Bis-nitrobenzoate 138.** A Schlenck tube was charged with 4-nitrobenzoyl chloride (59 mg,



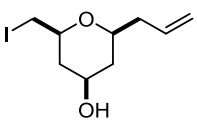

0.32 mmol), DMAP (1.6 mg, 0.013 mmol) and pyridine (52 µL, 0.64 mmol) before a solution of diol **136** (10. Mg, 0.064 mmol) in $CH_2Cl_2$ (0.32 mL) was added. The reaction mixture was stirred for 3 hours before the reaction was quenched by addition of sat. $NH_4Cl$ solution (5 mL). It was extracted with EtOAc

(3 x 5 ml) and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The yellow residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give an off-white solid (27.3 mg, 94%) $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.23 – 8.18 (m, 4H), 8.11 – 8.05 (m, 4H), 5.77 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 2H), 5.31 (dq, *J* = 7.3, 6.0 Hz, 2H), 5.17 – 5.05 (m, 4H), 2.49 (ddt, *J* = 7.2, 6.0, 1.2 Hz, 4H), 2.13 (dd, *J* = 7.1, 5.8 Hz, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.1, 150.3, 135.6, 132.4, 130.6, 123.5, 118.9, 71.1, 39.0, 37.4 ppm; IR (film): $\tilde{\nu}$ = 1719, 1607, 1254, 1410, 1347, 1319, 1268, 1117, 1102, 1014, 993, 922, 872, 836, 783, 718 cm$^{-1}$; MS (EI) *m/z* (%): 413 (13), 246 (5), 151 (8), 150 (100), 120 (9), 104 (14), 92 (4), 76 (5). HRMS (ESIpos): *m/z*: calcd for $C_{23}H_{22}N_2O_8Na$: 477.1268, found 477.1266.

HPLC: 250 mm Chiralpak IB (Ø 4.6 mm), *n*-heptane/2-propanol 85:15, 1.0 mL/min, 298 K, 4.4 MPa: $R_t$ = 8.54 min (major), 10.64 min (meso), 15.44 min (minor).



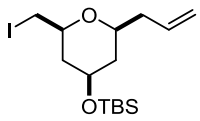

**(2*S*,4*R*,6*S*)-2-Allyl-6-(iodomethyl)tetrahydro-2*H*-pyran-4-ol (139).** $NaHCO_3$ (4.18 g, 49.8 mmol)




was added at −40 °C to a solution of diol **136** (3.11 g, 19.9 mmol) in MeCN (360 mL) and the resulting suspension was vigorously stirred for 10 min. $I_2$ (15.2 g, 59.7 mmol) was carefully added in three portions and the resulting brown mixture stirred for 15 h at −40 °C. The mixture was poured into sat. $Na_2S_2O_3$-solution (200 mL) and the flask was rinsed with EtOAc (2 x 50 mL). After extraction of the aqueous phase with EtOAc (2 x 150 mL), the combined organic layers were dried over $Na_2SO_4$ and concentrated. The brown residue was purified by flash chromatography (hexanes/EtOAc 3:1) to yield a 5:1 mixture of diastereoisomers (based on $^1$H-NMR integration, solvent: $C_6D_6$) as a colorless oil (4.55 g, 81%). This mixture was purified by flash chromatography ($SiO_2$ 60 (15 x 40 µm), $CH_2Cl_2$/$Et_2O$ 5:1) to give the desired all-*cis* diastereomer as a colorless oil (3.54 g, 63%), which solidified upon prolonged storage at −20 °C. $[\alpha]_D^{20}$ = +25.7 (c = 0.37, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dddd, *J* = 16.8, 10.2, 7.5, 6.5 Hz, 1H), 5.11 – 5.02 (m, 2H), 3.80 (m, 1H), 3.36 (m, 2H), 3.19 (dd, *J* = 5.8, 3.8 Hz, 2H), 2.42 –

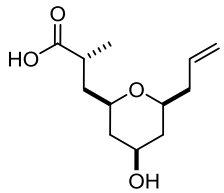
2.30 (m, 1H), 2.26 – 2.12 (m, 2H), 1.90 (ddt, *J* = 12.5, 4.3, 2.0 Hz, 1H), 1.63 (s, 1H), 1.14 (m, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 134.3, 117.1, 75.4, 75.0, 67.8, 40.7, 40.2, 40.1, 8.7 ppm. IR (film): $\tilde{\nu}$ = 3346, 2942, 2917, 2850, 1641, 1446, 1430, 1414, 1368, 1325, 1270, 1185, 1136, 1080, 1038, 998, 916, 854 cm$^{-1}$. MS (EI) *m/z* (%) = 282 (0.3), 241 (100), 223 (23), 197 (38), 73 (14), 67 (17), 45 (15), 43 (10). HRMS (ESIpos): *m/z*: calcd for $C_9H_{15}O_2INa$: 305.0009; found: 305.0009.

**(((2*S*,4*R*,6*S*)-2-Allyl-6-(iodomethyl)tetrahydro-2*H*-pyran-4-yl)oxy)(*tert*-butyl)-dimethylsilane (141).** A solution of alcohol **139** (3.10 g, 11.0 mmol) in $CH_2Cl_2$ (38 mL) was cooled to 0 °C before




2,6-lutidine (1.79 mL, 15.4 mmol) and TBSOTf (3.03 mL, 13.2 mmol) were added dropwise via syringe. The mixture was stirred for 1 h at 0 °C before the reaction was quenched with sat. $NH_4Cl$ solution (40 mL). After phase separation, the aqueous layer was extracted with EtOAc (2 x 25 mL) and the combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 29:1) to yield the desired silyl ether as a colorless oil (4.18 g, 96%). $[\alpha]_D^{20}$ = +15.8 (c = 1.21, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.90 – 5.77 (m, 1H), 5.12 – 4.97 (m, 2H), 3.74 (dddd, *J* = 10.8, 10.7, 4.8, 4.7 Hz, 1H), 3.35 – 3.24 (m, 2H), 3.16 (dd, *J* = 5.9, 1.5 Hz, 2H), 2.33 (dtt, *J* = 13.3, 6.6, 1.5 Hz, 1H), 2.18 (dddd, *J* = 14.4, 7.1, 5.7, 1.3 Hz, 1H), 2.00 (dddd, *J* = 12.4, 4.1, 1.9, 1.8 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.23 – 1.11 (m, 2H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.92 (dddd, *J* = 16.7, 10.9, 8.3, 6.3 Hz, 1H), 5.09 – 4.98 (m, 2H), 3.54 (dddd, *J* = 10.8, 10.7, 4.9, 4.7 Hz, 1H), 3.07 (dddd, *J* = 11.5, 6.7, 5.1, 1.8 Hz, 1H), 2.93 (dddd, *J* = 11.2, 6.6, 4.6, 2.0 Hz, 1H), 2.85 (dd, *J* = 10.1, 6.7 Hz, 1H), 2.76 (dd, *J* = 10.1, 4.6 Hz, 1H), 2.29 (dtt, *J* = 13.2, 8.1, 6.6, 5.1 Hz, 1H), 2.08 (dddt, *J* = 14.0, 7.5, 5.2, 1.1 Hz, 1H), 1.74 (ddt, *J* = 12.3, 47, 2.0, 1H), 1.63 (dddd, *J* = 12.6, 4.6, 2.0, 2.0 Hz, 1H), 1.21 (ddd, *J* = 12.6, 11.1, 11.1 Hz, 1H), 1.11 (ddd, *J* = 12.2, 11.1, 11.0 Hz, 1H), 0.97 (s, 9H), 0.05 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 134.5, 116.8, 75.4, 75.1, 68.3, 41.1, 40.7, 40.2, 25.8, 18.0, 8.9, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2950, 2928, 2856, 1642, 1471, 1462, 1383, 1251, 1126, 1087, 1068, 1005, 916, 833, 773, 669 cm$^{-1}$. MS (EI) *m/z* (%) = 340 (14), 339 (81), 271 (27), 269 (10), 172 (14), 171 (100), 141 (14), 129 (42), 101 (38), 79 (21), 75 (37), 73 (23), 67 (11), 59 (14), 43 (25), 41 (18). HRMS (ESIpos): *m/z*: calcd for $C_{15}H_{29}O_2SiINa$: 419.0872; found: 419.0874.

**Acid 143.** A solution of *n*-BuLi (1.58 M in hexanes, 368 µL, 0.582 mmol) was added dropwise to a

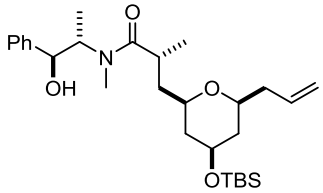



stirred solution of diisopropylamine (85 µL, 0.61 mmol) in THF (1.1 mL) at 0 °C. After 5 min, the ice bath was removed and the reaction mixture allowed to warm to ambient temperature. After 25 min equilibration, prolinolamide **R11** (43.6 mg, 0.277 mmol) was added dropwise via syringe and the reaction was stirred for another 90 min. HMPA (101.3 µL, 0.582 mmol) was added and the reaction mixture recooled to 0 °C. A solution of alkyl iodide **141** (100 mg, 0.252 mmol) in THF (0.3 mL) was added dropwise via

syringe and the mixture stirred for 6 h before the reaction was quenched with water (8 mL). The mixture was extracted with EtOAc (3 x 6 mL) and the combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography to yield a pale yellow oil (79.6 mg, 74%), which was immediately engaged in the next step. HRMS (ESIpos): *m/z*: calcd for $C_{23}H_{43}N_1O_4Si_1Na$: 448.2854, found 448.2858.

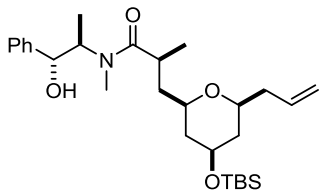
Aqueous HCl (1 N, 0.6 mL) was added to a flask containing amide **142** (27 mg, 63 µmol) and the resulting emulsion was heated to 100 °C for 4.5 h. The reaction mixture was cooled to 0 °C, aqueous NaOH solution (1 M, 1.3 mL) was added and the resulting mixture stirred for 20 min. It was then neutralized with conc. HCl and the aqueous phase extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The desired acid **143** was obtained as a colorless oil and judged pure by $^1$H NMR analysis. $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.99 – 5.71 (m, 1H), 5.10 – 4.95 (m, 2H), 3.36 (tt, *J* = 11.1, 4.7 Hz, 1H), 3.11 – 2.93 (m, 2H), 2.68 (ddq, *J* = 7.0, 7.0, 6.9 Hz, 1H), 2.26 (dtt, *J* = 13.3, 6.6, 1.4 Hz, 1H), 2.16 – 1.97 (m, 2H), 1.59 (dddt, *J* = 18.5, 12.2, 4.4, 2.0 Hz, 2H), 1.37 – 1.22 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 – 0.93 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 182.4, 135.1, 116.8, 75.3, 73.4, 68.0, 41.5, 40.8, 40.7, 39.7, 36.7, 17.1 ppm; MS (ESIneg) *m/z* (%): 226.9 (100 ($M$-H$^+$)). HRMS (ESI): *m/z*: calcd. for $C_{12}H_{20}O_4Na$ [$M$+Na$^+$]: 251.1254, found 251.1253.

**(*R*)-3-((2*R*,4*R*,6*S*)-6-Allyl-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpropanamide (144).** A flame-dried 3-necked round-bottom flask equipped with a stirbar, a reflux condenser and a dropping funnel was charged with dry LiCl (5.13 g, 121 mmol), diisopropylamine (6.24 mL, 44.4 mmol) and THF (75 mL). After cooling to −78 °C, a solution of *n*-BuLi (1.50 M in hexanes, 29.0 mL, 43.5 mmol) was added dropwise over 20 min and the mixture was stirred for 10 min before it was warmed to 0 °C. After 10 min, the mixture was cooled to −78 °C and a solution of (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionic amide (**R12**) (4.69 g, 21.2 mmol) in THF (115 mL) was added over 45 min via dropping funnel. The resulting yellow suspension was stirred for 1 h at −78 °C, for 30 min at 0 °C and for 20 min at RT before it was re-cooled to 0 °C. A solution of alkyl iodide **141** (4.01 g, 10.1 mmol) in THF (6 mL + 2 x 2 mL rinse) was then added dropwise over 5 min via syringe. The mixture was warmed to 45 °C and stirred at this temperature for 48 h. After cooling to RT, the reaction was quenched with sat. $NH_4Cl$ solution (300 mL) and the aqueous layer was extracted with EtOAc (4 x 200 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 2:1) to give the alkylated compound as a white foam that collapsed to a colorless syrup upon storage (3.83 g, 76%).[$\propto$ $]_D^{20}$ = +50.7 (c = 0.96, $CH_2Cl_2$). $^1$H and $^{13}$C NMR spectra were complex and broadened due to the presence of amide bond rotamers. IR (film): $\tilde{\nu}$ = 3387, 2933, 2930, 2856, 1619, 1462, 1409, 1374,



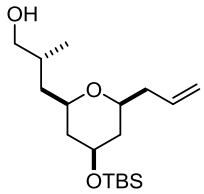
1252, 1115, 1072, 913, 835, 774, 700, 673 $cm^{-1}$. MS (EI) *m/z* (%) = 433 (31), 432 (97), 383 (16), 382 (31), 325 (19), 258 (20), 257 (100), 216 (31), 193 (16), 171 (10), 148 (21), 129 (10), 119 (11), 101 (12), 99 (19), 79 (11), 75 (22), 73 (25), 58 (39). HRMS (ESIpos): *m/z*: calcd for $C_{28}H_{47}NO_4SiNa$: 512.3167; found: 512.3166.

**(*S*)-3-((2*R*,4*R*,6*S*)-6-Allyl-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpropanamide (216).** Prepared analogously from




(1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionic amide (*ent*-**R12**) and alkyl iodide **141** (3.08 g, 7.77 mmol) as a sticky syrup (3.20 g, 84%). $[\propto]_{20}^{D}$ = −24.3 (c = 0.77, $CH_2Cl_2$). $^1$H and $^{13}$C NMR spectra were complex and partially broadened due to the presence of amide bond rotamers. IR (film): $\tilde{\nu}$ = 3376, 2934, 2930, 2856, 1619, 1472, 1463, 1374, 1328, 1306, 1254, 1120, 1073, 1006, 915, 857, 836, 775, 702, 671 $cm^{-1}$. MS (EI) *m/z* (%) = 474 (5), 433 (28), 432 (89), 383 (15), 382 (26), 325 (22), 258 (20), 257 (100), 222 (17), 193 (13), 148 (18), 119 (10), 99 (19), 75 (15), 73 (17), 58 (23). HRMS (ESIpos): *m/z*: calcd for $C_{28}H_{47}NO_4SiNa$: 512.3167; found: 512.3169.

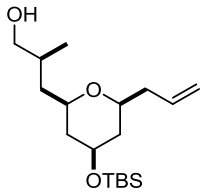
**(*R*)-3-((2*R*,4*R*,6*S*)-6-Allyl-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-2-methylpropan-1-ol (145).** A solution of *n*-BuLi (1.60 M in hexanes, 23.1 mL, 37.0 mmol) was added over 15




min at −78 °C to a solution of diisopropylamine (5.57 mL, 39.6 mmol) in THF (34 mL) and the resulting mixture was stirred at this temperature for 15 min and for 45 min at 0 °C. Solid $NH_3{\cdot}BH_3$ (90%, 1.31 g, 38.1 mmol) was then added in one portion and the resulting mixture stirred for 40 min at 0 °C and for 45 min at ambient temperature. After cooling to 0 °C, a solution of amide **144** (3.80 g, 7.62 mmol) in THF (34 mL) was slowly added over 10 min. After stirring for 3 h at 0 °C, the mixture was warmed to ambient temperature and stirring continued for 1 h before the reaction was quenched with sat. $NH_4Cl$ solution (200 mL). The mixture was vigorously stirred for 45 min before the phases were separated, the aqueous phase was extracted with EtOAc (3 x 120 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give the desired alcohol as a colorless oil (2.42 g, 96%). $[\alpha]_D^{20}$ = +17.8 (c = 0.83, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.85 (dddd, *J* = 16.0, 9.2, 6.6, 6.6 Hz, 1H), 5.07 – 5.00 (m, 2H), 3.63 (dddd, *J* = 10.7, 10.4, 5.1, 5.1 Hz, 1H), 3.46 (ddd, *J* = 10.5, 5.2, 5.1 Hz, 1H), 3.36 (ddd, *J* = 10.4, 5.1, 5.1 Hz, 1H), 3.19 – 3.04 (m, 2H), 2.26 (dddt, J = 14.1, 7.0, 7.0, 1.2 Hz, 1H), 2.22 – 2.15 (br t, 1H), 2.12 – 2.04 (m, 1H), 1.78 (dq, *J* = 12.4, 6.2 Hz, 1H), 1.75 – 1.61 (m, 2H), 1.55 (ddd, *J* = 14.4, 9.6, 7.3 Hz, 1H), 1.34 – 1.21 (m, 2H), 1.09 (ddd, *J* = 14.4, 6.4, 2.3 Hz, 1H), 1.00 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 134.9, 117.2, 75.3, 74.8, 69.1, 68.2, 43.0, 41.4, 41.2, 40.8, 34.5, 26.0, 18.2, 18.0, −4.3 ppm. IR (film): $\tilde{\nu}$ = 3395, 2926, 2929, 2856, 1643, 1472, 1462, 1375, 1253, 1152, 1123, 1070, 975, 914, 835, 774, 671 $cm^{-1}$. MS (EI)

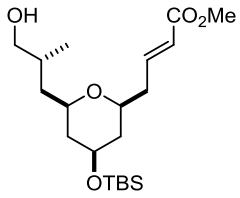
*m/z* (%) = 271 (33), 201 (20), 179 (37); 171 (47), 161 (16), 159 (47), 145 (46), 131 (12), 129 (69), 127 (12), 125 (15), 119 (15), 111 (12), 109 (65), 107 (12), 105 (22), 101 (44), 93 (18), 85 (93), 81 (28), 79 (26), 75 (100), 73 (49), 67 (43), 59 (22), 57 (14), 55 (24), 43 (17), 41 (32). HRMS (ESIpos): *m/z*: calcd for $C_{18}H_{36}O_3SiNa$: 351.2326; found: 351.2326.

**(*S*)-3-((2*R*,4*R*,6*S*)-6-Allyl-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-2-methylpropan-1-ol (**11-*epi*-**145).** Prepared analogously from amide **216** (3.20 g, 6.53 mmol) as a colorless




oil (1.86 g, 87%). $[\alpha]_D^{20}$ = +1.8 (c = 1.03, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.85 (dddd, *J* = 17.7, 9.6, 7.0, 7.0 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.65 (dddd, *J* = 10.7, 10.7, 5.0, 4.8 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.36 (dd, *J* = 10.7, 6.6 Hz, 1H), 3.28 (dddd, *J* = 11.5, 8.3, 3.5, 1.9 Hz, 1H), 3.11 (dddd, *J* = 11.4, 7.1, 5.3, 1.9 Hz, 1H), 2.25 (dtt, *J* = 14.0, 7.0, 1.4 Hz, 1H), 2.08 (dddd, *J* = 14.1, 8.6, 4.0, 2.6 Hz, 1H), 2.01 (br s, 1H), 1.86 (qt, *J* = 6.8, 5.3 Hz, 1H), 1.77 – 1.64 (m, 2H), 1.52 (ddd, *J* = 13.9, 8.3, 5.4 Hz, 1H), 1.43 – 1.20 (m, 3H), 0.99 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 135.0, 117.0, 75.3, 73.5, 69.2, 67.5, 42.3, 41.6, 40.8, 40.0, 32.9, 26.0, 18.2, 17.6, –4.3 ppm. IR (film): $\tilde{\nu}$ = 3394, 2950, 2929, 2857, 1375, 1254, 1151, 1123, 1072, 1005, 914, 836, 775, 672 cm$^{-1}$. MS (EI) *m/z* (%) = 271 (33), 201 (20), 179 (37); 171 (47), 161 (16), 159 (47), 145 (46), 131 (12), 129 (69), 127 (12), 125 (15), 119 (15), 111 (12), 109 (65), 107 (12), 105 (22), 101 (44), 95 (41), 93 (18), 85 (93), 81 (28), 79 (26), 75 (100), 73 (49), 67 (43), 59 (22), 57 (14), 55 (24), 43 (17), 41 (32). HRMS (ESIpos): *m/z*: calcd for $C_{18}H_{36}O_3SiNa$: 351.2326; found: 351.2327.

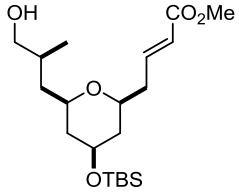
**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-3-hydroxy-2-methylpropyl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (146).** Hoveyda-Grubbs 2$^{nd}$ gen. catalyst **C7** (137 mg,




0.219 mmol) was added to a solution of the terminal alkene **145** (2.40 g, 7.30 mmol) and methylacrylate (3.27 mmol, 36.5 mmol) in $CH_2Cl_2$ (70 mL). The mixture was stirred for 7.5 h at ambient temperature allowing the generated ethene to evaporate. After concentration, the residue (*E/Z* = 12:1 based on $^1$H NMR integration of a crude sample) was purified by flash chromatography (hexanes/EtOAc 5:1 to 4:1) to give the title compound as a pale brown oil (2.33 g, single isomer, 83%). $[\alpha]_D^{20}$ = +9.0 (c = 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 7.09 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.90 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.57 (dddd, *J* = 10.8, 10.6, 4.9, 4.8 Hz, 1H), 3.40 (s, 3H) 3.39 – 3.29 (m, 2H), 3.09 (dddd, *J* = 11.7, 9.7, 2.3, 2.3 Hz, 1H), 2.96 (dddd, *J* = 11.7, 7.0, 4.7, 1.9 Hz, 1H), 2.09 (dddd, *J* = 14.8, 7.4, 7.3, 1.5 Hz, 1H), 1.94 (dddd, *J* = 8.6, 8.6, 5.1, 2.0 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.67 – 1.56 (m, 2H), 1.51 (ddd, *J* = 14.4, 9.6, 6.9 Hz, 1H), 1.29 – 1.12 (m, 2H), 1.07 – 1.01 (m, 1H), 0.99 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 166.4, 145.1, 123.5, 74.6, 74.2, 68.9, 68.1, 51.0, 42.7, 41.5, 40.7, 38.7, 34.0, 26.0, 18.2, 17.7, –4.3, –4.3 ppm. IR (film): $\tilde{\nu}$ = 3436, 2933, 2929, 2856, 1725, 1659, 1462, 1436, 1376, 1324, 1255, 1175, 1122, 1069, 985, 855, 836,

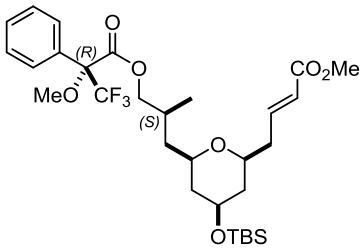
775, 669 $cm^{-1}$. MS (EI) *m/z* (%) = 329 (14), 237 (54), 229 (17), 203 (11), 159 (26), 137 (11), 131 (12), 129 (20), 109 (30), 101 (23), 97 (20), 93 (21), 89 (11), 85 (100), 81 (15), 75 (46), 73 (32), 67 (18), 59 (13), 55 (12), 41 (15). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{38}O_5SiNa$: 409.2381; found: 409.2381.

**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-3-hydroxy-2-methylpropyl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (**11-*epi*-**146).** Prepared analogously from terminal alkene




11-*epi*-**145** (1.82 g, 5.63 mmol) as a colorless oil (1.99 g, 91%). $[\propto]_D^{20}$ = –0.4 (c = 1.09, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 7.09 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.90 (dt, *J* = 15.7, 1.5 Hz, 1H), 3.59 (tt, *J* = 10.5, 4.7 Hz, 1H), 3.40 (m, 5H), 3.21 (dddd, *J* = 11.6, 8.6, 3.4, 1.8 Hz, 1H), 2.99 (dddd, *J* = 11.7, 7.4, 4.4, 2.1 Hz, 1H), 2.16 – 2.04 (m, 1H), 2.04 – 1.97 (br s, 1H), 1.93 (dddd, *J* = 14.9, 7.1, 4.5, 1.5 Hz, 1H), 1.84 (tdd, *J* = 12.8, 7.3, 1.3 Hz, 1H), 1.67 (ddt, *J* = 12.6, 4.8, 1.9 Hz, 1H), 1.59 (ddt, *J* = 12.4, 4.8, 1.9 Hz, 1H), 1.43 (ddd, *J* = 14.1, 8.3, 5.7 Hz, 1H), 1.35 (ddd, *J* = 14.2, 7.2, 3.9 Hz, 1H), 1.26 (ddd, *J* = 11.8, 11.6, 11.1 Hz, 1H), 1.19 (ddd, *J* = 11.7, 11.6, 11.2 Hz, 1H), 0.98 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.06 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 166.6, 145.5, 123.3, 74.2, 73.8, 69.0, 67.5, 51.0, 42.2, 41.7, 40.0, 38.7, 32.9, 26.0, 18.2, 17.7, –4.3, –4.3 ppm. IR (film): $\tilde{\nu}$ = 3436, 2951, 2930, 2857, 1726, 1660, 1463, 1436, 1376, 1330, 1256, 1175, 1154, 1122, 1072, 987, 854, 837, 776 $cm^{-1}$. MS (EI) *m/z* (%) = 329 (14), 237 (54), 229 (17), 203 (11), 159 (26), 137 (11), 131 (12), 129 (20), 109 (30), 101 (23), 97 (20), 93 (21), 89 (11), 85 (100), 81 (15), 75 (46), 73 (32), 67 (18), 59 (13), 55 (12), 41 (15). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{38}O_5SiNa$: 409.2381; found: 409.2382.

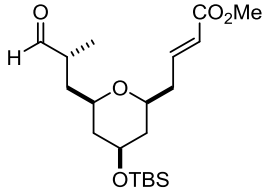
**(*R*)-Mosher Ester 218b** (*all 4 possible Mosher Esters were prepared analogously):* Pyridine



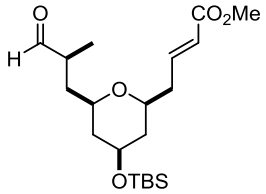

(10.5 µL, 129 µmol) and (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (9.77 µL, 51.8 µmol) were successively added to a solution of primary alcohol 11-*epi*-**146** (10.0 mg, 25.9 µmol) in $CH_2Cl_2$ (300 µL). The mixture was stirred for 90 min before the reaction was quenched by addition of $NH_4Cl$-solution (3 mL). The aqueous phase was extracted with EtOAc (2 x 3 mL), the combined extracts were washed with $NaHCO_3$-solution, dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give the desired (*R*)-mosher ester as a colorless oil (14.5 mg, 93%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.54 – 7.46 (m, 2H), 7.43 – 7.34 (m, 3H), 6.93 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.84 (dt, *J* = 15.8, 1.4 Hz, 1H), 4.21 (dd, *J* = 10.8, 5.8 Hz, 1H), 4.13 (dd, *J* = 10.8, 5.0 Hz, 1H), 3.70 (m, 4H), 3.52 (q, *J* = 1.2 Hz, 3H), 3.33 (dddd, *J* = 11.6, 7.0, 5.0, 1.9 Hz, 1H), 3.25 (tdd, *J* = 9.2, 4.1, 2.0 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.12 – 1.99 (m, 1H), 1.75 (ddt, *J* = 12.5, 4.1, 1.8 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.43 (ddd, *J* = 14.7, 8.8, 6.0 Hz, 1H), 1.34 (ddd, *J* = 14.2, 7.5, 4.0 Hz, 1H), 1.14 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 166.6, 145.4, 132.4, 129.6, 128.4, 127.4,

122.9, 74.1, 73.4, 70.5, 68.5, 55.4, 51.4, 41.8, 41.2, 39.0, 38.7, 29.4, 25.8, 18.1, 17.6, –4.5, –4.5 ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ = –71.6 ppm. MS (ESIpos) *m/z* (%) = 625.4 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{30}H_{45}F_3O_7SiNa$: 625.2779; found: 625.2774.

**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-2-methyl-3-oxopropyl)tetrahydro-2*H*-pyran-2-yl)but-2-enoate (147).** A solution of Dess-Martin periodinane (524 mg, 1.24 mmol) in $CH_2Cl_2$ (2 mL) was cooled to 0 °C before a solution of alcohol **146** (398 mg, 1.03 mmol) in $CH_2Cl_2$ (2 mL + 1 mL rinse) was added dropwise via syringe. After 5 min, the mixture was allowed to warm to ambient temperature and stirring was continued for 3 h. The reaction was quenched by addition of aq. sat. $Na_2S_2O_3$ and $NaHCO_3$ solution (1:1, 15 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3x 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 12:1 to 9:1) to yield the desired aldehyde as a colorless oil (305 mg, 77%). $[\alpha]_D^{20}$ = +3.4 (c = 0.81, hexanes). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.55 (d, *J* = 2.3 Hz, 1H), 6.91 (dd, *J* = 15.7, 7.3, 7.2 Hz, 1H), 5.83 (ddd, *J* = 15.7, 1.5, 1.5 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.71 (s, 3H), 3.39 – 3.25 (m, 2H), 2.52 (dqd, *J* = 7.1, 7.0, 2.4 Hz, 1H), 2.43 – 2.24 (m, 2H), 1.93 (ddd, *J* = 14.3, 9.9, 7.0 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.38 (ddd, *J* = 14.3, 7.1, 3.0 Hz, 1H), 1.26 – 1.14 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.8, 166.8, 145.2, 123.0, 74.2, 73.4, 68.4, 51.5, 43.8, 41.8, 41.1, 38.6, 37.3, 25.8, 18.1, 13.8, –4.5 ppm. MS (EI) *m/z* (%) = 328 (15), 327 (60), 309 (27), 235 (20), 229 (49), 227 (16), 203 (51), 201 (22), 199 (22), 185 (15), 183 (36), 175 (16), 157 (33), 145 (30), 129 (33), 109 (15), 107 (23), 101 (48), 97 (29), 93 (29), 89 (22), 85 (31), 83 (25), 81 (36), 79 (15), 75 (100), 73 (54), 59 (27), 41 (25). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{36}O_5SiNa$: 407.2228; found: 407.2224.

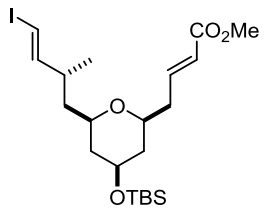



**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-2-methyl-3-oxopropyl)tetrahydro-2*H*-pyran-2-yl)but-2-enoate (**11-*epi*-**147).** *A slightly modified procedure had to be used:* A solution of Dess-Martin periodinane (783 mg, 1.85 mmol) in $CH_2Cl_2$ (2 mL) was cooled to 0 °C and $NaHCO_3$ (358 mg, 4.27 mmol) was added as a solid, followed by addition of a solution of alcohol 11-*epi*-**146** (550 mg, 1.42 mmol) in $CH_2Cl_2$ (2 mL + 1 mL rinse). After 5 min, the mixture was allowed to reach ambient temperature and stirring was continued for 3 h. The mixture was filtered and the filtrate loaded onto $SiO_2$. Purification by flash chromatography (hexanes/EtOAc 12:1 to 9:1) gave the desired aldehyde as a colorless oil (414 mg, 76%). $[\alpha]_D^{20}$ = +17.7 (c = 1.105, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 1.4 Hz, 1H), 6.90 (dt, *J* = 15.7, 7.2 Hz, 1H), 5.82 (dt, *J* = 15.7, 1.5 Hz, 1H), 3.71 (m, 4H), 3.39 – 3.26 (m, 2H), 2.61 – 2.48 (m, 1H), 2.41 – 2.23 (m, 2H), 1.79 (ddd, *J* = 14.4, 8.1, 3.4 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.65 (ddd, *J* = 14.0, 9.2, 4.4 Hz, 1H), 1.24 – 1.12 (m, 2H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.5, 166.8, 145.2,



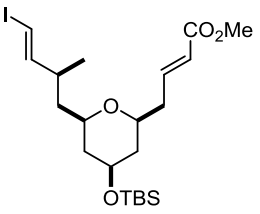
122.9, 74.1, 72.8, 68.4, 51.4, 42.8, 41.6, 41.1, 38.6, 36.9, 25.8, 18.0, 13.8, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2951, 2939, 2856, 1725, 1660, 1462, 1436, 1376, 1330, 1255, 1175, 1122, 1072, 853, 776 $cm^{-1}$. MS (EI) *m/z* (%) = 328 (14), 327 (60), 309 (29), 235 (20), 229 (49), 227 (16), 203 (51), 201 (22), 199 (22), 185 (15), 183 (36), 175 (16), 157 (33), 155 (13), 153 (15), 151 (17), 145 (30), 143 (10), 129 (33), 109 (15), 107 (23), 101 (48), 97 (29), 93 (29), 89 (22), 85 (31), 83 (25), 81 (36), 79 (15), 75 (100), 73 (54), 67 (17), 59 (27), 43 (17), 41 (25). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{36}O_5SiNa$: 407.2224; found: 407.2224.

**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*,*E*)-4-iodo-2-methylbut-3-en-1-yl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (150).** A flame-dried Schlenk tube was charged with



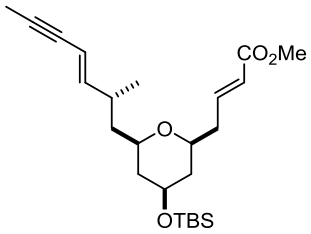

$CrCl_2 \cdot 1.7$ THF (1.21 g, 4.94 mmol) which was suspended in degassed THF (11.5 mL). The suspension was cooled to –8 °C, before solid $CHI_3$ (642 mg, 1.63 mmol) was added under vigorous stirring, causing a color change from green-grey to brown. After 5 min, a solution of aldehyde **147** (190 mg, 0.494 mmol) in degassed THF (1 mL + 2 x 0.5 mL rinse) was added dropwise. After 3 h at –8 °C, the reaction was quenched by addition of aq. serine/$KHCO_3$ solution (1 M, pH = 8, 25 mL) and hexanes/EtOAc (1:1, 40 mL). The mixture was allowed to warm to room temperature and was vigorously stirred for 30 min. After phase separation, the deep violet aqueous phase was extracted with hexanes/EtOAc (1:1, 3 x 40 mL) and the combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 100:0 (until all $CHI_3$ was removed) to 99:1 to 49:1 to 39:1 to 29:1) to yield the desired (*E*)-vinyl iodide as a colorless oil (181 mg, 72%) along with the isomeric (*Z*)-vinyl-iodide (18.8 mg, 8%). $[\propto]_D^{20}$ = –29.6 (c = 1.20, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.94 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.43 (dd, *J* = 14.4, 8.0 Hz, 1H), 5.95 (dd, *J* = 14.4, 1.0 Hz, 1H), 5.86 (dt, *J* = 15.7, 1.5 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.71 (s, 3H), 3.41 – 3.30 (m, 1H), 3.25 (dddd, *J* = 10.0, 8.4, 4.8, 1.8 Hz, 1H), 2.47 – 2.25 (m, 3H), 1.75 (m, 2H), 1.62 (ddd, *J* = 13.8, 8.4, 6.5 Hz, 1H), 1.28 (ddd, *J* = 13.9, 7.0, 4.9 Hz, 1H), 1.25 – 1.09 (m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.9, 152.0, 145.4, 122.8, 74.1, 73.3, 73.2, 68.6, 51.4, 41.9, 41.6, 41.3, 38.7, 37.1, 25.8, 19.1, 18.1, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2949, 2929, 2856, 1725, 1660, 1435, 1376, 1329, 1269, 1255, 1174, 1069, 950, 836, 775, 670 $cm^{-1}$. MS (EI) *m/z* (%) = 452 (23), 451 (100), 229 (47), 197 (11), 181 (37), 169 (10), 157 (11), 131 (34), 129 (31), 101 (19), 93 (12), 89 (13), 75 (28), 73 (21), 59 (11). HRMS (ESIpos): *m/z*: calcd for $C_{21}H_{37}O_4SiINa$: 531.1398; found: 531.1402.

**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*,*E*)-4-iodo-2-methylbut-3-en-1-yl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (**11-*epi*-**150).** Prepared analogously from aldehyde 11-*epi*-




**147** (404 mg, 1.05 mmol) as a mixture of olefin isomers (384 mg, 72%, *E*/*Z* = 10:1). An aliquot (340 mg, 0.669 mmol) was purified by preparative HPLC (2 runs with 170 mg each, Nucleodur C18 HTec 10 µm, length: 250 mm, Ø: 40 mm, MeOH/$H_2O$ =93:7, 75 mL/min) to give the desired (*E*)-isomer as a colorless syrup (286 mg, 84%). $[\propto]_D^{20}$ = +92.8 (c = 1. 01, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.95 (dt, *J* = 15.7, 7.1 Hz, 1H), 6.27 (dd, *J* = 14.3, 9.2 Hz, 1H), 6.00 (dd, *J* = 14.3, 0.7 Hz, 1H), 5.86 (dt, *J* = 15.7, 1.5 Hz, 1H), 3.73 (m, 4H), 3.30 (dddd, *J* = 11.5, 8.2, 4.3, 1.9 Hz, 1H), 3.18 (dddd, *J* = 12.0, 10.4, 3.1, 1.5 Hz, 1H), 2.49 (tdd, *J* = 9.2, 6.8, 3.9 Hz, 1H), 2.38 (dddd, *J* = 15.3, 8.4, 7.1, 1.5 Hz, 1H), 2.29 (dddd, *J* = 9.1, 7.1, 3.6, 1.4 Hz, 1H), 1.80 – 1.64 (m, 2H), 1.50 (ddd, *J* = 14.2, 10.2, 4.2 Hz, 1H), 1.29 – 1.11 (m, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 151.2, 145.9, 122.6, 74.4, 74.3, 73.2, 68.5, 51.5, 42.4, 41.9, 41.5, 38.6, 37.4, 25.8, 20.6, 18.1, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2950, 2928, 2855, 1724, 1660, 1435, 1375, 1253, 1219, 1175, 1156, 1126, 1067, 987, 955, 869, 834, 774, 669 cm$^{-1}$. MS (EI) *m/z* (%) = 452 (24), 451 (100), 229 (41), 181 (22), 131 (26), 129 (20), 101 (11), 75 (14), 73 (10). HRMS (ESIpos): *m/z*: calcd for $C_{21}H_{37}O_4SiINa$: 531.1398; found: 531.1393.

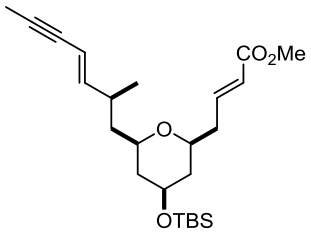
**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*R*,*E*)-2-methylhept-3-en-5-yn-1-yl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (**(*E*)-**148).** A flame-dried two-necked round-bottom flask



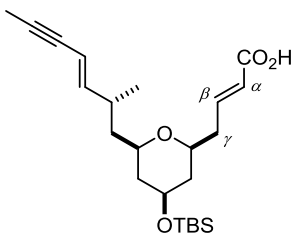

equipped with a reflux condenser was charged with 1-propynylsodium (42.1 mg, 0.677 mmol), which was suspended in degassed THF (4 mL). Trimethyl borate (76.9 µL, 0.677 mmol) was added dropwise via syringe at rt. After stirring for 20 min, [Pd(dppf)$Cl_2$]·$CH_2Cl_2$ (42.5 mg, 0.0521 mmol) was added, causing the reaction mixture to turn dark red. Next, a solution of (*E*)-vinyl iodide **150** (265 mg, 0.521 mmol) in degassed THF (3 mL + 1 mL rinse) was added and the mixture stirred at 65 °C. After 2 h, the pale orange mixture was allowed to cool to ambient temperature, the reaction was quenched with sat. $NH_4Cl/H_2O$ (1:1 v/v, 15 mL) and the aqueous phase was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc 49:1 to 39:1 to 29:1) to give the title compound as a pale yellow oil (177 mg, 81%). $[\propto]_D^{20}$= –30.0 (c = 0.92, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.94 (dt, *J* = 15.7, 7.2 Hz, 1H), 5.93 (ddd, *J* = 15.9, 7.9, 0.8 Hz, 1H), 5.85 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.37 (dqd, *J* = 15.9, 2.2, 1.1 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.71 (s, 3H), 3.39 – 3.30 (m, 1H), 3.25 (dddd, *J* = 11.2, 7.4, 5.5, 1.7 Hz, 1H), 2.47 – 2.25 (m, 3H), 1.90 (d, *J* = 2.2 Hz, 3H), 1.75 (dt, *J* = 4.8, 1.5 Hz, 1H), 1.75 (dt, *J* = 4.8, 1.5 Hz, 1H), 1.61 (dddd, *J* = 7.1, 7.1, 7.0, 6.9 Hz, 1H), 1.28 (ddd, *J* = 13.6, 7.7, 5.7 Hz, 1H), 1.24 – 1.09 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.9, 148.5, 145.5,

122.8, 108.2, 84.4, 78.3, 74.1, 73.2, 68.6, 51.4, 42.3, 41.5, 41.3, 38.7, 33.4, 25.8, 19.6, 18.1, 4.2, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2951, 2928, 2856, 1725, 1660, 1435, 1376, 1328, 1255, 1174, 1068, 985, 962, 836, 775, 670 $cm^{-1}$. MS (EI) *m/z* (%) = 420 (19), 364 (11), 363 (40), 313 (13), 288 (11), 229 (53), 189 (17), 181 (37), 171 (12), 169 (13), 159 (16), 157 (14), 145 (32), 131 (24), 129 (37), 123 (10), 121 (10), 120 (13), 119 (37), 108 (13), 105 (23), 101 (33), 97 (18), 93 (100), 91 (45), 89 (21), 81 (19), 79 (13), 77 (41), 75( 48), 73 (46), 59 (17), 41 (14). HRMS (ESIpos): *m/z*: calcd for $C_{24}H_{40}O_4SiNa$: 443.2588; found: 443.2592.

**Methyl (*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*,*E*)-2-methylhept-3-en-5-yn-1-yl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (**11-*epi*-(*E*)-**148)**. Prepared analogously from vinyl iodide 11-*epi*-**150** (185 mg, 1.05 mmol) as a pale yellow oil (117 mg, 76%). $[\alpha]_D^{20}$ = +93.8 (c = 0.99, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.96 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.86 (dt, *J* = 15.8, 1.5 Hz, 1H), 5.79 (ddd, *J* = 15.8, 9.0, 0.8 Hz, 1H), 5.41 (dqd, *J* = 15.9, 2.3, 0.8 Hz, 1H), 3.72 (m, 4H), 3.38 – 3.25 (m, 1H), 3.20 (dddd, *J* = 11.8, 10.2, 3.0, 1.9 Hz, 1H), 2.53 – 2.34 (m, 2H), 2.30 (tdd, *J* = 7.7, 4.6, 1.6 Hz, 1H), 1.91 (d, *J* = 2.3 Hz, 3H), 1.79 – 1.70 (m, 1H), 1.71 – 1.63 (m, 1H), 1.53 (ddd, *J* = 14.0, 10.1, 4.0 Hz, 1H), 1.28 – 1.10 (m, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 148.0, 145.8, 122.7, 109.2, 84.2, 78.4, 74.1, 73.3, 68.6, 51.4, 42.9, 42.0, 41.4, 38.6, 33.9, 25.8, 21.1, 18.1, 4.2, –4.5, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2951, 2929, 2856, 1727, 1660, 1435, 1375, 1329, 1257, 1218, 1155, 1118, 1072, 962, 852, 837, 776 $cm^{-1}$. MS (EI) *m/z* (%) = 420 (19), 364 (11), 363 (40), 313 (13), 288 (11), 229 (53), 189 (17), 181 (37), 171 (12), 169 (13), 159 (16), 157 (14), 145 (32), 131 (24), 129 (37), 123 (10), 121 (10), 120 (13), 119 (37), 107 (13), 105 (23), 101 (33), 97 (18), 93 (100), 91 (45), 89 (21), 81 (19), 79 (14), 77 (41), 75( 48), 73 (46), 59 (17), 41 (14). HRMS (ESIpos): *m/z*: calcd for $C_{24}H_{40}O_4SiNa$: 443.2588; found: 443.2586.

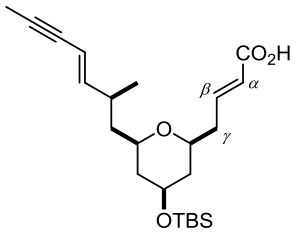



**(*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-((*R*,*E*)-2-methylhept-3-en-5-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)but-2-enoic acid (151).** KOTMS (90%, 246 mg, 1.73 mmol) was added to a solution of methyl ester (*E*)-**148** (145 mg, 0.345 mmol) in $Et_2O$ (7.0 mL). After stirring for 1h, additional KOTMS (90%, 246 mg, 1.73 mmol) was introduced and stirring of the yellow suspension continued for 5 h. Excess base was quenched with aq. HCl (0.5 M, 10 mL) and the aqueous layer was extracted with EtOAc (5 x 15 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated, and the residue purified by flash chromatography (hexanes/EtOAc 6:1 with 0.1% AcOH) to give the desired acid as a colorless oil (112 mg, 80%). As a by-product, the β,γ-olefin was isolated as a colorless oil (9.8 mg, 7%). $[\alpha]_D^{20}$ = –28.2 (c = 1.37, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 13.0 – 10.4 (br s, 1H), 7.06 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.93



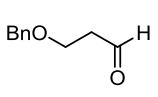
(dd, *J* = 15.9, 7.8 Hz, 1H), 5.84 (dt, *J* = 15.7, 1.2 Hz, 1H), 5.37 (ddd, *J* = 15.9, 2.1, 1.1 Hz, 1H), 3.72 (m, 1H), 3.43 – 3.31 (m, 1H), 3.31 – 3.19 (m, 1H), 2.51 – 2.28 (m, 3H), 1.90 (d, *J* = 2.3 Hz, 3H), 1.80 – 1.73 (m, 2H), 1.61 (dddd, *J* = 7.1, 7.0, 7.0, 6.9 Hz, 1H), 1.29 (ddd, *J* = 13.6, 7.7, 5.7 Hz, 1H), 1.25 – 1.08 (m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.4, 148.5, 148.2, 122.4, 108.2, 84.4, 78.3, 73.9, 73.3, 68.6, 42.3, 41.5, 41.4, 38.8, 33.4, 25.8, 19.6, 18.1, 4.2, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2928, 2926, 2855, 1698, 1654, 1462, 1443, 1376, 1282, 1255, 1152, 1068, 960, 852, 835, 815, 774, 699, 669 cm$^{-1}$. MS (EI) *m/z* (%) = 418 (5), 349 (8), 257 (13), 237 (24), 169 (23), 160 (12), 145 (27), 131 (33), 129 (11), 121 (10), 119 (28), 107 (12), 105 (12), 101 (24), 93 (100), 91 (37), 79 (13), 77 (37), 75 (47), 73 (32), 59 (11), 41 (11). HRMS (ESIpos): *m/z*: calcd for $C_{23}H_{38}O_4SiNa$: 429.2427; found: 429.2431.

**(*E*)-4-((2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*S*,*E*)-2-methylhept-3-en-5-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)but-2-enoic acid (11-*epi*-151).** Prepared analogously from methyl ester 11-*epi*-(*E*)-**148** (116 mg, 0.276 mmol) as a colorless oil (101 mg, 88%), along with the corresponding β,γ-olefin as a colorless oil (8.2 mg, 7%). $[\alpha]_D^{20}$ = +84.0 (c = 1.02, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 13.6 – 9.40 (br s, 1H), 7.08 (dt, *J* = 15.8, 7.0 Hz, 1H), 5.87 (d, *J* = 15.7 Hz, 1H), 5.79 (ddd, *J* = 15.9, 8.9, 0.9 Hz, 1H), 5.41 (ddt, *J* = 16.0, 2.7, 1.9 Hz, 1H), 3.79 – 3.63 (m, 1H), 3.34 (dddd, *J* = 12.6, 6.1, 4.0, 1.7 Hz, 1H), 3.22 (dddd, *J* = 10.9, 10.4, 2.1, 1.8 Hz, 1H), 2.53 – 2.37 (m, 2H), 2.34 (m, 1H), 1.90 (dd, *J* = 2.3, 0.7 Hz, 3H), 1.81 – 1.63 (m, 2H), 1.53 (ddd, *J* = 14.1, 10.0, 4.1 Hz, 1H), 1.30 – 1.10 (m, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.5, 148.3, 148.0, 122.4, 109.2, 84.3, 78.4, 74.0, 73.4, 68.5, 42.9, 41.9, 41.5, 38.7, 33.9, 25.8, 21.1, 18.1, 4.2, –4.5, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2952, 2928, 2856, 1696, 1653, 1421, 1375, 1304, 1283, 1254, 1154, 1117, 976, 960, 924, 852, 834, 774, 739, 669 cm$^{-1}$. MS (EI) *m/z* (%) = 418 (6), 349 (8), 257 (13), 237 (25), 169 (23), 160 (12), 145 (27), 131 (33), 129 (11), 121 (10), 119 (28), 107 (12), 105 (11), 101 (24), 93 (100), 91 (39), 79 (13), 77 (37), 75 (49), 73 (32), 59 (12). HRMS (ESIneg): *m/z*: calcd for $C_{23}H_{37}O_4Si$: 405.2467; found: 405.2468.




### 5.3.2 Synthesis of alcohol 194.

**3-(Benzyloxy)propanal (153).** According to the procedure of Stahl *et. al.*,[58] a 1 L-round-bottom flask was charged with 3-(benzyloxy)propanol (**156**) (7.20 g, 43.3 mmol) and MeCN (HPLC grade, 210 mL). $[Cu(MeCN)_4]BF_4$ (683 mg, 2.17 mmol) and 2,2'-bipyridine (339 mg, 2.17 mmol) were added as solids, followed by *N*-methyl imidazole (346 µL, 4.34 mmol) and TEMPO (339 mg, 2.17 mmol). The resulting red/brown mixture was vigorously stirred open to air for 3 h until the reaction mixture turned dark green. After concentration at reduced pressure, the residue was purified by flash chromatography (hexanes/EtOAc 6:1 to 5:1 to 4:1) to give the desired aldehyde as a colorless oil with an unpleasant smell (6.69 g, 94%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* =

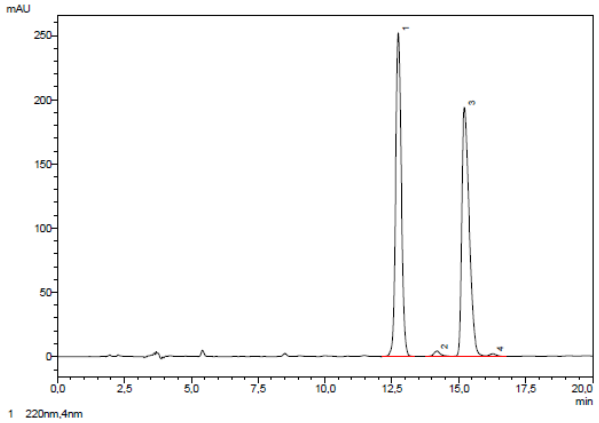


1.8 Hz, 1H), 7.41 – 7.22 (m, 5H), 4.52 (s, 2H), 3.80 (td, *J* = 6.1, 1.2 Hz, 2H), 2.68 (tt, *J* = 6.1, 1.6 Hz, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 201.1, 137.8, 128.4, 127.7, 127.7, 73.2, 63.8, 43.9 ppm. IR (film): $\tilde{\nu}$ = 3031, 2860, 2733, 1721, 1496, 1454, 1394, 1362, 1205, 1091, 1027, 899, 885, 736, 697 cm$^{-1}$. MS (EI) *m/z* (%) = 108 (79), 107 (85), 92 (17), 91 (66), 79 (100), 78 (14), 77 (56), 65 (14), 56 (29), 55 (22), 51 (18), 39 (10), 28 (11), 27 (22), 26 (11). HRMS (ESIpos): *m/z*: calcd for $C_{10}H_{12}O_2H$: 165.0916; found: 165.0914.

**(3*R*,4*R*)-1-(Benzyloxy)-4-methylhex-5-en-3-ol (157).** A solution of crotylsilane (*R*,*R*)-**R17**[167] (1.0 M in $CH_2Cl_2$, 6.62 mmol, 6.62 mL) was added dropwise at −78 °C via syringe to a solution of aldehyde **153** (906 mg, 5.52 mmol) in $CH_2Cl_2$ (56 mL). Next, solid $Sc(OTf)_3$ (136 mg, 0.276 mmol) was added and the mixture stirred for 15 min at −78 °C before it was allowed to reach 0 °C. Stirring was continued for 2 h. At this point, NMR analysis of an aliquot (50 µL) confirmed full consumption of the aldehyde. The mixture was concentrated and treated with aq. HCl (1 M, 70 mL) and $Et_2O$ (70 mL) under vigorous stirring for 1 h. The white precipitate formed was filtered off and washed with $Et_2O$ (2 x 10 mL) (treatment of this solid with NaOH allowed the diamine ligand to be recovered after chromatographic purification in > 90%). The phases of the filtrate were separated and the aqueous layer extracted with $Et_2O$ (3 x 50 mL). The combined extracts were washed with $NaHCO_3$ (70 mL), dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give the crotylated alcohol as a colorless oil (995 mg, 82% yield, 94% ee, 98:2 d.r.). The enantiomeric excess was determined by HPLC of the TBS ether (see conditions below). $[\alpha]_D^{20}$ = +16.5 (c = 1.18, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.25 (m, 5H), 5.77 (ddd, *J* = 17.7, 10.4, 7.6 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.50 (s, 2H), 3.75 – 3.59 (m, 3H), 2.80 (br s, 1H), 2.25 (m, 1H), 1.82 – 1.62 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 141.0, 137.9, 128.4, 127.7, 127.7, 114.9, 74.5, 73.3, 69.4, 43.9, 33.5, 15.0 ppm. IR (film): $\tilde{\nu}$ = 3471, 3031, 2943, 2865, 1638, 1496, 1454, 1418, 1363, 1206, 1092, 1071, 1028, 997, 949, 913, 736, 697 cm$^{-1}$. MS (EI) *m/z* (%) = 220 (0.1), 165 (3), 107 (14), 92 (13), 91 (100), 79 (7), 65 (8), 55 (7). HRMS (ESIpos): *m/z*: calcd for $C_{14}H_{20}O_2Na$: 243.1355; found: 243.1356.

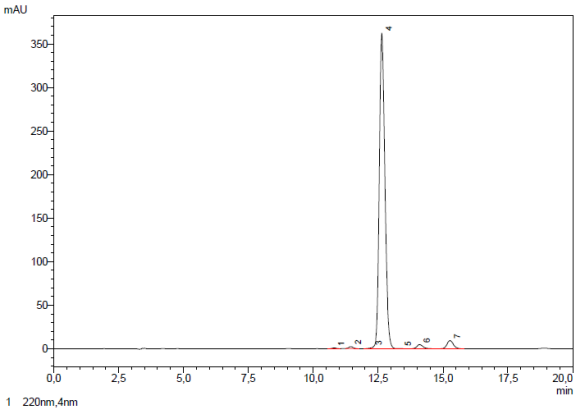
**(3*S*,4*S*)-1-(Benzyloxy)-4-methylhex-5-en-3-ol (*ent*-157).** Prepared analogously from aldehyde **153** (1.98 g, 12.0 mmol) and crotylsilane (*S*,*S*)-**R17** (1.0 M in $CH_2Cl_2$, 8.21 mmol, 8.21 mL) as a colorless oil (2.13 g, 80% yield, 94.6% ee, 98:2 d.r.). The enantiomeric excess was determined by HPLC of the TBS ether (see conditions below).

**(((3*R*,4*R*)-1-(Benzyloxy)-4-methylhex-5-en-3-yl)oxy)(tert-butyl)dimethylsilane (158).** TBSOTf (782 µL, 3.40 mmol) and 2,6-lutidine (463 µL, 3.98 mmol) were added to a solution of alcohol **157** (625 mg, 2.84 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before the reaction was quenched by addition of sat. $NH_4Cl$ solution (30 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 35:1) yielded the target silyl ether as a colorless oil (908 mg, 96%). $[\alpha]_D^{20}$= +37.4 (c = 1.39, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.30 (m, 4H), 7.30 – 7.24 (m, 1H), 5.87 (ddd, *J* = 17.3, 10.7, 6.8 Hz, 1H), 5.03 – 4.95 (m, 2H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 3.75 – 3.69 (m, 1H), 3.55 – 3.49 (m, 2H), 2.35 – 2.25 (m, 1H), 1.75 (dtd, *J* = 13.9, 7.4, 4.0 Hz, 1H), 1.65 (ddt, *J* = 13.9, 7.8, 6.2 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.5, 128.3, 127.6, 127.5, 114.2, 72.9, 72.9, 67.1, 43.0, 33.4, 25.9, 18.1, 14.9, −4.3, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2928, 2885, 2856, 1472, 1461, 1455, 1361, 1253, 1092, 1050, 1028, 1005, 912, 835, 774, 733, 696 cm$^{-1}$. MS (EI) *m/z* (%) = 279 (11), 173 (21), 131 (8), 91 (100), 73 (13). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{34}O_2SiNa$: 357.2220; found: 357.2219. HPLC: 150 mm Chiralcel OJ-3R (Ø 4.6 mm), MeCN/water 70:30, 0.5 mL/min, 308 K, 9.2 MPa: $R_t$ = 12.64 min (major *syn*), 14.10 min (*anti*), 15.27 min (minor *syn*).




PDA Ch1 220nm

| Peak # | Ret. Time | Area % | Name |
|---|---|---|---|
| 1 | 12,74 | 49,16 | 1. Enantiomer |
| 2 | 14,18 | 1,00 | |
| 3 | 15,21 | 49,32 | 2. Enantiomer |
| 4 | 16,27 | 0,52 | |
| Total | | 100,00 | |



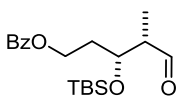

PDA Ch1 220nm

| Peak # | Ret. Time | Area % | Name |
|---|---|---|---|
| 1 | 10,80 | 0,18 | |
| 2 | 11,44 | 0,46 | |
| 3 | 12,25 | 0,14 | |
| 4 | 12,64 | 95,00 | 1. Enantiomer 94.3 % ee |
| 5 | 13,38 | 0,06 | |
| 6 | 14,10 | 1,39 | |
| 7 | 15,27 | 2,78 | 2. Enantiomer |
| Total | | 100,00 | |

**(2*S*,3*R*)-5-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal (152).** The terminal alkene **158** (900 mg, 2.67 mmol) was dissolved in $CH_2Cl_2$ and the resulting solution cooled to −78 °C. Ozone was bubbled through the solution (~30 g/Nm$^3$) until TLC analysis showed complete conversion of the alkene (30 min) and the solution turned blue. Argon was then bubbled for 10 min through the solution, which turned colorless. Triphenylphosphine (842 mg, 3.21 mmol) was added as a solid and the reaction mixture was allowed to warm to ambient temperature and stirred for 3.5 h. The volatiles were then removed under reduced

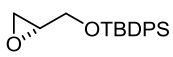
pressure and the residue purified by flash chromatography (hexanes/EtOAc 29:1 to 19:1) to yield the desired aldehyde as a colorless liquid (823 mg, 91%) along with the benzoate as a by-product. $[\alpha]_D^{20}$ = +42.5 (c = 1.34, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.76 (d, *J* = 0.9 Hz, 1H), 7.37 – 7.24 (m, 5H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.30 (ddd, *J* = 7.3, 5.6, 3.6 Hz, 1H), 3.56 – 3.45 (m, 2H), 2.46 (qdd, *J* = 6.9, 3.7, 1.0 Hz, 1H), 1.89 – 1.69 (m, 2H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 205.1, 138.3, 128.4, 127.6, 73.0, 69.3, 66.6, 51.6, 34.6, 25.8, 18.0, 7.9, −4.5, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2953, 2929, 2856, 1725, 1496, 1472, 1455, 1361, 1252, 1148, 1099, 1028, 1005, 938, 834, 774, 734, 697 cm$^{-1}$. MS (EI) *m/z* (%) = 279 (1), 187 (4), 173 (9), 145 (10), 131 (16), 115 (5), 92 (9), 91 (100), 59 (5). HRMS (ESIpos): *m/z*: calcd for $C_{19}H_{32}O_3SiNa$: 359.2013; found: 357.2010.

**(3*R*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-5-oxopentyl benzoate (159).** Obtained as a by-




product from the reaction described above as a colorless oil (37 mg, 4%) $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.76 (d, *J* = 1.0 Hz, 1H), 8.04 – 7.89 (m, 2H), 7.56 – 7.45 (m, 1H), 7.44 – 7.33 (m, 2H), 4.38 (dt, *J* = 11.7, 6.0 Hz, 1H), 4.33 – 4.22 (m, 2H), 2.50 (qdd, *J* = 7.0, 3.7, 1.0 Hz, 1H), 1.97 (dddd, *J* = 14.1, 7.8, 6.2, 5.1 Hz, 1H), 1.86 (ddt, *J* = 14.3, 7.7, 5.7 Hz, 1H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.82 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.6, 166.4, 133.0, 130.1, 129.5, 128.4, 69.2, 61.6, 51.6, 33.5, 25.7, 18.0, 8.2, −4.5, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2911, 2876, 1455, 1414, 1363, 1238, 1091, 1004, 911, 840, 725, 695 cm$^{-1}$. MS (EI) *m/z* (%) = 293 (1), 213 (3), 201 (1), 179 (25), 172 (14), 171 (100), 141 (10), 127 (8), 115 (32), 105 (74), 97 (41), 91 (10), 77 (25), 59 (14). HRMS (ESIpos): *m/z*: calcd for $C_{19}H_{30}O_4SiNa$: 373.1806; found: 373.1807.

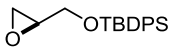
**(*R*)-*tert*-Butyl(oxiran-2-ylmethoxy)diphenylsilane (160).** A solution of TBDPSCl (18.1 mL,



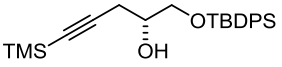

69.4 mmol) in $CH_2Cl_2$ (50 mL) was added over 15 min via a dropping funnel to a solution of (*S*)-glycidol (**155**) (4.41 mL, 66.1 mmol) and imidazole (5.99 g, 87.9 mmol) in $CH_2Cl_2$ (200 mL) at 0 °C. A white solid started to precipitate after 5 min and the reaction mixture was allowed to warm to rt. After 2 h, $H_2O$ (250 mL) was added and the aqueous phase extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 19:1 to 9:1) to give the desired silyl ether as a colorless oil (19.5 g, 94%). $[\alpha]_D^{20}$ = +0.9 (c = 1.41, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.61 (m, 4H), 7.47 – 7.32 (m, 6H), 3.84 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.70 (dd, *J* = 11.8, 4.7 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.73 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.60 (dd, *J* = 5.2, 2.7 Hz, 1H), 1.05 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.6, 135.5, 132.3, 129.7, 127.0, 64.3, 52.3, 44.4, 26.8, 19.2 ppm. IR (film): $\tilde{\nu}$ = 3071, 3049, 2998, 2930, 2894, 2857, 1472, 1427, 1390, 1361, 1254, 1159, 1136, 1111, 1091, 1030, 980, 917, 823, 739, 700, 690 cm$^{-1}$. MS (EI) *m/z* (%) = 256 (11), 255 (53), 226 (20), 225 (100), 211 (22), 184 (16), 183 (87),

181 (20), 177 (46), 117 (38), 105 (13), 77 (99). HRMS (ESIpos): *m/z*: calcd for $C_{19}H_{24}O_2SiNa$: 335.1438; found: 335.1435.

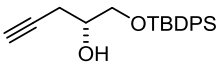
***(S)*-*tert*-Butyl(oxiran-2-ylmethoxy)diphenylsilane (*ent*-160).** Prepared analogously from (*R*)-glycidol (*ent*-**155**) (3.0 g, 40.5 mmol) as a colorless oil (12.0 g, 95%).




**(*R*)-1-((tert-Butyldiphenylsilyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-ol (161).** A solution of *n*-BuLi (1.65 M in hexane, 40.6 mL, 66.9 mmol) was added dropwise via dropping funnel over 12 min to a solution of trimethylsilylacetylene (7.17 g, 73.0 mmol) in THF (300 mL) at −78 °C. The resulting yellow solution was stirred for 15 min at −78 °C, when $BF_3{\cdot}Et_2O$ (9.26 mL, 73.0 mmol) was added dropwise via syringe over 5 min. A solution of epoxide **160** (18.3 g, 58.6 mmol) in THF (15 mL) was then added dropwise via syringe over 6 min and the reaction mixture allowed to stir for further 90 min. The reaction was then quenched by careful addition of sat. $NH_4Cl$ solution (300 mL) and EtOAc (200 mL) and the mixture subsequently warmed to ambient temperature. After phase separation, the aqeuos phase was extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (short column (~9cm), hexanes/EtOAc 14:1) yielded the desired alcohol as a colorless oil (21.9 g, 91%). $[\alpha]_D^{20} = -5.3$ (c = 0.99, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.69 – 7.62 (m, 4H), 7.46 – 7.32 (m, 6H), 3.75 (ddd, *J* = 10.1, 4.3, 0.7 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.69 (ddd, *J* = 10.1, 5.9, 0.8 Hz, 1H), 2.58 – 2.42 (m, 3H), 1.06 (s, 9H), 0.10 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.1, 129.8, 127.8, 127.7, 102.6, 87.1, 70.2, 66.4, 26.9, 24.7, 19.3, 0.0 ppm. IR (film): $\tilde{\nu}$ = 3487, 2958, 2931, 2858, 2177, 1472, 1428, 1391, 1362, 1249, 1112, 1188, 1112, 1030, 1008, 970, 936, 840, 823, 759, 739, 700 cm$^{-1}$. MS (EI) *m/z* (%) = 353 (17), 272 (12), 271 (45), 242 (21), 241 (100), 223 (12), 221 (9), 211 (6), 200 (13), 199 (74), 193 (13), 163 (31), 105 (6), 73 (14). HRMS (ESIpos): *m/z*: calcd for $C_{24}H_{34}O_2Si_2Na$: 433.1990; found: 433.1987.



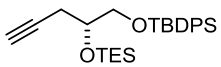

**(*R*)-1-((tert-Butyldiphenylsilyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-ol (162).** The secondary alcohol **161** (21.8 g, 53.1 mmol) was dissolved in MeOH (200 mL) and the solution cooled to 15 °C. Potassium carbonate (14.6 g, 106 mmol) was added slowly and the reaction mixture stirred vigorously. After 1h, the reaction was quenched with sat. $NH_4Cl$ solution (200 mL) and the mixture extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue (17.5 g, 97%) thus obtained turned out to be a 8:1 mixture of alkynes **162** and **163** as the result of 1,2-silyl migration.




A part of the residue (16.7 g, 49.3 mmol) was dissolved in $CH_2Cl_2$ (250 mL), cooled to −78 °C, and treated with triethylamine (1.16 mL, 8.4 mmol), TESCl (1.24 mL, 7.4 mmol) and DMAP (30 mg, 0.25 mmol). The mixture was stirred for 4 h at −78 °C before the reaction was quenched with sat. $NH_4Cl$ solution (200 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 x 200 mL) and the

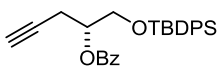
combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 13:1 to 4:1) to yield pure secondary alcohol **162** as a colorless oil (12.7 g, 76%). $[\alpha]_D^{20}$ = −2.5 (c = 1.36, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.71 – 7.62 (m, 4H), 7.46 – 7.35 (m, 6H), 3.88 (qd, *J* = 6.2, 4.3 Hz, 1H), 3.75 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.69 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.46 m, 3H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.07 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.5, 135.5, 133.0, 133.0, 129.8, 127.8, 80.3, 70.4, 70.1, 66.3, 26.8, 23.2, 19.2 ppm. IR (film): $\tilde{\nu}$ = 3433, 3301, 3072, 2931, 2858, 1472, 1427, 1391, 1361, 1259, 1188, 1111, 1072, 1043, 1007, 998, 971, 936, 909, 822, 798, 739, 699 cm$^{-1}$. MS (EI) *m/z* (%) = 281 (12), 242 (10), 241 (51), 200 (18), 199 (100), 181 (12), 163 (16), 139 (12), 135 (8), 105 (8), 77 (8). HRMS (ESIpos): *m/z*: calcd for $C_{21}H_{26}O_2Si_1Na$: 361.1594; found: 361.1591.

**(*R*)-8,8-Diethyl-2,2-dimethyl-3,3-diphenyl-6-(prop-2-yn-1-yl)-4,7-dioxa-3,8-disiladecane (164)**.




The secondary alcohol **162** (1.96 g, 5.79 mmol) was dissolved in $CH_2Cl_2$ (29 mL) and cooled to 0 °C. Triethylamine (0.96 mL, 6.93 mmol) and TESCl (1.08 mL, 6.40 mmol) were added slowly via syringe, followed by DMAP (7.1 mg, 58 µmol) as a solid. The mixture was stirred for 3 h at 0 °C before the reaction quenched by addition of sat. $NH_4Cl$ solution (12 mL). After separation of the layers, the aqueous phase was further extracted with EtOAc (3 x 7 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 29:1) yielded the desired silyl ether as a colorless oil (2.28 g, 87%). $[\alpha]_D^{20}$ = +7.3 (c = 1.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.72 – 7.63 (m, 4H), 7.46 – 7.31 (m, 6H), 3.91 – 3.80 (m, 1H), 3.68 – 3.56 (m, 2H), 2.60 (dddd, *J* = 16.7, 5.5, 2.7, 0.8 Hz, 1H), 2.38 (dddd, *J* = 16.7, 5.9, 2.7, 0.8 Hz, 1H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.04 (d, *J* = 0.8 Hz, 9H), 0.90 (dd, *J* = 8.3, 7.5 Hz, 9H), 0.54 (q, *J* = 8.0 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.6, 135.6, 133.6, 133.4, 129.6, 127.6, 81.6, 71.4, 69.6, 66.8, 26.8, 24.4, 19.2, 6.8, 4.8 ppm. IR (film): $\tilde{\nu}$ = 3312, 2954, 2933, 2876, 1472, 1462, 1427, 1390, 1361, 1239, 1111, 1072, 1003, 938, 855, 823, 807, 736, 699 cm$^{-1}$. MS (EI) *m/z* (%) = 423 (19), 396 (11), 395 (30), 315 (11), 314 (30), 313 (100), 285 (30), 243 (10), 197 (15), 183 (7), 163 (10), 143 (11), 135 (32), 87 (14). HRMS (ESIpos): *m/z*: calcd for $C_{27}H_{40}O_2Si_2Na$: 475.2459; found: 475.2461.

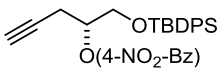
**(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)pent-4-yn-2-yl benzoate (165).** The secondary Alcohol **162**




(1.20 g, 3.55 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and the solution cooled to 0 °C. Triethylamine (0.589 mL, 4.25 mmol) and benzoyl chloride (0.452 mL, 3.89 mmol) were added slowly via syringe, followed by DMAP (21.7 mg, 178 µmol) as a solid. The mixture was stirred for 1 h at 0 °C and 3 h at ambient temperature before the reaction was quenched by addition of sat. $NH_4Cl$ solution (15 mL). After separation of the layers, the aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography

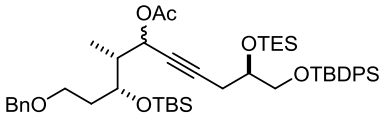
(hexanes/EtOAc 9:1) yielded the desired silyl ether as a pale yellow oil (1.24 g, 79%). $[\alpha]_D^{20}$ = −11.7 (c = 1.69, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.11 – 7.97 (m, 2H), 7.68 – 7.62 (m, 4H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.25 (m, 8H), 5.36 – 5.24 (m, 1H), 3.97 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.92 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.81 (ddd, *J* = 16.7, 6.5, 2.3 Hz, 1H), 2.72 (ddd, *J* = 16.7, 5.6, 2.2 Hz, 1H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.04 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.8, 135.5, 133.1, 133.0, 130.2, 129.7, 129.7, 128.3, 127.7, 127.7, 79.5, 72.6, 70.4, 63.6, 26.7, 20.6, 19.3 ppm. IR (film): $\tilde{\nu}$ = 3305, 2958, 2931, 2858, 1718, 1602, 1588, 1472, 1451, 1427, 1391, 1361, 1315, 1266, 1176, 1108, 1069, 1047, 1026, 997, 823, 796, 738, 701, 615 cm$^{-1}$. MS (EI) *m/z* (%) = 386 (16), 385 (54), 304 (22), 303 (88), 259 (17), 105 (100), 77 (11). HRMS (ESIpos): *m/z*: calcd for $C_{28}H_{30}O_3Si_1Na$: 465.1856; found: 465.1857.

**(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)pent-4-yn-2-yl 4-nitrobenzoate (166)**. The secondary Alcohol




**162** (2.00 g, 5.91 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and cooled to 0 °C. Triethylamine (0.98 mL, 7.1 mmol) and 4-nitrobenzoyl chloride (1.21 g, 6.50 mmol) were added slowly, followed by DMAP (36.1 mg, 296 µmol) as a solid. The mixture was stirred for 1.5 h at 0 °C before the reaction was quenched by addition of sat. $NH_4Cl$ solution (15 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 9:1) yielded the desired silyl ether as a yellow oil (2.52 g, 87%). $[\alpha]_D^{20}$ = −13.3 (c = 1.01, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.66 – 7.59 (m, 4H), 7.43 – 7.27 (m, 6H), 5.36 – 5.27 (m, 1H), 3.97 (dd, *J* = 11.0, 4.7 Hz, 1H), 3.93 (dd, *J* = 10.7, 4.2 Hz), 2.79 (ddd, *J* = 17.0, 6.4, 2.6 Hz, 1H), 2.73 (ddd, *J* = 17.1, 6.1, 2.7 Hz, 1H), 1.03 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.9, 150.6, 135.5, 135.5, 133.0, 132.9, 130.8, 129.8, 127.7, 127.7, 123.5, 79.0, 73.6, 70.7, 63.5, 26.7, 20.6, 19.2 ppm. IR (film): $\tilde{\nu}$ = 3297, 3072, 2931, 2858, 1725, 1608, 1527, 1472, 1427, 1348, 1320, 1269, 1112, 1102, 1044, 1014, 997, 873, 823, 783, 741, 718, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 431 (11), 430 (35), 349 (26), 348 (100), 302 (8), 150 (30), 104 (11). HRMS (ESIpos): *m/z*: calcd for $C_{27}H_{40}O_2Si_2Na$: 475.2459; found: 475.2461.

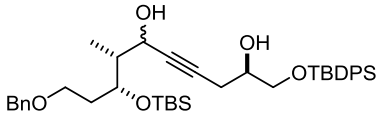
**(5*R*,6*R*,11*R*)-5-(2-(Benzyloxy)ethyl)-2,2,3,3,6,15,15-heptamethyl-14,14-diphenyl-11-((triethylsilyl) oxy)-4,13-dioxa-3,14-disilahexadec-8-yn-7-yl acetate (167)**. A solution of *n*-BuLi (1.60 M in hexane,




221 µL, 353 µmol) was added dropwise over 2 min to a −78 °C solution of terminal alkyne **164** (160 mg, 353 µmol) in THF (2.0 mL). After 25 min stirring at −78 °C, a solution of aldehyde **152** (120 mg, 357 µmol) in THF (1.0 mL) was added dropwise. After 2 h, the reaction mixture was warmed to 0 °C and stirred for another 2 h. Acetyl chloride (25.5 µL, 0.357 mmol) was added, the reaction mixture allowed to warm to ambient temperature and stirred for another 2 h. The reaction was

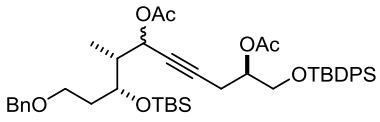
quenched by addition of water (5 mL) and brine (5 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography to give the desired propargylic acetate as a colorless oil as a mixture of diastereomers (2.9:1 d.r., 104 mg, 35%). $^1$H NMR (400 MHz, $C_6D_6$, only the peaks of the major isomer are listed): δ = 7.86 – 7.77 (m, 4H), 7.33 – 7.23 (m, 8H), 7.23 – 7.17 (m, 2H), 7.10 (tt, *J* = 7.3, 1.4 Hz, 1H), 5.90 (dt, *J* = 7.6, 2.0 Hz, 1H), 4.38 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.35 – 4.27 (m, 2H), 3.99 – 3.91 (m, 1H), 3.87 – 3.76 (m, 2H), 3.47 – 3.35 (m, 2H), 2.76 (ddd, *J* = 16.6, 5.6, 1.8 Hz, 1H), 2.53 (ddd, *J* = 16.5, 5.9, 2.2 Hz, 1H), 2.13 (qdd, *J* = 7.1, 7.0, 3.3 Hz, 1H), 1.89 (q, *J* = 6.4 Hz, 2H), 1.72 (s, 3H), 1.16 (s, 9H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.57 (q, J = 8.1 Hz, 6H), 0.23 (s, 3H), 0.13 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$, only the peaks of the major isomer are listed): δ = 169.1, 139.2, 136.0, 136.0, 134.0, 133.8, 130.0, 128.5, 128.1, 128.1, 127.7, , 127.6, 83.7, 79.9, 73.1, 72.0, 70.5, 67.4, 67.0, 66.3, 43.5, 35.4, 27.1, 26.2, 25.0, 20.6, 19.5, 18.4, 10.1, 7.1, 5.2, −4.1, −4.2 ppm. IR (film): $\tilde{\nu}$ = 2953, 2931, 2877, 2857, 1744, 1472, 1462, 1428, 1362, 1230, 1111, 1016, 971, 940, 862, 835, 775, 737, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 641 (6), 639 (6), 623 (6), 435 (9), 383 (6), 313 (21), 285 (16), 281 (12), 279 (43), 241 (10), 237 (21), 197 (11), 181 (10), 175 (15), 174 (12), 173 (85), 171 (17), 135 (28), 131 (43), 117 (31), 115 (10), 91 (100), 87 (11). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{74}O_6Si_3Na$: 853.4685; found: 853.4685.

**((6*R*,11*R*,12*R*)-12-(2-(Benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yne-6,10-diol**. A solution of *n*-BuLi (1.60 M in hexane, 0.240 mL, 0.384 mmol) was added dropwise to a solution of alkyne **162** in THF (1.0 mL) at −78 °C. The resulting pale yellow solution was stirred for 5 min at −78 °C, 15 min at −30 °C and recooled to −78 °C, when aldehyde **152** (51.5 µL, 0.148 mmol) was added dropwise via syringe. The mixture was stirred for 1.5 h at −78 °C before the reaction was quenched by the addition of aqueous HCl (0.1 M, 4 mL) and EtOAc (3 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtoAc 5:1) to yield two inseparable diastereomers (48 mg, 60%, 1.4:1 mixture of diastereomers) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$, the peaks of both diastereomers are listed): δ = 7.65 (d, *J* = 7.1 Hz, 4H), 7.47 – 7.20 (m, 11H), 4.54 – 4.41 (m, 2H), 4.40 – 4.24 (m, 1H), 4.14 – 4.04 (m, 1H), 3.89 – 3.81 (m, 1H), 3.74 – 3.66 (m, 2H), 3.51 – 3.40 (m, 2H), 2.59 (br s, 1H), 2.54 – 2.42 (m, 2H), 1.96 – 1.69 (m, 3H), 1.35 – 1.24 (m, 1H), 1.06 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 1.7H), 0.86 (m, 10.3H), 0.13 – 0.01 (m, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, the peaks of both diastereomers are listed): δ = 138.3, 135.5, 133.0, 129.8, 128.3, 128.3, 127.8, 127.8, 127.7, 127.6, 127.5, 127.5, 83.1, 83.0, 81.8, 81.3, 72.9, 72.1, 71.5, 70.4, 70.4, 66.8, 66.5, 65.4, 65.2, 43.9, 43.6, 41.3, 36.0, 34.6, 33.7, 32.7, 29.7, 29.0, 27.6, 26.9, 26.8, 25.8, 25.8, 23.6, 23.6, 22.6, 20.4, 19.4, 19.2, 18.7, 18.0, 17.9, 14.3, 12.2, 11.4, 9.3, −4.3, −4.5, −4.6, −4.7 ppm. IR

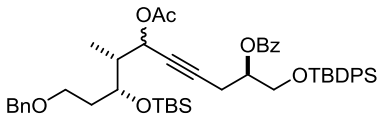


(film): $\tilde{\nu}$ = 3413, 2953, 2929, 2885, 2856, 1471, 1462, 1427, 1389, 1361, 1252, 1111, 1027, 1005, 938, 834, 775, 738, 699 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 697.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{40}H_{58}O_5Si_2Na$: 697.3715; found: 697.3712.

**(6*R*,11*R*,12*R*)-12-(2-(Benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yne-6,10-diyl diacetate (168)**. A diastereomeric mixture of the diol described above (97.0 mg, 0.144 mmol) was dissolved in $CH_2Cl_2$ (0.8 mL) and the resulting solution cooled to 0 °C. Triethylamine (44.8 µL, 0.323 mmol) and acetic anhydride (29.2 µL, 0.309 mmol) were added via syringe, followed by the addition of DMAP (1.8 mg, 14 µmol) as a solid. The mixture was stirred for 1 h at 0 °C before the reaction was quenched by addition of sat. $NH_4Cl$ solution (5 mL). The aqueous phase was then extracted with $CH_2Cl_2$ (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 14:1 to 12:1) to give the bisacetate as a colorless oil (1.5:1 mixture of diastereomers, 91.6 mg, 84%). $[\alpha]_D^{20}$ = +9.7 (c = 1.09, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$, the peaks of both diastereomers are listed): δ = 7.69 – 7.59 (m, 4H), 7.43 – 7.24 (m, 11H), 7.23 – 7.19 (m, 1H), 5.34 (d, *J* = 7.0 Hz, 0.6H, major isomer), 5.19 (d, *J* = 7.6 Hz, 0.4H, minor isomer), 5.02 – 4.93 (m, 1H), 4.50 – 4.37 (m, 2H), 4.01 (td, *J* = 6.1, 3.4 Hz, 0.6H, major isomer), 3.91 (6.1 Hz, 3.1 Hz, 0.4H, minor isomer), 3.80 – 3.67 (m, 2H), 3.49 – 3.38 (m, 2H), 2.70 – 2.48 (m, 2H), 2.03 – 1.95 (m, 6H), 1.89 – 1.69 (m, 3H), 1.01 (s, 9H), 0.93 (dd, *J* = 7.0 Hz, 1.2H, minor isomer), 0.91 (d, *J* = 6.9 Hz, 1.8H, major isomer), 0.83 (m, 9H), 0.03 (s, 1.8H, major isomer), 0.00 (s, 1.8H, major isomer), −0.01 (s, 1.2H, minor isomer), −0.05 (s, 1.2H, minor isomer) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, the peaks of both diastereomers are listed): δ = 170.1, 169.8, 169.7, 138.5, 138.4, 135.5, 135.5, 133.3, 133.2, 129.7, 128.3, 127.7, 127.7, 127.5, 127.5, 127.5, 81.9, 81.4, 79.6, 79.2, 72.9, 72.1, 72.0, 69.9, 68.6, 67.0, 66.8, 65.9, 65.8, 63.9, 63.8, 43.0, 41.9, 34.6, 34.5, 26.7, 25.9, 22.6, 21.0, 21.0, 21.0, 20.9, 20.8, 19.3, 18.1, 18.1, 10.1, 9.8, −4.2, −4.4, −4.5, −4.9 ppm. IR (film): $\tilde{\nu}$ = 2956, 2931, 2857, 1744, 1472, 1428, 1371, 1231, 1113, 1050, 1010, 836, 776, 740, 701 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 781.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{44}H_{62}O_7Si_2Na$: 781.3926; found: 781.3921.

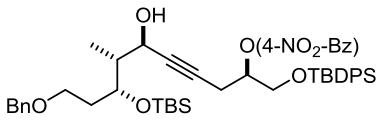



**(6*R*,11*R*,12*R*)-10-Acetoxy-12-(2-(benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yn-6-yl benzoate (169)**. A solution of *n*-BuLi (1.60 M in hexane, 0.111 mL, 0.178 mmol) was added dropwise to a solution of diisopropylamine (24.7 µL, 0.178 mmol) in THF (0.6 mL) at −78 °C. The resulting pale yellow solution was stirred for 5 min at −78 °C, 30 min at 0 °C and recooled to −78 °C, when a solution of alkyne **165** (85.2 mg, 0.192 mmol) in THF (0.4 mL) was added dropwise. The reaction mixture was stirred for another 20 min at −78 °C before aldehyde **152** (51.5 µL, 0.148 mmol) was added carefully. The mixture was stirred for 2 h at



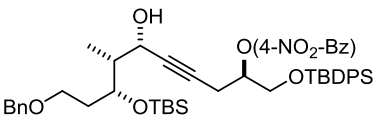
−78 °C and 30 min at 0 °C before the reaction was quenched by the addition of sat. $NH_4Cl$ solution (3 mL) and EtOAc (3 mL). The aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtoAc 9:1 to 7:1 to 5:1) and yielded a mixture of two inseparable diastereomers as a pale yellow liquid (67 mg, 58%, 90% purity). This mixture (2.4:1 d.r., 67.0 mg, 85.9 µmol) was dissolved in $CH_2Cl_2$ (0.6 mL) and the solution cooled to 0 °C. Triethylamine (13.7 µL, 98.8 µmol), acetic anhydride (8.9 µL, 95 µmol) and DMAP (1.05 mg, 8.6 µmol) were added successively and the mixture was stirred for 1 h at 0 °C. The reaction was then quenched by addition of sat. $NH_4Cl$ solution (4 mL) and the aqueous phase extracted with $CH_2Cl_2$ (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 19:1 to 14:1) yielded the desired propargylic acetate as a colorless oil (2.4:1 d.r., 42.6 mg, 60%). $^1$H NMR (400 MHz, $CDCl_3$, the peaks of both diastereoisomers are listed): δ = 8.04 – 7.95 (m, 2H), 7.65 – 7.56 (m, 4H), 7.51 (dd, *J* = 9.2, 5.9 Hz, 1H), 7.42 – 7.20 (m, 13H), 5.33 (d, *J* = 7.1 Hz, 0.8H), 5.28 – 5.15 (m, *J* = 10.2, 8.6, 4.7 Hz, 1.2H), 4.45 – 4.33 (m, 2H), 3.96 (td, *J* = 6.2, 3.4 Hz, 0.8H), 3.92 – 3.78 (m, 2.2H), 3.43 – 3.32 (m, 2H), 2.86 – 2.64 (m, 2H), 1.93 (s, 2.1H), 1.90 (s, 0.85H), 1.82 – 1.60 (m, 3H), 0.99 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 0.85H), 0.87 (d, *J* = 6.8 Hz, 2.1H), 0.82 – 0.78 (m, 9H), −0.02 – −0.09 (m, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, only the peaks of the major isomer are listed): δ = 169.7, 165.7, 138.4, 135.5, 133.1, 133.0, 130.2, 129.7, 129.7, 129.7, 128.3, 127.7, 127.7, 127.5, 127.5, 127.4, 81.4, 79.8, 72.9, 72.7, 69.9, 66.9, 65.8, 63.7, 43.0, 34.5, 26.7, 25.8, 20.9, 19.2, 18.0, 9.8, −4.4, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2930, 2856, 1743, 1721, 1472, 1462, 1453, 1362, 1314, 1268, 1228, 1176, 1106, 1045, 1026, 971, 938, 835, 794, 775, 739, 700 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 843.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{49}H_{63}N_1O_9Si_2Na$: 843.4083; found: 843.4090.

**(6*R*,10*R*,11*R*,12*R*)-12-(2-(Benzyloxy)ethyl)-10-hydroxy-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yn-6-yl 4-nitrobenzoate**.[246] A solution of *n*-BuLi (1.60 M in hexane, 0.111 mL, 0.178 mmol) was added dropwise to a solution of diisopropylamine (24.7 µL, 0.178 mmol) in THF (0.6 mL) at −78 °C. The resulting pale yellow solution was stirred for 5 min at −78 °C, 25 min at 0 °C and recooled to −78 °C, when a solution of alkyne **166** (93.7 mg, 0.192 mmol) in THF (0.4 mL + 2 x 0.1 mL rinse) was introduced dropwise via syringe. The reaction mixture was stirred for another 20 min at −78 °C before aldehyde **152** (51.5 µL, 0.148 mmol) was added carefully. The mixture was stirred for 2 h at −78 °C before the reaction was quenched by the addition of sat. $NH_4Cl$ solution (3 mL) and EtOAc (3 mL). The aqueous phase was further extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtoAc 8:1 to 7:1) to yield two separable diastereomers (major: 34.5 mg, 27%; minor: 17.3 mg, 13%) as pale yellow



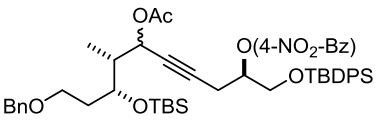
liquids. The two diastereomers were combined prior to the next step. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.6 Hz, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.64 – 7.54 (m, 4H), 7.40 – 7.24 (m, 10H), 7.21 (t, *J* = 4.8 Hz, 1H), 5.31 – 5.22 (m, 1H), 4.46 – 4.34 (m, 3H), 4.00 – 3.94 (m, 1H), 3.95 – 3.86 (m, 2H), 3.40 (t, *J* = 6.3 Hz, 2H), 2.78 (dd, *J* = 16.8, 6.2 Hz, 1H), 2.71 (dd, *J* = 16.9, 6.1 Hz, 1H), 2.57 (br s, 1H), 1.91 – 1.66 (m, 3H), 0.99 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), −0.01 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.9, 150.5, 138.3, 135.5, 135.5, 133.0, 133.0, 130.8, 129.8, 128.3, 127.7, 127.7, 127.5, 127.5, 123.4, 83.2, 80.3, 74.0, 72.9, 72.4, 66.7, 65.3, 63.7, 43.4, 34.4, 26.7, 25.8, 20.9, 19.2, 18.0, 9.3, −4.3, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2953, 2931, 2877, 2857, 1744, 1472, 1462, 1428, 1362, 1230, 1111, 1016, 971, 940, 862, 835, 775, 737, 701 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 846.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{61}N_1O_8Si_2Na$: 846.3828; found: 846.3836.

**(6*R*,10*R*,11*R*,12*R*)-12-(2-(Benzyloxy)ethyl)-10-hydroxy-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yn-6-yl 4-nitrobenzoate**. Obtained as the minor




diastereomer from the reaction described above. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.5 Hz, 2H), 7.65 – 7.57 (m, 4H), 7.40 – 7.26 (m, 11H), 5.31 (p, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.27 (d, *J* = 9.2 Hz, 1H), 4.04 (dt, *J* = 7.9, 3.8 Hz, 1H), 3.98 – 3.88 (m, 2H), 3.56 – 3.38 (m, 3H), 2.82 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.70 (dd, *J* = 16.8, 6.3 Hz, 1H), 1.84 – 1.70 (m, 3H), 1.01 (s, 9H), 0.84 (s, 9H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.9, 150.5, 138.3, 135.6, 135.5, 133.0, 130.8, 129.8, 128.4, 127.7, 127.7, 127.6, 127.6, 123.5, 83.3, 80.1, 73.9, 73.0, 71.8, 66.7, 65.2, 63.8, 44.0, 32.4, 26.7, 25.8, 21.0, 19.2, 17.9, 12.5, −4.5, −4.8 ppm. IR (film): $\tilde{\nu}$ = 2954, 2931, 2878, 2857, 1745, 1471, 1462, 1429, 1362, 1231, 1110, 1016, 972, 940, 863, 835, 776, 737, 702 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 846.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{61}N_1O_8Si_2Na$: 846.3831; found: 846.3836.

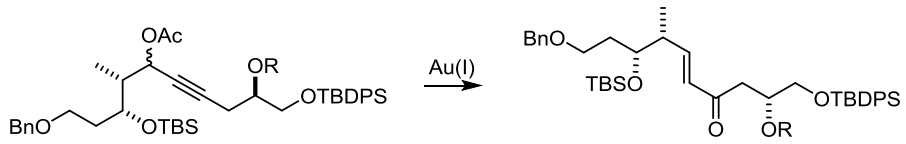
**(6*R*,11*R*,12*R*)-10-Acetoxy-12-(2-(benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-8-yn-6-yl 4-nitrobenzoate (170)**. A mixture of the propargylic




alcohols described above (2.2:1 d.r., 39.0 mg, 47.4 µmol) was dissolved in $CH_2Cl_2$ (0.5 mL) and the solution cooled to 0 °C. Triethylamine (7.6 µL, 55 µmol), acetic anhydride (4.9 µL, 52 µmol) and DMAP (0.3 mg, 2.4 µmol) were added successively and the mixture stirred for 1h at 0 °C. The reaction was then quenched by addition of sat. $NH_4Cl$ solution (3 mL) and extracted with $CH_2Cl_2$ (3 x 3 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 9:1) yielded the desired propargylic acetate as a yellow oil (2.2:1 d.r., 29.5 mg, 76%). $^1$H NMR (400 MHz, $CDCl_3$, only the peaks of the major isomer are listed): δ = 8.25 (dd, *J* = 8.7, 4.4 Hz, 2H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.67

– 7.57 (m, 4H), 7.43 – 7.27 (m, 10H), 7.24 – 7.19 (m, 1H), 5.36 – 5.16 (m, 2H), 4.50 – 4.36 (m, 2H), 3.95 – 3.85 (m, 2H), 3.43 (q, *J* = 6.9 Hz, 2H), 2.89 – 2.66 (m, 2H), 1.96 (s, 3H), 1.90 – 1.63 (m, 3H), 1.02 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 9H), −0.02 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, only the peaks of the major isomer are listed): δ = 169.7, 163.8, 150.5, 138.4, 135.5, 135.5, 133.0, 133.0, 130.8, 129.8, 128.3, 127.8, 127.7, 127.5, 127.5, 127.5, 123.4, 80.8, 80.1, 73.7, 72.9, 69.9, 66.9, 65.8, 63.7, 42.9, 34.5, 26.7, 25.8, 25.8, 20.9, 20.9, 19.2, 9.8, −4.4, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2951, 2930, 2857, 1737, 1733, 1608, 1529, 1472, 1428, 1349, 1271, 1231, 1113, 1103, 1015, 835, 776, 741, 719, 702 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 888.45 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{49}H_{63}N_1O_9Si_2Na$: 888.3934; found: 888.3936.

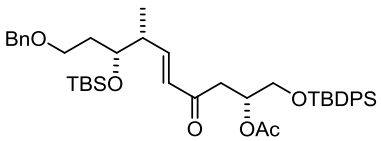
**General Procedure for Au(I)-catalyzed Meyer-Schuster rearrangement of propargylic acetate**




*A stock solution of the catalyst was prepared as follows:* A Schlenck tube is charged with Au(IPr)Cl (8.5 mg, 13.7 µmol) and dry $AgSbF_6$ (3.7 mg, 13.7 µmol). THF (500 µL) was added and the resulting mixture stirred for 10 min. The white precipitate formed was allowed to settle and the supernatant used as catalyst solution (0.0274 M).

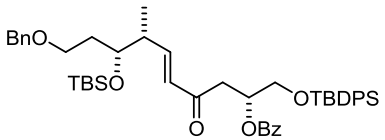
A flame-dried Young tube was charged with a solution of propargylic acetate (1.00 equiv.) in THF/$H_2O$ (39:1, 22.3 µL per µmol substrate). An aliquot of the catalyst solution (0.06 equiv., 2.47 µL per µmol substrate) was added via syringe. The Young tube was sealed and placed in a pre-heated oil bath and stirred at 60 °C for 15 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (hexanes/EtoAc 19:1 to 14:1 to 9:1) to give the desired enone.

**(6*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-8-oxo-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl acetate (174).** Obtained from compound **168** (10.0 mg, 13.2 µmol) following the general procedure as a colorless oil (7.5 mg, 79%). $[\alpha]_D^{20}$ = +21.2 (c = 0.68, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.60 (m, 4H), 7.43 – 7.26 (m, 11H), 6.91 (dd, *J* = 16.2, 6.8 Hz, 1H), 6.06 (dd, *J* = 16.2, 1.4 Hz, 1H), 5.37 (td, *J* = 6.5, 3.4 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 3.83 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.81 – 3.71 (m, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.92 (dd, *J* = 6.5, 4.4 Hz, 2H), 2.54 – 2.43 (m, 1H), 1.95 (s, 3H), 1.75 (dtd, *J* = 14.3, 7.4, 3.9 Hz, 1H), 1.05 – 0.99 (m, 12H), 0.86 (s, 9H), 0.02 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 196.8, 170.1, 150.1, 138.3, 135.6, 135.5, 135.4, 133.2, 130.1, 129.8, 129.7, 128.4, 127.8, 127.7, 127.7, 127.6, 127.6, 73.0, 72.3, 70.7, 66.7, 64.5, 42.3, 40.3, 33.7, 26.8, 26.8, 25.9, 25.9, 21.0, 19.3, 18.1, 14.1, −4.3, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1742, 1673, 1627, 1472, 1462, 1428,

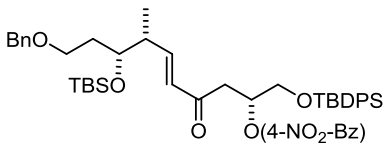


1363, 1238, 1188, 1112, 1045, 983, 939, 836, 775, 739, 701 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 697.5 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{42}H_{60}O_6Si_2Na$: 739.3821; found: 739.3823.

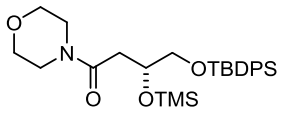
**(6*R*,11*R*,12*R*,*E*)-12-(2-(benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-8-oxo-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl benzoate (175).** Obtained from compound **169** (42.0 mg, 51.2 µmol) following the general procedure as a colorless oil (29.2 mg, 73%). $[\alpha]_D^{20}$ = +16.4 (c = 0.97, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.91 (m, 2H), 7.60 – 7.54 (m, 4H), 7.39 – 7.25 (m, 10H), 7.23 – 7.18 (m, 3H), 6.90 (dd, *J* = 16.2, 6.8 Hz, 1H), 6.06 (dd, *J* = 16.1, 1.4 Hz, 1H), 5.60 (tt, *J* = 6.7, 4.0 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 3.87 (dd, *J* = 4.0, 2.2 Hz, 2H), 3.78 (dt, *J* = 8.3, 4.3 Hz, 1H), 3.43 (t, *J* = 6.0 Hz, 2H), 3.08 (dd, *J* = 16.3, 6.4 Hz, 1H), 3.03 (dd, *J* = 16.2, 6.7 Hz, 1H), 2.48 – 2.39 (m, 1H), 1.69 (dtd, *J* = 14.1, 7.1, 4.2 Hz, 1H), 1.54 (ddt, *J* = 13.9, 8.0, 5.8 Hz, 1H), 0.98 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), −0.03 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 196.8, 165.6, 150.2, 138.4, 135.5, 135.4, 133.1, 132.8, 130.3, 130.1, 129.7, 129.7, 129.7, 128.3, 128.2, 127.7, 127.6, 127.5, 73.0, 72.3, 71.4, 66.7, 64.6, 42.2, 40.4, 33.7, 26.8, 25.8, 19.2, 18.1, 14.1, −4.4, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1720, 1673, 1626, 1472, 1452, 1428, 1361, 1314, 1270, 1176, 1110, 1026, 983, 938, 836, 775, 739, 701 $cm^{-1}$. MS (EI) *m/z* (%) = 721 (3), 599 (8), 492 (12), 435 (4), 361 (4), 303 (11), 280 (10), 279 (45), 174 (15), 173 (100), 171 (10), 135 (15), 131 (71), 117 (8), 105 (27), 101 (13), 91 (98), 73 (24). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{62}O_6Si_2Na$: 801.3977; found: 801.3976.




**(6*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-2,2,11,14,14,15,15-heptamethyl-8-oxo-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl 4-nitrobenzoate (176).** Obtained from compound **170** (31.0 mg, 35.8 µmol) following the general procedure as a colorless oil (21.2 mg, 73%). $[\alpha]_D^{20}$ = +8.8 (c = 0.94, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.59 (ddt, *J* = 8.1, 2.7, 1.3 Hz, 4H), 7.42 – 7.25 (m, 11H), 6.95 (dd, *J* = 16.1, 6.8 Hz, 1H), 6.09 (dd, *J* = 16.1, 1.5 Hz, 1H), 5.68 (td, *J* = 6.4, 3.2 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.92 (d, *J* = 4.0 Hz, 2H), 3.84 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.49 (t, *J* = 6.5 Hz, 2H), 3.09 (d, *J* = 6.4 Hz, 2H), 2.55 – 2.44 (m, 1H), 1.75 (dtd, *J* = 14.3, 7.1, 4.2 Hz, 1H), 1.64 – 1.63 (m, 1H), 1.01 (d, *J* = 8.0 Hz, 12H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 196.3, 163.7, 150.5, 150.5, 138.3, 135.7, 135.5, 135.4, 133.0, 133.0, 130.7, 129.9, 129.8, 129.8, 128.4, 127.8, 127.7, 127.7, 127.6, 127.6, 123.4, 73.0, 72.3, 72.3, 66.8, 64.5, 42.3, 40.2, 33.7, 26.8, 25.8, 19.2, 18.1, 14.1, −4.4, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2954, 2929, 2857, 1726, 1672, 1528, 1471, 1462, 1348, 1318, 1270, 1188, 1101, 1029, 1014, 982, 939, 871, 836, 775, 737, 719, 700, 614 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 846.5 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{61}N_1O_8Si_2Na$: 846.3828; found: 846.3824.

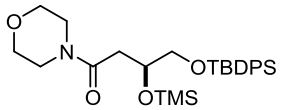


**(*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-morpholino-3-((trimethylsilyl)oxy)butan-1-one (180).**



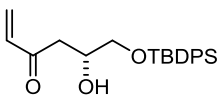

According to a modified protocol from Jacobsen et. al.,[173] a flame-dried two-necked round-bottom flask was charged with $Co_2(CO)_8$ (274 mg, 0.8 mmol). The flask was evacuated (1 x $10^{-1}$ mbar)[247] and backfilled with CO (1 atm, from a balloon, 3 cycles). Dry EtOAc (15 mL) was introduced and the suspension stirred for 10 min, after which freshly distilled *N*-trimethylsilyl morpholine (2.66 mL, 15.0 mmol) and silylated epoxide **160** (3.12 g, 10.0 mmol) were added via syringe. The brown mixture was vigorously stirred under a CO atmosphere (balloon) for 15 h, before it was concentrated. The residue was quickly purified by flash chromatography (hexanes/EtOAc 5:1 to 4:1) to yield the desired morpholine amide as a colorless oil (3.70 g, 74%). $[\alpha]_D^{20}$ = +21.1 (c = 0.915, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.65 (m, 4H), 7.43 – 7.34 (m, 6H), 4.25 (ddt, *J* = 8.5, 5.9, 4.3 Hz, 1H), 3.63 (m, 7H), 3.56 – 3.44 (m, 3H), 2.62 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.53 (dd, *J* = 14.4, 8.3 Hz, 1H), 1.04 (s, 9H), 0.02 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.1, 135.6, 135.6, 133.4, 129.7, 129.7, 127.7, 127.7, 70.7, 67.8, 66.9, 66.7, 46.5, 41.9, 37.5, 26.8, 26.8, 19.2, 0.1 ppm. IR (film): $\tilde{\nu}$ = 2958, 2930, 2857, 1644, 1460, 1428, 1249, 1186, 1111, 1070, 1033, 959, 840, 824, 741, 701, 612 $cm^{-1}$. MS (EI) *m/z* (%) = 484 (11), 444 (13), 443 (36), 442 (100), 364 (23), 271 (13), 230 (6), 193 (14), 135 (5), 114 (7), 73 (4). HRMS (ESIpos): *m/z*: calcd for $C_{27}H_{41}NO_4Si_2Na$: 522.2466; found: 522.2465.

**(*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-morpholino-3-((trimethylsilyl)oxy)butan-1-one (*ent*-180).**




Prepared analogously from epoxide *ent*-**160** (3.12 g, 10.0 mmol) as a pale yellow oil (3.67 g, 74%).

**(*R*)-6-((*tert*-butyldiphenylsilyl)oxy)-5-hydroxyhex-1-en-3-one (179).** A solution of vinylmagnesium chloride (1.6 M in THF, 0.65 mL, 1.03 mmol) was added dropwise over 10 min at −78 °C to a solution of amide **180** (246 mg, 0.492 mmol) in THF (5 mL) and the resulting mixture was warmed to 0 °C for 2 h. The mixture was cooled to −78 °C and slowly transferred via canula into a vigorously stirred aq. sat. $NH_4Cl$ solution (10 mL). The reaction flask was rinsed with EtOAc (2 x 5 mL), which was also transferred to the aqueous layer. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give the desired enone as a colorless oil (74.6 mg, 41%). $[\alpha]_D^{20}$ = +20.1 (c = 0.46, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.60 (m, 4H), 7.45 – 7.33 (m, 6H), 6.34 (dd, *J* = 17.8, 10.5 Hz, 1H), 6.20 (d, *J* = 17.6 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 4.22 (dd, *J* = 8.7, 3.3 Hz, 1H), 3.72 – 3.58 (m, 2H), 2.91 (s, 1H), 2.78 (d, *J* = 6.0 Hz, 2H), 1.05 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 200.0, 136.8, 135.5, 135.5, 133.1, 133.1, 129.8, 129.0, 127.8, 68.3, 67.0, 42.3, 26.9, 19.3 ppm. IR (film): $\tilde{\nu}$ = 3459, 2952, 2931, 2858, 1681, 1614, 1472, 1428, 1400, 1112, 997, 962,



824, 741, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 391.1 (100 ($M+Na^+$)), 759.2 (79 ($2M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{22}H_{28}O_3Si_1Na$: 391.1700; found: 391.1698.

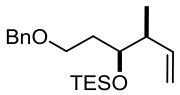
**(*R*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-hydroxyhept-2-en-4-one (181).** A solution of propenylmagnesium bromide (0.5 M in THF, 8.6 mL, 4.30 mmol) was added dropwise over 10 min at 0 °C to a solution of amide **180** (565 mg, 1.131 mmol) in THF (9 mL) and the resulting mixture was stirred at 0 °C for 2 h. The mixture was cooled to −78 °C and slowly transferred via canula into a vigorously stirred aq. solution of HCl (0.75 M, 130 mL). The reaction flask was rinsed with EtOAc (2 x 10 mL), which was also transferred to the aqueous acid layer. After stirring for 15 min at ambient temperature, EtOAc (20 mL) was added, the phases were separated and the aqueous phase extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9:1 to 7.5:1 to 6:1) to give the desired enone as an inconsequential mixture of olefin isomers (*E*/*Z* = 2:1, 360 mg, 83%). $^1$H NMR (300 MHz, $CDCl_3$, only the peaks assigned to the major isomer are given): δ = 7.70 – 7.57 (m, 4H), 7.47 – 7.31 (m, 6H), 6.84 (dq, *J* = 15.7, 6.8 Hz, 1H), 6.11 (dq, *J* = 15.8, 1.6 Hz, 1H), 4.25 – 4.14 (m, 1H), 3.65 (d, *J* = 5.5 Hz, 2H), 3.02 (d, *J* = 4.1 Hz, 1H), 2.72 (d, *J* = 5.9 Hz, 2H), 1.89 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.05 (s, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$ only the peaks assigned to the major isomer are given): δ = 199.6, 143.7, 135.5, 135.5, 133.2, 133.1, 132.3, 129.8, 127.7, 68.5, 67.0, 42.8, 26.8, 19.2, 18.3 ppm. IR (film): $\tilde{\nu}$ = 3462, 3071, 2930, 2587, 1680, 1663, 1628, 1472, 1428, 1362, 1188, 1112, 969, 823, 741, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 405.2 (100 ($M+Na^+$)), 787.3 (85 (($2M+Na^+$). HRMS (ESIpos): *m/z*: calcd for $C_{23}H_{30}O_3SiNa$: 405.1856; found: 405.1856.

**(*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-6-hydroxyhept-2-en-4-one (*ent*-181).** Prepared analogously from morpholine amide *ent*-**180** (3.67 g, 10.0 mmol) as a pale yellow oil (*E*/*Z* = 2:1, 2.21 g, 79%).

**(((3*R*,4*R*)-1-(Benzyloxy)-4-methylhex-5-en-3-yl)oxy)triethylsilane (182).** $NEt_3$ (0.951 mL, 6.86 mmol) and TESCl (1.05 mL, 6.29 mmol) were added via syringe at 0 °C to a solution of alcohol **157** (1.26 g, 5.72 mmol) in $CH_2Cl_2$ (28.6 mL). DMAP (34.9 mg, 0.286 mmol) was then introduced and the mixture stirred for 90 min at 0 °C and for another 30 min at RT before the reaction was quenched with sat. $NH_4Cl$-solution. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 30 mL), the combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 35:1) yielded the target silyl ether as a colorless oil (1.72 g, 90%). $[\alpha]_D^{20}$ = +38.6 (c = 1.13, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.24 (m, 5H), 5.86 (ddd, *J* = 17.3, 10.5, 6.6 Hz, 1H), 5.03 – 4.95

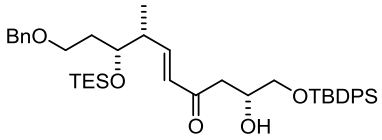
(m, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 3.74 (dt, *J* = 8.2, 4.3, 4.2 Hz, 1H), 3.53 (t, *J* = 6.7 Hz, 2H), 2.35 – 2.22 (m, 1H), 1.83 – 1.70 (m, 1H), 1.70 – 1.59 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (dd, *J* = 7.7 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.6, 128.3, 127.7, 127.5, 114.3, 73.2, 73.0, 67.2, 43.4, 33.7, 15.0, 7.0, 5.2 ppm. IR (film): $\tilde{\nu}$ = 2954, 2911, 2876, 1455, 1414, 1363, 1238, 1091, 1004, 911, 840, 725, 695 cm$^{-1}$. MS (EI) *m/z* (%) = 305 (8), 279 (17), 173 (33), 159 (6), 117 (9), 115 (10), 91 (100), 87 (9), 59 (5). HRMS (ESIpos): *m/z*: calcd for $C_{20}H_{34}O_2SiNa$: 357.2220; found: 357.2222.

**(((3*S*,4*S*)-1-(Benzyloxy)-4-methylhex-5-en-3-yl)oxy)triethylsilane (*ent*-182).**

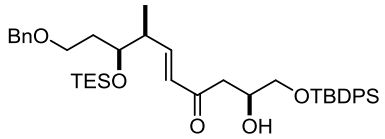



Prepared analogously from alcohol *ent*-**157** (1.70 g, 7.72 mmol) as a colorless oil (2.46 g, 91%).

**(6*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-14,14-diethyl-6-hydroxy-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-8-one (183).** A flame-dried two necked round-bottom flask equipped with a reflux condenser and a septum was charged with a solution of olefin **182** (495 mg, 1.48 mmol) in $CH_2Cl_2$ (15 mL). Zhan-catalyst 1B **C8** (39.4 mg, 53.7 µmol) was added and the resulting mixture was heated to 45 °C while a solution of enone **181** (514 mg, 1.34 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise through the septum over the course of 1 h via syringe pump. After 16 h, the mixture was cooled to RT, another batch of Zhan-catalyst 1B **C8** (19.7 mg, 26.9 µmol) was added and stirring continued at 45 °C. This procedure was repeated once again after additonal stirring for 12 h. After an overall reaction time of 48 h, the mixture was concentrated and the residue purified by flash chromatography (hexanes/EtOAc 14:1 to 12:1 to 9:1) to yield the title compound as a pale orange oil (716 mg, 79%). $[\alpha]_D^{20}$ = +41.2 (c = 0.96, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.60 (ddd, *J* = 7.9, 3.8, 1.7 Hz, 4H), 7.44 – 7.34 (m, 6H), 7.34 – 7.25 (m, 5H), 6.92 (dd, *J* = 16.2, 6.8 Hz, 1H), 6.06 (dd, *J* = 16.2, 1.5 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.25 – 4.16 (m, 1H), 3.85 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.64 (dd, *J* = 5.5, 1.5 Hz, 2H), 3.55 – 3.43 (m, 2H), 3.04 (d, *J* = 3.9 Hz, 1H), 2.82 – 2.66 (m, 2H), 2.53 – 2.41 (m, 1H), 1.79 – 1.69 (m, 1H), 1.62 – 1.52 (m, 1H), 1.05 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 199.8, 150.5, 138.4, 135.5, 135.5, 133.2, 133.2, 130.4, 129.8, 128.3, 127.7, 127.7, 127.6, 73.0, 72.4, 68.5, 67.1, 66.8, 42.6, 42.6, 33.9, 26.9, 19.3, 14.2, 7.0, 5.1 ppm. IR (film): $\tilde{\nu}$ = 3512, 3071, 2955, 2932, 2875, 1664, 1624, 1456, 1427, 1362, 1238, 1186, 1112, 1007, 823, 739, 701 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 697.5 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{40}H_{58}O_5Si_2Na$: 697.3715; found: 697.3720.

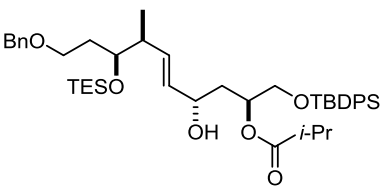


**(6*S*,11*S*,12*S*,*E*)-12-(2-(Benzyloxy)ethyl)-14,14-diethyl-6-hydroxy-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-8-one (*ent*-183).** Prepared analogously from *ent*-**182** (2.25 g, 6.43 mmol) and enone *ent*-**181** (2.05 g, 5.36 mmol) as a pale yellow oil (2.65 g, 73%) along with recovered enone (255 mg, 12%).

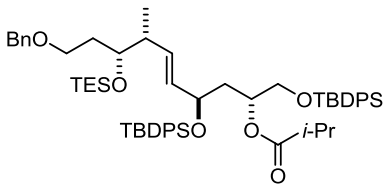



**(6*R*,8*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-14,14-diethyl-8-hydroxy-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl isobutyrate (184).** A freshly prepared solution of $SmI_2$ (0.096 M in THF, 3.80 mL, 0.363 mmol) was slowly added at –50 °C alongside the cold wall of the flask to a solution of enone **24** (700 mg, 1.04 mmol) and freshly distilled isobutyraldehyde (473 µL, 5.19 mmol) in degassed THF (9.4 mL). The mixture was stirred for 1 h at –50 °C before it was poured into sat. aq. $NaHCO_3$ solution (65 mL). The mixture was diluted with EtOAc (40 mL overall) and vigorously stirred until it reached ambient temperature. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (60 mL), dried over $Na_2SO_4$ and concentrated. During concentration, a small amount of $SiO_2$ was added and the crude product loaded on a silica gel column, from which the title compound was eluted with hexanes/EtOAc (12:1 to 9:1); colorless oil (598 mg, 78%). $[\alpha]_D^{20}$ = +27.2 (c = 1.32, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.61 (m, 4H), 7.44 – 7.27 (m, 11H), 5.69 (ddd, *J* = 15.8, 6.9, 1.2 Hz, 1H), 5.43 (ddd, *J* = 15.6, 6.2, 1.3 Hz, 1H), 5.16 (ddt, *J* = 9.4, 5.5, 4.1 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 3.99 (ddd, *J* = 9.8, 6.3, 3.5 Hz, 1H), 3.71 (m, 3H), 3.50 (dd, *J* = 7.4, 5.9 Hz, 2H), 2.73 (br s, 1H), 2.56 (hep, *J* = 7.0 Hz, 1H), 2.33 – 2.21 (m, 1H), 1.77 – 1.53 (m, 4H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.02 (s, 9H), 0.95 – 0.89 (m, 12H), 0.56 (q, *J* = 8.1 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.0, 138.5, 135.6, 135.5, 133.3, 133.3, 133.2, 131.8, 129.8, 129.7, 128.3, 127.7, 127.7, 127.5, 73.2, 73.0, 71.9, 68.3, 67.2, 65.7, 42.0, 39.0, 34.2, 33.7, 26.7, 19.2, 19.2, 19.0, 15.3, 7.0, 5.2 ppm. IR (film): $\tilde{\nu}$ = 3502, 2956, 2932, 2875, 1732, 1457, 1428, 1388, 1362, 1239, 1196, 1160, 1111, 1007, 975, 823, 738, 701, 612 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 769.5 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{44}H_{66}O_6Si_2Na$: 769.4290; found: 769.4291.

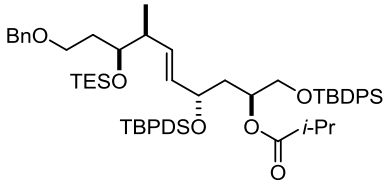
**(6*S*,8*S*,11*S*,12*S*,*E*)-12-(2-(Benzyloxy)ethyl)-14,14-diethyl-8-hydroxy-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl isobutyrate (*ent*-184).** Prepared analogously from *β*-hydroxy ketone *ent*-**183** (2.30 g, 3.41 mmol) as a colorless oil (1.88 g, 74%).



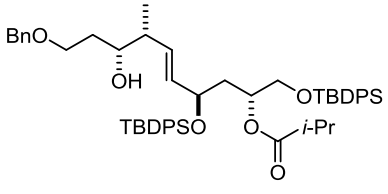
**(6*R*,8*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-8-((*tert*-butyldiphenylsilyl)oxy)-14,14-diethyl-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl isobutyrate.** TBDPSCl (284 µL, 1.09 mmol) was added at 0 °C to a solution of the homoallylic alcohol **184** (584 mg, 0.782 mmol) and imidazole (90.5 mg, 1.33 mmol) in $CH_2Cl_2$ (5.2 mL). After 5 min, the mixture was allowed to reach ambient temperature and stirring was continued for 17 h before the reaction was quenched with sat. $NH_4Cl$ solution (25 mL). The aqueous phase was extracted with $CH_2Cl_2$ (4 x 20 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 39:1) to afford the title compound as a colorless syrup (671 mg, 87%). $[\alpha]_D^{20}$ = +36.7 (c = 1.00, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.60 (m, 8H), 7.44 – 7.25 (m, 17H), 5.34 (dd, *J* = 15.9, 6.8 Hz, 1H), 5.27 (dd, *J* = 15.8, 5.5 Hz, 1H), 5.20 – 5.10 (m, 1H), 4.51 – 4.46 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.14 (td, *J* = 7.5, 5.3 Hz, 1H), 3.67 – 3.53 (m, 3H), 3.49 – 3.36 (m, 2H), 2.43 (hep, *J* = 7.0 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.89 (ddd, *J* = 14.0, 7.7, 4.9 Hz, 1H), 1.77 (ddd, *J* = 14.1, 7.9, 5.3 Hz, 1H), 1.62 – 1.52 (m, 1H), 1.45 – 1.34 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 6H), 1.02 (s, 18H), 0.89 (t, *J* = 7.9 Hz, 9H), 0.73 (d, *J* = 6.9 Hz, 3H), 0.52 (q, *J* = 7.9 Hz, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.1, 138.7, 136.0, 135.9, 135.6, 135.5, 134.7, 134.0, 133.5, 133.5, 133.3, 129.6, 129.6, 129.4, 129.2, 128.3, 127.6, 127.6, 127.4, 127.2, 73.0, 72.9, 72.0, 71.4, 67.2, 65.2, 41.7, 39.8, 34.1, 33.5, 27.0, 26.8, 19.2, 19.0, 18.9, 15.0, 7.0, 5.1 ppm. IR (film): $\tilde{\nu}$ = 2956, 2932, 2875, 2858, 1734, 1471, 1427, 1387, 1361, 1259, 1191, 1157, 1105, 1007, 977, 822, 736, 698 cm$^{-1}$. MS (EI) *m/z* (%) = 927 (2), 820 (2), 561 (2), 509 (6), 493 (7), 469 (4), 467 (4), 377 (5), 322 (3), 319 (3), 280 (22), 279 (97), 269 (26), 199 (16), 174 (15), 173 (100), 171 (14), 135 (22), 131 (44), 91 (57), 73 (16). HRMS (ESIpos): *m/z*: calcd for $C_{60}H_{84}O_6Si_3Na$: 1007.5468; found: 1007.5473.




**(6*R*,8*R*,11*R*,12*R*,*E*)-12-(2-(Benzyloxy)ethyl)-8-((*tert*-butyldiphenylsilyl)oxy)-14,14-diethyl-2,2,11-trimethyl-3,3-diphenyl-4,13-dioxa-3,14-disilahexadec-9-en-6-yl isobutyrate.** Prepared analogously from alcohol *ent*-**184** (1.82 g, 2.44 mmol) as a colorless oil (1.96 g, 82%).

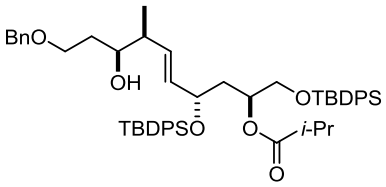



**(6*R*,8*R*)-8-((3*R*,4*R*,*E*)-6-(Benzyloxy)-4-hydroxy-3-methylhex-1-en-1-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (185).** Camphorsulfonic acid (47.7 mg, 0.205 mmol) was added at 0 °C to a solution of the tris-silylether described above (675 mg, 0.685 mmol) in $CH_2Cl_2$/MeOH (2:1, 12.6 mL). The resulting mixture was stirred for 90 min before the reaction was carefully quenched with sat. $NaHCO_3$ (40 mL)

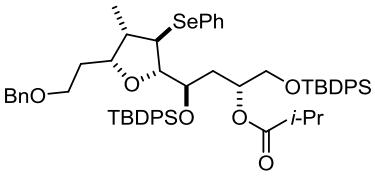


solution. After extraction with $CH_2Cl_2$ (3 x 40 mL), the combined organic phases were washed with brine, dried over $Na_2SO_4$ and concentrated to give a colorless oil, which was purified by flash chromatography (hexanes/EtOAc 8:1) to give the title compound as a colorless oil (576 mg, 97%). $[\alpha]_D^{20}$ = +22.9 (c = 1.32, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.64 – 7.57 (m, 8H), 7.43 – 7.25 (m, 18H), 5.35 (dd, *J* = 15.5, 7.9 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.98 (dd, *J* = 15.5, 7.9 Hz, 1H), 4.45 (s, 2H), 4.08 (q, *J* = 7.0 Hz, 1H), 3.57 (d, *J* = 4.8 Hz, 2H), 3.51 – 3.37 (m, 2H), 3.30 (br t, 1H), 2.51 – 2.37 (m, 2H), 1.91 (ddd, *J* = 11.5, 7.4, 4.6 Hz, 2H), 1.73 (dt, *J* = 13.6, 6.5 Hz, 1H), 1.44 – 1.29 (m, 3H), 1.09 (d, *J* = 6.9 Hz, 6H), 0.99 (d, *J* = 7.7 Hz, 18H), 0.79 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): 176.2, 138.0, 135.9, 135.9, 135.6, 135.5, 134.6, 134.2, 133.6, 133.4, 133.4, 132.8, 129.6, 129.6, 129.6, 129.3, 128.4, 127.7, 127.6, 127.5, 127.3, 74.0, 73.3, 72.0, 69.3, 65.2, 42.3, 39.7, 34.1, 33.5, 26.9, 26.7, 19.2, 19.0, 19.0, 15.0 ppm. IR (film): $\tilde{\nu}$ = 3511, 2960, 2931, 2858, 1734, 1472, 1427, 1389, 1361, 1260, 1193, 1158, 1111, 1082, 976, 822, 739, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 527 (5), 467 (8), 393 (28), 363 (27), 319 (11), 271 (12), 270 (18), 269 (81), 209 (11), 200 (13), 199 (71), 197 (19), 135 (48), 108 (21), 91 (100), 81 (11), 43 (15). HRMS (ESIpos): *m/z*: calcd for $C_{54}H_{70}O_6Si_2Na$: 870.4711; found: 870.4715.

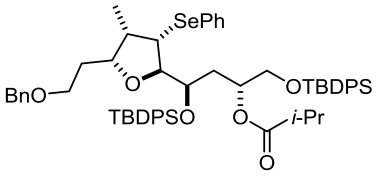
**(6*R*,8*R*)-8-((3*R*,4*R*,*E*)-6-(Benzyloxy)-4-hydroxy-3-methylhex-1-en-1-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-185).** Prepared analogously from the tris-silylether described above (1.93 g, 1.96 mmol) as a colorless oil (1.69 g, 99%).




**(6*R*,8*R*)-8-((2*S*,3*R*,4*S*,5*R*)-5-(2-(Benzyloxy)ethyl)-4-methyl-3-(phenylselanyl) tetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (186).** According to a modified protocol from Denmark,[181a] a solution of alcohol **185** (574 mg, 0.659 mmol) in $CH_2Cl_2$ (10 mL) was prepared and cooled to −40 °C. *N*-(Phenylseleno)phthalimide (239 mg, 0.791 mmol) followed by a solution of triphenylphosphine sulfide (23.3 mg, 79.1 µmol) and trifluoroacetic acid (56.7 µL, 0.791 mmol) in $CH_2Cl_2$ (1 mL) were added via syringe over 5 min. After complete addition, the mixture was allowed to warm to −20 °C and stirring was continued for 3 h before the mixture was poured into a stirred emulsion of sat. aq. $NaHCO_3$ solution and $CH_2Cl_2$ (1:1, 40 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL), the combined organic extracts were dried over $Na_2SO_4$ and concentrated. $^1$H NMR and HPLC analysis of the crude mixture revealed a d.r. of 14:1. The residue was purified by flash chromatography (hexanes/EtOAc 100:0 to 49:1 to 29:1 to 24:1) to give the cyclized product as a colorless oil (560 mg, 83% yield, 14:1 d.r.). An analytically pure sample was obtained by preparative

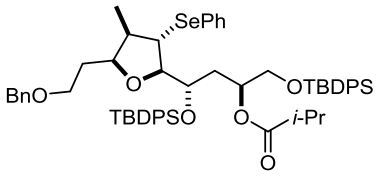


HPLC (Triart C18 5 µm, 12 nm, 150x30 mm, 100% MeCN, 35 °C, 35bar, 35mL/min). $[\propto]_D^{20}$ = +1.1 (c = 0.93, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.69 – 7.66 (m, 2H), 7.64 – 7.60 (m, 6H), 7.44 – 7.24 (m, 19H), 7.23 – 7.16 (m, 3H), 5.15 – 5.09 (m, 1H), 4.32 (s, 2H), 3.85 (ddd, *J* = 8.2, 5.5, 5.0 Hz, 1H), 3.68 (ddd, *J* = 6.9, 6.9, 3.8 Hz, 1H), 3.63 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.52 (dd, *J* = 10.9, 4.1 Hz, 1H), 3.45 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.14 – 3.09 (m, 2H), 2.93 (dd, *J* = 6.3, 3.5 Hz, 1H), 2.40 (hept, *J* = 7.0 Hz, 1H), 2.16 (ddd, *J* = 14.6, 9.8, 3.9 Hz, 1H), 2.07 (ddq, *J* = 12.4, 7.1, 3.6 Hz, 1H), 1.73 (ddd, *J* = 14.7, 7.1, 2.8 Hz, 1H), 1.49 – 1.44 (m, 2H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H) 0.49 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 176.0, 138.7, 136.1, 135.8, 135.6, 135.6, 134.4, 134.4, 133.6, 133.4, 133.3, 129.6, 129.6, 129.3, 129.2, 129.1, 128.3, 127.7, 127.7, 127.6, 127.4, 127.3, 127.1, 85.8, 72.9, 72.7, 71.6, 67.9, 65.3, 49.6, 44.6, 36.1, 34.1, 30.6, 29.7, 27.1, 26.7, 19.7, 19.2, 19.0, 18.8, 14.9 ppm. IR (film): $\tilde{\nu}$ = 2961, 2929, 2855, 1733, 1472, 1427, 1361, 1260, 1192, 1111, 1021, 821, 802, 738, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 970 (6), 969 (9), 883 (9), 882 (13), 881 (22), 880 (8), 879 (11), 805 (11), 724 (11), 723 (11), 563 (11), 467 (10), 361 (25), 349 (11), 319 (13), 296 (11), 295 (45), 270 (23), 269 (100), 241 (14), 239 (34), 200 (13), 199 (73), 197 (30), 136 (12), 135 (93), 91 (84), 43 (13). HRMS (ESIpos): *m/z*: calcd for $C_{60}H_{74}O_6Si_2SeNa$: 1049.4081; found: 1049.4072.

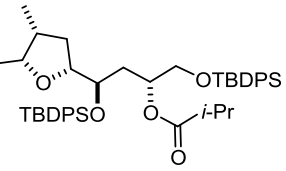
**(6*R*,8*R*)-8-((2*R*,3*S*,4*S*,5*R*)-5-(2-(Benzyloxy)ethyl)-4-methyl-3-(phenylselanyl) tetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (187).** 

Obtained as the minor isomer by preparative HPLC (conditions see above) as a colorless oil. $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.70 – 7.67 (m, 3H), 7.63 – 7.60 (m, 2H), 7.60 – 7.56 (m, 4H), 7.53 – 7.49 (m, 1H), 7.40 – 7.24 (m, 17H), 7.23 – 7.14 (m, 3H), 5.06 – 4.99 (m, 1H), 4.48 (d, *J* = 13.8 Hz, 2H), 4.04 (ddd, *J* = 7.9, 4.1, 1.4, 1H), 3.98 (ddd, *J* = 8.8, 4.5, 4.5 Hz, 1H), 3.92 (dd, *J* = 9.9, 1.3 Hz, 1H), 3.67 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.59 (ddd, *J* = 9.1, 7.7, 5.4 Hz, 1H), 3.53 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.50 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.41 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.27 (hept, *J* = 7.0 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.99 (ddd, *J* = 14.5, 9.9, 4.3 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.73 (ddd, *J* = 13.7, 7.3, 5.0 Hz, 1H), 1.01 (s, 9H) 1.00 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.97 (s, 9H), 0.86 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 176.1, 138.5, 136.1, 136.0, 135.6, 135.5, 134.2, 133.5, 133.4, 133.4, 133.1, 132.5, 130.9, 130.6, 129.6, 129.6, 129.4, 129.0, 128.8, 128.4, 127.7, 127.6, 127.6, 127.5, 127.3, 127.0, 83.3, 78.7, 73.0, 71.9, 71.6, 68.0, 65.3, 48.1, 40.2, 34.0, 33.6, 31.9, 27.1, 26.7, 19.4, 19.2, 19.0, 18.9, 11.6 ppm. IR (film): $\tilde{\nu}$ = 2962, 2930, 2854, 1732, 1472, 1427, 1360, 1260, 1192, 1110, 1021, 823, 799, 738, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 970 (6), 969 (9), 883 (10), 882 (14), 881 (22), 880 (8), 879 (11), 805 (11), 724 (11), 723 (11), 563 (11), 467 (11), 361 (25), 349 (11), 319 (13), 296 (12), 295 (47), 270 (23), 269 (100), 241 (14), 239 (34), 200 (13), 199 (73), 197 (30), 135 (93), 91 (84). HRMS (ESIpos): *m/z*: calcd for $C_{60}H_{74}O_6Si_2SeNa$: 1049.4081; found: 1049.4075.

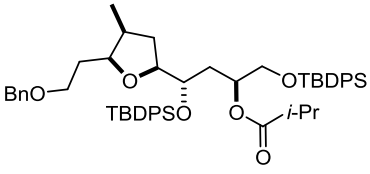
**(6*S*,8*S*)-8-((2*R*,3*S*,4*R*,5*S*)-5-(2-(Benzyloxy)ethyl)-4-methyl-3-(phenylselanyl) tetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-186).** Prepared analogously from alcohol *ent*-**185** (1.59 g, 1.82 mmol) as a colorless oil (1.53 g, 82%).



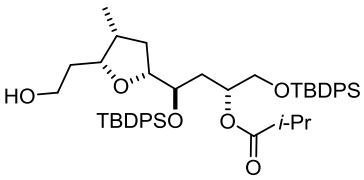

**(6*R*,8*R*)-8-((2*R*,4*R*,5*R*)-5-(2-(Benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (188).** A flame-dried two-necked round-bottom flask equipped with a reflux condenser was charged with a solution of selenoether **186** (560 mg, 0.546 mmol) in degassed toluene (22 mL). ($n$-Bu)$_3$SnH (177 µL, 0.655 mmol) was added via syringe, followed by solid AIBN (0.9 mg, 5.5 µmol). The resulting mixture was stirred at 80 °C for 90 min under Argon, allowing the generated $N_2$ to evaporate. After cooling to room temperature, the mixture was concentrated and the residue purified by flash chromatography (hexanes/EtOAc 100:0 to 49:1 to 39:1 to 29:1) to yield the title compound as a sticky colorless syrup (440 mg, 93% yield, single diastereomer). $[\alpha]_D^{20}$ = +34.1 (c = 0.95, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.71 – 7.61 (m, 8H), 7.42 – 7.25 (m, 17H), 5.24 – 5.17 (m, 1H), 4.30 (s, 2H), 3.72 – 3.63 (m, 2H), 3.61 – 3.54 (m, 3H), 3.15 – 3.03 (m, 2H), 2.36 (hep, *J* = 7.0 Hz, 1H), 2.05 (dddd, *J* = 13.3, 11.7, 6.7, 5.4 Hz, 1H), 1.94 (ddd, *J* = 12.3, 7.3, 7.2 Hz, 1H), 1.83 (ddd, *J* = 14.1, 9.1, 0.2 Hz, 1H), 1.72 (ddd, *J* = 14.4, 7.6, 2.9 Hz, 1H), 1.51 – 1.37 (m, 2H), 1.06 – 0.99 (m, 25H), 0.61 (d, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.1, 138.8, 136.2, 135.9, 135.6, 135.5, 135.0, 133.8, 133.5, 133.4, 129.6, 129.3, 129.0, 128.3, 127.7, 127.6, 127.6, 127.6, 127.4, 127.3, 127.0, 80.8, 78.3, 73.2, 72.8, 71.3, 68.2, 63.4, 36.1, 35.6, 35.2, 34.0, 31.0, 27.2, 26.7, 19.6, 19.3, 19.0, 18.8, 15.6 ppm. IR (film): $\tilde{\nu}$ = 2959, 2930, 2856, 1734, 1471, 1427, 1388, 1361, 1258, 1192, 1157, 1110, 998, 937, 822, 738, 700 cm$^{-1}$. MS (EI) *m/z* (%) = 814 (16), 813 (25), 726 (18), 725 (29), 563 (14), 558 (17), 557 (37), 469 (12), 319 (12), 301 (13), 296 (13), 295 (47), 271 (11), 270 (23), 269 (100), 241 (24), 239 (29), 200 (14), 199 (77), 197 (25), 163 (13), 136 (10), 135 (80), 91 (96). HRMS (ESIpos): *m/z*: calcd for $C_{54}H_{70}O_6Si_2Na$: 893.4603; found: 893.4594.



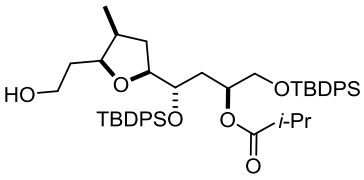

**(6*S*,8*S*)-8-((2*S*,4*S*,5*S*)-5-(2-(Benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-188).** Prepared analogously from selenoether *ent*-**186** (1.53 g, 1.49 mmol) as a colorless oil (1.26 g, 97%, single d.r.).



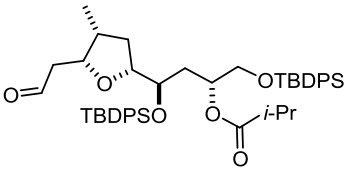
**(6*R*,8*R*)-8-((2*R*,4*R*,5*R*)-5-(2-Hydroxyethyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (189).** A flame-dried Schlenk tube was charged with $Pd(OH)_2/C$ (20 wt. %, 35.5 mg, 50.5 µmol). The flask was evacuated (5 x $10^{-1}$ mbar) and backfilled with $H_2$ from a balloon (two cycles). EtOH (27 mL) was added and the suspension vigorously stirred for 10 min before a solution of benzyl ether **188** (440 mg, 0.505 mmol) in EtOAc (3 mL) was introduced. After stirring for 7.5 h under a $H_2$ atmosphere (balloon), the mixture was filtered through a short pad of Celite® that was carefully rinsed with EtOAc (3 x 20 mL). The combined filtrates were concentrated and the residue was purified by flash chromatography (hexanes/EtOAc 4:1) to yield the desired product as a white foam (345 mg, 88%). $[\alpha]_D^{20}$ = +24.2 (c = 0.88, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.71 – 7.60 (m, 8H), 7.44 – 7.28 (m, 12H), 5.12 (ddd, *J* = 9.6, 4.8, 4.9, 3.1 Hz, 1H), 3.75 – 3.66 (m, 3H), 3.58 – 3.51 (m, 2H), 3.49 – 3.35 (m, 2H), 2.36 (hep, *J* = 7.0 Hz, 1H), 2.14 (dddd, *J* = 14.1, 14.1, 7.1, 6.9 Hz, 1H), 2.00 – 1.89 (m, 3H), 1.88 (dd, *J* = 9.6, 3.0 Hz, 1H), 1.73 (ddd, *J* = 14.3, 7.4, 3.1 Hz, 1H), 1.50 – 1.37 (m, 1H), 1.24 – 1.16 (m, 1H), 1.06 – 1.00 (m, 24H), 0.74 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.1, 136.1, 135.8, 135.6, 135.5, 134.7, 133.5, 133.4, 133.3, 129.6, 129.6, 129.5, 129.2, 127.6, 127.6, 127.4, 127.2, 80.9, 80.3, 72.2, 71.2, 65.3, 61.4, 35.5, 35.3, 35.2, 34.0, 32.9, 27.1, 26.7, 19.5, 19.2, 19.0, 18.8, 15.5 ppm. IR (film): $\tilde{\nu}$ = 3487, 2960, 2930, 2857, 1735, 1472, 1428, 1388, 1259, 1193, 1158, 1112, 998, 823, 740, 702, 610 cm$^{-1}$. MS (EI) *m/z* (%) = 723 (12), 646 (10), 645 (18), 636 (13), 635 (23), 563 (12), 558 (20), 557 (41), 437 (16), 379 (31), 319 (13), 301 (18), 295 (34), 270 (18), 269 (82), 241 (32), 239 (32), 200 (18), 199 (97), 197 (38), 183 (12), 181 (14), 163 (14), 145 (11), 139 (12), 137 (12), 136 (14), 135 (100), 85 (29), 71 (14), 43 (26). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{64}O_6Si_2Na$: 803.4134; found: 803.4135.




**(6*S*,8*S*)-8-((2*S*,4*S*,5*S*)-5-(2-Hydroxyethyl)-4-methyltetrahydrofuran-2-yl)-2,2,11,11-tetramethyl-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-189).** Prepared analogously from benzyl ether *ent*-**188** (1.25 g, 1.43 mmol) as a colorless oil (907 mg, 81%).

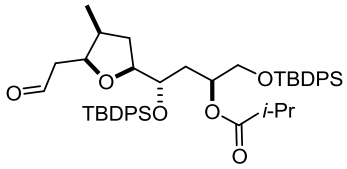



**(6*R*,8*R*)-2,2,11,11-Tetramethyl-8-((2*R*,4*R*,5*R*)-4-methyl-5-(2-oxoethyl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (190).** A solution of alcohol **189** (341 mg, 0.437 mmol) in $CH_2Cl_2$ (1 mL + 2 x 0.5 mL rinse) was added dropwise at 0 °C to a solution of Dess-Martin periodinane (463 mg, 1.09 mmol) in $CH_2Cl_2$ (2.6 mL). After complete addition, the ice bath was removed and stirring continued at rt for 4.5 h before the

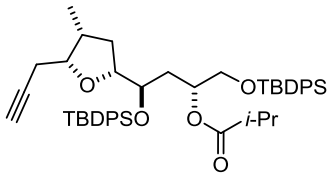


reaction was quenched with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ solution (1:1, 20 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified flash chromatography (short column, hexanes/EtOAc 19:1) to give the desired aldehyde as a colorless sticky syrup (310 mg, 91%). $[\alpha]_D^{20}$ = +35.2 (c = 0.57, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.13 (t, *J* = 2.2 Hz, 1H), 7.70 – 7.59 (m, 8H), 7.46 – 7.25 (m, 12H), 5.18 (dddd, *J* = 9.5, 4.8, 4.7, 3.0 Hz, 1H), 3.93 (ddd, *J* = 8.8, 6.5, 4.7 Hz, 1H), 3.75 – 3.63 (m, 2H), 3.58 (d, *J* = 4.7 Hz, 2H), 2.37 (hep, *J* = 7.0 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.16 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.10 (ddd, *J* = 16.2, 4.9, 2.5 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.83 (ddd, *J* = 14.2, 9.5, 2.5 Hz, 1H), 1.73 (ddd, *J* = 14.4, 7.6, 3.1 Hz, 1H), 1.14 – 1.09 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H), 0.63 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 202.1, 176.1, 136.1, 135.7, 135.6, 135.5, 134.8, 133.7, 133.4, 133.4, 129.7, 129.4, 129.1, 127.7, 127.7, 127.3, 127.0, 81.3, 76.3, 72.9, 71.2, 65.3, 44.8, 35.8, 35.5, 35.2, 34.0, 27.1, 26.7, 19.6, 19.3, 19.0, 18.8, 15.6 ppm. IR (film): $\tilde{\nu}$ = 2959, 2929, 2856, 1729, 1472, 1427, 1388, 1240, 1192, 1158, 1111, 998, 822, 740, 701 cm$^{-1}$. MS (EI) *m/z* (%) = 721 (7), 635 (16), 634 (42), 633 (80), 563 (7), 377 (15), 319 (11), 295 (31), 270 (22), 269 (100), 241 (14), 239 (21), 225 (10), 200 (12), 199 (66), 197 (29), 183 (13), 179 (15), 163 (12), 136 (10), 136 (78), 43 (19). HRMS (ESIpos): *m/z*: calcd for $C_{47}H_{62}O_6Si_2Na$: 801.3977; found: 801.3977.

**(6*S*,8*S*)-2,2,11,11-Tetramethyl-8-((2*S*,4*S*,5*S*)-4-methyl-5-(2-oxoethyl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-190).** Prepared analogously from alcohol *ent*-**189** (907 mg, 1.16 mmol) as a colorless oil (847 mg, 94%).

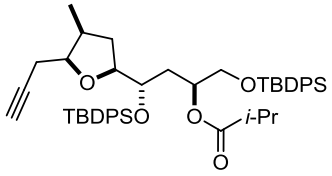



**(6*R*,8*R*)-2,2,11,11-Tetramethyl-8-((2*R*,4*R*,5*R*)-4-methyl-5-(prop-2-yn-1-yl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (191).** A flame-dried Schlenk tube was charged with dimethyl-1-diazo-2-oxopropylphosphonate (**R18**) (306 mg, 1.592 mmol) and THF (8 mL). The resulting solution was cooled to −78 °C before a freshly prepared solution of NaOMe[248] (0.5 M, 3.18 mL, 1.592 mmol) was added over the course of 10 min via syringe, causing the mixture to turn intensively yellow. After stirring for 15 min at −78 °C, a precooled (−78 °C) solution of aldehyde **190** (310 mg, 0.398 mmol) in THF (5 mL + 2 x 1 mL rinse) was added slowly via canula. The reaction flask was then equipped with an Argon bubbler to allow the generated $N_2$ to evaporate. The mixture was slowly warmed to −50 °C, causing a heavy gas evolution. After stirring for 90 min at −50 °C, the reaction was quenched by addition of sat. $NH_4Cl$ solution (20 mL) and $H_2O$ (4 mL) and the aqueous layer was extracted with EtOAc (4 x 30 mL). The combined

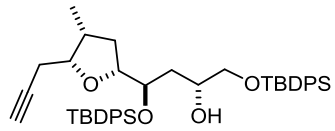


extracts were washed with brine (35 mL), dried over $Na_2SO_4$ and concentrated. The orange residue was purified by flash chromatography (hexanes/EtOAc 39:1) to yield the desired alkyne as a white foam that collapsed upon storage (287 mg, 93%). $[\alpha]_D^{20}$ = +19.4 (c = 1.10, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.72 – 7.57 (m, 8H), 7.48 – 7.25 (m, 12H), 5.13 (dddd, *J* = 9.5, 4.7, 4.6, 2.9 Hz, 1H), 3.78 – 3.64 (m, 3H), 3.57 (d, *J* = 4.7 Hz, 2H), 2.35 (hep, *J* = 7.0 Hz, 1H), 2.24 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 2.05 – 2.00 (m, 2H), 1.97 – 1.84 (m, 2H), 1.83 (t, *J* = 2.7 Hz, 1H), 1.71 (ddd, *J* = 14.5, 7.8, 3.0 Hz, 1H), 1.27 – 1.15 (m, 1H), 1.06 – 0.98 (m, 24H), 0.81 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 176.1, 136.1, 135.9, 135.6, 135.5, 134.7, 134.0, 133.5, 133.4, 129.6, 129.6, 129.3, 129.1, 127.7, 127.6, 127.3, 127.0, 81.6, 81.0, 79.3, 72.7, 71.2, 69.1, 65.3, 35.2, 35.1, 34.0, 27.2, 26.7, 20.6, 19.6, 19.2, 19.0, 18.8, 14.8 ppm. IR (film): $\tilde{\nu}$ = 2960, 2930, 2857, 1735, 1472, 1428, 1388, 1260, 1192, 1158, 1112, 1006, 822, 740, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 797.5 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{62}O_5Si_2Na$: 797.4028; found: 797.4028.

**(6*S*,8*S*)-2,2,11,11-Tetramethyl-8-((2*S*,4*S*,5*S*)-4-methyl-5-(prop-2-yn-1-yl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-yl isobutyrate (*ent*-191).** Prepared analogously from aldehyde *ent*-**190** (847 mg, 1.087 mmol) as a colorless syrup (809 mg, 96%).

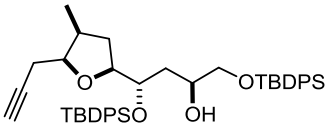



**(6*R*,8*R*)-2,2,11,11-Tetramethyl-8-((2*R*,4*R*,5*R*)-4-methyl-5-(prop-2-yn-1-yl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-ol (194).** A solution of DIBAl-H in toluene (1.0 M, 1.10 mL, 1.10 mmol) was added dropwise at −78 °C to a solution of ester **191** (285 mg, 0.368 mmol) in toluene (24 mL) and the resulting mixture was stirred for 30 min at this temperature. The mixture was then poured via canula into a stirred sat. solution of Rochelle salt (150 mL), the flask was rinsed with EtOAc (2 x 20 mL) and the emulsion was vigorously stirred at ambient temperature for 4 h. The layers were separated, the aqueous phase was extracted with EtOAc (3 x 40 mL), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The crude residue was purified by flash chromatography (hexanes/EtOAc 24:1 to 19:1) to give the title compound as a sticky colorless syrup (252 mg, 97%). $[\alpha]_D^{20}$ = +18.2 (c = 1.07, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.68 (m, 4H), 7.64 – 7.59 (m, 4H), 7.45 – 7.28 (m, 12H), 4.06 (ddd, *J* = 6.7, 6.6, 4.1 Hz, 1H), 3.90 – 3.74 (m, 3H), 3.43 (d, *J* = 5.6 Hz, 2H), 2.60 (d, *J* = 3.4 Hz, 1H), 2.30 (hep, *J* = 7.1 Hz, 1H), 2.13 (ddd, *J* = 16.7, 6.0, 2.5 Hz, 1H), 2.07 (ddd, *J* = 16.6, 7.6, 2.6 Hz, 1H), 1.95 (ddd, *J* = 12.5, 7.8, 6.9 Hz, 1H), 1.86 (t, *J* = 2.7 Hz, 1H), 1.62 (ddd, *J* = 14.3, 9.3, 4.2 Hz, 1H), 1.56 (ddd, *J* = 14.4, 6.9, 3.1 Hz, 1H), 1.30 (ddd, *J* = 12.5, 9.0, 7.4 Hz, 1H), 1.06 (s, 9H), 1.03 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 136.1, 136.0, 135.5, 135.5, 134.2, 134.1, 133.4, 133.4, 129.7,



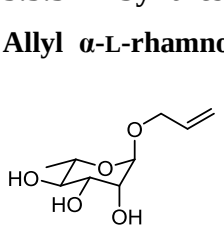
129.4, 129.4, 127.7, 127.4, 127.2, 81.6, 81.0, 79.5, 73.2, 69.3, 68.8, 68.3, 36.6, 35.2, 35.1, 27.1, 26.8, 20.8, 19.6, 19.2, 14.8 ppm. IR (film): $\tilde{\nu}$ = 3311, 2957, 2928, 2856, 1472, 1469, 1427, 1390, 1362, 1269, 1189, 1111, 999, 822, 739, 701 $cm^{-1}$. MS (EI) *m/z* (%) = 570 (22), 569 (48), 491 (8), 417 (7), 319 (18), 299 (10), 259 (12), 257 (14), 241 (35), 239 (19), 223 (11), 221 (35), 200 (19), 199 (100), 197 (40), 183 (17), 181 (14), 175 (16), 163 (22), 149 (34), 139 (13), 136 (12), 135 (88), 117 (17), 93 (12), 91 (22), 79 (12). HRMS (ESIpos): *m/z*: calcd for $C_{44}H_{56}O_4Si_2Na$: 727.3609; found: 727.3610.

**(6*S*,8*S*)-2,2,11,11-Tetramethyl-8-((2*S*,4*S*,5*S*)-4-methyl-5-(prop-2-yn-1-yl)tetrahydrofuran-2-yl)-3,3,10,10-tetraphenyl-4,9-dioxa-3,10-disiladodecan-6-ol (*ent*-194).** Prepared analogously from ester *ent*-**191** (803 mg, 1.04 mmol) as a colorless syrup (709 mg, 97%).

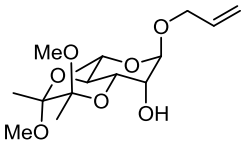



### 5.3.3 Synthesis of sugar fragment 201.

**Allyl α-L-rhamnopyranoside (196)**. L-Rhamnose (**195**) (4.0 g, 22 mmol) was dissolved in allyl alcohol (30 mL) and conc. $H_2SO_4$ (0.4 mL) was added. The mixture was stirred at 100 °C for 1 h while its color changed to brown. After cooling to ambient temperature, solid $K_2CO_3$ (60 mg) was added and excess allyl alcohol was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to yield the targeted compound as a highly viscous colorless oil (3.5 g, 78%). $[\alpha]_D^{20}$ = –83.0 (c = 1.29, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.85 (dddd, *J* = 17.2, 10.3, 6.1, 5.2 Hz, 1H), 5.25 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.16 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.77 (d, *J* = 1.5 Hz, 1H), 4.74 – 4.56 (br s, 1H), 4.39 – 4.23 (br s, 1H), 4.30 – 4.17 (br s, 1H), 4.12 (ddt, *J* = 13.0, 5.3, 1.5 Hz, 1H), 4.03 – 3.86 (m, 2H), 3.75 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.61 (dq, *J* = 9.4, 6.2 Hz, 1H), 3.44 (t, *J* = 9.5 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 133.7, 117.5, 98.9, 72.8, 71.7, 71.0, 68.2, 68.0, 17.5 ppm. IR (film): $\tilde{\nu}$ = 3371, 2977, 2915, 1450, 1422, 1383, 1265, 1128, 1046, 980, 880, 835, 808, 734, 685 $cm^{-1}$. MS (EI) *m/z* (%) = 131 (5), 100 (46), 87 (21), 85 (11), 83 (5), 74 (7), 73 (18), 72 (5), 71 (63), 61 (13), 60 (96), 59 (11), 58 (46), 57 (26), 56 (6), 55 (10), 45 (18), 43 (41), 42 (15), 41 (100), 39 (21), 31 (18), 29 (25), 27 (11). HRMS (ESIpos): *m/z*: calcd for $C_9H_{16}O_5Na$: 227.0889; found: 227.0891.




**Bisacetal 197**. Trimethylorthoacetate (44.8 mL, 350 mmol) and 2,3-butadione (7.7 mL, 88 mmol) were dissolved in MeOH (200 mL) and the solution treated with *p*TsOH·$H_2O$ (1.25 g, 6.57 mmol) before the mixture was stirred at 75 °C for 24 h. After cooling to ambient temperature, a solution of rhamnoside **196** (3.02 g, 14.8 mmol) in MeOH (7 mL+7 mL rinse) was added and the mixture stirred at



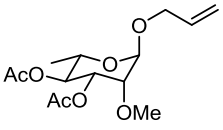
75 °C overnight. After cooling to ambient temperature, $NEt_3$ (1.2 mL) was added to neutralize the medium prior to evaporation of the solvents under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give the desired bisacetal as a highly viscous colorless syrup (3.21 g, 72%). $[\propto]_D^{20}$ = –182.6 (c = 0.99, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dddd, *J* = 16.8, 10.3, 6.3, 5.2 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.79 (d, *J* = 1.5 Hz, 1H), 4.13 (ddt, *J* = 12.9, 5.2, 1.5 Hz, 1H), 4.00 – 3.87 (m, 3H), 3.78 (dq, *J* = 9.7, 6.0 Hz, 1H), 3.68 (t, *J* = 9.9 Hz, 1H), 3.22 (s, 3H), 3.19 (s, 3H), 2.46 (d, *J* = 2.3 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.22 (d, *J* = 6.1 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 133.8, 117.4, 100.2, 99.8, 98.9, 69.9, 68.4, 68.2, 67.9, 66.5, 48.0, 47.6, 17.8, 17.6, 16.5 ppm. IR (film): $\tilde{\nu}$ = 3464, 2932, 2834, 1454, 1376, 1138, 1111, 1076, 1034, 984, 929, 915, 882, 848, 734, 701, 672 $cm^{-1}$. MS (EI) *m/z* (%) = 116 (7), 113 (7), 101 (33), 85 (7), 84 (100), 83 (23), 75 (16), 73 (11), 57 (5), 55 (11), 43 (34), 41 (21), 29 (7). HRMS (ESIpos): *m/z*: calcd for $C_{15}H_{27}O_7Na$: 341.1571; found: 341.1571.

**Methylated bisacetal 198**. A solution of bisacetal **197** (3.17 g, 10.4 mmol) in DMF (10 mL) was slowly added at 0 °C to a suspension of NaH (748 mg, 31.2 mmol) in DMF (60 mL). The resulting mixture was stirred for about 30 min at 0 °C until gas evolution had ceased. MeI (1.95 mL, 31.2 mmol) was then added dropwise, causing a color change to yellow. The mixture was warmed to room temperature overnight before the reaction was quenched with sat. $NH_4Cl$ solution (300 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL), the combined organic extracts were washed with brine (200 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give the methylated product as pale yellow oil (2.21 g, 64%). $[\propto]_D^{20}$ = –214.0 (c = 0.88, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.91 (m, 1H), 5.24 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.15 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.82 (d, *J* = 1.5 Hz, 1H), 4.13 (m, 1H), 3.99 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.93 (m, 1H), 3.75 (dq, *J* = 9.8, 6.0 Hz, 1H), 3.68 (dd, *J* = 9.9, 9.8 Hz, 1H), 3.44 (dd, *J* = 3.0, 1.5 Hz, 1H), 3.47 (s, 3H), 3.24 (s, 3H), 3.22 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.23 (d, *J* = 6.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 133.9, 117.3, 99.8, 99.5, 97.1, 78.8, 68.7, 68.4, 67.9, 66.9, 59.2, 47.9, 47.6, 17.8, 17.8, 16.6 ppm. IR (film): $\tilde{\nu}$ = 2932, 2832, 1453, 1375, 1197, 1138, 1114, 1083, 1037, 994, 932, 882, 848, 815 $cm^{-1}$. MS (EI) *m/z* (%) = 116 (9), 115 (11), 101 (25), 99 (11), 98 (100), 97 (17), 83 (16), 75 (5), 73 (16), 71 (5), 67 (9), 55 (7), 45 (10), 43 (30), 41 (29), 39 (6), 29 (7). HRMS (ESIpos): *m/z*: calcd for $C_{16}H_{28}O7Na$: 355.1727; found: 355.1725.

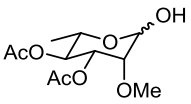
**Allyl 2-O-methyl-α-L-rhamnopyranoside**. Trifluoroacetic acid (19 mL) was added to an emulsion of compound **199** (2.05 g, 6.17 mmol) in $H_2O$ (1 mL) at 0 °C. The mixture turned slightly yellow and was allowed to stir for 7 min at this temperature. The mixture was diluted with $CH_2Cl_2$ (300 mL), the organic phase was dried over $Na_2SO_4$ and concentrated to give the diol as a pale orange oil that was used in the next step without further

purification (1.32 g, 98%, 95% purity). An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc = 1:1 to 1:2). $[\alpha]_D^{20}$ = –46.3 (c = 1.00, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dddd, *J* = 17.2, 10.4, 6.1, 5.0 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.14 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.84 (d, *J* = 1.6 Hz, 1H), 4.13 (ddt, *J* = 13.0, 5.1, 1.6 Hz, 1H), 3.92 (ddt, *J* = 13.0, 6.1, 1.4 Hz, 1H), 3.75 – 3.66 (br s, 1H), 3.56 (dq, *J* = 9.2, 6.2 Hz, 1H), 3.50 – 3.42 (br s, 1H), 3.43 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.41 (s, 3H), 3.33 (t, *J* = 9.5 Hz, 1H), 3.24 – 3.11 (m, 1H), 1.24 (d, *J* = 6.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 133.7, 117.2, 95.4, 80.4, 73.5, 71.4, 67.9, 67.8, 58.8, 17.5 ppm. IR (film): $\tilde{\nu}$ = 3416, 2976, 2932, 2907, 2832, 1453, 1382, 1192, 1133, 1103, 1075, 1038, 990, 975, 926, 912, 874, 836, 807 cm$^{-1}$. MS (EI) *m/z* (%) = 157 (8), 156 (16), 129 (18), 125 (7), 116 (28), 115 (8), 114 (17), 113 (15), 103 (5), 96 (13), 87 (22), 85 (13), 83 (12), 74 (50), 45 (9), 43 (100), 41 (20).

**Allyl 3,4-bis-O-acetyl-2-O-methyl-α-L-rhamnopyranoside (199)**. Triethylamine (2.8 mL, 21 mmol) and acetic anhydride (1.4 mL, 21 mmol) were successively added via syringe at 0 °C to a solution of DMAP (152 mg, 1.2 mmol) and the crude diol described above (1.4 g, 6.2 mmol) in $CH_2Cl_2$ (40 mL). The ice bath was removed and stirring continued for 2 h at ambient temperature, before sat. $NH_4Cl$ (20 mL) was added and the aqueous phase extracted with EtOAc (3 x 7 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give the desired bisacetate as a white crystalline solid (1.28 g, 68%). $[\alpha]_D^{20}$ = –72.3 (c = 0.98, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dddd, *J* = 17.3, 10.4, 6.1, 5.1 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.22 – 5.15 (m, 2H), 5.07 (t, *J* = 9.9 Hz, 1H), 4.82 (d, *J* = 1.8 Hz, 1H), 4.15 (ddt, *J* = 12.9, 5.1, 1.5 Hz, 1H), 3.96 (ddt, *J* = 12.9, 6.1, 1.3 Hz, 1H), 3.78 (dq, *J* = 9.6, 5.2 Hz, 1H), 3.59 (dd, *J* = 3.3, 1.9 Hz, 1H), 3.43 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.8, 133.5, 117.5, 96.4, 78.4, 71.6, 71.5, 68.1, 66.4, 59.5, 20.9, 20.7, 17.4 ppm. IR (film): $\tilde{\nu}$ = 2924, 1740, 1455, 1370, 1239, 1219, 1107, 1074, 1036, 1000, 976, 915, 835, 798 cm$^{-1}$. MS (EI) *m/z* (%) = 157 (8), 156 (16), 129 (18), 125 (7), 116 (28), 115 (8), 114 (17), 113 (15), 103 (5), 96 (13), 87 (22), 85 (13), 83 (12), 74 (50), 45 (9), 43 (100), 41 (20). HRMS (ESIpos): *m/z*: calcd for $C_{14}H_{22}O_7Na$: 325.1258; found: 325.1255.

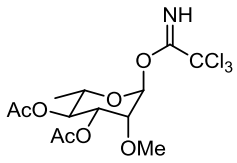



**3,4-Bis-O-acetyl-2-O-methyl-α-L-rhamnopyranose (200)**. $SeO_2$ (488 mg, 4.40 mmol) was added to a solution of compound **199** (1.20 g, 3.97 mmol) and acetic acid (183 µL, 3.20 mmol) in 1,4-dioxane (10 mL) and the resulting suspension was stirred at reflux temperature for 2 h. After cooling to room temperature, the mixture was neutralized with triethylamine (0.44 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give the desired hemiacetal as a white solid (0.891 g, 86%). $[\alpha]_D^{20}$ = –42.3 (c = 0.94, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$, data of the major



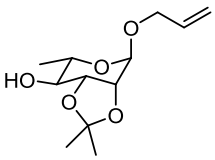
anomer only): δ = 5.26 – 5.17 (m, 2H), 5.05 (t, *J* = 9.9 Hz, 1H), 4.04 (dq, *J* = 9.8, 6.2 Hz, 1H), 3.66 (d, *J* = 3.8 Hz, 1H), 3.61 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.43 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.13 (d, *J* = 6.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, data of the major anomer only): δ = 170.4, 170.0, 92.0, 78.6, 71.5, 71.3, 66.3, 59.5, 20.9, 20.7, 17.4 ppm. IR (film): $\tilde{\nu}$ = 3453, 2923, 2854, 1741, 1456, 1373, 1243, 1225, 1108, 1074, 1050, 916, 797 cm$^{-1}$. MS (EI) *m/z* (%) = 156 (14), 129 (34), 116 (12), 115 (5), 114 (14), 113 (7), 87 (54), 85 (6), 83 (7), 74 (56), 45 (7), 43 (100), 29 (6). HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{18}O_7Na$: 285.0945; found: 285.0947.

**Trichloroacetimidate 201**. $Cl_3CCN$ (0.934 mL, 9.31 mmol) was added dropwise to a suspension of




hemiacetal **200** (348 mg, 0.19 mmol) and $Cs_2CO_3$ (86.7 mg, 0.039 mmol) in $CH_2Cl_2$ (7.0 mL). After stirring for 3 h at room temperature, the mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give the desired trichloroacetimidate as a white solid (532 mg, 98%). $[\propto]_D^{20}$ = –59.9 (c = 1.06, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 5.28 – 5.10 (m, 2H), 3.98 (dq, *J* = 9.0, 6.3 Hz, 1H), 3.80 (dd, *J* = 3.0, 2.0 Hz, 1H), 3.48 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.20 (d, *J* = 6.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.3, 160.0, 94.6, 90.5, 76.1, 70.7, 70.2, 69.0, 59.2, 20.5, 20.4, 17.2 ppm. IR (film): $\tilde{\nu}$ = 3332, 2988, 2922, 2851, 1741, 1673, 1448, 1368, 1279, 1236, 1219, 1156, 1107, 1056, 1039, 968, 943, 926, 842, 831, 793, 734 cm$^{-1}$. MS (EI) *m/z* (%) = 245 (28), 184 (19), 143 (14), 142 (24), 129 (16), 125 (28), 116 (18), 113 (13), 87 (22), 74 (34), 43 (100). HMRS (ESIpos): *m/z*: calcd for $C_{13}H_{18}O_7NCl_3Na$: 428.0041; found: 428.0042.

**Acetal 202.** 2,2-Dimethoxypropane (4.4 mL, 35.3 mmol) was added dropwise to a stirred solution of



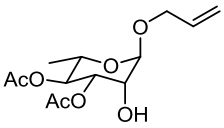

rhamnoside **196** (3.60 g, 17.6 mmol) and *p*TsOH·$H_2O$ (60.6 mg, 0.352 mmol) in DMF (17.6 mL) at ambient temperature. The reaction mixture was stirred for 16 h and used as a solution for the next step. An aliquot (0.5 mL) was removed from the reaction mixture and used to obtain an analytically pure sample. This aliquot was diluted with $NH_4Cl$ solution (3 mL) and the aqueous phase was extracted with $Et_2O$ (2 x 3 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:1) to yield the desired compound as a colorless oil. $[\propto]_D^{20}$ = −27.1 (c = 0.67, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.74 (dddd, *J* = 17.2, 10.4, 6.0, 5.1 Hz, 1H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.09 (s, 1H), 5.00 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.21 – 4.12 (m, 2H), 4.02 (ddt, *J* = 13.0, 5.2, 1.5 Hz, 1H), 3.81 – 3.71 (m, 2H), 3.50 (ddd, *J* = 9.5, 6.9, 4.2 Hz, 1H), 3.17 (d, *J* = 4.2 Hz, 1H), 1.48 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 3H), 1.23 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 134.4, 116.9, 109.4, 96.8, 79.3, 76.5, 74.9, 67.9, 66.2, 28.2, 26.3, 17.8 ppm. IR (film): $\tilde{\nu}$ = 3461, 2986, 2936, 2922, 1454, 1382, 1372, 1243, 1219, 1171, 1139, 1106, 1072, 1050, 1021, 993, 919, 858, 818, 787, 734, 668 cm$^{-1}$. MS (EI) *m/z* (%) = 229 (9), 187 (8), 129 (6), 111 (5), 101 (18), 100 (100), 85 (40),

71 (31), 59 (31), 57 (10), 55 (13), 43 (29), 41 (34). HRMS (ESIpos): *m/z*: calcd for $C_{12}H_{20}O_5Na$: 267.1203; found: 267.1202.

**Acetylated Acetal 203.** Pyridine (20 mL) and acetyl chloride (4.25 mL, 70.4 mmol) were added to the crude reaction mixture (see above) at 0 °C. The icebath was removed after 5 min and the reaction mixture was stirred at ambient temperature for further 24 h. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and washed with aq. HCl (1 N, 30 mL), water (30 mL) and sat. $NaHCO_3$ solution (30 mL). The organic extract was dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 21:1 to 15:1 to 9:1) to give a colorless oil (3.87 g, 73% over 2 steps). $[\alpha]_D^{20}$ = −23.0 (c = 0.82, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.73 (dddd, *J* = 17.2, 10.4, 5.9, 5.1 Hz, 1H), 5.29 (dd, *J* = 10.1, 7.8 Hz, 1H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.10 (s, 1H), 5.00 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.26 – 4.16 (m, 2H), 3.98 (ddt, *J* = 13.1, 5.2, 1.5 Hz, 1H), 3.79 – 3.67 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.21 (d, *J* = 0.8 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 169.5, 134.3, 116.9, 109.8, 96.8, 76.6, 76.3, 74.8, 68.0, 64.5, 28.0, 26.6, 20.5, 17.2 ppm. IR (film): $\tilde{\nu}$ = 2985, 2938, 2925, 1742, 1455, 1373, 1219, 1176, 1139, 1122, 1082, 1045, 1027, 999, 923, 888, 857, 840, 814, 785, 740 cm$^{-1}$. MS (EI) *m/z* (%) = 271 (28), 229 (15), 169 (9), 151 (7), 142 (6), 129 (7), 113 (17), 112 (50), 111 (17), 101 (15), 100 (89), 85 (40), 83 (26), 82 (15), 71 (10), 59 (11), 43 (100), 41 (34). HRMS (ESIpos): *m/z*: calcd for $C_{14}H_{22}O_6Na$: 309.1309; found: 309.1309.

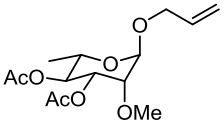
**Monoacetylated Diol 204.** Compound **203** (2.30 g, 7.63 mmol) was dissolved in 90% AcOH (15 mL) and the resulting solution stirred at 110 °C for 1 h. After cooling back to ambient temperature, the reaction mixture was concentrated and the residue was purified by flash chromatography (hexanes/EtOAc 1:1) to yield the desired diol as a white solid (1.83 g, 97% yield). $[\alpha]_D^{20}$ = −94.1 (c = 1.46, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.88 (dddd, *J* = 17.2, 10.4, 6.0, 5.1 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.85 (d, *J* = 1.7 Hz, 1H), 4.78 (t, *J* = 9.6 Hz, 1H), 4.16 (ddt, *J* = 13.0, 5.1, 1.5 Hz, 1H), 3.98 (ddt, *J* = 13.0, 6.1, 1.4 Hz, 1H), 3.94 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.88 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.80 (ddt, *J* = 9.8, 6.6, 5.9 Hz, 1H), 2.11 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.1, 133.6, 117.5, 98.4, 75.6, 71.0, 70.3, 68.1, 65.6, 21.0, 17.4 ppm. IR (film): $\tilde{\nu}$ = 3327, 2982, 2940, 2895, 1735, 1459, 1426, 1378, 1295, 1241, 1133, 1104, 1070, 1044, 1002, 982, 923, 834, 793, 700 cm$^{-1}$. MS (EI) *m/z* (%) = 189 (5), 142 (5), 131 (4), 129 (5), 116 (13), 101 (25), 100 (39), 83 (4), 71 (42), 60 (26), 43 (100), 41 (38). HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{18}O_6Na$: 269.0996; found: 269.0997.

**Bisacetylated alcohol 205.** Diol **204** (1.00 g, 4.06 mmol) and 2-aminoethyl diphenylborinate




(91.4 mg, 0.406 mmol) were dissolved in MeCN (20 mL). Diispropylethylamine (0.880 mL, 5.28 mmol) and acetylchloride (0.319 mL, 5.28 mmol) were added dropwise at ambient temperature. The mixture was stirred for 3 hours and the reaction quenched by addition of $H_2O$ (20 mL). The aqueous phase was then extracted with EtOAc (3 x 15 mL), the combined organic extracts were dried over $Na_2SO_4$ and concentrated. $^1$H NMR analysis of the crude mixture revealed a ratio of regioisomers of 10:1. The residue was purified by flash chromatography ($CH_2Cl_2$/$Et_2O$ =3:1) to give several pure fractions of the desired isomer (440 mg, 38%) along with mixed fractions (700 mg, 59% 5:1 ratio of regioisomers). $[\propto]_D^{20}$ = −83.0 (c = 1.51, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 5.66 (dddd, *J* = 17.2, 10.4, 6.0, 5.1 Hz, 1H), 5.53 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.49 – 5.42 (m, 1H), 5.13 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.96 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.76 (d, *J* = 1.7 Hz, 1H), 4.06 (s, 1H), 3.97 – 3.86 (m, 2H), 3.70 (ddt, *J* = 13.1, 6.0, 1.4 Hz, 1H), 2.22 (d, *J* = 4.5 Hz, 1H), 1.74 (s, 3H), 1.69 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 169.7, 169.6, 134.0, 117.1, 99.0, 72.3, 71.8, 69.9, 68.1, 66.8, 20.5, 20.4, 17.6 ppm. IR (film): $\tilde{\nu}$ = 3466, 2983, 2937, 1738, 1427, 1369, 1316, 1220, 1176, 1126, 1100, 1068, 1036, 984, 937, 922, 832, 801, 699, 601 cm$^{-1}$. MS (EI) *m/z* (%) = 231 (3), 171 (2), 142 (14), 115 (11), 113 (11), 102 (15), 100 (31), 83 (12), 82 (14), 71 (17), 60 (4), 43 (100), 41 (21). HRMS (ESIpos): *m/z*: calcd for $C_{13}H_{20}O_7Na$: 311.1101; found: 311.1099.

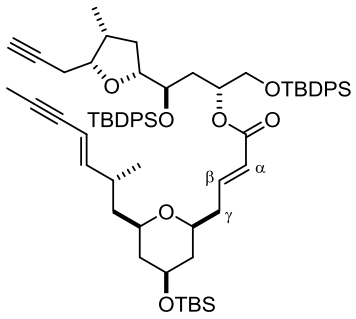
**Allyl 3,4-bis-O-acetyl-2-O-methyl-α-L-rhamnopyranoside (199).** Alcohol **205** (50.0 mg,




0.173 mmol) was dissolved in $CH_2Cl_2$ (0.7 mL) and the solution cooled to 0 °C. Aqueous $HBF_4$ (48%, 45.0 µL, 0.347 mmol) was added via syringe, followed by trimethylsilyldiazomethane (1.51 M in hexane, 0.70 mL, 1.0 mmol). The resulting solution was stirred for 2 hours at 0 °C, when the addition of $HBF_4$ (48%, 45.0 µL, 0.347 mmol) and trimethylsilyldiazomethane (1.51 M in hexane, 0.70 mL, 1.0 mmol) was repeated. After 1h, a third portion of both reagents was added and the reaction mixture stirred for one more hour. It was then carefully quenched by addition of sat. $NaHCO_3$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 5:1) to give the methylated compound as a colorless oil (37.0 mg, 71%). The physical and spectroscopic data were identical with those of the sample obtained by the alternative route outlined above.

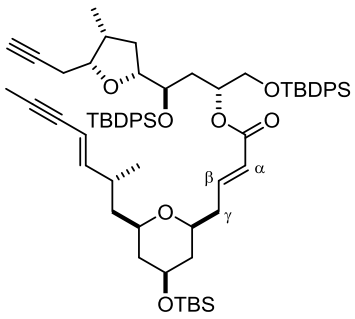
### 5.3.4 Fragment assembly, endgame and structure reassignment.

**Diyne 207.** A flame-dried Schlenk tube was charged with a solution of alcohol **194** (224 mg, 0.318 mmol) in $CH_2Cl_2$ (1.8 mL) and a solution of acid **151** (142 mg, 0.350 mmol) in $CH_2Cl_2$ (0.3 mL). DMAP (194 mg, 1.59 mmol) and DCC (138 mg, 0.668 mmol) were introduced as solids and the resulting mixture was stirred at ambient temperature for 18 h. The white precipitate was filtered off through a short pad of Celite® that was rinsed with $CH_2Cl_2$. The combined filtrates were concentrated and the residue purified by flash chromatography (hexanes/EtOAc 24:1) to give the diyne as a mixture of *α,β*- and *β,γ*-olefins (1.5:1, 222 mg, 64%) as a white foam, along with recovered alcohol **194** (63.1 mg, 28%) as a colorless oil.



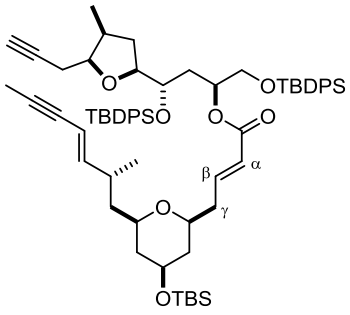

A solution of DBU (0.5 M in MeCN, 102 µL, 0.051 mmol) was added to a solution of the just mentioned mixture of isomeric diynes (222 mg, 0.203 mmol) in MeCN (25 mL) and the resulting solution was stirred at 50 °C for 70 h. After cooling to ambient temperature, sat. $NH_4Cl$ solution (30 mL) containing 10 drops of 1 M HCl was added, the aqueous phase was extracted with EtOAc (4 x 30 mL), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 24:1) to yield the desired *α,β*-olefin as a white foam (202 mg, 91%). $[\alpha]_D^{20}$ = –10.5 (c = 1.03, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 8H), 7.47 – 7.25 (m, 12H), 6.85 (dt, *J* = 15.5, 7.2 Hz, 1H), 5.90 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.72 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.36 (ddd, *J* = 15.9, 2.0, 0.2 Hz, 1H), 5.22 – 5.11 (m, 1H), 3.79 (ddd, *J* = 7.9, 6.4, 3.3 Hz, 1H), 3.76 – 3.67 (m, 3H), 3.61 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.57 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.33 (ddd, *J* = 11.4, 5.8, 5.8 Hz, 1H), 3.26 (dd, *J* = 11.6, 6.2, 6.1 Hz, 1H), 2.45 – 2.19 (m, 4H), 2.11 – 2.01 (m, 2H), 1.96 – 1.87 (m, 2H), 1.90 (d, *J* = 2.1 Hz, 3H), 1.83 (t, *J* = 2.6 Hz, 1H), 1.80 – 1.73 (dd, *J* = 11.7, 3.7 Hz, 3H), 1.61 (ddd, *J* = 13.8, 7.4, 7.2 Hz, 1H), 1.37 – 1.27 (m, 1H), 1.23 – 1.07 (m, 3H), 1.01 (s, 9H), 1.00 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.6, 148.4, 144.7, 136.0, 136.0, 135.9, 135.6, 135.6, 134.6, 134.0, 133.5, 133.4, 129.6, 129.3, 129.1, 127.6, 127.6, 127.3, 127.1, 123.4, 108.3, 84.4, 81.7, 80.9, 79.3, 78.3, 74.1, 73.2, 72.3, 69.2, 68.6, 65.2, 42.3, 41.4, 41.3, 38.8, 35.1, 35.0, 34.6, 33.3, 27.2, 26.8, 25.8, 20.7, 19.8, 19.6, 19.2, 18.1, 3.2, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2856, 1720, 1656, 1472, 1462, 1427, 1376, 1361, 1257, 1175, 1111, 1071, 1006, 836, 823, 776, 740, 701 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1115.7 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{67}H_{92}O_7Si_3Na$: 1115.6043; found: 1115.6049.

**Diyne** 11-*epi*-**207.** Prepared analogously from acid 11-*epi*-**207** (34.9 mg, 85.8 µmol) and alcohol **194**



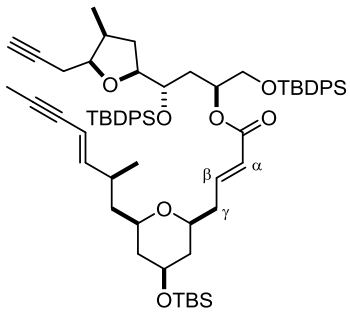

(55 mg, 78.0 µmol) as a white foam (1st step: 216 mg, 71% yield, 2nd step: 56 mg, 92%). $[\alpha]_D^{20}$ = +32.5 (c = 0.72, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.58 (m, 8H), 7.44 – 7.25 (m, 12H), 6.86 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.81 (dd, *J* = 15.8, 8.7 Hz, 1H), 5.73 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.42 (dd, *J* = 15.7, 2.2 Hz, 1H), 5.22 – 5.14 (m, 1H), 3.81 (ddd, *J* = 7.8, 6.6, 3.1 Hz, 1H), 3.77 – 3.67 (m, 3H), 3.64 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.58 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.37 – 3.28 (m, 1H), 3.27 – 3.18 (m, 1H), 2.51 – 2.34 (m, 2H), 2.34 – 2.19 (m, 2H), 2.07 – 2.02 (m, 2H), 1.96 – 1.88 (m, 2H), 1.86 (d, *J* = 2.2 Hz, 3H), 1.83 (t, *J* = 2.6 Hz, 1H), 1.81 – 1.67 (m, 3H), 1.54 (ddd, *J* = 14.0, 9.7, 4.2 Hz, 1H), 1.26 – 1.12 (m, 4H), 1.02 (s, 9H), 1.01 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.5, 148.0, 144.7, 136.0, 135.9, 135.9, 135.6, 135.5, 134.6, 133.9, 133.5, 133.4, 129.6, 129.3, 129.1, 127.6, 127.6, 127.3, 127.1, 123.3, 109.2, 84.3, 81.6, 81.0, 79.3, 78.4, 74.0, 73.3, 72.3, 71.4, 69.2, 68.6, 65.2, 42.9, 41.9, 41.3, 38.8, 35.1, 35.0, 34.7, 33.9, 27.2, 26.8, 25.8, 21.0, 20.7, 19.5, 19.2, 18.1, 14.8, 4.2, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2856, 1721, 1472, 1462, 1428, 1361, 1258, 1112, 1075, 1006, 836, 776, 740, 702, 612 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1115.7 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{67}H_{92}O_7Si_3Na$: 1115.6043; found:1115.6053.

**Diyne 220.** Prepared analogously from acid **151** (170 mg, 0,418 mmol) and alcohol *ent*-**194** (268 mg,



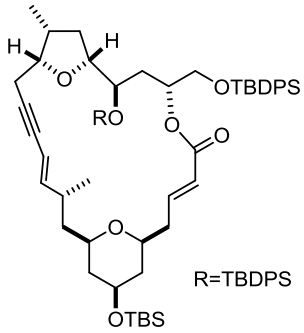

0.380 mmol) as a white foam (1st step: 216 mg, 52% yield, 2nd step: 183 mg, 85%). $[\alpha]_D^{20}$ = –9.0 (c = 1.53, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.58 (m, 8H), 7.42 – 7.24 (m, 12H), 6.86 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.91 (dd, *J* = 15.8, 8.0 Hz, 1H), 5.72 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.37 (ddd, *J* = 15.9, 2.2, 1.1 Hz, 1H), 5.16 (dtd, *J* = 7.9, 4.6, 3.0 Hz, 1H), 3.82 – 3.69 (m, 4H), 3.61 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.58 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.35 (ddd, *J* = 11.0, 5.5, 5.4 Hz, 1H), 3.27 (ddd, *J* = 11.4, 5.8, 5.7 Hz, 1H), 2.46 – 2.20 (m, 4H), 2.10 – 2.01 (m, 2H), 1.97 – 1.87 (m, 5H), 1.84 (t, *J* = 2.6 Hz, 1H), 1.81 – 1.67 (m, 3H), 1.69 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.34 – 1.20 (m, 3H), 1.17 – 1.11 (m, 1H), 1.01 (s, 9H), 1.01 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.6, 148.4, 144.7, 136.0, 135.9, 135.6, 135.5, 135.5, 134.5, 133.8, 133.4, 133.4, 129.6, 129.3, 129.1, 127.7, 127.6, 127.6, 127.6, 127.3, 127.1, 123.4, 108.2, 84.4, 81.6, 80.9, 79.3, 78.3, 74.1, 73.2, 72.2, 71.3, 69.2, 68.6, 65.2, 42.3, 41.3, 41.3, 38.8, 35.1, 34.9, 34.5, 33.3, 27.2, 26.7, 25.8, 20.7, 19.8, 19.5, 19.2, 18.1, 14.8, 4.2, –4.5, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2856, 1720, 1472, 1462, 1428, 1377, 1257, 1176, 1110, 1070, 1006, 836, 776, 739, 702, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1115.8 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{67}H_{92}O_7Si_3Na$: 1115.6043; found:1115.6052.

**Diyne** (11-*epi*-**220**)**.** Prepared analogously from acid 11-*epi*-**151** (89 mg, 0.219 mmol) and alcohol *ent*-




**194** (140 mg, 0.199 mmol) as a white foam (1st step: 116 mg, 53% yield, 2nd step: 108 mg, 93%). $[\alpha]_D^{20}$ = +40.9 (c = 0.90, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 8H), 7.41 – 7.25 (m, 12H), 6.85 (dt, *J* = 15.6, 7.1 Hz, 1H), 5.80 (dd, *J* = 15.8, 8.7 Hz, 1H), 5.72 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.41 (dd, *J* = 15.8, 2.2 Hz, 1H), 5.16 (dtd, *J* = 9.0, 4.6, 4.1 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.76 – 3.67 (m, 3H), 3.62 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.57 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.33 (dtd, *J* = 11.8, 5.8, 0.7 Hz, 1H), 3.26 – 3.17 (m, 1H), 2.49 – 2.35 (m, 2H), 2.31 (ddd, *J* = 6.3, 6.2, 1.3 Hz, 1H), 2.23 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.05 (t, *J* = 3.0 Hz, 1H), 2.03 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.89 (d, *J* = 2.2 Hz, 3H), 1.84 (t, *J* = 2.7 Hz, 1H), 1.80 – 1.65 (m, 3H), 1.53 (ddd, *J* = 13.9, 9.7, 4.2 Hz, 1H), 1.27 – 1.21 (m, 2H), 1.21 – 1.14 (m, 2H), 1.00 (s, 9H), 0.99 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.6, 148.1, 144.8, 136.0, 135.9, 135.6, 135.5, 134.5, 133.8, 133.4, 133.4, 129.7, 129.6, 129.3, 129.1, 127.6, 127.6, 127.4, 127.1, 123.3, 109.1, 84.3, 81.6, 80.9, 79.3, 78.4, 73.9, 73.3, 72.2, 71.3, 69.2, 68.5, 65.2, 42.9, 41.9, 41.3, 38.8, 35.1, 34.9, 34.6, 33.9, 27.2, 27.1, 26.7, 26.7, 25.8, 21.0, 20.6, 19.5, 19.2, 18.1, 14.8, 4.2, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1721, 1472, 1462, 1428, 1361, 1257, 1155, 1112, 1071, 1006, 836, 776, 702, 610 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1115.6 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{67}H_{92}O_7Si_3Na$: 1115.6043; found:1115.6047.

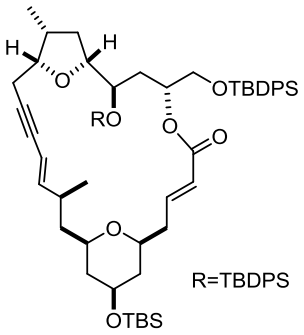
**Macrocyclic Enyne 209.** A flame-dried Schlenk tube was charged with powdered 4 Å molecular




sieves (~1.2 g) and 5 Å molecular sieves (~1.5 g). The flask was then evacuated and the molecular sieves were flame-dried. After reaching ambient temperature, a solution of diyne **207** (191 mg, 0.175 mmol) in toluene (85 mL) was added and the resulting suspension was stirred for 45 min. In a separate flame-dried Schlenk tube, a solution of the molybdenum alkylidyne complex **C1** (18.2 mg, 17.5 µmol) in toluene (2 mL) was prepared. This solution was added dropwise to the flask containing the diyne via syringe and the resulting mixture was stirred at ambient temperature for 3 h. The mixture was filtered through a short pad of Celite® that was carefully rinsed with $Et_2O$ (100 mL). The combined filtrates were evaporated and the brown residue was purified by flash chromatography (hexanes/EtOAc 29:1 to 24:1 to 19:1) to yield the target macrocycle as a white foam (133 mg, 72%). $[\alpha]_D^{20}$ = –7.4 (c = 0.87, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.60 (m, 8H), 7.45 – 7.24 (m, 12H), 6.87 (ddd, *J* = 15.7, 8.2, 5.7 Hz, 1H), 5.97 (dd, *J* = 16.0, 7.3 Hz, 1H), 5.73 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.32 (dq, *J* = 15.9, 1.7 Hz, 1H), 5.22 – 5.15 (m, 1H), 4.09 (ddd, *J* = 9.6, 5.7, 2.6 Hz, 1H), 3.82 –

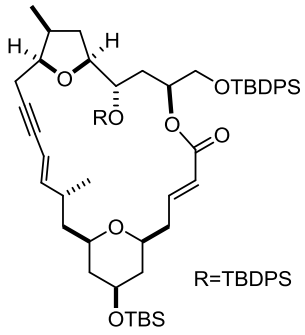
3.74 (m, 2H), 3.74 – 3.69 (m, 1H), 3.67 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.62 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.27 (dddd, *J* = 11.2, 9.2, 2.1, 1.8 Hz, 1H), 3.22 – 3.14 (m, 1H), 2.31 (tdd, *J* = 9.1, 4.6, 1.5 Hz, 1H), 2.26 – 2.12 (m, 5H), 2.10 (ddd, *J* = 14.2, 9.3, 2.5 Hz, 1H), 1.86 – 1.67 (m, 4H), 1.61 – 1.50 (m, 1H), 1.35 – 1.30 (m, 2H), 1.22 – 1.11 (m, 2H), 1.03 (s, 9H), 1.01 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 148.5, 144.9, 135.9, 135.8, 135.6, 135.2, 135.0, 134.9, 133.9, 133.6, 133.0, 129.5, 129.3, 129.2, 127.9, 127.6, 127.6, 127.4, 127.2, 123.6, 107.8, 86.8, 81.3, 81.2, 78.5, 75.6, 74.5, 71.9, 71.7, 68.6, 65.5, 43.2, 42.2, 41.8, 38.4, 36.5, 35.1, 34.0, 33.8, 29.7, 27.2, 26.8, 25.8, 21.6, 19.6, 19.3, 18.1, 13.8, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2856, 1718, 1472, 1462, 1428, 1361, 1328, 1256, 1174, 1112, 1071, 986, 836, 823, 775, 737, 700 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1075.7 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{88}O_7Si_3Na$: 1075.5730; found: 1075.5725.

**Macrocyclic Enyne** 11-*epi*-**209.** Prepared analogously (at room temperature) from diyne 11-*epi*-**207**



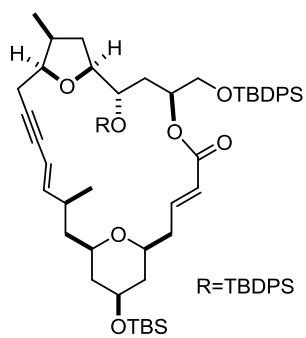

(52 mg, 47.5 µmol) as a white foam (32 mg, 64%). $[\alpha]_D^{20}$ = +54.6 (c = 1.04, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.69 (ddd, *J* = 7.7, 3.3, 1.7 Hz, 4H), 7.63 – 7.56 (m, 4H), 7.44 – 7.25 (m, 12H), 6.97 (ddd, *J* = 15.4, 8.2, 7.0 Hz, 1H), 5.73 (dt, *J* = 15.5, 1.1 Hz, 1H), 5.60 (dd, *J* = 15.7, 9.6 Hz, 1H), 5.30 (dt, *J* = 15.7, 1.8 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.16 (ddd, *J* = 8.8, 6.8, 1.8 Hz, 1H), 3.85 (ddd, *J* = 8.2, 5.8, 3.9 Hz, 1H), 3.80 – 3.68 (m, 2H), 3.65 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.47 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.20 – 3.08 (m, 2H), 2.63 – 2.50 (m, 1H), 2.39 – 2.17 (m, 3H), 2.13 (dd, *J* = 12.9, 7.9, 1H), 2.07 (ddd, *J* = 16.9, 5.7, 0.2 Hz, 1H), 1.90 (ddd, *J* = 14.5, 7.1, 2.1 Hz, 1H), 1.80 – 1.64 (m, 4H), 1.59 – 1.51 (m, 1H), 1.51 – 1.41 (m, 1H), 1.30 – 1.14 (m, 3H), 1.02 (s, 9H), 1.01 (m, 3H), 1.00 (s, 9H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.3, 146.2, 146.0, 135.9, 135.9, 135.6, 134.8, 134.6, 133.6, 133.6, 129.5, 129.2, 129.1, 127.6, 127.5, 127.3, 127.2, 123.3, 110.4, 86.6, 81.6, 81.0, 78.8, 75.5, 74.1, 72.9, 72.9, 68.7, 65.8, 42.6, 42.2, 41.9, 38.6, 36.6, 35.8, 35.3, 33.8, 27.3, 26.8, 25.8, 23.1, 21.3, 19.7, 19.3, 18.1, 13.7, –4.5, –4.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1722, 1472, 1462, 1428, 1361, 1327, 1257, 1176, 1112, 1067, 854, 836, 823, 776, 739, 701, 608 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1075.6 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{88}O_7Si_3Na$: 1075.5730; found:1075.5722.

**Macrocyclic Enyne 221.** *A slightly modified procedure had to be used:* A flame-dried Schlenk tube




was charged with powdered 4 Å molecular sieves (~0.7 g) and 5 Å molecular sieves (~0.9 g). The flask was then evacuated and the molecular sieves were flame-dried. After reaching ambient temperature, a solution of diyne **220** (90 mg, 82.3 µmol) in toluene (40 mL) was added and the resulting suspension was stirred for 45 min. The solution was then placed in a pre-heated oilbath (85 °C). In a separate flame-dried Schlenk tube, a solution of the molybdenum alkylidyne complex **C1** (8.6 mg, 8.2 µmol) in toluene (2 mL) was prepared. This solution was added dropwise to the flask containing the diyne via syringe at 85 °C and the resulting mixture was stirred for 2 h. After cooling to room temperature, the mixture was filtered through a short pad of Celite® that was carefully rinsed with $Et_2O$ (100 mL). The combined filtrates were evaporated and the brown residue was purified by flash chromatography (hexanes/EtOAc 29:1 to 24:1 to 19:1) to yield the targeted macrocycle as a white foam (64 mg, 74%). $[\propto]_D^{20}$ = +8.5 (c = 1.31, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.58 (m, 8H), 7.42 – 7.25 (m, 12H), 6.82 (ddd, *J* = 15.9, 5.3, 5.3 Hz, 1H), 5.87 (dd, *J* = 15.9, 7.8 Hz, 1H), 5.74 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.36 (dt, *J* = 15.9, 1.9 Hz, 1H), 5.13 – 5.05 (m, 1H), 4.08 (ddd, *J* = 9.9, 5.4, 1.1 Hz, 1H), 3.86 (ddd, *J* = 8.0, 8.0, 4.2 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.70 (dd, *J* = 10.7,4.4 Hz, 1H), 3.67 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.42 (dd, *J* = 11.0, 9.5 Hz, 1H), 3.22 (dt, *J* = 10.4, 5.4 Hz, 1H), 2.38 – 2.07 (m, 7H), 1.86 – 1.67 (m, 4H), 1.52 (ddd, *J* = 13.8, 8.2, 5.5 Hz, 1H), 1.47 (d, *J* = 10.9 Hz, 1H), 1.39 (ddd, *J* = 13.9, 6.3, 4.0 Hz, 1H), 1.28 (q, *J* = 11.5 Hz, 1H), 1.14 (dq, *J* = 11.1, 10.2 Hz, 1H), 1.05 (s, 9H), 1.00 (s, 9H), 0.99 (d, *J* = 7.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ =165.9, 147.8, 145.0, 135.9, 135.8, 135.6, 134.9, 134.7, 133.7, 133.6, 133.4, 129.6, 129.5, 129.2, 129.2, 127.9, 127.7, 127.6, 127.4, 127.2, 122.3, 108.8, 86.2, 81.2, 80.5, 78.6, 74.2, 73.2, 71.4, 71.2, 68.7, 65.3, 42.7, 41.9, 41.4, 37.3, 36.4, 34.5, 33.4, 33.3, 27.2, 27.1, 26.8, 25.8, 23.2, 21.5, 19.5, 19.3, 18.1, 13.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2856, 1720, 1472, 1462, 1428, 1361, 1331, 1257, 1178, 1111, 1070, 937, 837, 823, 776, 739, 702, 610 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1075.7 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{88}O_7Si_3Na$: 1075.5730; found: 1075.5736.

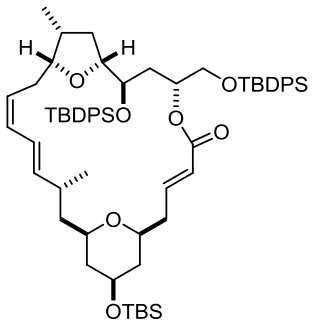
**Macrocyclic Enyne** 11-*epi*-**221.** Prepared analogously (at room temperature) from diyne 11-*epi*-**220**




(107 mg, 97.8 µmol) as a white foam (85.1 mg, 83%). $[\propto]_D^{20}$ = +57.4 (c = 0.56, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.72 – 7.60 (m, 8H), 7.42 – 7.25 (m, 12H), 6.85 (dt, *J* = 15.9, 5.2 Hz, 1H), 5.73 (dt, *J* = 15.8, 1.6 Hz, 1H), 5.69 (dd, *J* = 15.8, 8.8 Hz, 1H), 5.56 (dt, *J* = 15.8, 1.7 Hz, 1H), 5.22 – 5.13 (m, 1H), 4.24 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.91 – 3.73 (m, 5H), 3.44 (t, *J* = 10.6 Hz, 1H), 3.27 (t, *J* = 11.1 Hz, 1H), 2.56 – 2.33 (m, 2H), 2.29 – 2.19 (m, 2H), 2.18 – 2.08 (m, 2H), 1.86 – 1.63 (m, 5H), 1.54 (ddd, *J* =

14.0, 11.3, 2.9 Hz, 1H), 1.34 – 1.14 (m, 4H), 1.05 (s, 9H), 1.04 (m, 3H), 1.01 (s, 9H), 0.90 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.0, 146.2, 145.7, 136.0, 135.8, 135.5, 135.5, 135.1, 134.0, 133.5, 133.4, 129.6, 129.5, 129.0, 128.9, 127.6, 127.3, 127.0, 121.6, 110.1, 87.1, 82.4, 81.7, 78.2, 73.5, 72.8, 72.2, 72.0, 68.6, 65.1, 43.0, 42.1, 37.8, 36.9, 33.9, 33.6, 33.2, 27.2, 26.8, 26.8, 25.9, 25.8, 23.0, 21.4, 19.5, 19.3, 18.1, 13.2, −4.5, −4.6 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2856, 1720, 1472, 1462, 1378, 1361, 1291, 1256, 1176, 1111, 1075, 1006, 837, 776, 739, 702, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1075.8 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{88}O_7Si_3Na$: *m/z*: 1075.5730; found:1075.5724.

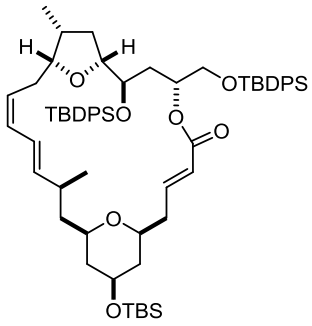
**Macrocyclic Diene 210.** *In order to obtain reproducible results, all solvents used for the preparation of the activated Zn(Cu/Ag) and the reaction were degassed by bubbling Ar through the solvent for at least 20 min.*




A Young tube was evacuated, backfilled with Argon and charged with a mixture of MeOH/$H_2O$ (1:1, 1.8 mL). Freshly prepared Zn(Cu/Ag)[96] (1.6 g) was added, followed by a solution of enyne **209** (130 mg, 0.123 mmol) in THF (0.5 mL + 2 x 0.2 mL rinse). The Young tube was sealed and placed in a preheated (45 °C) oil bath. The suspension was vigorously stirred at this temperature for 70 h before it was allowed to reach ambient temperature. The mixture was filtered through a short pad of Celite® that was rinsed with EtOAc/EtOH (9:1, 75 mL). The combined filtrates were concentrated to ≈1/10 of the original volume before brine (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 29:1 to 24:1 to 19:1) to give the desired diene as a white foam (115 mg, 89%). $[\propto]_D^{20}$ = –47.9 (c = 0.70, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.64 – 7.54 (m, 8H), 7.40 – 7.22 (m, 12H), 6.84 (ddd, *J* = 15.7, 8.0, 5.5 Hz, 1H), 6.19 (dd, *J* = 15.4, 10.8 Hz, 1H), 5.88 (t, *J* = 10.8 Hz, 1H), 5.76 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.55 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.18 – 5.08 (m, 2H), 3.99 (ddd, *J* = 8.8, 6.0, 2.3 Hz, 1H), 3.73 (td, *J* = 7.9, 6.3 Hz, 1H), 3.66 (dt, *J* = 10.0, 4.8 Hz, 1H), 3.64 – 3.59 (m, 2H), 3.56 (dt, *J* = 7.0, 5.7 Hz, 1H), 3.28 – 3.14 (m, 2H), 2.43 – 2.33 (m, 1H), 2.32 – 2.24 (m, 1H), 2.20 (ddd, *J* = 16.0, 8.2, 2.7 Hz, 1H), 2.14 – 1.95 (m, 3H), 1.90 (dt, *J* = 15.7, 7.5 Hz, 1H), 1.85 – 1.77 (m, 2H), 1.75 – 1.64 (m, 3H), 1.34 (ddd, *J* = 12.7, 7.3, 5.2 Hz, 1H), 1.29 – 1.25 (m, 1H), 1.23 – 1.17 (m, 2H), 1.17 – 1.07 (m, 1H), 0.99 (s, 9H), 0.97 (s, 9H), 0.94 (d, *J* = 6. 7 Hz, 3H), 0.83 (s, 9H), 0.76 (d, *J* = 7.1 Hz, 3H), 0.00 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.8, 145.0, 140.2, 136.0, 136.0, 135.6, 135.6, 134.7, 133.9, 133.5, 133.5, 129.6, 129.5, 129.4, 127.6, 127.6, 127.4, 127.2, 126.4, 124.3, 123.3, 81.4, 80.1, 74.2, 73.4, 72.0, 71.6, 68.7, 65.4, 43.1, 41.9, 41.9, 38.5, 35.4, 34.4, 34.3, 32.1, 30.0, 27.2, 26.8, 25.8, 20.7, 19.5, 19.3, 18.1, 15.4, –4.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1721, 1654, 1472, 1462, 1428, 1375, 1257, 1175, 1112, 1073, 1006, 836, 823, 775, 739, 702 cm$^{-1}$. MS (ESIpos)

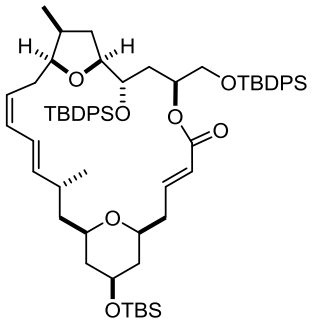
*m/z* (%) = 1077.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{90}O_7Si_3Na$: 1077.5887; found: 1075.5884.

**Macrocyclic Diene** 11-*epi*-**210.** Prepared analogously from enyne 11-*epi*-**209** (31.0 mg, 29.4 µmol) as




a white foam (26.8 mg, 86%). $[\propto]_D^{20}$ = +15.2 (c = 1.22, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.53 (m, 8H), 7.42 – 7.20 (m, 12H), 7.09 (ddd, *J* = 15.1, 10.3, 4.3 Hz, 1H), 6.21 (dd, *J* = 14.9, 11.1 Hz, 1H), 5.89 (tt, *J* = 10.9, 1.9 Hz, 1H), 5.74 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.25 (dd, *J* = 14.9, 9.7 Hz, 1H), 5.12 – 5.02 (m, 2H), 3.92 – 3.82 (m, 2H), 3.77 – 3.65 (m, 2H), 3.41 (dd, *J* = 11.2, 3.3 Hz, 1H), 3.34 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.71 – 2.59 (m, 1H), 2.40 (tdd, *J* = 9.6, 4.6, 1.9 Hz, 1H), 2.26 – 2.11 (m, 4H), 2.03 (dt, *J* = 15.1, 7.4 Hz, 1H), 1.93 (dt, *J* = 14.6, 5.9 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.66 (dd, *J* = 12.5, 4.7 Hz, 1H), 1.56 (ddd, *J* = 14.0, 10.6, 2.9 Hz, 2H), 1.49 – 1.38 (m, 1H), 1.25 – 1.12 (m, 4H), 1.01 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 9H), 0.85 (s, 9H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.02 (s, 3H), 0.02 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.2, 145.7, 139.8, 135.9, 135.8, 135.7, 135.6, 134.1, 133.9, 133.7, 133.4, 129.6, 129.5, 127.6, 127.5, 127.5, 127.4, 125.9, 125.6, 122.8, 81.3, 80.7, 75.1, 73.0, 72.3, 72.0, 68.5, 65.1, 43.5, 42.3, 42.1, 39.3, 35.6, 34.6, 34.6, 33.9, 29.4, 27.1, 26.7, 25.8, 22.1, 19.4, 19.2, 18.1, 15.1, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2957, 2928, 2856, 1724, 1427, 1257, 1157, 1113, 1076, 833, 822, 778, 741, 703, 557 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1077.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{90}O_7Si_3Na$: 1077.5887; found: 1077.5884.

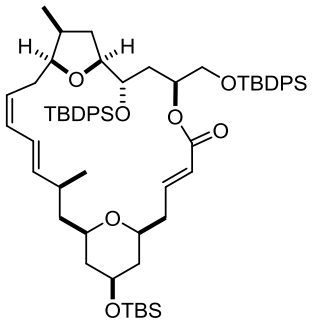
**Macrocyclic Diene 222.** Prepared analogously from enyne **221** (26.3 mg, 25.0 µmol) as a white foam




(24.1 mg, 91%). $[\propto]_D^{20}$ = +13.2 (c = 1.21, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.58 (m, 8H), 7.42 – 7.25 (m, 12H), 6.88 (ddd, *J* = 15.7, 7.6, 6.2 Hz, 1H), 6.21 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.93 (t, *J* = 10.7 Hz, 1H), 5.83 (dt, *J* = 15.7, 1.2 Hz, 1H), 5.20 (dd, *J* = 15.2, 8.1 Hz, 1H), 5.24 – 5.13 (m, 2H), 4.01 (ddd, *J* = 8.6, 5.6, 3.0 Hz, 1H), 3.80 – 3.66 (m, 2H), 3.64 – 3.57 (m, 2H), 3.54 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.40 – 3.32 (m, 1H), 3.31 – 3.23 (m, 1H), 2.40 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.36 – 2.29 (m, 1H), 2.20 – 2.08 (m, 2H), 1.99 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.93 (dt, *J* = 14.6, 5.9 Hz, 1H), 1.91 (ddd, *J* = 14.5, 8.4, 3.0 Hz, 1H), 1.85 – 1.69 (m, 4H), 1.36 (dt, *J* = 12.8, 7.6 Hz, 1H), 1.34 – 1.25 (m, 2H), 1.23 – 1.13 (m, 2H), 1.00 (s, 18H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H) 0.87 (s, 9H), 0.05 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.7, 145.2, 140.1, 136.0, 135.9, 135.6, 135.6, 134.7, 134.0, 133.5, 133.4, 129.9, 129.5, 129.3, 127.6, 127.3, 127.3, 126.8, 124.3, 123.3, 81.2, 80.1, 73.8, 73.2, 72.7, 71.6, 68.8, 65.5, 43.0, 41.9, 41.8, 38.5, 35.7, 34.4, 34.1, 33.3, 30.2, 27.2, 26.7, 25.8, 20.2, 19.5, 19.2, 18.1, 15.2, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1722, 1428, 1293, 1258, 1177,

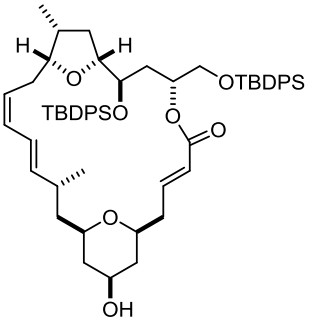
1107, 741, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1077.7 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{90}O_7Si_3Na$: 1077.5887; found: 1077.5896.

**Macrocyclic Diene** 11-*epi*-**222.** Prepared analogously from enyne 11-*epi*-**221** (71.0 mg, 67.4 µmol) as




a white foam (59.2 mg, 83%). $[\propto]_D^{20}$ = +79.1 (c = 1.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 8H), 7.42 – 7.25 (m, 12H), 6.84 (ddd, *J* = 15.8, 7.2, 5.6 Hz, 1H), 6.26 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.98 (t, *J* = 10.9 Hz, 1H), 5.72 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.36 (dd, *J* = 15.1, 8.6 Hz, 1H), 5.22 (td, *J* = 10.0, 6.3 Hz, 1H), 5.02 – 4.94 (m, 1H), 4.10 (ddd, *J* = 8.8, 4.9, 2.3 Hz, 1H), 3.82 (td, *J* = 7.8, 4.8 Hz, 1H), 3.76 – 3.61 (m, 4H), 3.28 (ddt, *J* = 10.9, 9.6, 1.6 Hz, 1H), 3.21 (t, *J* = 10.9 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.45 – 2.16 (m, 5H), 2.09 (dtd, *J* = 14.7, 5.4, 1.1 Hz, 1H), 1.90 (dt, *J* = 13.0, 7.8 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.69 – 1.62 (m, 1H), 1.59 – 1.48 (m, 2H), 1.28 – 1.13 (m, 3H), 1.03 (s, 9H), 1.01 (s, 9H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H) 0.82 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.7, 145.0, 141.2, 135.9, 135.9, 135.6, 135.5, 134.3, 133.6, 133.4, 133.3, 130.0, 129.6, 129.5, 129.4, 129.4, 127.6, 127.6, 127.5, 127.4, 126.8, 125.5, 122.9, 81.3, 79.7, 73.8, 73.2, 72.4, 70.8, 68.5, 65.4, 44.2, 42.4, 42.3, 39.0, 35.7, 33.3, 33.3, 33.1, 30.8, 27.1, 26.7, 25.8, 22.9, 19.4, 19.2, 18.1, 15.3, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2931, 2857, 1718, 1472, 1462, 1428, 1257, 1177, 1155, 1112, 1076, 1005, 836, 776, 737, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1077.7 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{64}H_{90}O_7Si_3Na$: 1077.5887; found: 1077.5878.

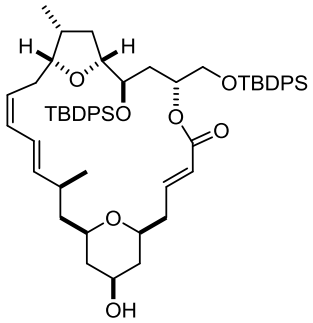
**Alcohol 211.** *p*TsOH·$H_2O$ (6.2 mg, 32.6 µmol) was added to a solution of silyl ether **210** (114 mg, 0.109 mmol) in $CH_2Cl_2$/MeOH (2:1, 12 mL) and the mixture was stirred for 5 h. The reaction was quenched by addition of sat. $NaHCO_3$ solution (12 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 8 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc 2:1) to yield the desired alcohol as a white foam (92 mg, 90%). $[\propto]_D^{20}$ = –42.5 (c = 0.89, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.58 (m, 8H),




7.43 – 7.25 (m, 12H), 6.87 (ddd, *J* = 15.8, 7.9, 5.7 Hz, 1H), 6.23 (ddt, *J* = 15.6, 10.8, 1.2 Hz, 1H), 5.92 (t, *J* = 10.8 Hz, 1H), 5.80 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.59 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.03 (ddd, *J* = 8.8, 6.0, 2.3 Hz, 1H), 3.83 – 3.71 (m, 2H), 3.71 – 3.56 (m, 3H), 3.35 – 3.21 (m, 2H), 2.46 – 2.30 (m, 2H), 2.27 (tdd, *J* = 7.5, 3.0, 1.3 Hz, 1H), 2.18 – 2.05 (m, 2H), 2.03 (ddd, *J* = 14.5, 10.1, 0.1 Hz, 1H), 1.99 – 1.81 (m, 5H), 1.76 (ddd, *J* = 14.0, 8.2, 6.0 Hz, 1H), 1.52 – 1.44 (br s, 1H), 1.38 (ddd, *J* = 12.8, 7.3, 5.4 Hz, 1H), 1.33 (ddd, *J* = 13.5, 8.1, 4.8 Hz, 1H), 1.22 (ddd, *J* = 11.5, 10.9, 10.6 Hz, 1H), 1.13 (ddd, *J* = 11.6, 11.3, 1.09 Hz, 1H), 1.03 (s, 9H), 1.01 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.7, 143.7, 140.0, 136.0,

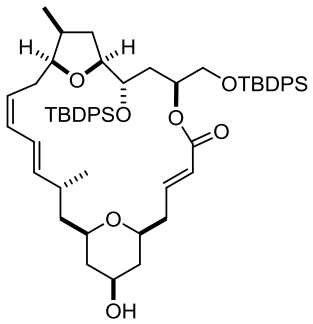
136.0, 135.6, 135.6, 134.6, 133.9, 133.5, 130.0, 129.6, 129.6, 129.4, 129.2, 127.6, 127.6, 127.4, 127.2, 126.4, 124.4, 123.3, 81.4, 80.1, 74.2, 73.4, 72.1, 71.6, 68.1, 65.4, 42.9, 41.4, 41.3, 38.4, 35.4, 34.5, 34.3, 32.1, 30.0, 27.2, 26.8, 20.9, 19.5, 15.4 ppm. IR (film): $\tilde{\nu}$ = 3454, 2957, 2930, 2857, 1720, 1654, 1472, 1427, 1361, 1265, 1176, 1112, 1006, 822, 739, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 963.6 (100 (M+Na). HRMS (ESIpos): *m/z*: calcd for $C_{58}H_{76}O_7Si_2Na$: 963.5022; found: 963.5028.

**Alcohol** 11-*epi*-**211.** Prepared analogously from silyl ether 11-*epi*-**210** (24.2 mg, 22.9 µmol) as a white




foam (19.3 mg, 89%). $[\propto]_D^{20}$ = +28.4 (c = 0.96, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.53 (m, 8H), 7.42 – 7.20 (m, 12H), 7.07 (ddd, *J* = 15.1, 10.2, 4.4 Hz, 1H), 6.20 (dd, *J* = 14.9, 11.0 Hz, 1H), 5.87 (tt, *J* = 10.9, 1.9 Hz, 1H), 5.75 (dd, *J* = 15.6, 1.7 Hz, 1H), 5.24 (dd, *J* = 14.9, 9.7 Hz, 1H), 5.11 – 5.01 (m, 2H), 3.93 – 3.83 (m, 2H), 3.79 – 3.68 (m, 2H), 3.41 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.35 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.21 – 3.07 (m, 2H), 2.64 (tt, *J* = 9.5, 3.4 Hz, 1H), 2.42 (tdd, *J* = 9.6, 4.7, 1.9 Hz, 1H), 2.27 – 2.10 (m, 4H), 2.02 (dd, *J* = 8.0, 7.7, 7.4 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.84 – 1.75 (m, 2H), 1.63 – 1.52 (m, 2H), 1.42 (ddd, *J* = 13.6, 7.2, 3.5 Hz, 1H), 1.23 – 1.11 (m, 3H), 1.01 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 9H), 0.78 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.2, 145.4, 139.6, 135.9, 135.8, 135.7, 135.6, 134.1, 133.9, 133.6, 133.5, 129.6, 129.5, 127.6, 127.5, 127.5, 127.4, 126.0, 125.7, 122.9, 81.3, 80.8, 75.0, 73.1, 72.4, 72.1, 68.0, 65.2, 43.4, 41.7, 41.6, 39.2, 35.6, 34.6, 34.6, 34.0, 29.5, 27.1, 26.7, 20.1, 19.4, 19.2, 15.1 ppm. IR (film): $\tilde{\nu}$ = 3414, 2957, 2930, 2857, 1722, 1655, 1472, 1428, 1361, 1326, 1262, 1177, 1111, 990, 822, 739, 702, 610 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 963.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{58}H_{76}O_7Si_2Na$: 963.5022; found: 963.5017.

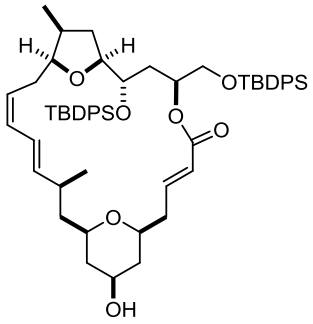
**Secondary alcohol 223.** Prepared analogously from silyl ether **222** (24.1 mg, 22.8 µmol) as a white




foam (18.4 mg, 86%). $[\propto]_D^{20}$ = +13.8 (c = 0.92, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 8H), 7.43 – 7.23 (m, 12H), 6.87 (ddd, *J* = 15.7, 7.3, 6.3 Hz, 1H), 6.25 (dd, *J* = 15.1, 10.9 Hz, 1H), 5.93 (t, *J* = 10.9 Hz, 1H), 5.83 (dt, *J* = 15.7, 1.0 Hz, 1H), 5.53 (dd, *J* = 15.1, 8.0 Hz, 1H), 5.25 – 5.13 (m, 2H), 4.02 (ddd, *J* = 8.8, 5.6, 3.1 Hz, 1H), 3.79 (ddt, *J* = 10.7, 10.2, 5.1 Hz, 1H), 3.70 (ddd, *J* = 7.7, 7.6, 5.7 Hz, 1H), 3.64 – 3.58 (m, 2H), 3.54 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.43 – 3.35 (m, 1H), 3.30 (dddd, *J* = 10.6, 8.9, 3.7, 1.7 Hz, 1H), 2.45 – 2.29 (m, 3H), 2.21 – 2.09 (m, 2H), 2.01 (dt, *J* = 13.9, 6.8 Hz, 1H), 1.97 – 1.81 (m, 4H), 1.75 (ddd, *J* = 14.5, 9.0, 3.4 Hz, 1H), 1.64 (ddd, *J* = 13.9, 8.6, 5.4 Hz, 1H), 1.60 – 1.47 (br d, 1H), 1.43 – 1.30 (m, 2H), 1.23 – 1.08 (m, 2H), 1.00 (s, 9H), 1.00 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.6, 144.9, 140.0, 136.0, 135.9, 135.6, 135.6, 134.6, 134.0, 133.4, 129.9, 129.5, 129.4, 127.6, 127.3, 127.3,

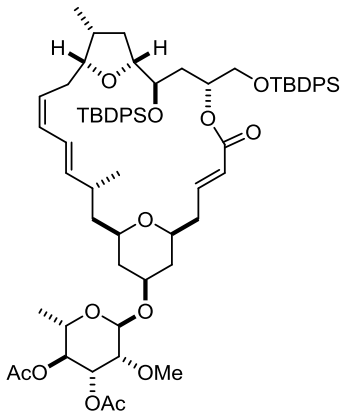
126.8, 124.3, 123.4, 81.2, 80.0, 73.7, 73.2, 72.5, 71.6, 68.1, 65.4, 43.0, 41.3, 41.3, 38.4, 35.6, 34.3, 34.0, 33.1, 30.2, 27.2, 26.7, 20.2, 19.5, 19.2, 15.2 ppm. IR (film): $\tilde{\nu}$ = 3422, 2957, 2931, 2857, 1719, 1656, 1472, 1428, 1362, 1265, 1177, 1111, 982, 823, 740, 702, 611 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 963.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{58}H_{76}O_7Si_2Na$: 963.5022; found: 963.5021.

**Alcohol** 11-*epi*-**223.** Prepared analogously from silyl ether 11-*epi*-**222** (23.1 mg, 21.9 µmol) as a white




foam (18.5 mg, 90%). $[\propto]_D^{20}$ = +100.5 (c = 0.92, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.55 (m, 8H), 7.42 – 7.23 (m, 12H), 6.82 (ddd, *J* = 15.8, 7.2, 5.4 Hz, 1H), 6.25 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.96 (t, *J* = 10.9 Hz, 1H), 5.71 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.34 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.22 (td, *J* = 10.2, 6.1 Hz, 1H), 5.02 – 4.95 (m, 1H), 4.10 (ddd, *J* = 8.9, 4.8, 2.3 Hz, 1H), 3.80 (td, *J* = 7.8, 4.8 Hz, 1H), 3.77 – 3.70 (m, 2H), 3.70 – 3.62 (m, 2H), 3.31 (ddt, *J* = 11.3, 9.5, 2.0 Hz, 1H), 3.24 (t, *J* = 10.7 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.42 (dddd, *J* = 16.4, 9.5, 5.4, 1.7 Hz, 1H), 2.38 – 2.16 (m, 4H), 2.08 (dt, *J* = 14.9, 5.2 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.82 – 1.73 (m, 2H), 1.60 – 1.50 (m, 2H), 1.25 – 1.12 (m, 4H), 1.03 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.7, 144.7, 141.0, 135.9, 135.9, 135.5, 135.5, 134.2, 133.5, 133.4, 133.3, 130.0, 129.6, 129.5, 129.4, 129.4, 127.6, 127.5, 127.4, 126.9, 125.6, 123.0, 81.3, 79.6, 73.6, 73.2, 72.3, 70.6, 67.9, 65.4, 44.2, 41.8, 41.7, 38.9, 35.6, 33.3, 33.2, 33.0, 30.8, 27.1, 26.7, 22.9, 19.4, 19.2, 15.4 ppm. IR (film): $\tilde{\nu}$ = 3456, 2957, 2931, 2857, 1714, 1472, 1462, 1428, 1362, 1268, 1180, 1110, 1089, 1048, 999, 908, 822, 731, 701, 610 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 963.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{58}H_{76}O_7Si_2Na$: 963.5022; found: 963.5024.

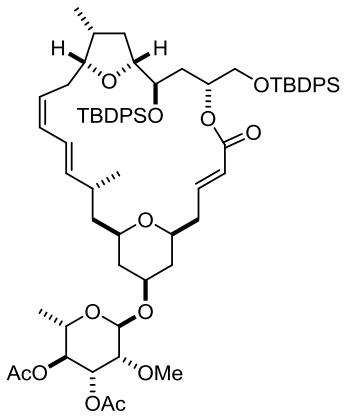
**Glycoside 212.** A Schlenk tube was charged with powdered 4 Å MS (400 mg) and flame-dried in




vacuo. After reaching RT, the molecular sieves were suspended in $CH_2Cl_2$ (10 mL) and a solution of alcohol **211** (87.0 mg, 92.4 µmol) in $CH_2Cl_2$ (1.6 mL) was introduced. Rhamnosyl donor **201** (56.3 mg, 139 µmol) was added as a solid and the resulting suspension was stirred for 45 min at ambient temperature before it was cooled to –50 °C. A solution of TESOTf (0.1 M, 277 µL, 27.7 µmol) was added dropwise via syringe over 1 min. After stirring for 30 min at –50 °C, the reaction was quenched with $NEt_3$ (0.1 mL), the mixture was filtered through a pad of Celite® and the filtrate was evaporated. The crude residue was purified by flash chromatography (hexanes/EtOAc 3:1) to yield the desired glycoside as a white foam (97.0 mg, 88% yield, 16:1 d.r.). $[\propto]_D^{20}$ = –61.5 (c = 0.82, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.70 – 7.55 (m, 8H), 7.43 – 7.24 (m, 12H), 6.85 (ddd, *J* = 15.8, 8.1, 5.5 Hz, 1H), 6.23 (dd, *J* = 15.4, 10.8 Hz, 1H), 5.91 (t, *J* = 10.8 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.1 Hz, 1H), 5.58 (dd, *J* = 15.4,

6.8 Hz, 1H), 5.23 – 5.14 (m, 3H), 5.08 (t, *J* = 9.9 Hz, 1H), 4.95 (d, *J* = 1.9 Hz, 1H), 4.02 (ddd, *J* = 8.8, 6.1, 2.4 Hz, 1H), 3.82 (dq, *J* = 9.7, 6.3 Hz, 1H), 3.79 – 3.70 (m, 2H), 3.65 (dd, *J* = 10.7, 4.5 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 1H), 3.54 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.45 (s, 3H), 3.32 – 3.23 (m, 2H), 2.44 – 2.37 (m, 1H), 2.37 – 2.31 (m, 1H), 2.25 (ddd, *J* = 15.3, 8.1, 2.6 Hz, 1H), 2.14 – 2.06 (m, 2H), 2.05 (s, 3H), 2.03 – 1.99 (m, 1H), 2.00 (s, 3H), 1.98 – 1.90 (m, 2H), 1.90 – 1.81 (m, 3H), 1.75 (ddd, *J* = 14.1, 8.5, 6.0 Hz, 1H), 1.37 (ddd, *J* = 12.7, 7.3, 5.1 Hz, 1H), 1.34 – 1.28 (m, 2H), 1.27 – 1.26 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 170.3, 169.9, 165.7, 144.5, 140.0, 136.0, 136.0, 135.6, 135.6, 135.6, 134.6, 133.9, 133.5, 130.0, 129.6, 129.6, 129.4, 129.2, 127.6, 127.6, 127.4, 127.2, 126.5, 124.4, 123.5, 95.4, 81.4, 80.1, 78.8, 74.1, 73.4, 73.2, 72.1, 71.7, 71.6, 71.6, 66.7, 65.4, 59.6, 43.0, 39.1, 38.5, 37.6, 35.4, 34.5, 34.3, 32.1, 29.9, 29.7, 27.2, 26.8, 21.0, 20.8, 19.5, 19.3, 17.5, 15.3 ppm. IR (film): $\tilde{\nu}$ = 2958, 2929, 2857, 1745, 1720, 1654, 1472, 1361, 1427, 1365, 1241, 1223, 1177, 1107, 1074, 1040, 998, 822, 803, 755, 702 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1207.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{69}H_{92}O_{13}Si_2Na$: 1207.5969; found: 107.5976.

**Glycoside 11-*epi*-212.** Prepared analogously from 11-*epi*-**211** (24.2 mg, 22.9 µmol) as a white foam



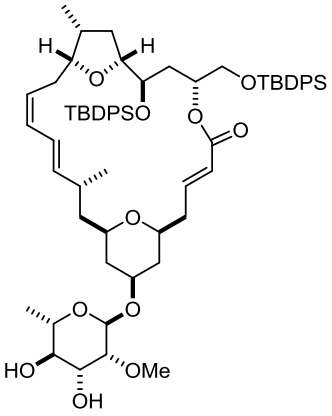

(20.6 mg, 87% yield, single diastereomer). $[\propto]_D^{20}$ = –17.4 (c = 0.87, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.52 (m, 8H), 7.43 – 7.24 (m, 11H), 7.23 – 7.20 (m, 1H), 7.05 (ddd, *J* = 15.2, 10.3, 4.4 Hz, 1H), 6.19 (dd, *J* = 14.9, 11.0 Hz, 1H), 5.87 (t, *J* = 11.0 Hz, 1H), 5.74 (dd, *J* = 15.6, 1.1 Hz, 1H), 5.24 (dd, *J* = 15.0 Hz, 9.7 Hz, 1H), 5.18 (dd, *J* = 10.1, 3.2 Hz, 1H), 5.12 – 5.00 (m, 3H), 4.91 (d, *J* = 1.9 Hz, 1H), 3.92 – 3.83 (m, 2H), 3.80 (dq, *J* = 9.5, 6.2 Hz, 1H), 3.77 – 3.66 (m, 2H), 3.52 (dd, *J* = 3.18, 1.98 Hz, 1H), 3.43 (s, 3H), 3.40 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.35 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.21 – 3.06 (m, 2H), 2.69 – 2.56 (m, 1H), 2.43 (dddd, *J* = 14.1, 9.3, 4.3, 1.5 Hz, 1H), 2.25 – 2.17 (m, 2H), 2.17 – 2.10 (m, 2H), 2.04 (s, 3H), 2.01 (s, 3H), 1.96 – 1.87 (m, 2H), 1.83 – 1.74 (m, 2H), 1.56 (dd, *J* = 14.0, 2.8 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.31 (q, *J* = 11.7 Hz, 2H), 1.23 – 1.16 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.00 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 9H), 0.78 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.9, 165.2, 145.3, 139.5, 135.9, 135.8, 135.6, 135.6, 134.1, 133.9, 133.6, 133.4, 129.6, 129.5, 129.5, 127.6, 127.5, 127.5, 127.4, 126.0, 125.7, 123.0, 95.4, 81.3, 80.8, 78.8, 75.0, 73.1, 73.1, 72.4, 72.1, 71.6, 71.6, 66.6, 65.1, 59.6, 43.4, 39.3, 39.3, 37.9, 35.6, 34.6, 33.9, 29.4, 27.0, 26.7, 22.0, 21.0, 20.8, 19.4, 19.2, 17.4, 15.1 ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1725, 1428, 1365, 1327, 1243, 1223, 1178, 1110, 1042, 912, 824, 736, 703, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1207.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{69}H_{92}O_{13}Si_2Na$: 1207.5969; found: 1207.5966.

**Glycoside 223a.** Prepared analogously from **223** (18.4 mg, 19.5 µmol) as a white foam (20.5 mg, 94% purity, 83% yield, single diastereomer). $[\propto]_D^{20}$ = –10.2 (c = 0.97, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.68 – 7.54 (m, 8H), 7.43 – 7.21 (m, 12H), 6.86 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.24 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.93 (t, *J* = 10.9 Hz, 1H), 5.82 (dt, *J* = 15.8, 1.2 Hz, 1H), 5.52 (dd, *J* = 15.1 Hz, 8.0 Hz, 1H), 5.26 – 5.13 (m, 3H), 5.08 (t, *J* = 9.8 Hz, 1H), 4.96 (d, *J* = 1.5 Hz, 1H), 4.00 (ddd, *J* = 8.4, 5.3, 3.2 Hz, 1H), 3.88 – 3.66 (m, 3H), 3.65 – 3.50 (m, 4H), 3.46 (s, 3H), 3.43 – 3.25 (m, 2H), 2.46 – 2.29 (m, 3H), 2.21 – 2.09 (m, 2H), 2.09 – 2.03 (m, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 – 1.90 (m, 2H), 1.84 (dd, *J* = 7.2, 5.4 Hz, 1H), 1.74 (ddd, *J* = 14.5, 9.0, 3.6 Hz, 1H), 1.64 (ddd, *J* = 13.9, 8.4, 5.4 Hz, 1H), 1.47 – 1.15 (m, 5H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.00 (s, 18H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.9, 165.6, 144.8, 140.0, 136.0, 135.9, 135.6, 135.5, 134.6, 134.0, 133.5, 133.4, 129.8, 129.5, 129.4, 127.6, 127.3, 126.9, 124.3, 123.5, 95.3, 81.2, 80.0, 78.8, 73.6, 73.3, 73.2, 72.6, 71.7, 71.6, 71.5, 66.6, 65.4, 59.6, 42.9, 39.1, 38.5, 37.4, 35.6, 34.4, 34.1, 33.2, 30.2, 27.1, 26.7, 21.0, 20.8, 20.2, 19.5, 19.2, 17.4, 15.2 ppm. IR (film): $\tilde{\nu}$ = 2957, 2930, 2857, 1725, 1472, 1461, 1428, 1365, 1242, 1224, 1110, 1043, 999, 913, 823, 736, 703, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1207.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{69}H_{92}O_{13}Si_2Na$: 1207.5969; found: 1207.5963.

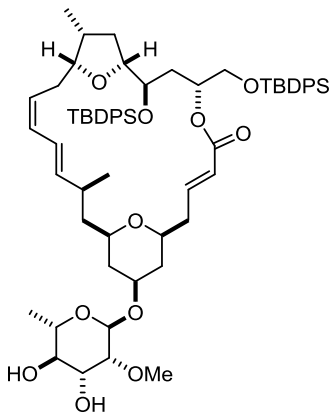
**Glycoside** 11-*epi*-**223a.** Prepared analogously from 11-*epi*-**223** (18.6 mg, 19.8 µmol) as a white foam (19.9 mg, 94% purity, 80% yield, single diastereomer). $[\propto]_D^{20}$ = +41.2 (c = 0.95, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.65 – 7.56 (m, 8H), 7.42 – 7.22 (m, 12H), 6.86 (ddd, *J* = 15.7, 7.1, 5.6 Hz, 1H), 6.24 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.96 (t, *J* = 10.9 Hz, 1H), 5.70 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.34 (dd, *J* = 15.2 Hz, 8.6 Hz, 1H), 5.26 – 5.19 (m, 1H), 5.20 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.08 (t, *J* = 9.9 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.97 (d, *J* = 1.7 Hz, 1H), 4.08 (ddd, *J* = 8.8, 4.7, 2.5 Hz, 1H), 3.86 – 3.77 (m, 2H), 3.76 – 3.61 (m, 4H), 3.55 (dd, *J* = 3.2, 1.9 Hz, 1H), 3.46 (s, 3H), 3.33 – 3.18 (m, 2H), 2.56 – 2.46 (m, 1H), 2.41 (dddd, *J* = 16.5, 9.5, 5.6, 1.7 Hz, 1H), 2.37 – 2.17 (m, 4H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 – 1.94 (m, 1H), 1.90 (dt, *J* = 13.0, 7.9 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.75 (ddd, *J* = 14.5, 8.9, 2.2 Hz, 1H), 1.58 – 1.49 (m, 2H), 1.34 – 1.26 (m, 1H), 1.27 – 1.20 (m, 2H), 1.20 – 1.15 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.9, 165.7, 144.5, 141.0, 135.9, 135.9, 135.5, 135.5, 134.2, 133.5, 133.4, 133.3, 130.0, 129.6, 129.5, 129.4, 127.6, 127.5, 127.4, 126.9, 125.6, 123.0, 95.4, 81.3, 79.6, 78.8, 73.6, 73.3, 73.2, 72.4, 71.6, 70.7, 66.6, 65.4, 59.6, 44.2, 39.7, 39.0, 37.9, 35.6, 33.3, 33.2,

33.0, 30.8, 27.1, 26.7, 22.9, 21.0, 20.8, 19.4, 19.2, 17.4, 15.4 ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1722, 1461, 1428, 1356, 1330, 1242, 1223, 1179, 1110, 1076, 1041, 999, 823, 739, 703, 611 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1207.7 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{69}H_{92}O_{13}Si_2Na$: 1207.5969; found: 1207.5967.

**Diol 213.** Dry $K_2CO_3$ (28.3 mg, 205 µmol) was added to a solution of compound **212** (96.9 mg, 81.8 µmol) in MeOH (11 mL) at 0 °C. The mixture was stirred at this temperature for 2 h before a second portion of $K_2CO_3$ (22.6 mg, 164 µmol) was introduced. After an additonal 2 h at 0 °C, the reaction was quenched with $NH_4Cl$ solution (15 mL) and the mixture allowed to reach ambient temperature. The aqueous phase was extracted with EtOAc (4 x 15 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 2:3) to give the desired product as a white foam (72.3 mg, 80%). $[\alpha]_D^{20}$ = –53.1 (c = 0.57, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.66 – 7.59 (m, 8H), 7.41 – 7.25 (m, 12H), 6.86 (ddd, *J* = 15.8, 8.2, 5.6 Hz, 1H), 6.22 (ddt, *J* = 15.5, 10.8, 1.2 Hz, 1H), 5.91 (t, *J* = 10.8 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.59 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.21 – 5.09 (m, 2H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.02 (ddd, *J* = 8.9, 6.2, 2.3 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.69 (td, *J* = 9.6, 3.7 Hz, 1H), 3.69 – 3.65 (m, 2H), 3.64 – 3.58 (m, 2H), 3.45 (s, 3H), 3.40 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.36 (dd, *J* = 9.6, 9.4 Hz, 1H), 3.35 – 3.25 (m, 2H), 2.45 – 2.39 (m, 1H), 2.38 – 2.31 (m, 2H), 2.31 – 2.23 (m, 2H), 2.13 – 2.06 (m, 2H), 2.02 (ddd, *J* = 14.9, 10.1, 2.5 Hz, 1H), 1.97 – 1.90 (m, 2H), 1.90 – 1.82 (m, 3H), 1.75 (ddd, *J* = 14.0, 8.4, 5.9 Hz, 1H), 1.37 (ddd, *J* = 12.8, 7.4, 5.3 Hz, 1H), 1.32 (ddd, *J* = 13.7, 8.0, 4.2 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.24 – 1.17 (m, 2H), 1.03 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.7, 144.5, 140.0, 136.0, 136.0, 135.6, 135.6, 135.5, 134.6, 134.0, 133.5, 130.0, 129.6, 129.6, 129.3, 129.2, 127.6, 127.6, 127.4, 127.2, 126.5, 124.4, 123.5, 93.9, 81.4, 80.6, 80.1, 74.0, 74.0, 73.5, 72.7, 72.1, 71.7, 71.4, 67.9, 65.4, 58.9, 43.0, 39.1, 38.5, 37.5, 35.4, 34.5, 34.4, 29.9, 27.2, 26.8, 20.8, 19.5, 19.3, 17.5, 15.4 ppm. IR (film): $\tilde{\nu}$ = 3411, 2958, 2930, 2857, 1719, 1656, 1462, 1428, 1360, 1327, 1263, 1176, 1111, 1076, 1045, 823, 740, 702 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1123.7 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{65}H_{88}O_{11}Si_2Na$: 1123.5757; found: 1123.5748.

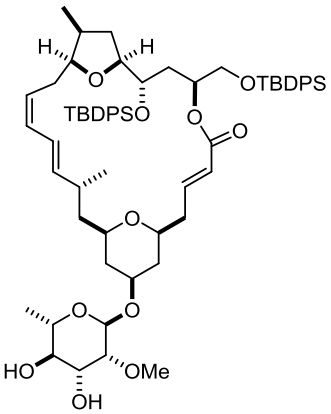


**Diol** 11-*epi*-**213.** Prepared analogously from compound 11-*epi*-**212** (20.0 mg, 16.9 µmol) as a white




foam (16.4 mg, 88%). $[\alpha]_D^{20}$ = –5.9 (c = 0.67, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.65 – 7.53 (m, 8H), 7.42 – 7.24 (m, 10H), 7.24 – 7.19 (m, 2H), 7.05 (ddd, *J* = 15.5, 10.3, 4.3 Hz, 1H), 6.20 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.88 (tt, *J* = 11.0, 1.9 Hz, 1H), 5.77 – 5.71 (m, 1H), 5.25 (dd, *J* = 14.9, 9.7 Hz, 1H), 5.11 – 5.00 (m, 2H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.91 – 3.83 (m, 2H), 3.76 – 3.69 (m, 2H), 3.67 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.61 (dq, *J* = 9.4, 6.2 Hz, 1H), 3.42 (s, 3H), 3.40 – 3.33 (m, 3H), 3.32 (t, *J* = 9.3 Hz, 1H), 3.17 (tt, *J* = 11.3, 1.9 Hz, 1H), 3.11 (tdd, *J* = 11.2, 3.3, 1.8 Hz, 1H), 2.70 – 2.57 (m, 1H), 2.43 (dddd, *J* = 14.4, 9.2, 4.3, 1.9 Hz, 1H), 2.36 – 2.28 (br s, 1H), 2.23 – 2.17 (m, 2H), 2.18 – 2.11 (m, 2H), 2.03 (dt, *J* = 13.1, 7.6 Hz, 1H), 1.97 – 1.88 (m, 2H), 1.83 – 1.75 (m, 2H), 1.56 (ddd, *J* = 14.1, 11.1, 3.1 Hz, 1H), 1.41 (ddd, *J* = 13.6, 7.7, 5.9 Hz, 1H), 1.31 – 1.22 (m, 2H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.22 – 1.10 (m, 2H), 1.00 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.78 (d, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.2, 145.3, 139.6, 135.9, 135.8, 135.7, 135.6, 134.1, 133.9, 133.6, 133.4, 129.6, 129.5, 129.5, 129.5, 127.6, 127.5, 127.5, 127.4, 126.0, 125.7, 123.0, 93.9, 81.3, 80.7, 80.6, 74.9, 74.0, 73.1, 72.6, 72.4, 72.1, 71.4, 67.8, 65.1, 58.8, 43.4, 39.3, 37.9, 35.6, 34.6, 34.6, 33.9, 29.4, 27.0, 26.7, 22.0, 19.4, 19.2, 17.5, 15.2 ppm. IR (film): $\tilde{\nu}$ = 3426, 2956, 2929, 2857, 1722, 1461, 1428, 1390, 1361, 1326, 1261, 1178, 1108, 1077, 1043, 909, 822, 734, 702, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 1123.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{65}H_{88}O_{11}Si_2Na$: 1123.5757; found: 1123.5754.

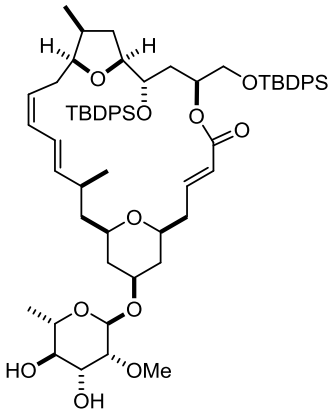
**Diol 223b.** Prepared analogously from compound **223a** (20.5 mg, 16.3 µmol) as a white foam



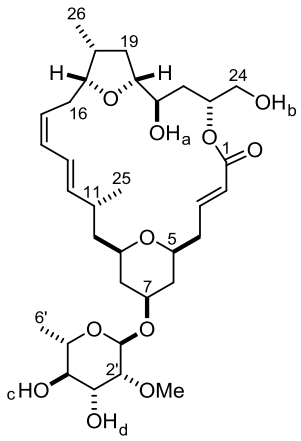

(17.3 mg, 96%). $[\alpha]_D^{20}$ = –2.2 (c = 0.80, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.65 – 7.57 (m, 8H), 7.42 – 7.24 (m, 12H), 6.86 (ddd, *J* = 15.7, 7.2, 6.6 Hz, 1H), 6.24 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.93 (tt, *J* = 10.9, 1.4 Hz, 1H), 5.82 (dt, *J* = 15.7, 1.3 Hz, 1H), 5.53 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.21 (dt, *J* = 10.0, 8.1 Hz, 1H), 5.16 (ddt, *J* = 8.2, 4.3, 4.1 Hz, 1H), 5.02 (d, *J* = 1.1 Hz, 1H), 4.00 (ddd, *J* = 8.8, 5.5, 3.3 Hz, 1H), 3.77 (tt, *J* = 10.8, 4.9 Hz, 1H), 3.70 (td, *J* = 7.8, 5.6 Hz, 1H), 3.70 – 3.65 (m, 1H), 3.63 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.61 (t, *J* = 6.2 Hz, 1H), 3.62 – 3.58 (m, 1H), 3.53 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.46 (s, 3H), 3.41 – 3.36 (m, 1H), 3.39 (dd, *J* = 3.9, 1.4 Hz, 1H), 3.34 (t, *J* = 9.4 Hz, 1H), 3.34 – 3.28 (m, 1H), 2.43 – 2.36 (m, 1H), 2.36 – 2.25 (m, 4H), 2.18 – 2.10 (m, 2H), 2.02 (ddt, *J* = 14.0, 6.9, 1.2 Hz, 1H), 1.99 – 1.95 (m, 1H), 1.93 (ddd, *J* = 14.5, 8.5, 3.3 Hz, 1H), 1.88 – 1.81 (m, 2H), 1.74 (ddd, *J* = 14.5, 8.9, 3.4 Hz, 1H), 1.63 (ddd, *J* = 14.0, 8.5, 5.5 Hz, 1H), 1.39 (dt, *J* = 12.7, 7.5 Hz, 1H), 1.33 (ddd, *J* = 13.7, 7.9, 3.9 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.26 – 1.22 (m, 2H), 1.00 (s, 9H), 0.99 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.6, 144.7, 140.0,

136.0, 135.9, 135.6, 135.6, 134.6, 134.0, 133.6, 133.4, 129.9, 129.5, 129.4, 129.3, 127.6, 127.6, 127.3, 127.3, 126.8, 124.4, 123.6, 93.9, 81.3, 80.6, 80.1, 74.0, 73.7, 73.3, 72.9, 72.6, 71.7, 71.4, 67.9, 65.5, 58.9, 43.0, 39.2, 38.5, 37.4, 35.7, 34.4, 34.1, 33.2, 30.3, 27.2, 26.7, 20.3, 19.5, 19.2, 17.5, 15.2 ppm. IR (film): $\tilde{\nu}$ = 3436, 2957, 2929, 2856, 1719, 1461, 1428, 1373, 1265, 1242, 1178, 1106, 1078, 1044, 985, 822, 739, 702, 609 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1123.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{65}H_{88}O_{11}Si_2Na$: 1123.5757; found: 1123.5760.

**Diol** 11-*epi*-**223b.** Prepared analogously from compound 11-*epi*-**223a** (19.1 mg, 15.1 µmol) as a white foam (15.4 mg, 92%). $[\propto]_D^{20}$ = +50.6 (c = 0.77, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.64 – 7.57 (m, 8H), 7.41 – 7.24 (m, 12H), 6.81 (ddd, *J* = 15.8, 7.2, 5.6 Hz, 1H), 6.25 (dd, *J* = 15.1, 10.7 Hz, 1H), 5.97 (tt, *J* = 10.9, 1.3 Hz, 1H), 5.71 (dt, *J* = 15.8, 1.6 Hz, 1H), 5.34 (dd, *J* = 15.1, 8.6 Hz, 1H), 5.21 (td, *J* = 10.1, 6.2 Hz, 1H), 5.03 (d, *J* = 1.1 Hz, 1H), 4.99 – 4.94 (m, 1H), 4.09 (ddd, *J* = 8.8, 4.8, 2.4 Hz, 1H), 3.81 (td, *J* = 7.9, 4.8 Hz, 1H), 3.76 – 3.60 (m, 6H), 3.47 (s, 3H), 3.40 (dd, *J* = 3.8, 1.4 Hz, 1H), 3.34 (t, *J* = 9.4 Hz, 1H), 3.29 (ddt, *J* = 11.2, 9.5, 1.9 Hz, 1H), 3.24 (tt, *J* = 10.9, 1.5 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.41 (dddd, *J* = 16.4, 9.4, 5.6, 1.7 Hz, 1H), 2.36 – 2.17 (m, 6H), 2.09 (dddd, *J* = 14.8, 5.5, 5.4, 0.7 Hz, 1H), 1.96 (ddt, *J* = 12.3, 3.9, 2.0 Hz, 1H), 1.90 (dt, *J* = 13.0, 7.9 Hz, 1H), 1.80 (ddt, *J* = 12.6, 4.1, 1.9 Hz, 1H), 1.75 (ddd, *J* = 14.5, 8.9, 2.4 Hz, 1H), 1.57 – 1.50 (m, 2H), 1.28 – 1.23 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.21 – 1.12 (m, 2H), 1.02 (s, 9H), 1.00 (s, 9H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.7, 144.5, 140.9, 135.9, 135.9, 135.6, 135.5, 134.3, 133.6, 133.5, 133.3, 130.0, 129.6, 129.5, 129.4, 129.4, 127.6, 127.5, 127.4, 126.9, 125.7, 123.1, 94.1, 81.3, 80.6, 79.7, 74.1, 73.7, 73.2, 72.9, 72.4, 71.5, 70.8, 67.9, 65.5, 58.8, 44.1, 39.7, 39.1, 38.0, 35.6, 33.4, 33.3, 33.1, 30.8, 27.1, 26.8, 22.9, 19.4, 19.2, 17.5, 15.4 ppm. IR (film): $\tilde{\nu}$ = 3428, 2957, 2931, 2857, 1717, 1462, 1428, 1361, 1267, 1179, 1111, 1079, 1045, 998, 910, 823, 736, 703, 611 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 1123.7 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{65}H_{88}O_{11}Si_2Na$: 1123.5757; found: 1123.5760.

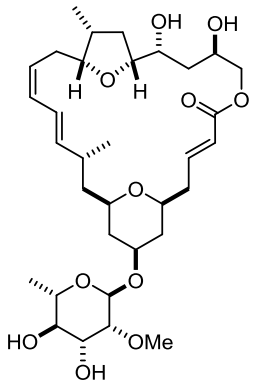


**Putative mandelalide A (124).** A Teflon vial was charged with diol **213** (42.0 mg, 38.1 µmol) and



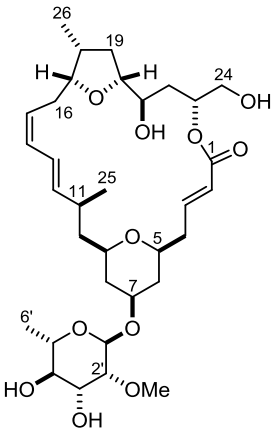

THF (2.5 mL). The solution was cooled to 0 °C before pyridine (2.5 mL) and HF·pyridine (2.5 mL) were slowly added via an Eppendorf pipette. After stirring for 5 min at 0 °C, the ice bath was removed and stirring continued at ambient temperature for 46 h. The mixture was diluted with EtOAc (10 mL) and carefully poured into $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with EtOAc/EtOH (9:1, 4 x 15 mL). The combined organic extracts were washed with $NH_4Cl$ solution (20 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH 97:3 to 96:4 to 95:5 to 96:4) to give the desired compound as a white amorphous solid (19.1 mg, 80%). $[\propto]_D^{23}$ = –29 (c = 0.25, MeOH). $^1$H NMR (600 MHz, $CDCl_3$): see table 5.7; $^{13}$C NMR (150 MHz, $CDCl_3$): see table 5.7; IR (film): $\tilde{\nu}$ = 3414, 2955, 2924, 2854, 1714, 1653, 1457, 1374, 1323, 1277, 1228, 1179, 1106, 1071, 1043, 988, 955, 911, 814, 732 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 647.4 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{33}H_{52}O_{11}Na$: 647.3402; found: 647.3406.

**Ring-expanded mandelalide A isomer (215).** Obtained as a by-product from the reaction described

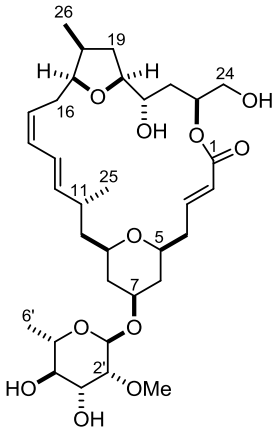



above. $[\propto]_D^{23}$ = +10 (c = 0.21, MeOH). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.04 (ddd, *J* = 15.8, 7.3, 6.6 Hz, 1H), 6.35 (ddt, *J* = 15.3, 10.9, 1.3 Hz, 1H), 6.08 (t, *J* = 10.9 Hz, 1H), 5.91 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.73 (dd, *J* = 15.3, 6.5 Hz, 1H), 5.36 (dt, *J* = 10.5, 8.1 Hz, 1H), 5.01 (d, *J* = 1.4 Hz, 1H), 4.16 (dd, *J* = 11.1, 5.6 Hz, 1H), 4.14 (dd, *J* = 11.2, 5.0 Hz, 1H), 4.10 – 4.04 (m, 2H), 3.81 – 3.74 (m, 2H), 3.68 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.66 (br s, 1H), 3.62 (dq, *J* = 9.3, 6.2 Hz, 1H), 3.45 (s, 3H), 3.39 (dd, *J* = 3.8, 1.5 Hz, 1H), 3.37 – 3.29 (m, 3H), 2.97 (br s, 1H), 2.64 – 2.48 (m, 2H), 2.47 – 2.38 (m, 2H), 2.38 – 2.32 (m, 2H), 2.32 – 2.23 (m, 3H), 1.99 (ddt, *J* = 12.2, 4.4, 1.7 Hz, 1H), 1.94 (ddd, *J* = 12.1, 7.2, 6.1 Hz, 1H), 1.86 (ddt, *J* = 12.5, 4.5, 1.7 Hz, 1H), 1.71 (ddd, *J* = 14.4, 8.9, 3.2 Hz, 1H), 1.67 – 1.56 (m, 1H), 1.64 (ddd, *J* = 14.1, 10.2, 4.7 Hz, 1H), 1.59 (ddd, *J* = 14.4, 8.6, 3.5 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.27 – 1.26 (m, 4H), 1.19 (td, *J* = 11.6, 11.5 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 166.4, 146.0, 142.0, 130.9, 126.4, 123.1, 122.8, 94.0, 81.4, 80.8, 80.6, 74.2, 74.0, 73.3, 72.7, 71.4, 71.1, 68.1, 68.0, 67.9, 58.9, 42.8, 39.3, 38.1, 37.5, 37.2, 36.9, 35.6, 32.7, 30.4, 18.0, 17.5, 14.5 ppm. IR (film): $\tilde{\nu}$ = 3427, 2924, 1714, 1653, 1454, 1373, 1323, 1275, 1179, 1106, 1043, 988, 734 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 647.3 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{33}H_{52}O_{11}Na$: 647.3402; found: 647.3404.

**11-*epi*-Isomer of putative mandelalide A** 11-*epi*-**124.** Prepared analogously from diol 11-*epi*-**213** (10.0 mg, 9.08 µmol) as a white amorphous solid (4.8 mg, 85%). $[\alpha]_D^{23}$ = –25.8 (c = 0.41, MeOH). $^1$H NMR (600 MHz, $CDCl_3$): see table 5.8. $^{13}$C NMR (150 MHz, $CDCl_3$): see table 5.8. IR (film): $\tilde{\nu}$ = 3411, 2924, 2854, 1716, 1654, 1457, 1373, 1246, 1178, 1107, 1045, 992, 812, 733 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 647.4 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{33}H_{52}O_{11}Na$: 647.3402; found: 647.3402.



**Reassigned mandelalide A** (**219**)**.** Prepared analogously from diol **223b** (14.0 mg, 12.7 µmol) as a white amorphous solid (5.6 mg, 71%). $[\alpha]_D^{23}$ = –40.1 (c = 0.27, MeOH). $^1$H NMR (600 MHz, $CDCl_3$): see table 5.9. $^{13}$C NMR (150 MHz, $CDCl_3$): see table 5.9. IR (film): $\tilde{\nu}$ = 3404, 2958, 2922, 1716, 1657, 1454, 1372, 1318, 1262, 1221, 1181, 1105, 1042, 985, 813, 734 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 647.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{52}O_{11}Na$: 647.3402; found: 647.3401.



**11-*epi*-Isomer of actual mandelalide A** 11-*epi*-**219.** Prepared analogously from diol 11-*epi*-**223b** (15.0 mg, 13.6 µmol) as a white amorphous solid (5.8 mg, 68%). $[\alpha]_D^{23}$ = –18.8 (c = 0.47, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): see table 5.10. $^{13}$C NMR (150 MHz, $CDCl_3$): see table 5.10. IR (film): $\tilde{\nu}$ = 3424, 2921, 1713, 1655, 1454, 1369, 1329, 1262, 1181, 1132, 1105, 1044, 990, 813 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 647.37 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{35}H_{52}O_{11}Na$: 647.3402; found: 647.3402.

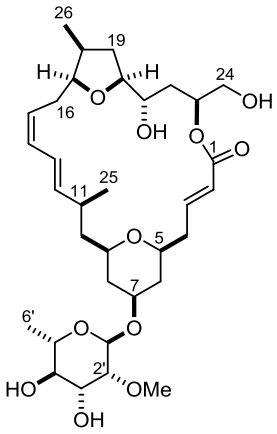


*Table 5.7:* $^{1}H$ & $^{13}C$ NMR data of putative Mandelalide A (**124**) (4.2 mg in 0.45 mL $CDCl_3$).

| atom n° | $^{1}H$ NMR ($CDCl_3$, 600 MHz) | | | | | $^{13}C$ NMR ($CDCl_3$, 150 | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 167.3 | - |
| 2 | 5.92 | dt | 15.6, 1.5 | 3, (4ab) | 3, 4(a)b, (25) | 123.1 | 1, (3), 4 |
| 3 | 7.02 | ddd | 15.5, 8.6, 5.5 | 2, 4a(b) | 2, 4a(b), (6a) | 146.3 | 1, 2, 4, 5 |
| 4a | 2.34 | ddd | 15.2, 6.5, 5.6, 1.8 | (3), 4b, 5 | (2), 3, 4b, 5 | 38.5 | 2, 3, 5, 6 |
| 4b | 2.46 | dddd | 15.2, 8.6, 3.7, 1.2 | 3, 4a, (5) | 2, 3, 4a, 5, 25 | | 2, 3, 5, (6) |
| 5 | 3.42 | m | - | 4a(b), 6a | (3), 4ab, 6b, 7, 9 | 73.4 | 3, (4), 7, 9 |
| 6a | 1.26 | m | - | 5, 6b, 7 | - | 36.7 | 5, 7, 8 |
| 6b | 1.94 | ddt | 12.0, 4.6, 1.9 | 6a, 7 | (5), 6a, 7, 1' | | 6, 8 |
| 7 | 3.77 | m | - | 6ab, 8ab | 5, 6b, 8b, 9, 1' | 72.8 | 6, 8, (1') |
| 8a | 1.22 | m | - | 7, 8b, 9 | - | 39.3 | - |
| 8b | 1.84 | dddd | 12.5, 4.2, 1.9, 1.9 | 7, 8a, (9) | 7, 8a, 9 | | 6, 7, 9 |
| 9 | 3.33 | m | - | 8a(b), 10ab | 5, 7, 8b, 10b, 25 | 73.1 | (5), (7), 8, 10 |
| 10a | 1.27 | m | - | 9, 10b, 11 | - | 42.9 | - |
| 10b | 1.69 | ddd | 14.1, 9.1, 5.1 | 9, 10a, (11) | 9, 10a | | 8, 9, 11, 12, 25 |
| 11 | 2.44 | m | - | 10a(b), 12, 25 | 9, 10a, 12, 13, 25 | 32.8 | 9, 10, 12, 13, 25 |
| 12 | 5.61 | dd | 15.2, 7.6 | 11, 13 | (10ab), 11, 13, 14, 25 | 140.9 | 10, 11, 14, (15), 25 |
| 13 | 6.22 | ddt | 15.2, 10.8, 1.0 | 12, 14 | 11, 12, 14, 16ab, 25 | 123.8 | 11, 14, 15 |
| 14 | 6.01 | tt | 10.8, 1.8 | 13, 15 | 12, 13, 15 | 130.5 | 12, 13, 16 |
| 15 | 5.27 | ddd | 10.8, 8.3, 7.5 | 14, 16ab | 14, 16ab, 17, (26) | 126.5 | 13, 16, 17 |
| 16a | 2.14 | dddd | 14.8, 6.8, 5.1, 1.9 | 15, 16b, 17 | 13, (15), 16a, (17), (26) | 31.2 | 14, 15, 17, 18 |
| 16b | 2.29 | dtd | 14.8, 8.5, 1.6 | 15, 16a, 17 | 13, 15, 16b, 17, 26 | | (13), 14, 15, 17, 18 |
| 17 | 4.03 | ddd | 8.6, 7.2, 4.9 | 16ab, 18 | 15, 16a(b), 18, (20), (26) | 81.3 | 15, 19, 20, 26 |
| 18 | 2.43 | m | - | 17, 19a(b), 26 | 17, 19ab, 20, 26 | 37.1 | 16, 17, 19, (20), 26 |
| 19a | 1.28 | m | - | 18, 19b, 20 | (18), 19b, 21, 26 | 36.0 | - |
| 19b | 2.04 | dt | 12.3, 6.7 | (18), 19a, 20 | 18, 19a, 20, (26) | | 17, 18, (20), 21, 26 |
| 20 | 3.71 | ddd | 8.4, 8.2, 6.7 | 19ab, 21 | 17, 18, 19b, 21, 22a(b) | 82.7 | (18), 19, 21, 22 |
| 21 | 3.45 | m | - | 20, 22(a)b | 19a, 20, 22b, 23, 25, 26 | 73.4 | (19), 20, 22, 23 |
| 22a | 1.54 | ddd | 14.4, 10.5, 2.5 | 21, 22b, (23) | 20, 21, 22b, 23, 24ab | 34.1 | 20, 23, 24 |
| 22b | 1.77 | ddd | 14.4, 10.8, 2.0 | (21), 22a, 23 | (19b), 21, 22a, 23, (24a) | | (20), 23, 24 |
| 23 | 5.24 | m | - | 22(a)b, 24ab | 21, 22a(b), 24ab | 72.5 | (22), (1) |
| 24a | 3.65 | m | - | 23, 24b | (22ab), 23, 24b | 65.7 | 22, 23 |
| 24b | 3.78 | dd | 12.1, 3.3 | 23, 24a | 21, 23, 24a | | 22, (23) |
| 25 | 1.00 | d | 6.7 | 11 | 2, 9, (10b), 11, 12, 13, 21 | 20.1 | 10, 11, 12 |
| 26 | 0.98 | d | 7.0 | 18 | 16a(b), (17), 18, (21) | 14.7 | 17, 18, 19 |
| 1' | 5.02 | d | 1.5 | 2' | 6b, 7, 2', 7' | 94.0 | 7, 2', 3', 5' |
| 2' | 3.40 | dd | 3.8, 1.5 | 1', 3' | 1', 7', 3' | 80.9 | 3', 4', 7' |
| 3' | 3.69 | m | - | 2', 4' | (2'), 5' | 71.7 | (2'), 4' |
| 4' | 3.34 | t | 9.4 | 3', 5' | 6', 7' | 74.2 | 3', 5' |
| 5' | 3.63 | dd | 9.4, 6.1 | 4', 6' | (2'), 3', 6' | 68.2 | (1'), 3', 4', (6') |
| 6' | 1.28 | d | 6.3 | 5' | 4', 5', 7' | 17.7 | (1'), 4', 5' |
| 7' | 3.46 | s | - | - | 1', 6' | 59.2 | 2' |
| OHa | 2.56-2.33 | - | - | 21 | | - | 21,22 |
| OHb | 2.56-2.33 | - | - | | | - | |
| OHc | 2.44-2.34 | - | - | 3' | | - | 3' |
| OHd | 2.78-2.64 | br s | - | 4' | | - | 4' |

*Table 5.8:* $^{1}H$ & $^{13}C$ NMR data of 11-*epi*-Isomer of putative mandelalide A (11-*epi*-**124**) (4.1 mg in 0.25 mL $CDCl_3$).

| atom | $^{1}H$ NMR ($CDCl_3$, 600 MHz) | | | | | $^{13}C$ NMR ($CDCl_3$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| n° | δ /ppm | m | *J* /Hz | COSY | NOESY | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 166.8 | - |
| 2 | 5.92 | dt | 15.6, 1.1 | 3, (4a) | 3, 4b | 123.6 | 1, 3, 4, (5) |
| 3 | 7.09 | ddd | 15.6, 8.2, 6.7 | 2, 4ab | 2, 4ab, 5, 11, 13, (21) | 146.1 | 1, 2, 4, 5 |
| 4a | 2.31 | dddd | 14.3, 8.2, 2.7, 0.8 | 3, 4b, (5) | 2, 3, 4b, 5, (6a) | 39.5 | 2, 3, 5, (6) |
| 4b | 2.39 | m | - | 3, 4a, 5 | 2, 3, 4b, 6a | | 2, 3, 5, 6 |
| 5 | 3.26 | dddd | 11.2, 10.5, 3.0, 2.1 | 4a, 4b, 6a(b) | 4a, 6b, 7, 9 | 74.0 | (3), (4), (9) |
| 6a | 1.15 | ddd | 11.8, 11.7, 11.6 | 5, 6b, 7 | 4b, 6b, 8a | 38.2 | 5, 7, 8 |
| 6b | 1.98 | ddt | 12.2, 4.7, 1.9 | 5, 6a, 7 | 4a, 5, 6a, 7, 1' | | (5), 7, 8 |
| 7 | 3.76 | m | - | 6a(b), 8a(b) | 5, 6b, 8b, 9, 1' | 72.7 | 8, (9), 1' |
| 8a | 1.27 | m | - | 7, 8b, 9 | 6a, 8b | 39.2 | 6, 7, 9, 10 |
| 8b | 1.75 | ddt | 12.4, 4.7, 1.9, 1.7 | 7, 8a, (9) | 7, 8a, 9, 10a | | 6, 7, 9 |
| 9 | 3.16 | tt | 11.1, 1.5 | 8a, 10(a)b | 5, 7, 8b, 10a | 73.2 | 5, 7, 10, 11 |
| 10a | 1.14 | m | - | (9), 10b, 11 | 8b, 9, 10b, (12), (25) | 43.5 | (5), 7, 8, 11, 12, 25 |
| 10b | 1.52 | ddd | 13.9, 11.0, 2.8 | 9, (11), 10a | (8a), 10a, 11, 25 | | 9, 11, 12, 25 |
| 11 | 2.48 | m | - | 10a, 12, 25 | 9, 10b, (12), 13, 25 | 34.1 | 9, 10, 12, 13, (25) |
| 12 | 5.32 | dd | 14.9, 9.7 | 11, 13 | (9), 10a, (11), 13, 14, 25 | 141.3 | 10, 11, 14, 25 |
| 13 | 6.10 | dd | 14.9, 11.0 | 12, 14 | (3), 11, 12, 16(a)b, (21) | 124.9 | 11, 14, 15 |
| 14 | 6.00 | ddt | 11.0, 10.9, 1.5 | (10ab), 13, 15 | 12, 15, 16b | 130.6 | 12, 13, 16 |
| 15 | 5.20 | m | - | 14, 16ab | 13, 14, 16ab, 17, 26 | 126.2 | 13, 16, 17 |
| 16a | 2.08 | ddd | 14.6, 5.9, 1.9 | 15, 16b, 17 | 13, 15, 16b, 17, 21, 26 | 31.0 | (13), 14, 15, 17, 18 |
| 16b | 2.25 | dddd | 14.7, 9.0, 7.5, 1.4 | (14), 15, 16a, 17 | 13, 15, 16a, 17, 19a, 26 | | 14, 15, 17, 18 |
| 17 | 3.99 | dt | 7.3, 6.2 | 18, 16ab | 16ab, 18, 20, (26) | 81.8 | 15, 19, 20, 26 |
| 18 | 2.46 | m | - | 17, 19ab, 26 | (15), 17, 19(a)b, 20, 26 | 36.9 | 16, 17, 20, 26 |
| 19a | 1.26 | m | - | 18, 19b, 20 | (18), 19b, 26 | 36.4 | 18, (20), 21, 26 |
| 19b | 2.09 | ddd | 12.3, 7.1, 7.1 | (18), 19a, 20 | 18, 19a, 20, 21 | | 18, 20, 21, 26 |
| 20 | 3.74 | m | - | 19ab, 21 | 17, 18, 19(a)b, 21, (22b) | 82.1 | 17, 19, 21, 22 |
| 21 | 3.46 | dddd | 9.1, 7.6, 2.8, 1.6 | 20, 22ab, OHa | (3), 19a, 20, 22ab, 23, OHa | 73.3 | 20, 22, 23 |
| 22a | 1.55 | ddd | 14.7, 9.2, 2.1 | 21, 22b, (23) | 21, 22b, 24ab | 34.7 | 20, 21, 24 |
| 22b | 1.88 | dddt | 14.4, 11.5, 1.4 | 21, 22a, 23 | 19a(b), 21, 22a, 24ab | | 20, 23, 24 |
| 23 | 5.23 | dddd | 11.2, 5.3, 2.8, 2.7 | 22(a)b, 24ab | 21, 22ab, 24ab | 73.9 | (1), 22 |
| 24a | 3.65 | m | - | 23, 24b | 22ab, 23, 24b | 65.7 | 22, 23 |
| 24b | 3.79 | m | - | 23, 24a | 22a(b), 23, 24a | | 22, 23 |
| 25 | 0.98 | d | 6.8 | 11 | 10ab, 11, 12 | 22.0 | 10, 11, 12 |
| 26 | 0.98 | d | 7.0 | 18 | 16a(b), (15), (17), 18 | 14.9 | 17, 18, 19 |
| 1' | 4.99 | d | 1.2 | 2' | 2', 7', 6b, 7 | 94.1 | 2', 3', 5', 7 |
| 2' | 3.38 | dd | 3.8, 1.5 | 1', 3' | 1', 3', 7' | 80.9 | 3', 4', 7' |
| 3' | 3.68 | td | 9.7, 3.8 | 2', 4', OHc | 2', 5', OHc, OHd | 71.6 | 1', 4' |
| 4' | 3.33 | td | 9.5, 1.9 | 3', 5', OHd | 5', 6', OHc, OHd | 74.2 | 3', 5', 6', 7' |
| 5' | 3.61 | dq | 9.4, 6.2 | 4', 6' | 3', 4', 6' | 68.2 | 1', 3', 4', 6' |
| 6' | 1.26 | d | 6.2 | 5' | 4', 5', 7' | 17.7 | 4', 5' |
| 7' | 3.44 | s | - | | 2', 6', OH3 | 59.1 | 2' |
| OHa | 2.74-2.72 | br s | - | 21 | | - | 21,22 |
| OHb | 2.40-2.36 | m | - | | | - | |
| OHc | 2.42-2.35 | m | - | 3' | | - | 3' |
| OHd | 2.48-2.44 | m | - | 4' | | - | 4' |

*Table 5.9:* $^{1}$H & $^{13}$C NMR data of synthetic mandelalide A (**219**) (4.6 mg in 0.25 mL $CDCl_3$).

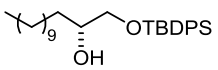
| atom n° | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | | $^{13}$C NMR ($CDCl_3$, 150 | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | δ | HMBC |
| 1 | - | - | - | - | - | 167.4 | - |
| 2 | 6.01 | dt | 15.5, 0.8 | 3, 4a | 3, 4ab, (5) | 123.1 | 1, 3, 4, (5) |
| 3 | 6.96 | ddd | 15.3, 10.4, 4.9 | 2, 4ab | 2, 4ab, 5, 25 | 147.1 | 1, 2, 4, 5 |
| 4a | 2.36 | m | - | 3, 4b, (5) | 2, 3, 5, 6a, 12, 13, 25 | 38.8 | 2, 3, 5, (6) |
| 4b | 2.39 | ddd | 13.9, 10.8, 10.7 | 3, 4a, 5 | | | 2, 3, 5, (6) |
| 5 | 3.37 | m | - | 4a, 4b, 6ab | 3, 4ab, 6b, 7 | 73.9 | 3, 4, 9 |
| 6a | 1.20 | m | - | 5, 6b, 7 | 6b, 8a, 10b | 37.6 | 4, 5, 7, 8 |
| 6b | 2.02 | dddd | 12.1, 5.6, 2.3, 1.6 | 5, 6a, 7, (8b) | 4b, (5), 6a, (12) | | (5), 7, 8, 2‘ |
| 7 | 3.82 | dddd | 11.3, 10.6, 4.8, 4.5 | 6ab, 8ab | 5, 6b, 8b, 9, 1‘ | 73.1 | 8, (9), 1' |
| 8a | 1.22 | m | - | 7, 8b, 9 | 8b, 10b, (12), 25 | 39.7 | 6, 7, 9, 10 |
| 8b | 1.87 | dddt | 13.2, 7.8, 5.3, 1.9 | 6b, 7, 8a, 9 | 7, 8a, 9, 10a, 1‘ | | 6, 7, 9 |
| 9 | 3.31 | tt | 10.7, 2.1 | 8ab, 10ab | 7, 8b, 10a, 25 | 72.5 | 5, 7 |
| 10a | 1.21 | m | - | 9, 10b, 11 | 10b, (11), 12, 25 | 43.1 | 8, 11, 12, 25 |
| 10b | 1.52 | ddd | 14.1, 11.1, 3.3 | 9, 10a, (11) | 10a, 11, (12) | | 8, 9, 11, 12, 25 |
| 11 | 2.37 | m | - | 10a, 12, 25 | 10ab, 12, 13, 14, 25 | 34.2 | 9, 10, 12, 13, 25 |
| 12 | 5.44 | dd | 14.9, 9.9 | 11, 13 | (10a), 11, 14, 25 | 141.5 | 10, 11, 14, 25 |
| 13 | 6.27 | dd | 14.8, 11.1 | 12, 14 | 11, 16b, 21, (25) | 123.9 | 10, 11, 14, 15 |
| 14 | 6.05 | dd | 10.9, 10.9 | 13, 15 | 12, 15 | 131.3 | 12, 13, 16, 17 |
| 15 | 5.28 | dt | 10.8, 5.6 | 14, 16ab | 14, 16ab, 17 | 126.9 | 13, 16, 17 |
| 16a | 1.88 | m | - | 15, 16b, 17 | 15, 16b, 17, 26 | 31.1 | 14, 15, 17, 18 |
| 16b | 2.25 | m | m | 15, 16a, 17 | 13, (15), 16a, 19a, 21, 26 | | 14, 15, 17, 18 |
| 17 | 3.98 | ddd | 10.9, 8.5, 1.7 | 16ab, 18 | 15, 16a, 18, 20 | 81.0 | 15, (18), 19, 20 |
| 18 | 2.52 | dddq | 12.3, 7.0, 7.0, 6.9 | 17, 19ab, 26 | 14, 17, 19b, 20, 26 | 37.4 | 16, 17, (20), 26 |
| 19a | 1.17 | ddd | 12.2, 12.1, 10.2 | 18, 19b, 20 | 16b, 19b, 21, 22b, 26 | 36.8 | 18, (20), 21, 26 |
| 19b | 2.01 | ddd | 11.8, 7.1, 6.0 | 18, 19a, 20 | 19a, 22b, 20 | | 17, 18, 21, (26) |
| 20 | 3.63 | m | - | 19ab, 21 | 17, 18, 19b, 22a | 83.2 | (17), (19), 21, 22 |
| 21 | 3.42 | ddd | 11.2, 8.9, 1.8 | 20, 22ab, (OHa) | 13, 18, 19a, 22b, 23 | 73.1 | 19, 20, 22, (23) |
| 22a | 1.46 | ddd | 14.2, 11.3, 1.9 | 21, 22b, 23 | 20, 22b, 23, 24b | 34.1 | 20, 21 |
| 22b | 1.76 | ddt | 12.8, 12.6, 1.5 | 21, 22a, 23 | (19ab), 20, 21, 22a, (23) | | 21, 24 |
| 23 | 5.23 | dddd | 11.6, 5.1, 3.1, 2.0 | 22ab, 24ab | (16b, 18), 22ab, 21, 24ab | 72.3 | 1, 22 |
| 24a | 3.61 | m | - | 23, 24b | 22a(b), 23, 24b | 66.1 | 22, 23 |
| 24b | 3.79 | m | - | 23, 24a | 22a, 23, 24 | | 22, 23 |
| 25 | 0.85 | d | 6.6 | 11 | 9, 10a, 11, 12 | 18.3 | 10, 11, 12 |
| 26 | 1.02 | d | 7.0 | 18 | 16a, (17), 18, 19a(b) | 14.5 | 17, 18, 19 |
| 1' | 5.02 | d | 1.1 | 2' | 6b, 7, 8b, 2‘, 7‘ | 94.2 | 2', 3', 5', 7 |
| 2' | 3.40 | dd | 3.9, 1.5 | 1', 3' | 1‘, 3‘ | 80.8 | 3', 4', 7' |
| 3' | 3.68 | td | 9.8, 3.7 | 2', 4', OHc | (1‘), 2‘, (4‘), OHd | 71.7 | 4' |
| 4' | 3.34 | dd | 10.5, 9.3 | 3', 5' | 3‘, (5‘), 6‘ | 74.3 | 2‘, 3', 5', 6' |
| 5' | 3.62 | dd | 9.9, 5.9 | 4', 6' | (4‘), 6‘ | 68.1 | 1', 3', 4', 6' |
| 6' | 1.26 | d | 6.3 | 5' | 4‘, 5‘ | 17.7 | 4', 5' |
| 7' | 3.45 | s | - | - | 1‘ | 59.1 | 2' |
| OHa | 2.69 | br s | - | 21 | | - | 21,22 |
| OHb | 2.31 | br s | - | 24ab | | - | (24) |
| OHc | 2.35 | m | - | 3' | | - | 3', 4’ |
| OHd | 2.53 | br s | - | 4' | | - | 2‘, 5‘ |

*Table 5.10:* $^{1}$H & $^{13}$C NMR data of 11-*epi*-isomer of actual mandelalide A 11-*epi*-**219** (4.1 mg in 0.25 mL $CDCl_3$).

| atom n° | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | $^{13}$C NMR ($CDCl_3$, 150 MHz) | |
|---|---|---|---|---|---|---|
| | δ /ppm | m | J/Hz | COSY | δ /ppm | HMBC |
| 1 | - | - | - | - | 167.4 | - |
| 2 | 5.93 | dd | 15.5, 0.7 | 3, (4a) | 123.4 | 1, 3, 4, 5 |
| 3 | 6.98 | ddd | 15.3, 8.1, 7.0 | 2, 4a | 146.8 | 1, 2, 4, 5 |
| 4a | 2.31 | m | - | 3, 4b, 5 | 39.5 | 2, 3, 5, 6 |
| 4b | 2.42 | ddd | 14.1, 6.3, 3.2 | 3, 4a, 5 | | 2, 3, 5, 6 |
| 5 | 3.30 | m | - | 4ab, 6a(b) | 74.2 | (3), 4, 6, 7, (9) |
| 6a | 1.17 | dt | 11.5, 11.4 | 5, 6b, 7 | 37.5 | 5, 7, 8 |
| 6b | 2.00 | m | - | (5), 6a, 7 | | 7, 8, 2’ |
| 7 | 3.75 | m | - | 6ab, 8ab | 73.1 | 8, 1’ |
| 8a | 1.23 | m | - | 7, 8b, 9 | 39.5 | 6, 7, 9, 10 |
| 8b | 1.82 | m | - | 7, 8a, 9 | | 6, 7, 9, 10 |
| 9 | 3.27 | tt | 9.9, 2.1 | 8a, 10ab | 72.9 | 8, 10, 11 |
| 10a | 1.37 | ddd | 14.1, 8.7, 2.7 | 9, 10b, 11 | 43.0 | 8, 11, 12, (25) |
| 10b | 1.49 | ddd | 14.3, 9.4, 5.1 | 9, 10a, 11 | | 8, 11, 12, 25 |
| 11 | 2.45 | m | - | 10ab, 12, 25 | 33.5 | 10, 12, 13, 25 |
| 12 | 5.60 | dd | 15.2, 7.7 | 11, 13 | 141.0 | 10, 11, 14, 25 |
| 13 | 6.20 | dd | 15.2, 10.7 | 12, 14 | 124.7 | 11, 14, (15) |
| 14 | 6.00 | dd | 10.8, 10.8 | 13, 15 | 130.5 | 12, 13, 16 |
| 15 | 5.28 | td | 10.5, 7.7 | 14, 16ab | 126.8 | 13, 16, 17 |
| 16a | 2.21 | m | - | (14), 15, 16b, 17 | 31.5 | 14, 15, 17, 18 |
| 16b | 2.20 | m | - | 15, 16a, 17 | | 14, 15, 17, 18 |
| 17 | 4.01 | q | 6.7 | 16ab, 18 | 80.9 | 15, (18), 19, 20, 26 |
| 18 | 2.44 | m | - | 17, 19a(b), 26 | 37.5 | 17, 19, 26 |
| 19a | 1.28 | m | - | 18, 19b, 20 | 35.8 | 17, 18, 21, 26 |
| 19b | 2.00 | m | - | 19a | | 18, 20, 21, 26 |
| 20 | 3.73 | ddd | 9.3, 6.9, 6.9 | 19ab, 21 | 82.5 | 19, 21, 22 |
| 21 | 3.76 | m | - | 20, 22ab | 73.1 | 19, 22 |
| 22a | 1.53 | m | - | 21, 22b, 23 | 33.8 | 21, 24 |
| 22b | 1.83 | ddd | 14.1, 11.0, 2.8 | 21, 22a, 23 | | 19, 20, 23 |
| 23 | 5.17 | ddd | 10.2, 8.1, 1.9 | 22ab, 24ab | 72.2 | 19, 21, 22 |
| 24a | 3.67 | m | - | 23, 24b | 65.6 | 22, 23 |
| 24b | 3.78 | m | - | 23, 24a | | 22, 23 |
| 25 | 1.00 | d | 6.9 | 11 | 21.4 | 10, 11, 12 |
| 26 | 0.98 | d | 6.9 | 18 | 14.7 | 17, 18, 19 |
| 1' | 5.00 | d | 1.3 | 2‘ | 94.3 | 7, 2‘, 3‘, 5‘ |
| 2' | 3.38 | dd | 3.6, 1.3 | 1‘, 3‘ | 80.8 | 3‘, 4‘, 7‘ |
| 3' | 3.69 | m | - | 2‘, 4‘ | 71.7 | 4‘ |
| 4' | 3.33 | dd | 9.4, 9.4 | 3‘, 5‘ | 74.4 | 3‘, 5‘, 6‘, 7‘ |
| 5' | 3.61 | m | - | 4‘, 6‘ | 68.1 | 3‘, 4‘, 6‘ |
| 6' | 1.26 | d | 6.2 | 4‘, 5‘ | 17.8 | 5‘ |
| 7' | 3.45 | d | 0.6 | - | 59.1 | 2‘ |
| OHa | not assigned | | | | | |
| OHb | not assigned | | | | | |
| OHc | not assigned | | | | | |
| OHd | not assigned | | | | | |

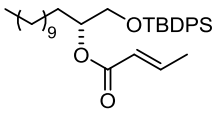
### 5.3.5 Synthesis of 2,3-*epi*-mandelalide C.

**1-((*tert*-Butyldiphenylsilyl)oxy)tridecan-2-ol (230).** A flame-dried Schlenck flask was charged with



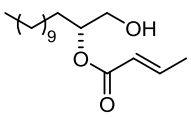

a solution of *n*-decylmagnesium bromide (1 M in $Et_2O$, 22 mL, 22 mmol), which was cooled to −15 °C. Copper cyanide (36 mg, 0.40 mmol) was, followed by a solution of (*R*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane (**160**) (6.25 g, 20.0 mmol) in THF (17 mL) via dropping funnel. After stirring for 30 min, the reaction mixture was quenched by pouring into sat. $NH_4Cl$ solution (100 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried over $NaSO_4$ and concentrated. The pale yellow residue (8.9 g, 98%) was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.62 – 7.56 (m, 4H), 7.37 – 7.26 (m, 6H), 3.68 – 3.52 (m, 2H), 3.41 (dd, *J* = 9.9, 7.3 Hz, 1H), 2.18 (br s, 1H), 1.37 – 1.27 (m, 2H), 1.22 – 1.13 (m, 18H), 0.99 (s, 9H), 0.83 – 0.78 (t, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.6, 135.5, 133.3, 133.3, 129.8, 127.7, 72.0, 68.1, 32.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 26.9, 25.5, 22.7, 19.3, 14.1 ppm. IR (film): $\tilde{\nu}$ = 3470, 2924, 2854, 1754, 1463, 1428, 1361, 1263, 1189, 1110, 1031, 1007, 938, 882, 823, 739, 700, 638, 613 cm$^{-1}$. MS (EI) *m/z* (%) = 397 (15), 229 (12), 200 (18), 199 (100), 139 (49), 111 (6), 97 (8) 69 (5). HRMS (ESIpos): *m/z*: calcd for $C_{29}H_{46}O_2Si_1Na$: 477.3159; found: 477.3158.

**(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)tridecan-2-yl (*E*)-but-2-enoate (231).** (*E*)-Crotonic acid (3.06 g,



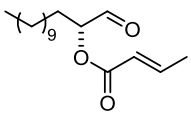

35.6 mmol), DMAP (7.25 g, 59.3 g) and *N*,*N'*-dicyclohexylcarbodiimide (8.98 g, 43.5 mmol) were added successively to a stirred solution of crude alcohol **230** (8.02 g, 19.8 mmol) in $CH_2Cl_2$ (100 mL) at ambient temperature. After 17 h, the reaction mixture was filtered through a pad of Celite®, which was rinsed with $CH_2Cl_2$ (2 x 10 mL). The filtrate was concentrated and the residue purified by flash chromatography (hexanes/EtOAc 15:1) to give the desired ester as a colorless oil (8.32 g, 81% yield). $[\alpha]_D^{20}$ = +12.4 (c = 0.89, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.72 – 7.58 (m, 4H), 7.45 – 7.31 (m, 6H), 6.94 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.83 (dq, *J* = 15.5, 1.7 Hz, 1H), 5.03 (ddd, *J* = 10.1, 7.4, 5.1 Hz, 1H), 3.70 (dd, *J* = 10.9, 5.4 Hz, 1H), 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.64 – 1.54 (m, 2H), 1.26 (s, 18H), 1.02 (s, 9H), 0.89 – 0.84 (m, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.1, 144.3, 135.6, 135.6, 133.5, 129.6, 127.6, 127.6, 127.6, 123.0, 74.1, 65.0, 34.9, 31.9, 30.5, 29.6, 29.6, 29.5, 29.5, 29.5, 29.3, 26.7, 25.4, 25.2, 24.7, 22.7, 19.2, 18.0, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2925, 2854, 2118, 1720, 1660, 1446, 1428, 1360, 1293, 1262, 1181, 1112, 1046, 1005, 969, 823, 802, 739, 700, 614 cm$^{-1}$. MS (EI) *m/z* (%) = 465 (14), 268 (22), 267 (100), 207 (25), 199 (16), 135 (5), 69 (19). HRMS (ESIpos): *m/z*: calcd for $C_{33}H_{50}O_3Si_1Na$: 545.3421; found: 545.3419.

**(*R*)-1-Hydroxytridecan-2-yl (*E*)-but-2-enoate (232).** Silyl ether **231** (5.01 g, 9.56 mmol) was



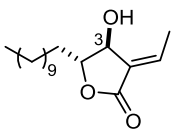
dissolved in THF (50 mL) and the solution cooled to 0 °C. Acetic acid (1.92 mL, 33.5 mmol) and a solution of TBAF (1 M in THF, 28.7 mL, 28.7 mmol) were added slowly. After 5 min stirring at 0 °C, the ice bath was removed and the mixture was allowed to warm to ambient temperature. After 3.5 h, it was diluted with EtOAc (20 mL), poured into sat. $NaHCO_3$ solution (40 mL) and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 8:1 to 6:1 to 4:1 to give the desired primary alcohol as a colorless oil (2.42 g, 89% yield). $[\propto]_D^{20}$ = +9.8 (c = 0.64, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.87 (dq, *J* = 15.5, 1.7 Hz, 1H), 4.95 (dtd, *J* = 7.4, 6.2, 3.2 Hz, 1H), 3.73 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.64 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.07 (br s, 1H), 1.89 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.65 – 1.54 (m, 2H), 1.31 – 1.22 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.9, 145.3, 122.6, 75.5, 65.0, 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 25.3, 22.7, 18.0, 14.1 ppm. IR (film): $\tilde{\nu}$ = 3428, 2955, 2923, 2854, 1719, 1658, 1465, 1444, 1377, 1308, 1292, 1265, 1182, 1101, 1057, 1002, 968, 919, 838, 722, 688 cm$^{-1}$. MS (EI) *m/z* (%) = 285 (1), 142 (9), 100 (8), 87 (12), 69 (100), 55 (6), 41 (12). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{32}O_3Na$: 307.2244; found: 307.2244.

**(*R*)-1-Oxotridecan-2-yl (*E*)-but-2-enoate (233).** Dess-Martin periodinane (4.65 g, 11.0 mmol) and



$NaHCO_3$ (2.13 g, 25.3 mmol) were added successively to a solution of primary alcohol **232** (1.20 g, 4.22 mmol) in $CH_2Cl_2$ (60 mL) at 0 °C. The icebath was removed after 5 min and the white suspension was stirred vigorously at ambient temperature for 4 h. The reaction was then poured into a sat. solution of $NaHCO_3$/$Na_2S_2O_3$ (1:1, 100 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 75 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (10 cm $SiO_2$, hexanes/EtOAc 19:1 to 15:1 to 12:1 to 9:1) to give the product as a colorless liquid (661 mg, 55% yield). $[\propto]_D^{20}$ = +31.0 (c = 0.64, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 0.9 Hz, 1H), 7.06 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.92 (dq, *J* = 15.5, 1.7 Hz, 1H), 4.99 (ddd, *J* = 8.3, 4.8, 0.9 Hz, 1H), 1.90 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.86 – 1.78 (m, 1H), 1.76 – 1.67 (m, 1H), 1.43 – 1.35 (m, 2H), 1.28 – 1.20 (m, 16H), 0.87 – 0.82 (t, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 198.8, 165.9, 146.5, 121.6, 78.1, 31.9, 29.6, 29.5, 29.3, 29.3, 29.2, 28.8, 24.9, 22.7, 18.1, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2923, 2854, 1721, 1657, 1465, 1444, 1377, 1292, 1258, 1175, 1102, 968, 837, 722, 688 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 337.3 (100 (M+MeOH+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{30}O_3Na$: 305.2087; found: 305.2085.

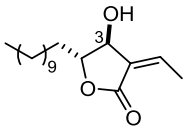
**Morita-Baylis-Hillman product (*E*)-(234).**A flame-dried Young tube was charged with a solution of



aldehyde **233** (150 mg, 0.531 mmol) in DMF (5 mL). Methyldiphenylphosphine (29.6 µL, 0.159 mmol) was added via syringe and the Young tube was sealed. It was

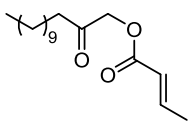
placed in a preheated oil-bath at 120 °C and the reaction mixture was stirred at this temperature for 22 h. After cooling to rt, it was poured into $NH_4Cl$ (15 mL) and the aqueous phase was extracted with $Et_2O$ (3 x 5 mL). The combined organic extracts were washed with brine (25 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1 to 3:1 to 2:1) to give the Baylis-Hillman alcohol (*E*)-**234** as a white solid (82 mg, 55% yield, 16:1 d.r. at C.3) along with the minor isomer (*Z*)-**234** (see below). $[\alpha]_D^{20}$ = +4.9 (c = 1.21, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$, data is given only for the major diastereomer): δ = 6.95 (qd, *J* = 7.2, 1.9 Hz, 1H), 4.53 (br s, 1H), 4.28 (ddd, *J* = 8.1, 6.0, 2.3 Hz, 1H), 2.78 (br s, 1H), 1.98 (dd, *J* = 7.3, 1.0 Hz, 3H), 1.59 – 1.44 (m, 2H), 1.43 – 1.30 (m, 2H), 1.25 – 1.15 (m, 16H), 0.84 – 0.78 (t, *J* = 7.0 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, data is given only for the major diastereomer): δ = 169.8, 143.4, 130.5, 86.5, 70.8, 34.0, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 24.7, 22.7, 15.4, 14.1 ppm. IR (film): $\tilde{\nu}$ = 3420, 2922, 2853, 1734, 1680, 1465, 1440, 1377, 1332, 1215, 1143, 1207, 980, 814, 722, 610 cm$^{-1}$. MS (EI) *m/z* (%) = 282 (1), 99 (6), 98 (100), 70 (22), 69 (6). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{30}O_3Na$: 305.2087; found: 305.2086.

**Morita-Baylis-Hillman product (*Z*)-(234).** Obtained as the minor isomer as a mixture of




diastereomers at C.3 (18.2 mg, 12% yield, 18:1 d.r.). $[\alpha]_D^{20}$ = +8.0 (c = 0.98, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$, data is given only for the major diastereomer): δ = 6.61 (qd, *J* = 7.3, 1.7 Hz, 1H), 4.37 (br s, 1H), 4.19 (ddd, *J* = 7.8, 5.7, 3.7 Hz, 1H), 2.55 (br s, 1H), 2.26 – 2.16 (dd, *J* = 7.4, 1.6 Hz, 3H), 1.66 – 1.55 (m, 2H), 1.50 – 1.36 (m, 2H), 1.23 (m, 16H), 0.88 – 0.82 (t, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, data is given only for the major diastereomer): δ = 168.6, 144.0, 129.8, 85.1, 74.1, 33.7, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 24.9, 22.7, 14.3, 14.1 ppm. IR (film): $\tilde{\nu}$ = 3429, 2922, 2853, 1735, 1677, 1465, 1439, 1378, 1353, 1207, 1123, 1075, 1038, 970, 865, 816, 722, 663 cm$^{-1}$. MS (EI) *m/z* (%) = 282 (1), 99 (6), 98 (100), 70 (22), 69 (6). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{30}O_3Na$: 305.2087; found: 305.2085.

**2-Oxotridecyl (*E*)-but-2-enoate (235).** DBU (5.3 µL, 35 µmol) was added to a solution of aldehyde




**233** (20.0 mg, 70.8 µmol) in $CH_3CN$ (0.7 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was stirred for 12 h at rt. The reaction was then quenched by addition of sat. $NH_4Cl$ solution (3 mL) and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude residue was purified by flash chromatography to yield the rearranged ketone as a colorless oil (16.1 mg, 80%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.05 (dq, *J* = 15.6, 6.9 Hz, 1H), 5.91 (dq, *J* = 15.5, 1.7 Hz, 1H), 4.67 (s, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.89 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.85 – 1.70 (m, 2H), 1.64 – 1.53 (m, 2H), 1.28 – 1.20 (m, 14H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 204.4, 165.6, 146.4, 121.6, 67.8, 38.8, 31.9, 29.6, 29.4, 29.3, 29.2, 28.8,

24.9, 22.7, 18.1, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2953, 2922, 2853, 1722, 1656, 1468, 1444, 1377, 1294, 1258, 1175, 1101, 969, 720 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 305.2 (100 ($M+Na^+$)). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{30}O_3Na$: 305.2087; found: 305.2084.

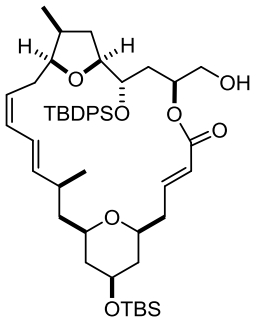
**(*R*)-1-Bromotridecan-2-yl (*E*)-but-2-enoate (237).** Alcohol **232** (362 mg, 1.27 mmol) was dissolved in $CH_2Cl_2$ (6.4 mL) and the resulting solution cooled to 0 °C. Triphenylphosphine (401 mg, 1.53 mmol) and $CBr_4$ (464 mg, 1.40 mmol) were added as solids at 0 °C. The ice bath was removed and the orange solution allowed to warm to ambient temperature and stirred for further 30 min. Hexane (14 mL) was added and the suspension filtered through Celite® (10 mL rinse with hexanes). The filtrate was washed with aq. $H_2O_2$ solution (5%, 10 mL) and the aqueous washings were extracted with hexanes/EtOAc (9:1, 2 x 10 mL). The combined organic fractions were dried over $Na_2SO_4$ and concentrated. The brown residue was purified by flash chromatography (hexanes/EtOAc 29:1 to 24:1) to give the desired alkyl bromide as a colorless oil (273 mg, 62% yield). $[\propto]_D^{20}$ = +11.7 (c = 0.76, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dq, *J* = 15.5, 6.9 Hz, 1H), 5.84 (dq, *J* = 15.5, 1.7 Hz, 1H), 5.02 (tt, *J* = 6.5, 4.9 Hz, 1H), 3.50 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.43 (dd, *J* = 10.8, 5.2 Hz, 1H), 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.71 – 1.63 (m, 2H), 1.29 – 1.20 (m, 18H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.8, 145.4, 122.4, 72.0, 34.4, 32.5, 31.9, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 25.0, 22.7, 18.0, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2922, 2853, 1721, 1658, 1465, 1443, 1293, 1259, 1172, 1101, 1017, 968, 837 $cm^{-1}$. MS (EI) *m/z* (%) = 349 (0.3), 347 (0.3), 267 (1), 180 (4), 111 (5), 97 (9), 87 (39), 69 (100), 41 (25). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{31}O_2BrNa$: 369.1400; found: 369.1396.

**(*R*)-1-Hydroxytridecan-2-yl (*Z*)-2-bromobut-2-enoate (239).** Alcohol **232** (117 mg, 0.411 mmol) was dissolved in $CH_2Cl_2$ (1.5 mL) and the resulting solution cooled to 0 °C. Bromine (31.6 µL, 0.617 mmol) was added dropwise via syringe. After 45 min at 0 °C, TLC analysis indicated full consumption of the s.m. and all volatiles were removed under vacuum. The residue was redissolved in $Et_2O$ (2 mL), before triethylamine (68.8 µL, 0.494 mmol) was added at ambient temperature. After stirring for 38 h, the white precipitate formed was filtered off. The filtrate was concentrated and purified by flash chromatography (hexanes/EtOAc 12:1 to 9:1 to 7:1) to give the title compound as a pale-yellow oil (86 mg, 58% yield). Due to the unstable nature (1,2-Acyl shift), it was immediately engaged in the next step. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38 (q, *J* = 6.8 Hz, 1H), 4.97 (dtd, *J* = 7.5, 6.0, 3.3 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.66 (dd, *J* = 12.2, 6.1 Hz, 1H), 2.05 – 1.89 (br s, 1H), 1.93 (d, *J* = 6.8 Hz, 3H), 1.70 – 1.55 (m, 2H), 1.36 – 1.18 (m, 18H), 0.88 – 0.82 (t, *J* = 6.7 Hz, 3H) ppm. IR (film): $\tilde{\nu}$ = 3428, 2923, 2853, 1715, 1630, 1465, 1376, 1335, 1249, 1227, 1108, 1036, 953, 845, 739 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 467.1 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{31}O_3BrNa$: 465.9611; found: 465.0611.

**(*R*)-1-Oxotridecan-2-yl (*Z*)-2-bromobut-2-enoate (240).** Dess-Martin periodinane (298 mg, 0.702 mmol) and $NaHCO_3$ (157 mg, 1.88 mmol) were added to a solution of primary alcohol **239** (85.1 mg, 0.234 mmol) in $CH_2Cl_2$ (2.4 mL) at 0 °C. After 5 min, the ice bath was removed and the white suspension allowed to warm to ambient temperature under vigorous stirring. After 100 min, the reaction mixture was poured into sat. $Na_2S_2O_3$/$NaHCO_3$ solution (1:1, 8 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 6 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9:1) to give a colorless oil (43 mg, 51% yield, 90% purity). $[\alpha]_D^{20}$ = +20.0 (c = 0.89, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 0.8 Hz, 1H), 7.47 (q, *J* = 6.9 Hz, 1H), 5.05 (dd, *J* = 8.2, 4.7 Hz, 1H), 1.96 (d, *J* = 6.8 Hz, 3H), 1.90 – 1.74 (m, 2H), 1.47 – 1.39 (m, *J* = 7.6 Hz, 2H), 1.26 (m, 16H), 0.86 – 0.82 (t, *J* = 6.7 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 197.8, 162.0, 143.0, 116.4, 79.9, 31.9, 29.6, 29.4, 29.3, 29.3, 29.2, 28.6, 24.8, 22.7, 18.0, 14.1 ppm. IR (film): $\tilde{\nu}$ = 2923, 2853, 1726, 1629, 1465, 1376, 1245, 1107, 1074, 1035, 944, 839, 775, 737 cm$^{-1}$. MS (EI) *m/z* (%) = 361 (1), 363 (1), 331 (0.5), 183 (8), 167 (16), 165 (11), 149 (100), 137 (99), 119 (9), 98 (36), 83 (7), 69 (10), 68 (9), 57 (12, 55 (14), 43 (19), 41 (14), 39 (12). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{29}O_3BrNa$: 383.1192; found: 383.1192.

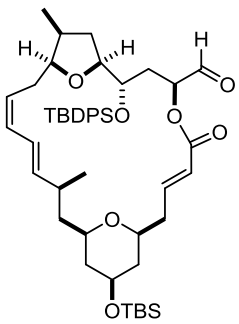
**(3*R*,4*R*,5*R*)-3,4-Dihydroxy-3-((*S*)-1-hydroxyethyl)-5-undecyldihydrofuran-2(3*H*)-one (245).** A flame-dried Schlenck tube was charged with a solution of alcohol (*E*)-**234** (16.0 mg, 56.7 µmol) in $CH_2Cl_2$ (3.0 mL) and the solution cooled to −78 °C. TMEDA (9.8 µL, 65 µmol) was added via syringe and the resulting solution was stirred for 5 min. A solution of $OsO_4$ (0.6 m in $CH_2Cl_2$, 104 µL, 62.3 µmol) was then added dropwise via syringe over the course of 4 min. After 20 min stirring at −78 °C, the cooling bath was removed and the reaction mixture concentrated by applying an Ar flow and finally dried under high vacuum. The residue was redissolved in THF (0.7 mL) and the solution treated with sat. $NaHSO_3$[249] (0.7 mL) for 36 h under vigorous stirring. The biphasic mixture was then diluted with sat. $NH_4Cl$ solution and extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2) to give the desired triol as a white solid (13.2 mg, 74%). $[\alpha]_D^{20}$ = +36.8 (c = 0.58, DMSO). $^1$H NMR (400 MHz, [D$_6$]-DMSO): δ = 5.46 (d, *J* = 6.8 Hz, 1H), 5.39 (s, 1H), 4.94 (d, *J* = 4.7 Hz, 1H), 4.03 (td, *J* = 7.8, 4.4 Hz, 1H), 3.96 (t, *J* = 7.1 Hz, 1H), 3.67 (qd, *J* = 6.4, 4.7 Hz, 1H), 1.70 (dtd, *J* = 9.5, 7.4, 6.4, 4.5 Hz, 1H), 1.60 – 1.51 (m, 1H), 1.46 – 1.33 (m, 2H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.31 – 1.21 (m, 16H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, [D$_6$]-DMSO): δ = 174.1, 81.4, 75.9, 72.4, 67.1, 32.3, 31.3, 29.1, 29.1, 29.0, 29.0, 28.9, 28.8, 25.0, 22.1, 16.7, 14.0 ppm. IR (film): $\tilde{\nu}$ = 3400, 2955, 2922, 2853, 1762, 1465, 1377, 1345, 1270, 1212, 1108, 1078, 1001, 967, 895, 798, 746, 721, 700 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 339.3 (100 (M+Na)), 655.2 (45 (2M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{17}H_{32}O_5Na$: 339.2142; found: 339.2142.

**Primary Alcohol** 11-*epi*-**247.** Ammoniumfluoride (52.6 mg, 1.42 mmol) was added to a solution of




diene **210** (14.0 mg, 0.133 mmol) in hexafluroisopropanol (1.4 mL) and the resulting solution stirred for 72 h at ambient temperature. The reaction mixture was then poured into sat. $NaHCO_3$ solution (6 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (5 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography to yield the title compound as a colorless oil (6.9 mg, 64%). $[\alpha]_D^{20}$ = +49.7 (c = 0.68, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.65 – 7.61 (m, 4H), 7.40 – 7.37 (m, 2H), 7.36 – 7.31 (m, 4H), 6.93 (ddd, *J* = 15.6, 7.8, 6.0 Hz, 1H), 6.22 (dd, *J* = 15.0, 10.9 Hz, 1H), 5.93 (tt, *J* = 10.8, 1.5 Hz, 1H), 5.71 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.33 (dd, *J* = 15.0, 8.9 Hz, 1H), 5.18 (dt, *J* = 10.8, 7.4 Hz, 1H), 4.55 (ddt, *J* = 9.2, 6.0, 3.1 Hz, 1H), 4.02 (ddd, *J* = 7.3, 4.8, 3.5 Hz, 1H), 3.90 (ddd, *J* = 9.1, 6.7, 4.7 Hz, 1H), 3.78 (td, *J* = 7.2, 5.9 Hz, 1H), 3.70 (tt, *J* = 10.7, 4.8 Hz, 1H), 3.57 (d, *J* = 12.3 Hz, 1H), 3.47 – 3.41 (m, 1H), 3.20 (tdd, *J* = 11.4, 9.7, 2.1 Hz, 1H), 3.16 (tt, *J* = 11.2, 1.5 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.41 (br t, 1H), 2.36 (ddd, *J* = 15.6, 9.6, 6.0, 1.6 Hz, 1H), 2.32 – 2.27 (dt, *J* = 14.9, 7.4 Hz, 1H), 2.26 – 2.15 (m, 4H), 1.97 (dt, *J* = 12.6, 7.0 Hz, 1H), 1.76 (ddt, *J* = 12.4, 4.2, 1.8 Hz, 1H), 1.67 – 1.63 (m, 1H), 1.62 (ddd, *J* = 14.6, 7.3, 3.9 Hz, 1H), 1.56 – 1.52 (m, 2H), 1.22 – 1.13 (m, 3H), 1.02 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 166.9, 146.5, 140.4, 135.9, 135.9, 133.9, 133.8, 129.7, 129.7, 129.6, 127.6, 127.6, 126.4, 125.6, 122.4, 81.2, 80.3, 75.6, 74.2, 73.1, 71.1, 68.5, 65.3, 43.7, 42.2, 42.1, 39.1, 35.9, 33.4, 33.4, 33.2, 30.9, 27.0, 25.8, 22.4, 19.4, 18.1, 14.9, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 3470, 2954, 2929, 2856, 1716, 1656, 1472, 1462, 1428, 1374, 1255, 1177, 1156, 1112, 1074, 967, 849, 837, 776, 739, 703, 610 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 839.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{72}O_7Si_2Na$: 839.4709; found: 839.4701.

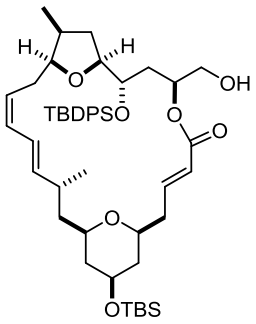
**Aldehyde 11-*epi*-227.** Sodium bicarbonate (4.8 mg, 56 µmol) and Dess-Martin periodinane (9.0 mg,




21 µmol) were added successively to a solution of alcohol 11-*epi*-**247** (5.8 mg, 7.1 µmol) in $CH_2Cl_2$ (1.4 mL) at 0 °C and the resulting suspension was vigorously stirred. After 5 min, the ice bath was removed and the reaction mixture was allowed to reach ambient temperature. After 90 min, the reaction mixture was poured into aq. $NaHCO_3/Na_2S_2O_3$ (1:1, 5 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was quickly purified by flash chromatography (short column < 8cm length, hexanes/EtOAc 12:1) keeping the contact time with silica gel as short as possible to give the rather unstable aldehyde as a colorless oil. (3.0 mg, 52%). $[\alpha]_D^{20}$ = +58 (c = 0.28, $CH_2Cl_2$). $^1$H NMR (600 MHz, $C_6D_6$): δ = 9.34 (d, *J* = 0.7 Hz, 1H), 7.85 – 7.74 (m, 4H), 7.30 – 7.21 (m, 7H), 6.58 (dd, *J* =14.6, 11.3 Hz, 1H), 6.07 (tt, *J* = 11.0, 2.2 Hz, 1H),

5.76 (dt, *J* = 15.7, 0.8 Hz, 1H), 5.30 (dd, *J* = 15.0, 9.3 Hz, 1H), 5.12 (dt, *J* = 10.8, 7.2 Hz, 1H), 4.59 (ddd, *J* = 10.8, 3.1, 1.5 Hz, 1H), 4.30 (ddt, *J* = 7.7, 4.7, 2.3 Hz, 1H), 3.69 (ddd, *J* = 8.7, 6.9, 4.7 Hz, 1H), 3.56 (ddd, *J* = 15.7, 10.5, 5.0 Hz, 1H), 3.15 (t, *J* = 11.0 Hz, 1H), 2.83 (tt, *J* = 10.6, 1.7 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.42 (ddd, *J* = 14.9, 11.0, 2.2 Hz, 1H), 2.34 (dddd, *J* = 16.7, 8.0, 4.9, 1.8 Hz, 1H), 2.30 – 2.24 (m, 1H), 2.19 – 2.14 (m, 1H), 2.12 (dddd, *J* = 15.1, 10.3, 5.0, 1.9 Hz, 1H), 1.98 (dq, *J* = 8.5, 7.0 Hz, 1H), 1.80 (dt, *J* = 12.8, 7.0 Hz, 1H), 1.73 (dddd, *J* = 15.3, 9.0, 2.4, 1.1 Hz, 1H), 1.63 (dd, *J* = 12.6, 5.0 Hz, 1H), 1.56 – 1.49 (m, 2H), 1.41 – 1.38 (m, 1H), 1.33 – 1.25 (m, 4H), 1.17 (s, 9H), 1.02 (s, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.09 (s, 6H) ppm. $^{13}$C NMR (150 MHz, $C_6D_6$): δ = 197.3, 165.7, 147.6, 140.5, 136.3, 136.3, 134.3, 134.2, 130.1, 130.0, 130.0, 126.6, 126.2, 121.8, 81.1, 80.5, 78.5, 73.9, 73.0, 71.6, 68.8, 44.1, 42.7, 42.6, 39.4, 36.4, 34.1, 33.7, 31.9, 31.3, 30.2, 27.3, 26.0, 22.3, 19.6, 18.2, 14.7, −4.3, −4.3 ppm. IR (film): $\tilde{\nu}$ = 2954, 2928, 2856, 1722, 1654, 1471, 1462, 1428, 1345, 1257, 1170, 1111, 1081, 1006, 989, 869, 837, 776, 739, 703, 610 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 837.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{70}O_7Si_2Na$: 837.4552; found: 837.4558.

**Alcohol 247.** Ammonium fluoride (328 mg, 8.86 mmol) was added as a solid to a stirred solution of diene **210** (85.0 mg, 80.5 µmol) in hexafluoroisopropanol (8.5 mL) at 5 °C. The reaction mixture was allowed to warm to 15 °C after 12 h and stirred at this temperature for further 36 h. The reaction was then quenched by pouring it into sat. $NH_4Cl$ solution (25 mL). The aqueous phase was extracted with $CH_2Cl_2$ (1 x 15 mL) and EtOAc (3 x 15 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 6:1) to give the desired primary alcohol as a white foam (43.0 mg, 65% yield). $[\alpha]_D^{20}$ = +11.8 (c = 0.96, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.69 – 7.61 (m, 4H), 7.42 – 7.29 (m, 6H), 6.91 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.23 (dd, *J* = 15.1, 10.9 Hz, 1H), 5.94 (t, *J* = 10.9 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.50 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.20 (dt, *J* = 10.4, 7.8 Hz, 1H), 4.96 (ddd, *J* = 12.4, 6.3, 3.1 Hz, 1H), 4.04 (ddd, *J* = 7.9, 5.6, 4.3 Hz, 1H), 3.81 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.74 (ddd, *J* = 10.7, 5.8, 4.9 Hz, 1H), 3.69 (dd, *J* = 6.7, 6.6 Hz, 1H), 3.51 (dd, *J* = 12.2, 2.7 Hz, 1H), 3.41 – 3.30 (m, 2H), 3.29 – 3.21 (m, 1H), 2.45 – 2.36 (m, 1H), 2.36 – 2.30 (m, 2H), 2.28 – 2.14 (m, 2H), 2.06 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.93 (dt, *J* = 13.0, 7.7 Hz, 1H), 1.90 – 1.81 (m, 2H), 1.78 (ddt, *J* = 12.4, 4.3, 1.9 Hz, 1H), 1.69 (ddt, *J* = 12.6, 4.2, 1.7 Hz, 1H), 1.64 – 1.54 (m, 2H), 1.41 (ddd, *J* = 12.7, 8.3, 6.6 Hz, 1H), 1.32 – 1.27 (m, 1H), 1.21 – 1.16 (m, 2H), 1.01 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.8, 146.5, 140.4, 136.0, 134.3, 134.0, 130.0, 129.6, 129.6, 127.6, 127.5, 127.5, 126.4, 124.1, 122.7, 81.2, 80.1, 73.7, 73.6, 73.2, 72.1, 68.8, 65.5, 42.8, 41.9, 41.7, 38.5, 35.3, 34.4, 33.9, 33.6, 30.1, 27.1, 25.8, 20.1, 19.5, 18.1, 15.2, −4.5 ppm. IR (film): $\tilde{\nu}$ = 3466, 2955, 2929, 2856, 1718, 1656, 1472, 1462, 1428, 1374, 1319, 1256, 1177, 1155, 1107, 1069, 961, 836, 775,



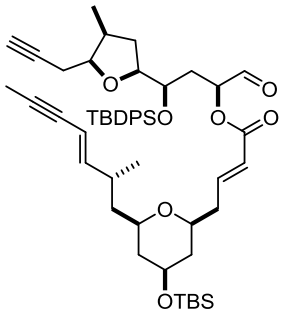
740, 703, 609 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 839.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{72}O_7Si_2Na$: 839.4709; found: 839.4703.

**Aldehyde 227.** Dess-Martin periodinane (46.8 mg, 0.110 mmol) and $NaHCO_3$ (25.3 mg, 0.301 mmol) were added as solids to a solution of alcohol **247** (41.0 mg, 50.2 µmol) in $CH_2Cl_2$ (9.6 mL) at 0 °C. The ice bath was removed 5 min after the addition and the reaction mixture allowed to warm to ambient temperature while stirring vigorously. After 2.5 h, the reaction mixture was quenched by pouring it into sat. $NaHCO_3/Na_2S_2O_5$ solution (1:1, 15 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (4 x 12 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (8 cm $SiO_2$, hexanes/EtOAc 9:1) keeping the contact time with silica gel as short as possible to yield the desired aldehyde as a white foam (34.3 mg, 84% yield). $[\alpha]_D^{20}$ = +15.6 (c = 0.98, $CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$): δ = 9.22 (s, 1H), 7.88 – 7.81 (m, 4H), 7.29 – 7.22 (m, 6H), 7.09 (ddd, *J* = 15.3, 8.7, 6.2 Hz, 1H), 6.50 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.11 (t, *J* = 10.8 Hz, 1H), 5.99 (dd, *J* = 15.7, 1.0 Hz, 1H), 5.54 (dd, *J* = 15.1, 8.3 Hz, 1H), 5.46 (dd, *J* = 9.9, 3.6 Hz, 1H), 5.19 (dt, *J* = 10.7, 7.7 Hz, 1H), 4.22 (ddd, *J* = 9.4, 6.3, 3.1 Hz, 1H), 3.82 (dt, *J* = 8.9, 6.7 Hz, 1H), 3.65 – 3.55 (m, 2H), 3.14 (td, *J* = 9.8, 1.6 Hz, 1H), 2.88 (td, *J* = 10.0, 0.8 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.11 (dt, *J* = 15.3, 7.6 Hz, 1H), 1.99 (dt, *J* = 15.0, 8.8 Hz, 1H), 1.92 – 1.75 (m, 5H), 1.73 – 1.62 (m, 2H), 1.56 – 1.46 (m, 2H), 1.21 (s, 9H), 1.19 – 1.12 (m, 4H), 1.04 – 0.99 (m, 12H), 0.70 – 0.65 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 6H). ppm. $^{13}$C NMR (100 MHz, $C_6D_6$): δ = 197.3, 165.6, 147.1, 140.3, 136.5, 136.4, 135.0, 134.5, 130.4, 129.9, 129.9, 127.9, 127.9, 126.9, 125.2, 122.7, 81.2, 81.0, 76.1, 73.7, 73.5, 72.8, 69.0, 43.5, 42.4, 42.0, 38.6, 36.3, 35.2, 33.7, 32.6, 30.7, 27.5, 26.0, 20.1, 19.9, 18.2, 14.7, −4.3 ppm. IR (film): $\tilde{\nu}$ = 2955, 2928, 2956, 1722, 1655, 1471, 1462, 1428, 1257, 1171, 1106, 1052, 1005, 982, 941, 836, 775, 738, 702, 609 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 837.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{70}O_7Si_2Na$: 837.4552; found: 837.4550.

**Alcohol 220a.** Ammonium fluoride (54.2 mg, 1.46 mmol) was added to a solution of diyne **220** (16.0 mg, 0.146 mmol) in 1,1,1,3,3,3-hexafluro-2-propanol (1.5 mL) and the resulting solution stirred for 40 h at ambient temperature. The reaction mixture was then poured into sat. aq. $NaHCO_3$ solution and the aqueous phase was extracted with $CH_2Cl_2$ (4 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 15:1 to 9:1 to 7:1 5:1) to yield the title compound as a white foam (8.8 mg, 70%). $[\alpha]_D^{20}$ = −16.4 (c = 0.86, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.61 (m, 4H), 7.40 – 7.35 (m, 2H), 7.35 – 7.28 (m, 4H), 6.87 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.92 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.71 (dt, *J* = 15.7,

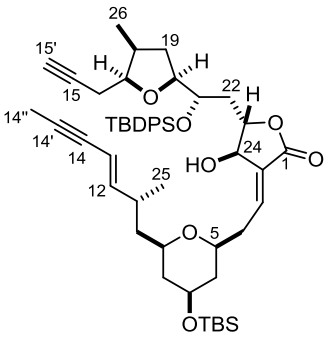
1.2 Hz, 1H), 5.36 (ddq, *J* = 15.9, 2.6, 1.3 Hz, 1H), 4.98 (ddt, *J* = 8.4, 4.7, 4.3 Hz, 1H), 3.84 (ddd, *J* = 7.1, 6.1, 3.9 Hz, 1H), 3.82 – 3.74 (m, 2H), 3.70 (tt, *J* = 10.6, 4.9 Hz, 1H), 3.58 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.47 (dd, *J* = 12.3, 5.7 Hz, 1H), 3.33 (dddd, *J* = 11.4, 6.6, 5.2, 1.2 Hz, 1H), 3.25 (dd, *J* = 11.2, 7.2, 5.8, 1.4 Hz, 1H), 2.44 – 2.24 (m, 4H), 2.18 – 2.04 (m, 3H), 2.01 – 1.89 (m, 2H), 1.90 (d, *J* = 2.2 Hz, 3H), 1.87 (t, *J* = 2.6 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.69 – 1.57 (m, 2H), 1.32 (ddd, *J* = 12.4, 8.4, 7.9 Hz, 1H), 1.35 – 1.26 (ddd, *J* = 13.4, 7.0, 6.4 Hz, 1H), 1.23 – 1.07 (m, 2H), 1.00 (s, 9H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.6, 148.5, 145.9, 136.0, 135.9, 134.1, 133.9, 129.5, 129.4, 127.5, 127.3, 122.9, 108.2, 84.5, 81.7, 81.0, 79.3, 78.3, 74.0, 73.3, 73.1, 71.8, 69.3, 68.6, 65.3, 42.3, 41.4, 41.3, 38.8, 35.2, 34.8, 34.4, 33.4, 27.1, 25.8, 20.9, 19.8, 19.5, 18.1, 14.7, 4.2, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 3466, 2954, 2929, 2856, 1718, 1656, 1472, 1462, 1428, 1377, 1256, 1219, 1177, 1109, 1069, 1005, 837, 776, 739, 703, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 877.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{51}H_{74}O_7Si_2Na$: 877.4865; found: 877.4860.

**Aldehyde 249.** Dess-Martin periodinane (9.8 mg, 23 µmol) and $NaHCO_3$ (5.2 mg, 62 µmol) were added as solids to a stirred solution of alcohol **220a** (6.6 mg, 7.7 µmol) in $CH_2Cl_2$ (2.4 mL) at room temperature. The resulting white suspension was stirred vigorously for 2.5 h. The reaction mixture was then poured into sat. $NaHCO_3/Na_2S_2O_5$ solution (1:1, 6 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (4 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (8 cm $SiO_2$, hexanes/EtOAc 12:1), keeping the contact time with silica gel as short as possible, to give the rather unstable aldehyde as a colorless oil (5.5 mg, 84% yield). $[\alpha]_D^{20}$ = −11.7 (c = 0.48, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 0.8 Hz, 1H), 7.65 – 7.60 (m, 4H), 7.39 – 7.35 (m, 2H), 7.33 – 7.29 (m, 4H), 6.91 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.91 (ddd, *J* = 15.9, 8.0, 0.8 Hz, 1H), 5.74 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.36 (dqd, *J* = 15.9, 2.3, 1.1 Hz, 1H), 5.03 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.93 (ddd, *J* = 8.3, 6.0, 3.4 Hz, 1H), 3.82 – 3.77 (m, 2H), 3.73 (tt, *J* = 10.8, 4.7 Hz, 1H), 3.36 (dddd, *J* = 11.8, 7.0, 5.0, 1.8 Hz, 1H), 3.26 (dddd, *J* = 11.2, 7.3, 5.7, 1.6 Hz, 1H), 2.41 (dtd, *J* = 14.2, 7.1, 1.6 Hz, 1H), 2.38 – 2.26 (m, 3H), 2.12 – 2.08 (m, 2H), 1.96 (dt, *J* = 12.8, 7.4 Hz, 1H), 1.92 – 1.89 (m, 1H), 1.90 (d, *J* = 2.2 Hz, 3H), 1.87 (t, *J* = 2.7 Hz, 1H), 1.80 – 1.73 (m, 2H), 1.62 (dt, *J* = 14.3, 7.1 Hz, 1H), 1.34 – 1.27 (m, 2H), 1.22 – 1.17 (m, 2H), 1.16 – 1.10 (m, 1H), 1.01 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 1H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 198.3, 165.5, 148.4, 147.0, 135.9, 133.8, 133.5, 129.6, 129.5, 127.6, 127.3, 121.9, 108.2, 84.4, 81.5, 80.6, 79.4, 78.3, 75.5, 73.9, 73.3, 71.0, 69.5, 68.6, 42.3, 41.4, 41.4, 38.9, 35.2, 34.7, 33.4, 31.8, 27.1, 25.8, 20.9, 19.7, 19.5, 14.7, 4.2, −4.5, −4.5.ppm. IR (film): $\tilde{\nu}$ = 2955, 2929, 2856, 1725, 1655, 1472, 1462, 1428, 1376, 1258, 1171, 1110, 1060, 1006, 962, 837, 776, 740, 703, 611 cm$^{-1}$. MS (ESIpos) *m/z*



(%) = 875.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{51}H_{72}O_7Si_2Na$: 875.4711; found: 875.4709.

**Baylis-Hillman alcohol 250.** A flame-dried Young tube was charged with a solution of aldehyde **249** (1.2 mg, 1.41 µmol) in DMF (30 µL) followed by a solution of dimethylphenylphosphine (0.05 M in DMF, 8.4 µL, 0.42 µmol). The Young tube was sealed and place in a preheated oil bath (90 °C). The reaction mixture was stirred at this temperature for 8 h before being cooled to room temperature. It was then poured into sat. $NH_4Cl$ solution (3 mL) and the aqueous phase was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 9.1 to 8:1 to 7:1 to 6:1 to 5:1) to give alcohol **250** as a white amorphous solid (0.45 mg, 38% yield, 6:1 E/Z, ~90% pure). $^1$H NMR (600 MHz, $C_6D_6$): δ = see table 5.11. $^{13}$C NMR (150 MHz, $C_6D_6$): δ = see table 5.11. IR (film): $\tilde{\nu}$ = 3461, 2956, 2931, 2855, 1724, 1658, 1472, 1463, 1428, 1376, 1256, 1172, 1111, 1060, 1005, 960, 835, 778, 742, 706 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 875.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{51}H_{72}O_7Si_2Na$: 875.4711; found: 875.4707.




**Baylis-Hillman alcohol ((24*R*)-226, major isomer).** A flame-dried Young-tube was charged with a solution of aldehyde **227** (34.3 mg, 42.1 µmol) in DMF (1.1 mL). A solution of dimethylphenylphosphine (0.2 M in DMF, 63.1 µL, 12.6 µmol) was added via syringe, the Young tube was sealed, placed in a preheated oil bath (90 °C) and the reaction mixture was stirred for 60 h at this temperature. After cooling to ambient temperature, the reaction mixture was poured into sat. $NH_4Cl$ solution (10 mL) and the aqueous phase was extracted with $Et_2O$ (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The pale yellow residue was purified by flash chromatography (hexanes/EtoAc 12:1 to 9:1 to 8:1 to 7:1) to yield alcohol (24*R*)-**226** (11.7 mg, 34% yield) along with its isomer (24*S*)-**226** (see below) and elimination product **251** (see below). $[\propto]_D^{20}$ = +47 (c = 0.28, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): see table 5.12. $^{13}$C NMR (100 MHz, $CDCl_3$): see table 5.12. IR (film): $\tilde{\nu}$ = 3426, 2955, 2930, 2894, 2857, 1760, 1744, 1683, 1462, 1428, 1376, 1362, 1331, 1252, 1195, 1111, 1077, 1029, 1006, 945, 856, 836, 775, 739, 704 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 837.5 (100 (M+Na)). HRMS (ESIpos): calcd for $C_{48}H_{70}O_7Si_2Na$: *m/z*: 837.4552; found: 837.4549.

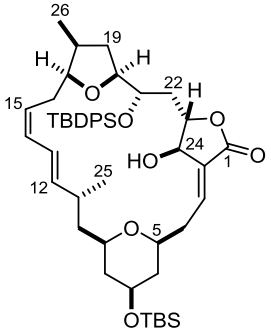


*Table 5.11:* Assignment of the $^{1}$H & $^{13}$C NMR data for the *anti*-Baylis-Hillman alcohol **250**.*

| atom n° | $^{1}$H NMR ($C_6D_6$, 600 MHz) | | | | | $^{13}$C NMR ($C_6D_6$, 150 MHz) δ /ppm |
|---|---|---|---|---|---|---|
| | δ /ppm | m | J/Hz | COSY | NOESY | |
| 1 | - | - | - | - | - | 168.2 |
| 2 | - | - | - | - | - | 134.3 |
| 3 | 6.95 | ddd | 9.8, 7.1, 2.0 | 4ab, 24 | 4a(b) | 139.8 |
| 4a | 2.33 | ddd | 14.0, 9.8, 4.0 | 3, 4b, 5 | 4b, 5, 24 | 34.9 |
| 4b | 1.95 | m | - | 3, 4a, 5 | 4a, 5 | |
| 5 | 2.95 | dtd | 11.5, 6.5, 1.4 | 4ab, 6ab | 4ab, 6b, 7, 9 | 73.7 |
| 6a | 1.53 | m | - | 5, 6b, 7 | 6b | 40.3 |
| 6b | 1.28 | m | - | 5, 6a, 7 | 5, 6a, 7 | |
| 7 | 3.50 | dddd | 10.5, 10.3, 5.0, 4.9 | 6ab, 8ab | 5, 6b, 8b, 9 | 68.9 |
| 8a | 1.60 | ddt | 12.9, 4.4, 2.1 | 7, 8b, 9 | 8b | 41.1 |
| 8b | 0.97 | m | - | 7, 8a, 9 | 7, 8a, 9, 11 | |
| 9 | 3.09 | dtd | 11.2, 6.7, 1.2 | 8ab, 10ab | 5, 7, 8b, 10a, (11), 25 | 74.2 |
| 10a | 1.47 | t | 11.3 | 9, 10b, 11 | 9, 10b, 12 | 42.0 |
| 10b | 1.08 | m | - | 9, 10a, 11 | 10a, (25) | |
| 11 | 2.16 | m | - | 10ab, 12 | 8b, (9), 10a(b), (12), 13, 25 | 33.8 |
| 12 | 5.96 | dd | 15.8, 8.3 | 11, 13 | 10a, (11), 25 | 147.9 |
| 13 | 5.52 | dqd | 15.9, 2.2, 0.9 | (11), 12, 14‘‘ | 11, (25) | 109.6 |
| 14 | - | - | - | - | - | 78.9 |
| 14‘ | - | - | - | - | - | 84.9 |
| 14‘‘ | 1.63 | d | 2.3 | 13 | - | 3.9 |
| 15‘ | 1.70 | t | 2.7 | 16ab | - | 70.0 |
| 15 | - | - | - | - | - | 81.7 |
| 16a | 2.03 | ddd | 16.7, 5.6, 2.7 | 16b, 17 | 16b, 17, 18 | 21.1 |
| 16b | 1.93 | m | - | 16a, 17 | 16a, 17 | |
| 17 | 3.64 | ddd | 7.8, 7.1, 5.6 | 16ab, 18 | 16ab, 18 | 79.7 |
| 18 | 1.93 | m | - | 17, 19a, 26 | 17, 19a, 26 | 35.6 |
| 19a | 1.53 | m | - | 18, 19b, 20 | 18, 19b, 20, 21 | 35.5 |
| 19b | 1.06 | m | - | 19a | 19a, (22b), 26 | |
| 20 | 3.68 | dt | 8.9, 6.7 | 19a, 21 | 19ab, 21, 22b, (23, (26) | 81.7 |
| 21 | 4.18 | ddd | 7.2, 7.0, 4.2 | 20, 22ab | 19a, 20, 22b, 23, 24 | 72.8 |
| 22a | 1.71 | m | - | 21, 22b, 23 | 20, 22b, 23 | 39.1 |
| 22b | 1.71 | m | - | 21, 22a, 23 | 20, 22a, 23 | |
| 23 | 4.82 | ddd | 9.0, 5.0, 2.4 | 22ab, 24 | (20), 21, 22b, 24 | 82.3 |
| 24 | 4.34 | dd | 2.4, 2.1 | 23, OH | 4ab, (21), 22b, 23 | 70.9 |
| 25 | 0.78 | d | 6.6 | 11 | 9, 10a(b), 11, 12, (13) | 20.0 |
| 26 | 0.66 | d | 7.0 | 18 | 18, 19, (20) | 14.6 |
| OH | 3.35 | br s | - | 23 | 24 | - |

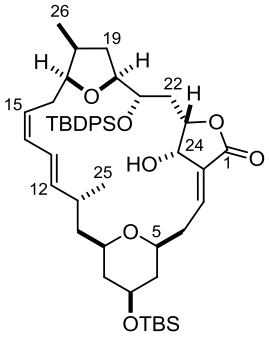
* The signals of the TBS & TBDPS group are not listed and appear as follows: $^{1}$H NMR (600 MHz, $C_6D_6$): δ = 7.93 – 7.88 (m, 4H), 7.30 – 7.22 (m, 6H), 1.23 (s, 9H), 0.99 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm. $^{13}$C NMR (150 MHz, $C_6D_6$): δ = 136.5, 134.8, 134.5, 129.9, 129.7, 127.9, 27.5, 26.0, −4.4 ppm.

*Table 5.12:* Assignment of the $^{1}$H & $^{13}$C NMR data for the *anti*-Baylis-Hillman alcohol (24*R*)-**226**.*

| atom n° | $^{1}$H ($CDCl_3$, 600 MHz) | | | | | $^{13}$C ($CDCl_3$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 168.7 | - |
| 2 | - | - | - | - | - | 132.8 | - |
| 3 | 6.85 | ddd | 9.7, 7.0, 2.1 | 4ab | 4ab, 5, 6a, (24), (25) | 142.3 | 1, (5), 24 |
| 4a | 2.63 | ddd | 14.0, 9.7, 8.3 | 3, 4b, (5) | 3, 4b, 5, (6a), 24 | 35.0 | 2, 3, 5 |
| 4b | 2.39 | ddd | 14.0, 7.1, 2.4 | 3, 4a, 5 | 3, 4a, 5, 24 | | 2, 5, 6 |
| 5 | 3.45 | dddd | 11.1, 8.5, 2.0, 1.7 | 4(a)b, 6a | 3, 4ab, 6b, 7, 9 | 74.3 | (3), 4, 5 |
| 6a | 1.29 | m | - | 5, 6b, 7 | 3, (4a), 6b, 8a | 40.7 | 5, 7 |
| 6b | 1.83 | ddt | 12.5, 4.7, 1.7 | 6a, 7 | 5, 6a, 7 | | 7, 8 |
| 7 | 3.75 | m | - | 6ab, 8ab | 5, 6b, 8b, 9, 25 | 68.6 | 6,8 |
| 8a | 1.16 | m | - | 7, 8b, 9 | 6a, 8b | 41.8 | 7, 9, 10 |
| 8b | 1.68 | ddt | 12.7, 4.7, 1.7 | 7, 8a, (9) | 7, 8a, 9 | | 6, 7 |
| 9 | 3.29 | tt | 10.9, 2.0 | 8a(b), 10b | 5, 7, 8b, 10b, 11, 25 | 73.1 | 7, 11 |
| 10a | 1.19 | m | - | 10b, 11 | 9, 10b, 11, 12 | 43.7 | 8, 12 |
| 10b | 1.47 | m | - | 9, 10a | 10a, 11, 12, 13 | | 9 |
| 11 | 2.31 | m | - | 10ab, 12, 25 | 9, 10a, 13, 24, 25, OH | 32.8 | 12 |
| 12 | 5.45 | dd | 15.1, 8.3 | 11, 13 | 10ab, (11), 12, 13, 25 | 141.0 | 11, 14, 25 |
| 13 | 6.34 | dd | 15.2, 10.9 | 12, 14 | 10a, 11, 16a, (17), (24), 25 | 125.0 | 11 |
| 14 | 5.93 | dd | 10.8, 10.8 | 13, 15 | 12, 15 | 130.5 | 16 |
| 15 | 5.28 | dt | 10.2, 6.6 | 14, 16ab | 14, 16ab, 17, (26) | 127.0 | 13, 17 |
| 16a | 2.00 | dddd | 14.5, 6.6, 3.1, 0.5 | 15, 16b, 17 | 13, 15, 16b, 17, 23, 26 | 30.4 | 14, 15, 17 |
| 16b | 2.36 | m | - | 15, 16a, 17 | 15, 17, 16a, 26 | | 14, 15 |
| 17 | 3.72 | ddd | 8.7, 7.3, 3.0 | 16ab, 18 | (13), 15, 16ab, 18, 20, 25 | 81.5 | 15 |
| 18 | 2.46 | ddq | 7.4, 7.3, 7.3 | 17, 19ab, 26 | 17, 19a, 20, 26 | 35.4 | 19, (20), 26 |
| 19a | 1.48 | m | - | 18, 19b, 20 | 18, 19b, 20 | 33.7 | 17, 18, (20), 26 |
| 19b | 1.92 | ddd | 12.9, 7.7, 7.0 | 18, 19a, 20 | 19a, 21, 22a, 23 | | 18, 20, (21), 26 |
| 20 | 3.83 | ddd | 9.3, 6.6, 4.9 | 19ab, 21 | 17, 18, 19a, 21 | 80.0 | (18), 22 |
| 21 | 4.34 | m | - | 20, 22ab | 19b, 20, 22a | 69.0 | 19, 23 |
| 22a | 1.74 | ddd | 14.2, 7.5, 5.9 | 21, 22b, 23 | 19b, 21, 22b, 23, 24 | 36.0 | 20, 21 23, 24 |
| 22b | 1.93 | ddd | 14.4, 8.2, 6.0 | 21, 22a, 23 | 22a | | (21), 23, 24 |
| 23 | 4.54 | ddd | 8.7, 5.9, 3.5 | 22ab, 24 | 16a, 19b, 22a, 24, 25, OH | 82.0 | (1) |
| 24 | 4.33 | ddd | - | 23, OH | (3), 4ab, 11, (13), 22a, 23 | 71.0 | |
| 25 | 0.86 | d | 6.4 | 11 | (3), 7, 9, 11, 12, (13) | 18.6 | 10, 11 |
| 26 | 0.95 | d | 7.1 | 18 | 16ab, 17, 18, 19b, 22, 23 | 15.7 | 17, 18, 19 |
| OH | 2.84 | br d | 4.4 | 23 | 11, 23, 24 | - | - |

*The signals of the TBS & TBDPS group are not listed and appear as follows: $^{1}$H NMR (600 MHz, $CDCl_3$): δ = 7.68 – 7.63 (m, 4H), 7.42 – 7.31 (m, 6H), 1.04 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 136.0, 133.8, 133.7, 129.7, 129.7, 127.6, 127.6, 127.5, 27.1, 25.8, 19.5, 18.1, −4.5, −4.6 ppm

**Baylis-Hillman alcohol ((24*S*)-226, minor isomer).** Obtained from the reaction described above as the minor isomer (6.4 mg, 19% yield). $[\alpha]_D^{20}$ = +46.1 (c = 0.67, $CH_2Cl_2$). $^1$H NMR (600 MHz, $C_6D_6$): δ = see table 5.13. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = see table 5.13. IR (film): $\tilde{\nu}$ = 3417, 2955, 2928, 2856, 2856, 1760, 1742, 1682, 1462, 1428, 1376, 1252, 1194, 1110, 1075, 1006, 945, 856, 836, 775, 739, 703 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 837.5 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{70}O_7Si_2Na$: 837.4552; found: 837.4551.




**Elimination product 251.** Obtained from the reaction described above as an unpolar by-product (1.6 mg, 5% yield). $[\alpha]_D^{20}$ = +27.8 (c = 0.34, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.61 (m, 4H), 7.40 – 7.30 (m, 6H), 6.40 (dd, *J* = 10.6, 6.5 Hz, 1H), 6.16 (dd, *J* = 15.0, 11.1 Hz, 1H), 5.99 (t, *J* = 11.0 Hz, 1H), 5.91 (s, 1H), 5.48 (dd, *J* = 15.0, 8.4 Hz, 1H), 5.31 (td, *J* = 10.1, 6.4 Hz, 1H), 4.30 (ddd, *J* = 8.3, 5.6, 4.4 Hz, 1H), 3.74 – 3.66 (m, 3H), 3.17 – 3.06 (m, 2H), 2.89 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.54 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.44 (ddd, *J* = 13.0, 10.7, 7.8 Hz, 1H), 2.33 – 2.23 (m, 4H), 2.12 – 2.06 (m, 1H), 1.93 (ddd, *J* = 12.4, 7.6, 6.2 Hz, 1H), 1.83 (ddt, *J* = 12.4, 4.7, 1.6 Hz, 1H), 1.68 (ddt, *J* = 12.5, 4.6, 1.6 Hz, 1H), 1.58 (dt, *J* = 12.4, 9.5 Hz, 1H), 1.47 (ddd, *J* = 13.8, 9.9, 6.2 Hz, 1H), 1.26 (dd, *J* = 6.6, 2.7 Hz, 1H), 1.21 – 1.13 (m, 2H), 1.01 (s, 9H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 168.1, 156.9, 141.5, 135.9, 135.9, 133.8, 133.7, 133.6, 130.9, 130.4, 129.7, 129.6, 127.6, 127.5, 126.5, 123.3, 103.6, 81.6, 79.7, 74.4, 73.5, 69.6, 68.7, 42.3, 42.1, 41.5, 36.5, 35.6, 34.4, 33.7, 32.3, 29.9, 27.0, 25.8, 19.6, 19.4, 18.1, 15.5, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 2955, 2928, 2856, 1782, 1655, 1471, 1462, 1428, 1376, 1324, 1254, 1151, 1105, 1081, 1006, 927, 867, 837, 823, 776, 740, 703 cm$^{-1}$. MS (EI) *m/z* (%) = 796 (14), 741 (16), 740 (34), 739 (58), 711 (29), 607 (22), 540 (38), 483 (17), 408 (51), 295 (38), 239 (25), 217 (26), 199 (63), 197 (44), 135 (100), 131 (18), 93 (20), 73 (32). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{68}O_6Si_2Na$: 819.4447; found: 819.4443.

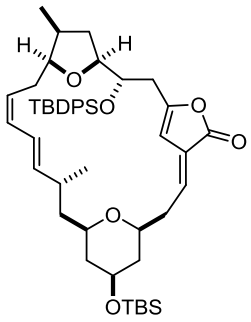


*Table 5.13:* Assignment of the $^{1}$H & $^{13}$C NMR data for the *syn*-Baylis-Hillman alcohol (24*S*)-**226**.*

| atom n° | $^{1}$H ($CDCl_3$, 600 MHz) | | | | | $^{13}$C ($CDCl_3$, 150 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | δ /ppm | HMBC |
| 1 | - | - | - | - | - | 168.7 | - |
| 2 | - | - | - | - | - | 134.8 | - |
| 3 | 6.79 | ddd | 11.3, 6.0, 1.6 | 4ab | 4ab, 5 | 140.0 | 1, 24 |
| 4a | 2.46 | m | - | 3, 4b, (5) | 3, 5, 23, OH | 36.7 | 2, 3, 5 |
| 4b | 2.46 | m | - | 3, 4a, 5 | 3, 5, 23, OH | | 2, 3, 5 |
| 5 | 3.38 | dddd | 11.3, 11.3, 3.5, 1.8 | 4(a)b, 6a | 3, 4ab, 6b, 7, 9 | 72.8 | 4, 7 |
| 6a | 1.31 | ddd | 11.9, 11.7, 11.2 | 5, 6b, 7 | 6b | 41.9 | 4, 5, 7 |
| 6b | 1.91 | m | - | 6a, 7 | 5, 6b, 7 | | 7, 8 |
| 7 | 3.79 | dddd | 10.6, 10.6, 4.8, 4.8 | 6ab, 8ab | 5, 6b, 8b, 9 | 68.3 | - |
| 8a | 1.24 | ddd | 12.5, 11.4, 11.3 | 7, 8b, 9 | 8b | 41.9 | 7, 9, 10 |
| 8b | 1.69 | ddt | 12.8, 4.8, 1.7 | 7, 8a, (9) | 7, 8a, 9, 10b | | 7 |
| 9 | 3.29 | tt | 11.2, 2.0 | 8a(b), 10b | 5, 7, 8b, 10b, 25 | 73.7 | 7 |
| 10a | 1.53 | m | - | 10b, 11 | (11), (25) | 43.5 | 25 |
| 10b | 1.15 | ddd | 14.2, 12.4, 1.1 | 9, 10a | 9, 10b, 25 | | 11, (12), 25 |
| 11 | 2.39 | m | - | 10b, 12, 25 | 13, 25, OH | 31.3 | 25 |
| 12 | 5.39 | dd | 15.2, 7.6 | 11, 13 | (13), 14, 25 | 141.2 | 11, (13), (17) |
| 13 | 6.35 | dd | 15.2, 10.9 | 12, 14 | 11, (12, 14), 16a, (OH) | 125.1 | 11, 14, 15 |
| 14 | 5.92 | dd | 10.9, 10.9 | 13, 15 | 12, (13), 15 | 130.3 | 11, 12, (13) |
| 15 | 5.17 | td | 10.9, 5.1 | 14, 16ab | 14, 16b, 17 | 127.6 | 11, 13, 17 |
| 16a | 2.33 | m | - | 15, 16b, 17 | 13, 16b | 31.2 | 14, 15, 17 |
| 16b | 1.92 | dddd | 14.6, 11.1, 2.3, 2.2 | 15, 16a, 17 | 16a, 17, 26 | | 14, 15, 17 |
| 17 | 3.85 | m | - | 16ab, 18 | 15, 16, 18 | 81.5 | 15, 19, (20), 26 |
| 18 | 2.24 | ddq | 10.8, 7.4, 7.1 | 17, 19b, 26 | 17, 19b, 20, 26 | 35.7 | 17, 19, 26 |
| 19a | 1.86 | ddd | 12.6, 6.4, 6.3 | 19b, 20 | 18, 19b, 20 | 33.2 | 17, 18, 21 |
| 19b | 1.51 | m | - | 18, 19a, 20 | 19a, 26 | | 18, 20, 21, 26 |
| 20 | 3.88 | m | - | 19ab, 21 | 19a, 21 | 80.0 | 21, 22 |
| 21 | 4.49 | ddd | 11.6, 4.8, 1.9 | 20, 22b | 20, 22b | 69.6 | 19, 20, 22 |
| 22a | 2.35 | m | - | 22b, 23 | 21, 22b | 29.7 | 23 |
| 22b | 1.81 | dd | 13.2, 0.5 | 21, 22a | 22a, 23, 24 | | 20, 21 |
| 23 | 4.51 | ddd | 12.4, 5.3, 1.6 | 22a, 24 | 22b, 24 | 78.5 | 20, 21, 22, 24 |
| 24 | 4.72 | dd | 5.3, 1.3 | (23), OH | 4ab, 23, OH | 65.8 | 1, (2, 3), 23 |
| 25 | 0.80 | d | 6.6 | 11 | 9, 10b, 11, 12 | 18.1 | 10, 11, 12 |
| 26 | 0.98 | d | 7.0 | 18 | 16b, 18 | 15.2 | 17, 18, 19 |
| OH | 4.23 | s | - | (23) | 4ab, 11, (13), 24 | - | 23, 24 |

*The signals of the TBS & TBDPS group are not listed and appear as follows: $^{1}$H NMR (500 MHz, $CDCl_3$): δ = 7.67 – 7.61 (m, 4H), 7.41 – 7.30 (m, 6H), 1.03 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 135.9, 135.9 133.9, 133.9, 129.7, 129.7, 127.5, 27.2, 27.1, 25.8, 19.7, 18.0, −4.5, −4.6 ppm.

**Triol 252.** A flame-dried Schlenck tube was charged with a solution of alcohol (24*R*)-**226** (10.0 mg, 12.3 µmol) in $CH_2Cl_2$ (1.3 mL) and the solution was cooled to −78 °C. A solution of TMEDA (0.2 M in $CH_2Cl_2$, 70.5 µL, 14.1 µmol) was introduced and the reaction mixture stirred at −78 °C for 5 min. A solution of osmium tetroxide (0.12 M in $CH_2Cl_2$, 103 µL, 12.4 µmol) was added dropwise via syringe through a septum over 3 min. After stirring at −78 °C for 20 min, the mixture was allowed to warm to rt, the volatiles were removed by first applying an Ar flow and the residue was dried under high vacuum. The residue was redissolved in THF (0.6 mL) and the solution treated with aq. sat. $NaHSO_3$ solution (0.6 mL) for 23 h under vigorous stirring. The resulting emulsion was diluted with EtOAc/NaCl solution (1:1, 6 mL) and the layers were separated. The aqueous phase was extracted with EtoAc (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The pale red residue was purified by flash chromatography (hexanes/EtOAc 5:1) to afford the triol as a white foam (6.8 mg, 65%). $[\alpha]_D^{20}$ = +13.6 (c = 0.59, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.67 – 7.61 (m, 4H), 7.42 – 7.38 (m, 2H), 7.36 – 7.32 (m, 4H), 6.16 (ddt, *J* = 15.2, 10.8, 1.1 Hz, 1H), 5.92 (tt, *J* = 10.9, 1.7 Hz, 1H), 5.55 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.25 (td, *J* = 9.8, 5.4 Hz, 1H), 4.35 (ddd, *J* = 8.5, 4.8, 3.4 Hz, 1H), 4.25 (ddd, *J* = 10.5, 7.7, 2.9 Hz, 1H), 3.94 – 3.87 (m, 2H), 3.84 (td, *J* = 8.0, 4.7 Hz, 1H), 3.75 (ddd, *J* = 10.7, 6.0, 4.7 Hz, 1H), 3.72 (br s, 1H), 3.59 (dd, *J* = 8.9, 8.0 Hz, 1H), 3.50 (d, *J* = 2.9 Hz, 1H), 3.46 (ddt, *J* = 11.3, 10.5, 1.9 Hz, 1H), 3.32 (ddt, *J* = 11.9, 9.9, 2.3 Hz, 1H), 2.78 (d, *J* = 9.3 Hz, 1H), 2.37 – 2.26 (m, 3H), 2.06 (dtd, *J* = 15.4, 5.1, 1.9 Hz, 1H), 2.01 (ddd, *J* = 14.5, 8.9, 2.9 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.85 (ddd, *J* = 14.2, 10.4, 3.4 Hz, 1H), 1.77 (ddt, *J* = 12.5, 4.2, 1.7 Hz, 1H), 1.70 (ddd, *J* = 12.5, 4.5, 2.0 Hz, 1H), 1.57 – 1.48 (m, 3H), 1.29 (ddd, *J* = 13.9, 10.0, 2.5 Hz, 1H), 1.25 – 1.18 (m, 2H), 1.05 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 175.8, 140.7, 135.9, 133.7, 133.6, 129.8, 129.8, 127.6, 126.7, 123.9, 80.9, 80.2, 79.9, 74.4, 74.1, 73.2, 72.9, 71.3, 69.1, 68.6, 44.0, 42.2, 41.7, 36.4, 35.8, 34.7, 33.6, 33.1, 31.0, 27.1, 25.8, 19.5, 19.3, 18.1, 14.9, −4.5, −4.5 ppm. IR (film): $\tilde{\nu}$ = 3477, 2956, 2930, 2857, 1763, 1472, 1462, 1428, 1376, 1362, 1255, 11943, 1111, 1078, 1031, 1006, 981, 922, 857, 837, 776, 739, 703, 611 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 871.59 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{72}O_9Si_2Na$: 871.4607; found: 871.4607.

2,3,24-*epi*-**Deacylmandelalide D (253).** A teflon vial was charged with a solution of triol **252** (5.0 mg, 5.9 µmol) in THF (0.5 mL) and pyridine (0.5 mL) and the mixture cooled to 0 °C. HF·pyr (500 µL) was then added slowly via an Eppendorf pipette. After stirring 5 min at 0 °C, the reaction mixture was allowed to warm to ambient temperature and stirred for further 24 h. The reaction was then quenched by pouring it into pH 7.2 buffer ($NaH_2PO_4/Na_2HPO_4$, 5 mL) and the buffered aqueous phase was extracted with EtOAc/EtOH (9:1, 4 x 6 mL). The

combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH 93:7 to 92:8 to 91:9 to 90:10) to yield the desired pentaol as a white solid (2.1 mg, 72% yield). $[\propto]_D^{27}$ = −2.0 (c = 0.34, MeOH). $^1$H NMR (600 MHz, $CD_3OD$): see table 5.14. $^{13}$C NMR (150 MHz, $CD_3OD$): δ = see table 5.14. IR (film): $\tilde{\nu}$ = 3379, 2957, 2924, 2873, 2856, 1763, 1650, 1455, 1375, 1261, 1375, 1214, 1109, 1063, 1036, 998, 948, 883, 732 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 519.20 (100 (M+Na)), 1016.37 (32 (2M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{26}H_{40}O_9Na$: 519.2565; found: 519.2564.

**Triol 254.** A flame-dried Schlenck tube was charged with a solution of alcohol (24*S*)-**226** (6.0 mg, 7.4 µmol) in $CH_2Cl_2$ (1.0 mL) and the resulting mixture cooled to −78 °C. A solution of TMEDA (0.2 m in $CH_2Cl_2$, 42.3 µL, 8.5 µmol) was introduced and the reaction mixture stirred 5 min at −78 °C. A solution of osmium tetroxide (0.12 M in $CH_2Cl_2$, 61.3 µL, 7.4 µmol) was added dropwise via syringe through a septum over 3 min. After stirring at −78 °C for 20 min, the cooling bath was removed and the volatiles were removed by first applying an Ar flow. The residue was finally dried under high vacuum before it was redissolved in THF (0.4 mL) and the solution treated with aq. sat. $NaHSO_3$ (0.4 mL) for 23 h under vigorous stirring. The resulting emulsion was diluted with EtOAc/NaCl solution (1:1, 6 mL) and the layers were separated. The aqueous phase was further extracted with EtoAc (3 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The pale red residue was purified by flash chromatography (hexanes/EtOAc 7:1 to 6:1) to afford the triol as a white foam (4.9 mg, 78%). $[\propto]_D^{20}$ = +30.2 (c = 0.42, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.67 – 7.61 (m, 4H), 7.41 – 7.37 (m, 2H), 7.36 – 7.32 (m, 4H), 6.30 (ddt, *J* = 15.3, 10.9, 1.2 Hz, 1H), 5.87 (ddt, *J* = 13.0, 10.7, 1.9 Hz, 1H), 5.43 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.16 (td, *J* = 9.6, 4.5 Hz, 1H), 4.87 (ddt, *J* = 11.2, 3.3, 1.6 Hz, 1H), 4.34 (ddd, *J* = 10.8, 4.8, 2.2 Hz, 1H), 4.26 (dt, *J* = 5.1, 2.1 Hz, 1H), 4.08 (t, *J* = 1.6 Hz, 1H), 4.01 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.00 – 3.92 (m, 2H), 3.78 (tt, *J* = 10.7, 4.7 Hz, 1H), 3.55 (tt, *J* = 11.3, 2.2 Hz, 1H), 3.48 (br s, 1H), 3.43 – 3.38 (m, 1H), 3.21 (br s, 1H), 2.43 – 2.30 (m, 4H), 2.18 (dddd, *J* = 16.3, 6.8, 4.7, 2.3 Hz, 1H), 1.90 – 1.83 (m, 2H), 1.79 (ddt, *J* = 15.8, 11.5, 1.6 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.67 – 1.62 (m, 1H), 1.59 (dd, *J* = 10.1, 2.5 Hz, 1H), 1.57 – 1.54 (m, 1H), 1.27 – 1.24 (m, 1H), 1.20 (dd, *J* = 4.0, 1.8 Hz, 1H), 1.17 (dd, *J* = 13.4, 2.0 Hz, 1H), 1.05 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 177.5, 140.2, 135.9, 135.9, 133.9, 133.4, 129.7, 129.7, 129.0, 127.6, 127.5, 127.1, 125.1, 81.5, 80.1, 79.1, 78.7, 74.9, 74.4, 74.1, 69.7, 68.2, 68.2, 44.1, 42.1, 41.9, 38.9, 36.5, 32.5, 32.5, 32.4, 29.5, 27.1, 25.8, 19.6, 19.4, 18.1, 14.4, −4.6, −4.6 ppm. IR (film): $\tilde{\nu}$ = 3374, 2956, 2929, 2856, 1759, 1471, 1461, 1427, 1375, 1362, 1332, 1259, 1203, 1107, 1069, 979, 856, 836, 801, 775, 737, 702 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 871.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{48}H_{72}O_9Si_2Na$: 871.4607; found: 871.4606.

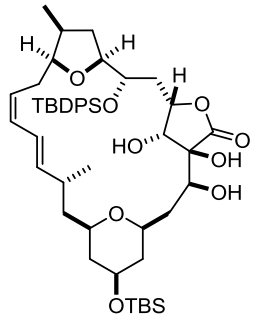


*Table 5.14:* $^{1}$H and $^{13}$C NMR data of 2,3,24-*epi*-deacylmandelalide D (**253**).

| atom n° | $^{1}$H NMR ($CD_3OD$, 600 MHz) | | | | | $^{13}$C NMR ($CD_3OD$, 600 MHz) δ /ppm |
|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | |
| 1 | - | - | | | - | 177.9 |
| 2 | - | - | | | - | 76.9 |
| 3 | 3.92 | m | - | 4ab, 5 | - | 73.3 |
| 4a | 1.74 | ddd | 14.9, 8.5, 2.3 | 3, 4b, 5 | 4b, 5, 6a | 38.0 |
| 4b | 1.96 | m | - | 3, 4a, 5 | 3, 4a | |
| 5 | 3.58 | dddd | 11.4, 10.0, 1.9, 1.8 | 4ab, 6ab | 3, 4a, 6b, 7, 9 | 74.2 |
| 6a | 1.19 | dt | 12.0, 11.3 | 5, 6b, 7 | 6b | 42.3 |
| 6b | 1.89 | ddt | 12.1, 4.2, 1.8 | 5, 6a, 7 | (4a), 6a, 5, 7 | |
| 7 | 3.78 | dddd | 11.0, 10.9, 4.8, 4.6 | 6ab, 8ab | 5, 6b, 8b, 9 | 68.8 |
| 8a | 1.11 | dt | 12.1, 11.3 | 7, 8b, 9 | 8b, (10a) | 42.9 |
| 8b | 1.88 | m | - | 7, 8a, 9 | 7, 8a, 9, (10b) | |
| 9 | 3.41 | ddt | 11.1, 10.1, 2.1 | 8ab, 10ab | 5, 7, 8b, 10a, (11), 25 | 74.2 |
| 10a | 1.35 | ddd | 13.7, 10.7, 2.9 | 10b, 11 | (8a), 10b, (11) | 45.3 |
| 10b | 1.54 | ddd | 13.8, 10.1, 3.8 | 10a, 11 | 8b, 9, 10a, 25 | |
| 11 | 2.52 | m | - | 10ab, 12, 25 | (9), (10b), 12, 13, 25 | 34.9 |
| 12 | 5.55 | dd | 15.2, 8.3 | 11, 13 | 3, (11), 14, 25 | 141.9 |
| 13 | 6.44 | ddt | 15.1, 10.8, 0.9 | 12, 14 | (10a), 11, 16b, (17), 25 | 126.2 |
| 14 | 5.98 | tq | 10.8, 0.7 | 13, 15 | 12, 15 | 131.6 |
| 15 | 5.33 | m | - | 14, 16ab | 14, 16a, 17, (26) | 127.9 |
| 16a | 2.16 | dddd | 15.1, 6.2, 4.3, 1.6 | 15, 16b, 17 | 15, 16b, 17, 26 | 31.8 |
| 16b | 2.38 | m | - | 15, 16a, 17 | 13, 16a, 17 | |
| 17 | 3.91 | m | - | - | - | 82.8* |
| 18 | 2.40 | m | - | 17, 19ab, 26 | 17, 19b, 26 | 37.9 |
| 19a | 1.51 | td | 12.4, 9.0 | 18, 19b, 20 | 19b, 20, (22ab), (26) | 35.1 |
| 19b | 2.05 | ddd | 12.4, 7.2, 6.3 | 18, 19a, 20 | 17, 18, 19a, 20 | |
| 20 | 3.90 | m | - | - | - | 83.0* |
| 21 | 3.91 | m | - | - | - | 75.3** |
| 22a | 1.95 | m | - | 21, 22b, 23 | 21, 22b, 23 | 36.3 |
| 22b | 1.96 | m | - | 21, 22a, 23 | 21, 22a | |
| 23 | 4.48 | ddd | 8.3, 6.0, 4.4 | 22ab, 24 | 22ab, 24 | 82.9 |
| 24 | 3.90 | m | - | - | - | 69.9** |
| 25 | 0.99 | d | 6.8 | 11 | 9, 10b, 11, 12 | 19.8 |
| 26 | 1.03 | d | 7.1 | 18 | 16ab, 19a | 15.3 |
| OH | not observed due to H/D exchange with $CD_3OD$ | | | | | |

*,**: Due to overlap in the spectra, these signals could not be assigned and appear arbitrary.

**2,3-*epi*-Deacylmandelalide D (255).** A teflon vial was charged with a solution of triol **254** (1.0 mg, 1.2 µmol) in THF (0.1 mL) and the mixture cooled to 0 °C. Pyridine (100 µL) and HF·pyr (100 µL) were added slowly via an Eppendorf pipette. After stirring for 5 min at 0 °C, the reaction mixture was allowed to warm to ambient temperature and stirred for further 41 h. The reaction was then quenched by pouring the mixture into pH 7.2 buffer ($NaH_2PO_4/Na_2HPO_4$, 5 mL) and the buffered aqueous phase was extracted with EtOAc/EtOH (9:1, 4 x 6 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH 93:7 to 92:8 to 91:9) to yield the desired pentaol as a white solid (0.5 mg, 86% yield). $[\propto]_D^{27}$ = +14 (c = 0.16, MeOH). $^1$H NMR (600 MHz, $CD_3OD$): see table 5.15. $^{13}$C NMR (150 MHz, $CD_3OD$): see table 5.15. IR (film): $\tilde{\nu}$ = 3357, 2956, 2922, 2853, 1758, 1665, 1632, 1609, 1510, 1458, 1408, 1376, 1249, 1205, 1102, 1086, 1046, 979, 707 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 519.3 (100 (M+Na)), 1016.37 (32 (2M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{26}H_{40}O_9Na$: 519.2565; found: 519.2563.

**Monobutyrate (2*R*,3*S*)-256.** Triol **254** (2.0 mg, 2.4 µmol) was dissolved in $CH_2Cl_2$ (0.2 mL) and the resulting solution cooled to 0 °C. Pyridine (4.8 µL, 59 µmol) was added via syringe followed by a solution of *n*-butyric anhydride (0.6 M in $CH_2Cl_2$, 8.6 µL, 5.2 µmol) and DMAP (1 crystal, ~0.1 mg). The ice bath was removed after 10 min and the reaction mixture was stirred for another 2 h at ambient temperature. The reaction was quenched by addition of sat. $NH_4Cl$ solution (5 mL) and the aqueous phase was extracted with EtOAc (4 x 4 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 12:1 to 9:1) to give the monobutyrate as a white amorphous solid (1.5 mg, 69% yield). $[\propto]_D^{20}$ = +26.2 (c = 0.31, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.66 – 7.61 (m, 4H), 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 4H), 6.30 (ddt, *J* = 15.2, 10.8, 1.1 Hz, 1H), 5.89 (t, *J* = 10.8 Hz, 1H), 5.48 (dd, *J* = 15.2, 7.3 Hz, 1H), 5.42 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.15 (td, *J* = 9.8, 4.7 Hz, 1H), 4.87 (br d, *J* = 10.7 Hz, 1H), 4.38 (br s, 1H), 4.35 (ddd, *J* =10.5, 4.7, 2.6 Hz, 1H), 4.00 (dd, *J* = 3.2, 2.2 Hz, 1H), 3.93 – 3.87 (m, 2H), 3.78 (tt, *J* = 10.4, 4.7 Hz, 1H), 3.70 (tt, *J* = 11.3, 1.7 Hz, 1H), 3.49 (dd, *J* = 11.6, 9.7 Hz, 1H), 2.89 (s, 1H), 2.53 – 2.45 (m, 1H), 2.41 (ddd, *J* = 16.0, 8.4, 6.8 Hz, 1H), 2.36 – 2.26 (m, 4H), 2.12 (dtd, *J* = 15.8, 5.1, 2.1 Hz, 1H), 2.02 (ddd, *J* = 16.3, 11.2, 2.8 Hz, 1H), 1.84 (dt, *J* = 12.6, 6.4 Hz, 1H), 1.78 (dt, *J* = 12.7, 2.6 Hz, 1H), 1.72 – 1.69 (m, 2H), 1.68 – 1.65 (m, 2H), 1.61 (ddd, *J* = 13.4, 10.0, 2.9 Hz, 1H), 1.55 (m, 1H), 1.28 – 1.24 (m, 1H), 1.22 – 1.18 (m, 1H), 1.20 – 1.12 (m, 2H), 1.04 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 173.1, 172.8, 140.6, 135.9, 135.9, 134.0, 133.6, 129.7, 129.6, 129.4, 127.6, 127.5, 127.1, 124.9, 81.5, 80.2, 78.8, 77.4, 75.2, 74.2, 73.7, 69.7, 69.3, 68.1, 43.9, 42.1, 41.8, 39.2, 36.3, 36.1, 32.6,

32.1, 32.1, 29.7, 29.5, 27.1, 25.8, 19.6, 19.2, 18.2, 18.1, 14.7, 13.7, −4.5, −4.6 ppm. IR (film): $\tilde{\nu}$ = 3380, 2956, 2928, 2856, 1782, 1743, 1462, 1428, 1376, 1362, 1257, 1177, 1110, 1070, 979, 858, 836, 776, 704 $cm^{-1}$. MS (ESIpos) *m/z* (%) = 941.6 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{52}H_{78}O_{10}Si_2Na$: 941.5026; found: 941.5022.

*Table 5.15:* $^{1}H$ and $^{13}C$ NMR data of 2,3-*epi*-deacylmandelalide D (**255**).

| atom n° | $^{1}H$ NMR ($CD_3OD$, 600 MHz) | | | | | $^{13}C$ NMR ($CD_3OD$, 600 MHz) | |
|---|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | δ /ppm | HMBC |
| 1 | - | - | | - | - | 178.9 | - |
| 2 | - | - | | - | - | 80.1 | - |
| 3 | 4.34 | dd | 6.6, 2.0 | 4ab | 4b, 5, 11, (24) | 69.5 | 1, 4, 5 |
| 4a | 1.70 | ddd | 15.3, 6.6, 2.0 | 3, 4b, 5 | (3), 4b, (5) | 40.4 | 3 |
| 4b | 1.90 | ddd | 15.4, 10.8, 2.0 | 3, 4a, 5 | 3, 4a, 24 | | 2, 5 |
| 5 | 3.64 | tt | 11.0, 1.8 | 4ab, 6ab | 3, 4a, 6b, 7, 9 | 75.2 | (4), 7 |
| 6a | 1.17 | m | - | 5, 6b, 7 | 6b | 42.5 | 4, 7, 8, (9) |
| 6b | 1.94 | ddt | 12.3, 4.4, 1.9 | 5, 6a, 7 | 5, 6a, 7 | | 7, 8 |
| 7 | 3.81 | tt | 11.0, 4.7 | 6ab, 8ab | 5, 6b, 8b, 9 | 68.6 | - |
| 8a | 1.15 | td | 11.6, 11.2 | 7, 8b, 9 | 8b, (10b) | 42.7 | 6, 7, 9, 10 |
| 8b | 1.85 | m | - | 7, 8a, 9 | 7, 8a, 9 | | 6, 7 |
| 9 | 3.50 | ddt | 11.2, 10.2, 1.8 | 8ab, 10ab | 5, 7, 8b (10a), (11), 25 | 74.8 | 7 |
| 10a | 1.28 | m | - | 9, 10b, 11 | (8b), (9), 10b, 25 | 45.2 | 11, 25 |
| 10b | 1.58 | ddd | 13.8, 10.3, 2.8 | 9, 10a, 11 | (8a), (11), 10a | | 9, 25 |
| 11 | 2.58 | m | - | 10ab, 12, 25 | 3, 10b, 13, 25 | 34.0 | (13) |
| 12 | 5.53 | dd | 15.1, 7.8 | 11, 13 | (11), 14, 25 | 141.9 | 10, 11, 14, 25 |
| 13 | 6.40 | ddt | 15.2, 11.1, 0.6 | 12, 14 | 11, 16b | 126.2 | 11, 14, 15 |
| 14 | 5.93 | tt | 10.9, 1.6 | 13, 15, (16ab) | 12, 15 | 130.8 | 12, 13, 16 |
| 15 | 5.23 | td | 9.8, 5.3 | 14, 16ab | 13, 16a, 17, 26 | 128.0 | 13, (16) |
| 16a | 2.27 | dtd | 15.8, 5.8, 2.1 | 15, 16b, 17 | (13), (15), 16a, (17), 26 | 33.1 | 14, 15, 17, 18 |
| 16b | 2.42 | dddd | 15.7, 9.1, 6.4, 1.6 | 15, 16a, 17 | 13, 16b, (17) | | 14, 15, 17 , (18) |
| 17 | 4.01 | td | 7.1, 6.2 | 16ab, 18 | 15, (16b), 18 | 83.4 | 15, 19, 20 |
| 18 | 2.47 | dqd | 7.1, 7.0, 3.9 | 17, 19ab, 26 | 17 ,19a, 26 | 38.4 | 16, 17, 19, 26 |
| 19a | 1.62 | m | - | 18, 19b, 20 | 17, 18, 19b, 20 | 34.1 | 17, 18, 20, 21, 26 |
| 19b | 2.00 | dt | 12.6, 6.6 | 18, 19a, 20 | 19a, (22b), 26 | | 17, 18, 20, 26 |
| 20 | 4.04 | ddd | 9.6, 6.3, 4.1 | 19ab, 21 | 17, 18, 19a, 21 | 83.0 | 22 |
| 21 | 3.95 | ddd | 11.0, 4.1, 2.2 | 20, 22ab | 20, 22a, 23 | 69.3 | 19 |
| 22a | 2.22 | ddd | 14.7, 8.7, 2.2 | 21, 22b, 23 | 21, 22b, (23) | 31.5 | 23, 24 |
| 22b | 1.85 | m | - | 21, 22a, 23 | 22a, 23 | | 21 |
| 23 | 4.95 | ddd | 8.7, 4.9, 3.6 | 22ab, 24 | 21, 22ab, 24 | 80.8 | (1) |
| 24 | 4.14 | d | 3.6 | 23 | (3), 4b, 23 | 77.1 | 1, 2, 23 |
| 25 | 1.00 | d | 6.7 | 11 | 9, 10a, 11, 12 | 20.0 | 10, 11, 12 |
| 26 | 1.04 | d | 7.0 | 18 | (15), 16(a)b, 18, 19b | 14.9 | 17, 18, 19 |
| OH | not observed due to H/D exchange with $CD_3OD$ | | | | | | |

**2,3-*epi*-Mandelalide C (257).** A teflon vial was charged with a solution of mono-butyrate **256** (1.5 mg, 1.6 µmol) in THF (0.15 mL). Pyridine (0.15 mL) was added and the reaction mixture was cooled to 0 °C. HF·pyr (0.15 mL) was added carefully and the ice bath was removed 5 min after the addition. The reaction mixture was stirred for 25 h before the reaction was quenched with EtOAc (3 mL) and pH 7.2 buffer ($NaH_2PO_4/Na_2HPO_4$, 5 mL). The aqueous phase was extracted with EtOAc/EtOH (9:1, 3 x 4 mL), the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH 97:3 to 96:4 to 95:5) to give a white amorphous solid (0.72 mg, 78% yield). $[\propto]_D^{20}$ = −19 (c = 0.14, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): see table 5.16. $^{13}$C NMR (150 MHz, $CDCl_3$): see table 5.16. IR (film): $\tilde{\nu}$ = 3377, 2961, 2930, 2875, 1775, 1737, 1455, 1413, 1367, 1329, 1262, 1179, 1102, 1057, 979, 947, 733 cm$^{-1}$. MS (ESIpos) *m/z* (%) = 589.4 (100 (M+Na)). HRMS (ESIpos): *m/z*: calcd for $C_{30}H_{46}O_{10}Na$: 589.2983; found: 589.2978.

*Table 5.16:* $^{1}$H and $^{13}$C NMR data for 2,3-*epi*-mandelalide C (**257**).

| atom n° | $^{1}$H NMR ($CDCl_3$, 600 MHz) | | | | | $^{13}$C NMR ($CDCl_3$, 150 MHz) δ /ppm |
|---|---|---|---|---|---|---|
| | δ /ppm | m | *J* /Hz | COSY | NOESY | |
| 1 | - | - | - | - | - | 172.5 |
| 2 | - | - | - | - | - | 78.3 |
| 3 | 5.51 | dd | 4.8, 4.8 | 4ab | 4a, 5, 11, (24), 28a OHd | 69.3 |
| 4a | 1.73 | ddd | 16.2, 4.6, 1.6 | 3, 4b, 5 | 3, 4b, 5, 6b | 38.6 |
| 4b | 2.11 | m | - | 3, 4a, 5 | 4a, (6b) | |
| 5 | 3.74 | dddd | 11.0, 11.0, 1.9, 1.7 | 4ab, 6ab | 6b, 7, 9 | 73.5 |
| 6a | 1.23 | ddd | 12.3, 11.7, 11.6 | 5, 6b, 7 | - | 41.2 |
| 6b | 1.93 | m | - | 6a | 4a(b), 5, 7 | |
| 7 | 3.85 | dddd | 11.0, 11.0, 4.8, 4.8 | 6ab, 8ab | 5, 6b, 8b, 9 | 67.5 |
| 8a | 1.33 | ddd | 12.6, 11.3, 11.3 | 7, 8b, 9 | - | 40.8 |
| 8b | 1.94 | m | - | 8a | 7, 9 | |
| 9 | 3.50 | m | - | 8ab, 10ab | 5, 7, 8b, 10ab, 12, (25) | 74.5 |
| 10a | 1.33 | ddd | 14.0, 9.9, 4.0 | 9, 10b, 11 | (8a), 9, 10b, (11), 25 | 42.6 |
| 10b | 1.71 | m | - | 9, 10a, 11 | 8b, 9, 10a, 11, 12, 24, 25, OHd | |
| 11 | 2.46 | m | - | 10ab, 12, 13 | 9, 10a, 11, 12, 13, (24), OHd | 30.6 |
| 12 | 5.72 | dd | 15.5, 5.2 | 11, 13 | 9, (10ab), 11, 14, 25 | 140.6 |
| 13 | 6.26 | dddd | 15.6, 10.7, 1.2, 1.1 | 11, 12, 14 | 10a, 11, 16a, 21, 25, OHc | 123.3 |
| 14 | 6.06 | dd | 10.7, 10.7 | 13, 15, 16ab | 12, 15 | 130.9 |
| 15 | 5.31 | ddd | 11.0, 5.0, 5.0 | 14, 16ab | 14, 16b, 17 | 127.3 |
| 16a | 1.98 | ddt | 14.0, 4.7, 2.1 | 14, 15, 16b, 17 | 15, 16b, 17, 18, 26 | 30.4 |
| 16b | 2.39 | m | - | 14, 15, 16a, 17 | 13, 16a, 21 | |
| 17 | 3.95 | ddd | 10.6, 7.2, 1.9 | 16ab, 18 | 16b, 18, 26 | 81.7 |
| 18 | 2.41 | m | - | 17, 19ab, 26 | 17, 19a, 20, 26 | 36.5 |
| 19a | 1.54 | m | - | 18, 19b, 20 | 18, 19b, 22b, 26 | 35.7 |
| 19b | 2.10 | m | - | 18, 19a, 20 | 18, 19a, 20, (21), 26 | |
| 20 | 3.80 | ddd | 8.5, 7.3, 3.6 | 19ab, 21 | 9, 17, 18, 19a, 22a | 81.1 |
| 21 | 3.46 | m | - | 20, 22ab, OHc | 13, 16a, (19a), 20, 23, 24 | 70.6 |
| 22a | 1.93 | m | - | 21, 22b, 23 | - | 31.7 |
| 22b | 2.24 | ddd | 14.1, 11.3, 11.3 | 21, 22a, 23 | 20, 22a, 23, 24, OHc, OHd | |
| 23 | 4.74 | ddd | 11.3, 4.3, 3.2 | 22ab, 24 | 21, 24 | 80.0 |
| 24 | 4.21 | dd | 3.1, 2.1 | 23, OHd | (3), 4a, 5, 23, OHa, OHc, OHd | 74.3 |
| 25 | 1.05 | d | 7.0 | 11 | 9, 10(a)b, 11, 12, 13 | 20.2 |
| 26 | 1.02 | d | 6.8 | 18 | 16a, 17, 18, 19ab | 14.8 |
| 27 | - | - | - | - | - | 172.9 |
| 28a | 2.42 | ddd | 15.9, 8.2, 6.8 | 28b, 29ab | 28b, 30 | 36.0 |
| 28b | 2.33 | ddd | 16.0, 8.1, 6.9 | 28a, 29ab | 28a, 30 | |
| 29 | 1.68 | m | - | 28ab, 30 | - | 18.2 |
| 30 | 0.94 | t | 7.4 | 29 | 28ab | 13.7 |
| OHa | 3.42 | br s | - | - | OH d | - |
| OHb | 1.56 | m | - | - | - | - |
| OHc | 2.87 | d | 6.6 | 21 | 13, 24 | - |
| OHd | 4.81 | d | 2.1 | (23), 24 | 3, 4b, 5, 10b, 11, 22a, 24 | - |

**(*E*)-3-((*Z*)-Hept-4-en-1-ylidene)dihydrofuran-2(3H)-one ((*E*)-261).** LiHMDS (475 mg, 2.83 mmol) was dissolved in THF (6 mL) and the solution cooled to −78 °C before a solution of γ-butyrolactone (**259**) (200 µL, 2.60 mmol) in THF (2.4 mL) was introduced via canula. The resulting yellow mixture was stirred for 30 min at −78 °C before a solution of *cis*-4-heptenal (**260**) (313 µL, 2.37 mmol) in THF (3.8 mL) was added via canula. The reaction mixture was allowed to stir for 1 h at −78 °C, when triethylamine (494 µL, 3.54 mmol) and methanesulfonyl chloride (0.238 mL, 3.07 mmol) were added via syringe. The reaction mixture was allowed to warm to ambient temperature and stirred for further 2 h. It was then cooled to 0 °C and DBU (530 µL, 3.54 mmol) was added via syringe. The cooling bath was removed after 5 min and the reaction mixture stirred for another 1 h at ambient temperature. The reaction was quenched by pouring the mixture into sat. $NaHCO_3$ solution (20 mL). After dilution with $Et_2O$ (15 mL), the organic phase was washed with sat. $NaHCO_3$ solution (15 mL) and the combined aqueous washings were re-extracted with $Et_2O$ (2 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (pentane/$Et_2O$ 4:1 to 3.5:1 to 3:1) to yield the major (*E*)-isomer (246 mg, 58%) as a pale yellow oil along with the minor (*Z*)-isomer (40 mg, 9%).$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.71 (ttd, *J* = 7.4, 2.9, 0.9 Hz, 1H), 5.44 – 5.36 (m, 1H), 5.27 (dtt, *J* = 10.6, 7.1, 1.6 Hz, 1H), 4.37 – 4.32 (m, 2H), 2.84 (tdd, *J* = 7.4, 3.0, 1.5 Hz, 2H), 2.26 – 2.15 (m, 4H), 2.06 – 1.95 (m, 2H), 0.93 (td, *J* = 7.5, 0.6 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 171.2, 140.2, 133.3, 126.9, 125.5, 65.3, 30.4, 25.6, 25.1, 20.5, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3005, 2963, 2932, 2873, 1746, 1679, 1440, 1378, 1352, 1306, 1282, 1217, 1197, 1177, 1139, 1028, 961, 868, 719, 614 cm$^{-1}$. MS (EI) *m/z* (%) = 112 (100), 91 (4), 83 (11), 79 (6), 77 (5), 69 (21), 67 (22), 41 (32). HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{16}O_2Na$: 203.1042; found: 203.1042.

**(*Z*)-3-((*Z*)-Hept-4-en-1-ylidene)dihydrofuran-2(3H)-one ((*Z*)-261).** Obtained as the minor isomer from the reaction described above. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.20 (tt, *J* = 7.7, 2.4 Hz, 1H), 5.43 – 5.35 (m, 1H), 5.34 – 5.26 (m, 1H), 4.28 (t, *J* = 7.4 Hz, 2H), 2.88 (tq, *J* = 7.4, 2.1 Hz, 2H), 2.75 (qt, *J* = 7.5, 2.0 Hz, 2H), 2.15 (qd, *J* = 7.3, 1.4 Hz, 2H), 2.05 – 1.96 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.1, 143.4, 132.7, 127.5, 123.7, 65.3, 29.1, 27.4, 26.5, 20.5, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3005, 2963, 2931, 2872, 1747, 1671, 1443, 1374, 1221, 1168, 1126, 1077, 1025, 958, 867, 866, 798, 756, 717 cm$^{-1}$. MS (EI) *m/z* (%) = 180 (6), 151 (8), 125 (5), 123 (9), 113 (7), 112 (100), 95 (10), 91 (15), 83 (15), 79 (20), 77 (11), 69 (16), 67 (37), 53 (14), 41 (34), 39 (13). HRMS (ESIpos): *m/z*: calcd for $C_{11}H_{16}O_2Na$: 203.1042; found: 203.1043.

**Diol 262.** A solution of diene (*E*)-**261** (10.0 mg, 55.5 µmol) was dissolved in $CH_2Cl_2$ (1.1 mL) and cooled to −78 °C. TMEDA (9.6 µL, 63.8 µmol) was added via syringe and the reaction mixture was equilibrated at −78 °C for 5 min. A solution of $OsO_4$ (0.6 M in $CH_2Cl_2$, 105 µL, 62.7 µmol) was then added dropwise until no more SM was detected by TLC analysis (after every three drops (~8-10 µL), the reaction mixture was controlled by TLC). Upon complete consumption of the s.m., all volatiles were removed under reduced pressure and the composition of the residue controlled by $^1$H NMR analysis (see below). The residue was redissolved in THF (0.7 mL) and treated with sat. $NaHSO_3$ (0.7 mL) under vigorous stirring for 16 h. For work up, brine (5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 3:2 to 1:1) to yield the desired diol as a colorless oil (8.5 mg, 72% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.46 – 5.37 (m, 1H), 5.28 (dddt, *J* = 10.9, 8.2, 6.8, 1.5 Hz, 1H), 4.44 (td, *J* = 8.8, 6.8 Hz, 1H), 4.32 (ddd, *J* = 9.0, 8.1, 3.4 Hz, 1H), 3.74 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.45 (br s, 1H), 3.38 (br s, 1H), 2.29 – 2.13 (m, 4H), 2.09 – 1.98 (m, 2H), 1.68 (dddd, *J* = 13.9, 10.6, 7.8, 5.4 Hz, 1H), 1.34 (dtd, *J* = 13.9, 8.2, 2.3 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 178.7, 133.1, 127.6, 75.1, 72.9, 66.3, 32.0, 29.6, 23.0, 20.5, 14.3 ppm. IR (film): $\tilde{\nu}$ = 3446, 3004, 2962, 2932, 2873, 1758, 1455, 1381, 1307, 1202, 1155, 1119, 1082, 1023, 984, 953, 690 cm$^{-1}$. MS (EI) *m/z* (%) = 196 (2), 178 (7), 123 (10), 115 (36), 109 (13), 102 (100), 95 (45), 83 (23), 67 (62), 56 (64), 55 (51), 41 (52). HRMS (ESIpos): *m/z*: calcd for $C_{13}H_{20}O_7Na$: 237.1097; found: 237.1097.

Four compounds were contained in the crude product, they were assigned to the following compounds on the basis of $^1$H NMR and ESI-MS.

ratio 8.0 : 1.0 : 0.4 : 0.2

# 6 List of abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | azobisisobutyronitrile |
| aq. | aqueous |
| Ar | aryl |
| BBN | 9-Borabicyclo(3.3.1)nonane |
| Bn | benzyl |
| br | broad |
| Bu | butyl |
| Bz | benzoyl |
| calcd | calculated |
| cm | centimeter |
| cod | cyclooctadienyl |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| d.r. | diastereomeric ratio |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| dd | doublet |
| DIBAl-H | diisobutylalumnium hydride |
| DMA | dimethylacetamide |
| DMAP | *N*,*N*-dimethyl 4-aminopyridine |
| DMF | dimethylformamide |
| DMP | Dess-Martin Periodinane |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone |
| DMS | dimethyl sulfide |
| DMSO | dimethylsulfoxide |
| EDCI | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| EDTA | ethylenediaminetetraacetic acid |
| *ee* | enantiomeric excess |
| *ent* | enantiomeric |
| *epi* | epimeric |
| Et | ethyl |
| g | gram |
| $GI_{50}$ | growth inhibition of 50% |
| h | hour |
| hep | heptet |
| HFIP | hexafluoroisopropanol |
| HMPA | hexamethylphosphoramide |
| HPLC | high pressure liquid chromatography |
| *i* | *iso* (branched) |
| $IC_{50}$ | half maximal inhibitory concentration |
| IR | infrared spectroscopy |

| | |
|---|---|
| KHMDS | potassium hexamethyldisilazide |
| l | liter |
| l.l.s. | longest linear sequence |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium hexamethyldisilazide |
| M | molar (mol/L) |
| m | multiplet |
| MBH | Morita Baylis-Hillman |
| Me | methyl |
| Mes | mesityl |
| mg | miligram |
| MIDA | *N*-methyliminodiacetic acid |
| min | minute |
| mL | mililiter |
| MOM | methoxy methyl |
| mp. | melting point |
| Ms | methanesulfonyl |
| MTBE | *tert*-butylmethylether |
| *n* | *normal* (linear) |
| n | normal (mol/kg) |
| µg | microgram |
| µL | microliter |
| NaHMDS | sodium hexamethyldisilazide |
| n.d. | not determined |
| NHC | *N*-heterocyclic carbene |
| NMI | *N*-Methylimidazole |
| NMR | nuclear magnetic resonance |
| 4-$NO_2$-Bz | 4-nitrobenzoyl |
| NOE | nuclear overhauser effect |
| NOESY | nuclear overhauser effect spectroscopy |
| *N*-PSP | *N*-(phenylseleno)phthalimide |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| pin | pinacol |
| PG | Protecting group |
| PMB | *para*-methoxybenzyl |
| Pr | propyl |
| q | quartet |
| quant | quantitative |
| r.r. | regioisomeric ratio |
| rac | racemic |
| RCAM | ring closing alkyne metathesis |
| RCM | ring closing (olefin) metathesis |
| ROESY | rotating frame nuclear overhauser effect spectroscopy |
| rt | room temperature |
| s | singlet |
| s.m. | starting material |

| | |
|---|---|
| sat. | saturated |
| t | triplet |
| TASF | tris(dimethylamino)sulfonium difluorotrimethylsilicate |
| 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 | trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Tol | *ortho*-tolyl |
| Ts | toluenesulfonyl |
| w/o | with or without |

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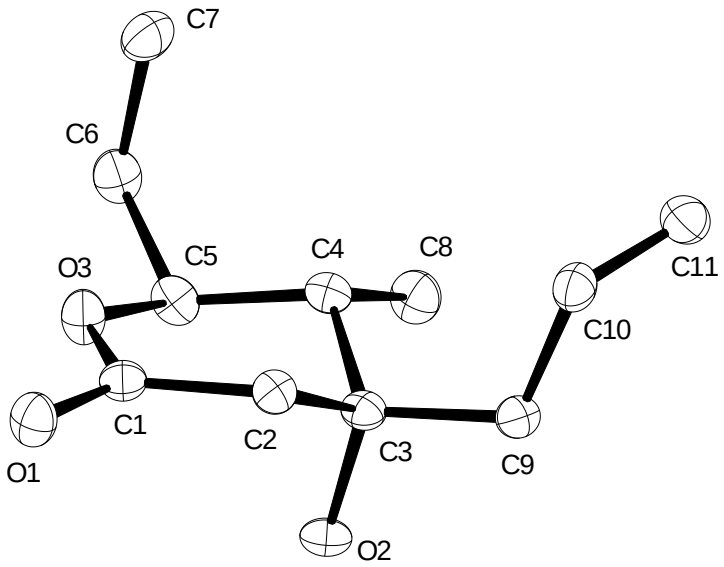
[245] Optimal results were obtained, when all solvents used during the preparation of Zn(Cu/Ag) couple were degassed prior to use.
[246] The configuration of the stereogenic center of the propgargylic alcohol was assigned by comparison with the result of a Carreira alkynylation (D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806) using (+)-*N*-methyl ephedrine, $Zn(OTf)_2$ and triethylamine. This alkynylation gave almost exclusively the alcohol, that was also the major diastereomer of the addition of lithiated alkyne. Although the overall yield was higher (72%), partial epimerization at the α-position of the aldehyde was observed.
[247] Due to the volatility of the catalyst, a higher vacuum should be avoided.
[248] A solution of NaOMe was prepared by adding an equimolar amount of MeOH to a suspension of NaH in THF at 0 °C, which was allowed to stir at room-temperature until gas evolution had ceased (~1 h).

[249] Obtained from Sigma Aldrich as an unspecified mixture of $NaHSO_3$ and $Na_2S_2O_5$. On this model system, use of sat. aq. $Na_2S_2O_5$ gave comparable results. It is presumed, that $NaHSO_3$ is formed from $Na_2S_2O_5$ upon contact with water.

# 8. Appendix

## 8.1 Crystallographic data

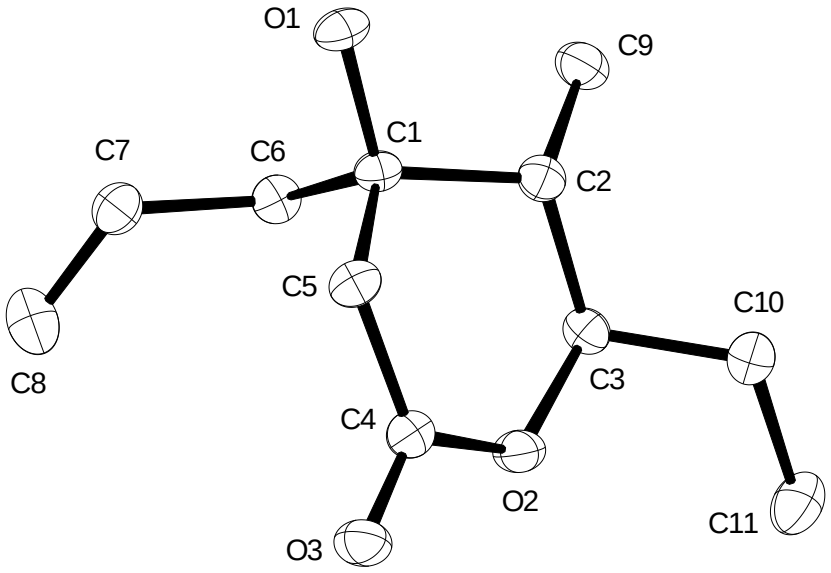
**Compound *epi-70***




| | | |
|---|---|---|
| Identification code (intern) | 7700 | |
| Empirical formula | $C_{11}H_{18}O_3$ | |
| Color | colourless | |
| Formula weight | 198.25 $g \cdot mol^{-1}$ | |
| Temperature | 100 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | MONOCLINIC | |
| Space group | **$P2_1$, (no. 4)** | |
| Unit cell dimensions | a = 9.1535(5) Å | α= 90°. |
| | b = 5.5655(3) Å | β= 103.613(2)°. |
| | c = 11.1241(6) Å | γ = 90°. |
| Volume | 550.78(5) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.195 $Mg \cdot m^{-3}$ | |
| Absorption coefficient | 0.695 $mm^{-1}$ | |
| F(000) | 216 e | |
| Crystal size | 0.30 x 0.11 x 0.07 $mm^3$ | |
| θ range for data collection | 4.09 to 67.00°. | |
| Index ranges | $-10 \le h \le 10$, $-6 \le k \le 6$, $-13 \le l \le 13$ | |
| Reflections collected | 12661 | |
| Independent reflections | 1825 [$R_{int}$ = 0.0418] | |
| Reflections with I>2σ(I) | 1780 | |
| Completeness to θ = 67.00° | 99.6 % | |

| | | |
|---|---|---|
| Absorption correction | Gaussian | |
| Max. and min. transmission | 0.96 and 0.86 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1825 / 1 / 138 | |
| Goodness-of-fit on $F^2$ | 1.096 | |
| Final R indices [I>2σ(I)] | $R_1$ = 0.0269 | $wR^2$ = 0.0648 |
| R indices (all data) | $R_1$ = 0.0276 | $wR^2$ = 0.0655 |
| Absolute structure parameter | 0.01(17) | |
| Largest diff. peak and hole | 0.116 and -0.158 e · $Å^{-3}$ | |

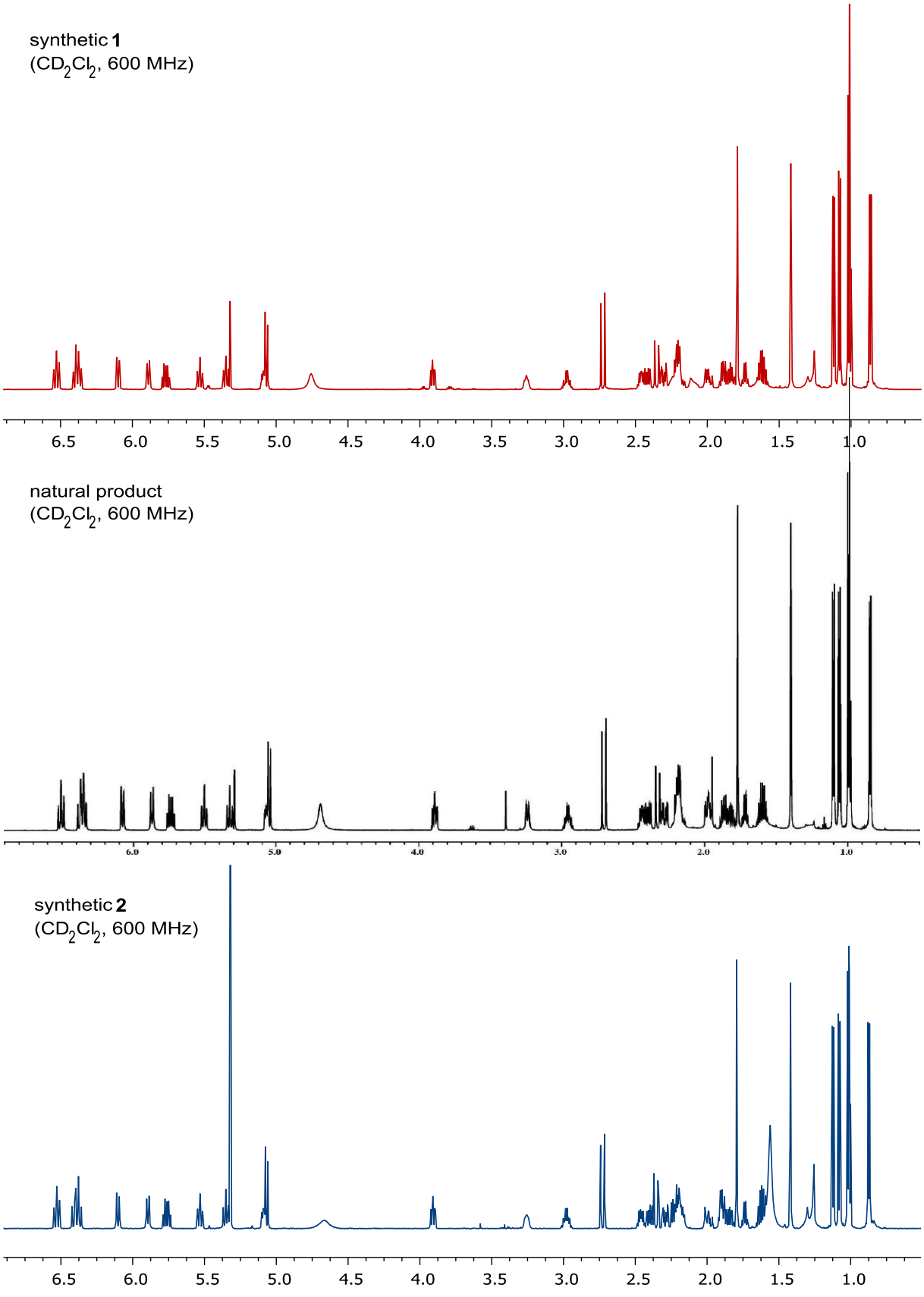
**Compound *ent-70***




| | | |
|---|---|---|
| Identification code (intern) | 7868 | |
| Empirical formula | $C_{11}H_{18}O_3$ | |
| Color | colourless | |
| Formula weight | 198.25 g · $mol^{-1}$ | |
| Temperature | 100 K | |
| Wavelength | 1.54184 Å | |
| Crystal system | MONOCLINIC | |
| Space group | **$P2_1$, (no. 4)** | |
| Unit cell dimensions | a = 7.1017(4) Å | α= 90°. |
| | b = 10.4344(5) Å | β= 113.6280(10)°. |
| | c = 8.2612(4) Å | γ = 90°. |
| Volume | 560.85(5) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.174 Mg · $m^{-3}$ | |

| | | |
|---|---|---|
| Absorption coefficient | 0.682 $mm^{-1}$ | |
| F(000) | 216 e | |
| Crystal size | 0.64 x 0.05 x 0.04 $mm^3$ | |
| θ range for data collection | 5.85 to 66.96°. | |
| Index ranges | $-8 \leq h \leq 8$, $-12 \leq k \leq 11$, $-9 \leq l \leq 9$ | |
| Reflections collected | 12794 | |
| Independent reflections | 1858 [$R_{int}$ = 0.0464] | |
| Reflections with I>2σ(I) | 1831 | |
| Completeness to θ = 66.96° | 99.1 % | |
| Absorption correction | Gaussian | |
| Max. and min. transmission | 0.98 and 0.80 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1858 / 1 / 131 | |
| Goodness-of-fit on $F^2$ | 1.038 | |
| Final R indices [I>2σ(I)] | $R_1$ = 0.0307 | $wR^2$ = 0.0833 |
| R indices (all data) | $R_1$ = 0.0311 | $wR^2$ = 0.0836 |
| Absolute structure parameter | -0.10(17) | |
| Extinction coefficient | 0.0086(19) | |
| Largest diff. peak and hole | 0.169 and -0.165 e · $Å^{-3}$ | |

## 8.2 Comparison of synthetic and natural leiodermatolide



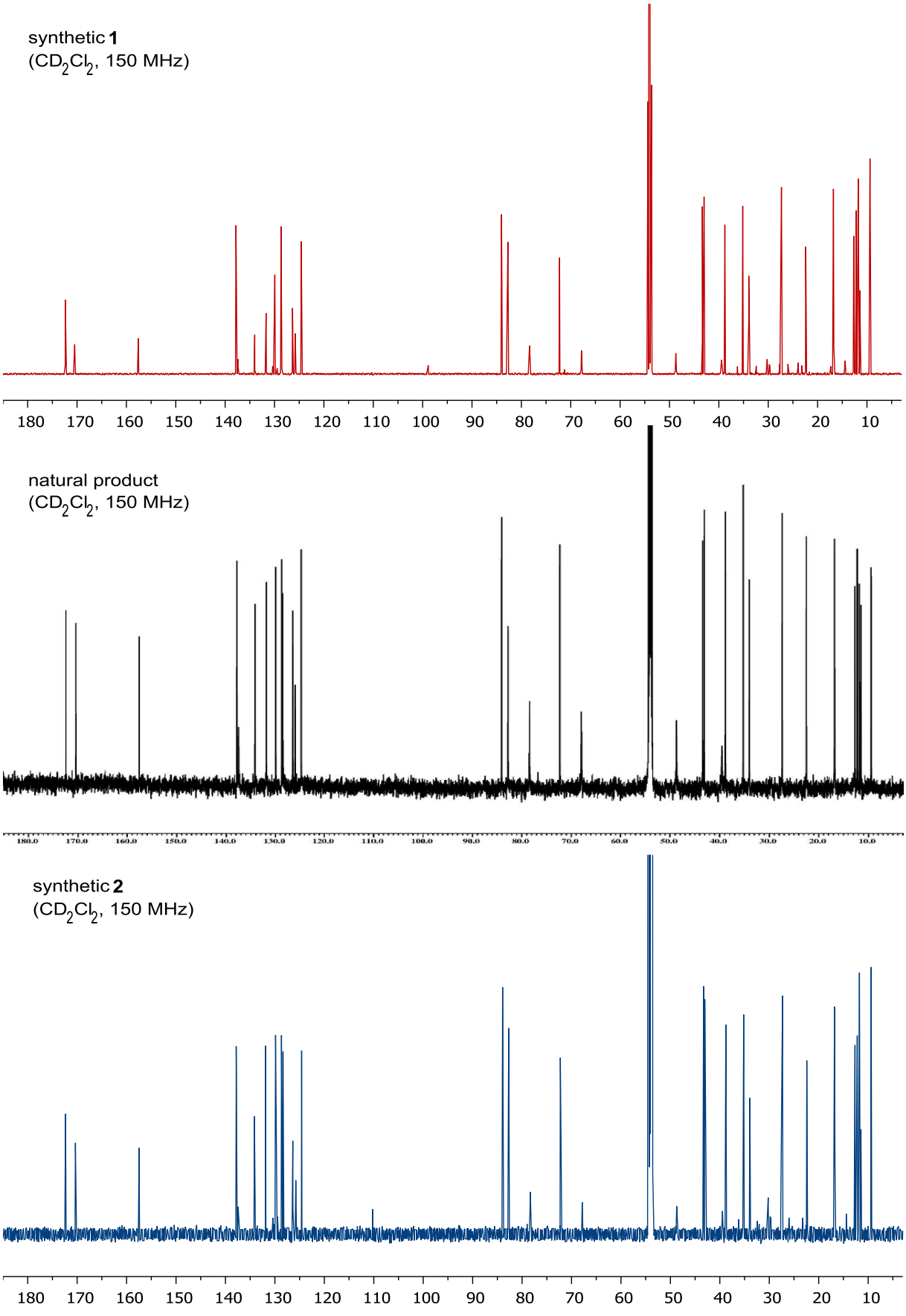

synthetic **1**
($CD_2Cl_2$, 150 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
natural product
($CD_2Cl_2$, 150 MHz)
synthetic **2**
($CD_2Cl_2$, 150 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

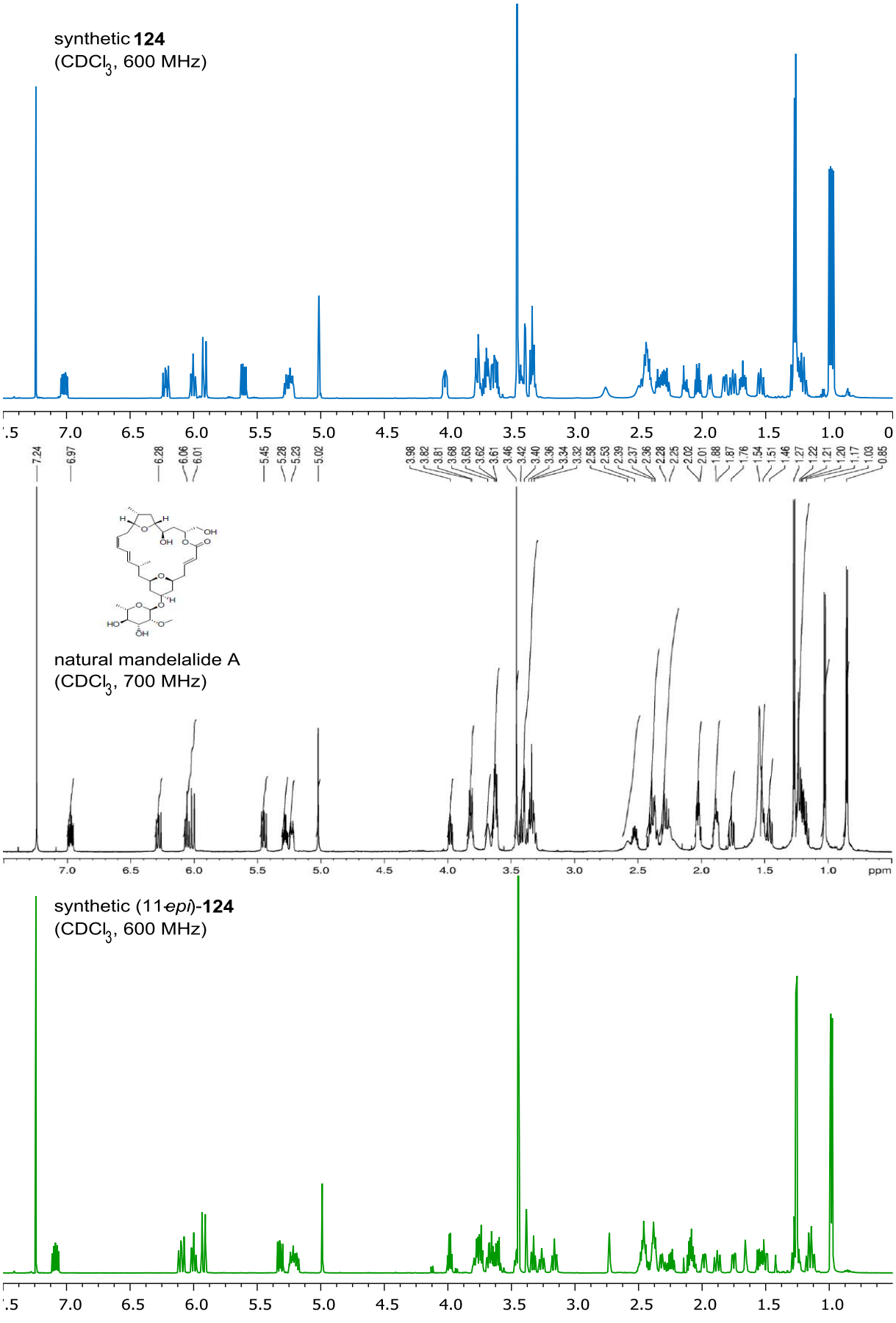
*Table 8.1:* Comparison of the $^{1}$H NMR shifts (600 MHz, $CD_2Cl_2$) of natural leiotermatolide (Lit.)[31] and the synthetic samples **1** and **2**. For this comparison, the spectra of the synthetic samples were calibrated on $CD_2Cl_2$ $\delta_H \equiv 5.29$ ppm; if the spectra are calibrated on $CD_2Cl_2$ $\delta_H \equiv 5.32$ ppm, all shifts systematically deviate by −0.3 ppm.

| **atom n°** | **δ (Lit.) /ppm** | **δ (synthetic 1) /ppm** | **Δδ (Lit-1)** | **δ (synthetic 2) /ppm** | **Δδ (Lit-1)** |
|---|---|---|---|---|---|
| 1 | - | - | | - | |
| 2a | 2.28 | 2.28 | 0.00 | 2.26 | 0.02 |
| 2b | 1.97 | 1.96 | 0.01 | 1.96 | 0.01 |
| 3 | 2.18 | 2.17 | 0.01 | 2.17 | 0.01 |
| 4 | 5.07 | 5.06 | 0.01 | 5.06 | 0.01 |
| 5 | - | - | - | - | - |
| 6 | 2.44 | 2.43 | 0.01 | 2.44 | 0.00 |
| 7 | 3.24 | 3.23 | 0.01 | 3.23 | 0.01 |
| 8 | 1.72 | 1.71 | 0.01 | 1.71 | 0.01 |
| 9 | 5.86 | 5.86 | 0.00 | 5.86 | 0.00 |
| 10 | 5.5 | 5.5 | 0.00 | 5.5 | 0.00 |
| 11 | 6.35 | 6.35 | 0.00 | 6.35 | 0.00 |
| 12 | 6.51 | 6.5 | 0.01 | 6.5 | 0.01 |
| 13 | 5.33 | 5.32 | 0.01 | 5.32 | 0.01 |
| 14 | 2.95 | 2.95 | 0.00 | 2.95 | 0.00 |
| 15 | 5.04 | 5.04 | 0.00 | 5.04 | 0.00 |
| 16 | - | - | - | - | - |
| 17 | 6.07 | 6.07 | 0.00 | 6.07 | 0.00 |
| 18 | 6.36 | 6.37 | -0.01 | 6.37 | -0.01 |
| 19 | 5.73 | 5.73 | 0.00 | 5.73 | 0.00 |
| 20a | 2.39 | 2.38 | 0.01 | 2.37 | 0.02 |
| 20b | 2.19 | 2.19 | 0 | 2.2 | -0.01 |
| 21 | - | - | - | - | - |
| 22 | 1.86 | 1.86 | 0 | 1.86 | 0.00 |
| 23 | 3.89 | 3.88 | 0.01 | 3.88 | 0.01 |
| 24a | 1.82 | 1.82 | 0.00 | 1.82 | 0.00 |
| 24b | 1.61 | 1.59 | 0.02 | 1.59 | 0.02 |
| 25 | 0.98 | 0.98 | 0.00 | 0.98 | 0.00 |
| 26 | 1.39 | - | - | - | - |
| 27 | 1.09 | 1.09 | 0.00 | 1.09 | 0.00 |
| 28 | 1.05 | 1.05 | 0.00 | 1.05 | 0.00 |
| 29 | 0.84 | 0.84 | 0.00 | 0.84 | 0.00 |
| 30 | 1.76 | 1.76 | 0.00 | 1.76 | 0.00 |
| 31 | 0.99 | 0.99 | 0.00 | 0.99 | 0.00 |
| 32a | 2.7 | 2.69 | 0.01 | 2.7 | 0.00 |
| 32b | 2.33 | 2.32 | 0.01 | 2.33 | 0.00 |
| 33 | - | - | - | - | - |
| 34 | - | - | - | - | - |
| $NH_2$ | 4.62 | 4.63 | -0.01 | 4.64 | -0.02 |

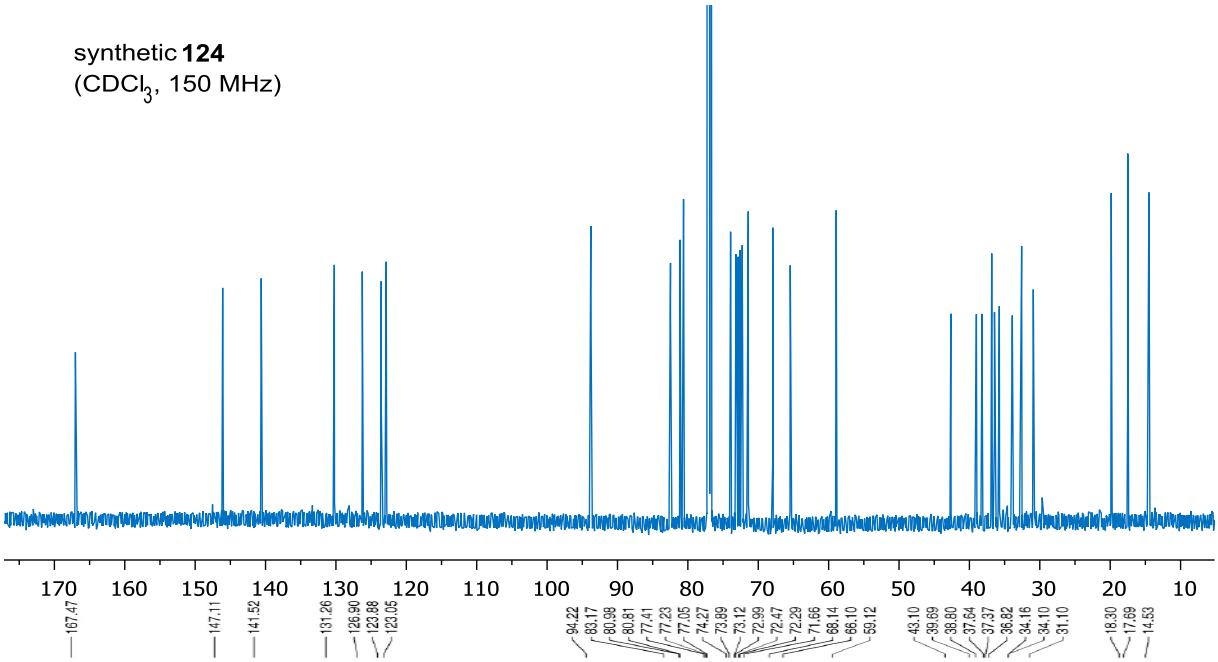
*Table 8.2:* Comparison of the $^{13}C$ NMR shifts (150 MHz, $CD_2Cl_2$) of natural leiotermatolide (Lit.)[31] and the synthetic samples **1** and **2**. For this particular comparison, the spectra of the synthetic samples were calibrated on the well resolved signal C.13 (≡ 137.869 ppm); if the spectra are calibrated on $CD_2Cl_2$ $\delta_C \equiv 53.8$ ppm, all shifts systematically deviate by +0.25 ppm.

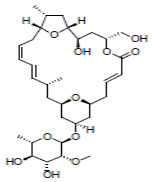
| **atom n°** | **δ (Lit.) /ppm** | **δ (synthetic 1) /ppm** | **Δδ (Lit-1)** | **δ (synthetic 2) /ppm** | **Δδ (Lit-1)** |
|---|---|---|---|---|---|
| 1 | 172.4 | 172.4 | 0.0 | 172.4 | 0.0 |
| 2 | 34.0 | 34.0 | 0.0 | 34.0 | 0.0 |
| 3 | 22.5 | 22.5 | 0.0 | 22.4 | 0.1 |
| 4 | 125.9 | 125.9 | 0.0 | 125.8 | 0.1 |
| 5 | 137.5 | 137.5 | 0.0 | 137.5 | 0.0 |
| 6 | 48.7 | 48.8 | −0.1 | 48.7 | 0.0 |
| 7 | 78.4 | 78.4 | 0.0 | 78.4 | 0.0 |
| 8 | 39.6 | 39.5 | 0.1 | 39.5 | 0.1 |
| 9 | 68.0 | 67.9 | 0.1 | 67.9 | 0.1 |
| 10 | 128.8 | 128.7 | 0.1 | 128.7 | 0.1 |
| 11 | 126.4 | 126.4 | 0.0 | 126.4 | 0.0 |
| 12 | 124.7 | 124.6 | 0.1 | 124.6 | 0.1 |
| 13 | 137.9 | 137.9 | 0.0 | 137.9 | 0.0 |
| 14 | 35.3 | 35.2 | −0.1 | 35.2 | 0.0 |
| 15 | 82.8 | 82.8 | 0.0 | 82.7 | 0.1 |
| 16 | 134.2 | 134.1 | 0.1 | 134.2 | 0.1 |
| 17 | 130.0 | 130.0 | 0.0 | 129.9 | 0.1 |
| 18 | 131.8 | 131.8 | 0.0 | 131.9 | −0.1 |
| 19 | 128.5 | 128.6 | −0.1 | 128.7 | −0.2 |
| 20 | 38.9 | 38.8 | 0.1 | 38.8 | 0.1 |
| 21 | 72.3 | 72.3 | 0.0 | 72.3 | 0.0 |
| 22 | 43.4 | 43.4 | 0.0 | 43.3 | 0.0 |
| 23 | 84.1 | 84.1 | 0.0 | 84.0 | 0.1 |
| 24 | 27.4 | 27.4 | 0.0 | 27.3 | 0.1 |
| 25 | 9.4 | 9.4 | 0.0 | 9.4 | 0.0 |
| 26 | 11.5 | 11.5 | 0.0 | 11.5 | 0.0 |
| 27 | 16.8 | 16.8 | 0.0 | 16.7 | 0.1 |
| 28 | 12.7 | 12.7 | 0.0 | 12.7 | 0.0 |
| 29 | 16.8 | 16.8 | 0.0 | 16.8 | 0.0 |
| 30 | 12.2 | 12.2 | 0.0 | 12.2 | 0.0 |
| 31 | 11.8 | 11.8 | 0.0 | 11.8 | 0.0 |
| 32 | 43.1 | 43.0 | 0.1 | 43.1 | 0.0 |
| 33 | 170.4 | 170.5 | −0.1 | 170.4 | 0.0 |
| 34 | 157.6 | 157.6 | 0.0 | 157.5 | 0.1 |

## 8.3 Comparison of synthetic isomers and natural mandelalide A

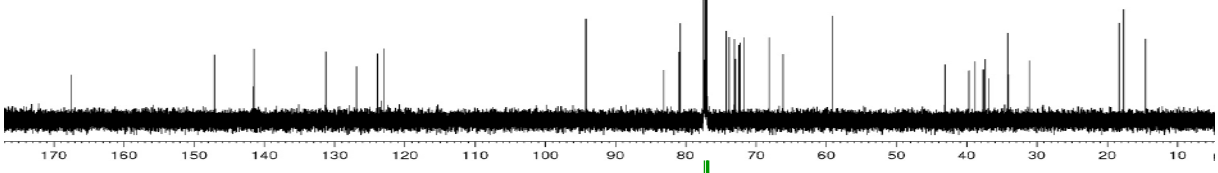


synthetic **124**
($CDCl_3$, 150 MHz)



natural mandelalide A
($CDCl_3$, 175 MHz)




synthetic (11-*epi*)-**124**
($CDCl_3$, 150 MHz)

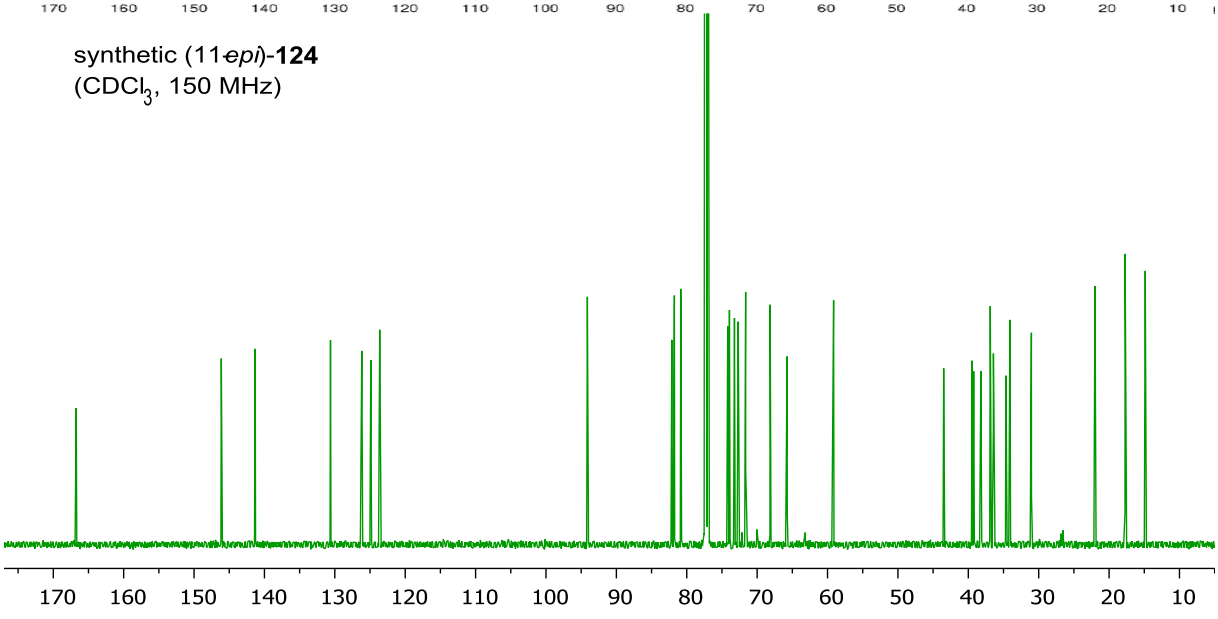
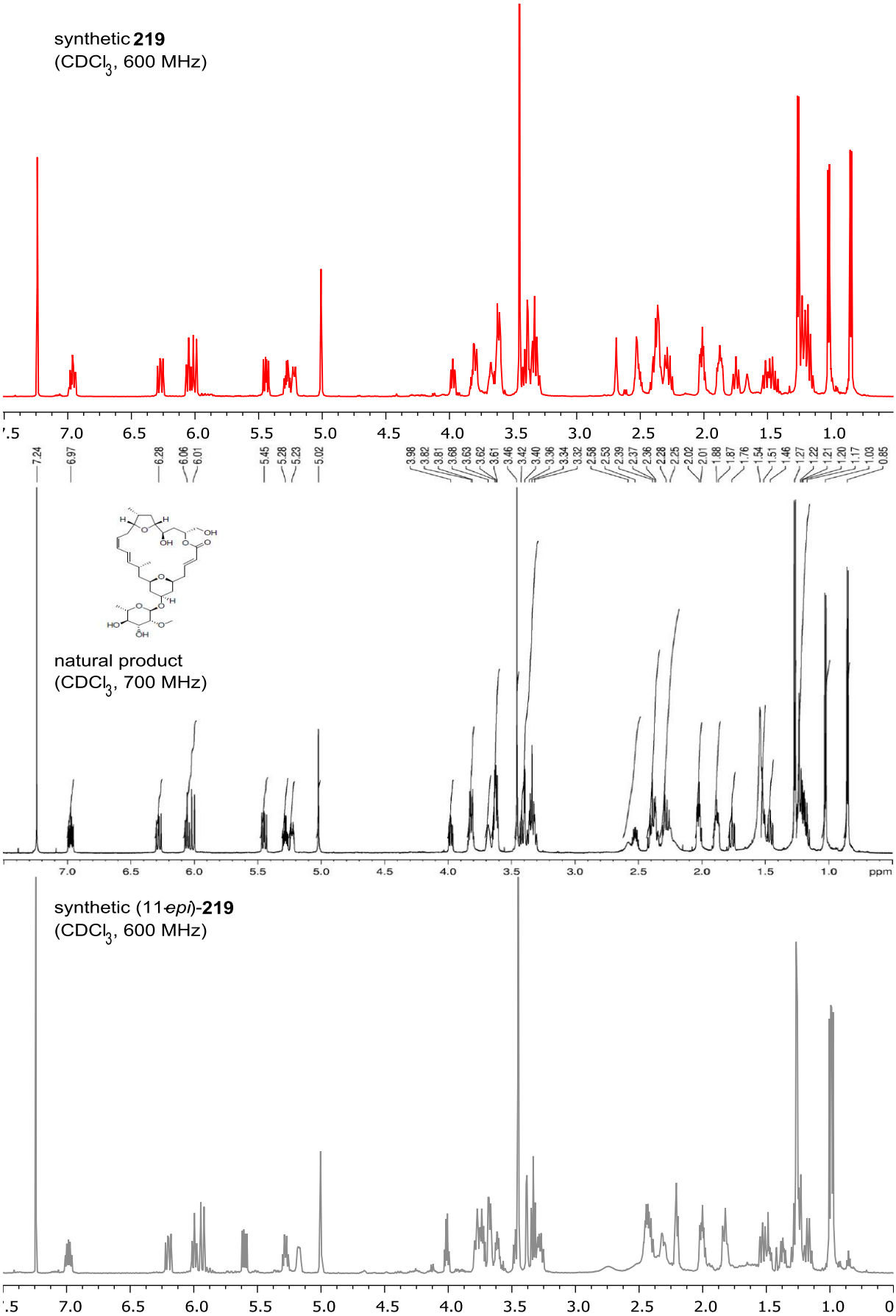


*Table 8.3*: Comparison of the $^{1}$H NMR chemical shifts of **124** (600 MHz, $CDCl_3$) and 11-*epi*-**124** with the data of the natural product (Lit.[141]; 700 MHz, $CDCl_3$).

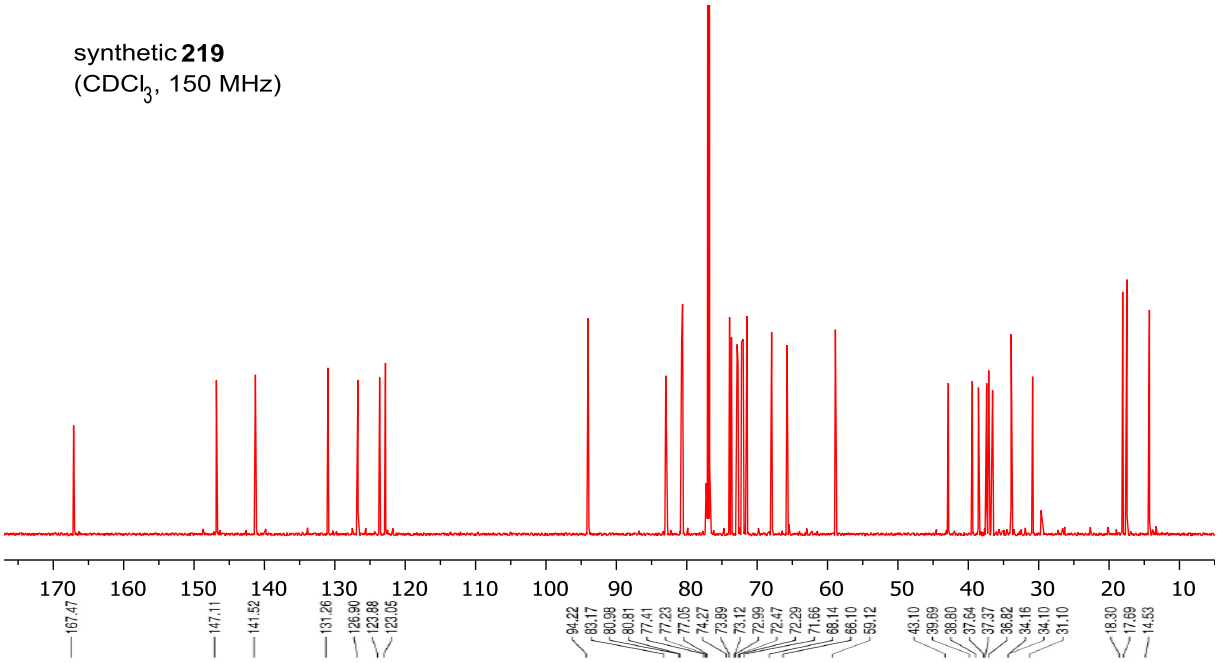
| atom n° | δ (Lit.) /ppm | δ(124) /ppm | Δδ (124–Lit.) | δ(11-*epi*-**124**) /ppm | Δδ (11-*epi*-1–Lit) |
|---|---|---|---|---|---|
| 1 | - | - | - | - | - |
| 2 | 6.01 | 5.92 | -0.09 | 5.92 | -0.09 |
| 3 | 6.97 | 7.02 | 0.05 | 7.09 | 0.12 |
| 4a | 2.36 | 2.34 | -0.02 | 2.31 | -0.05 |
| 4b | 2.39 | 2.46 | 0.07 | 2.39 | 0.00 |
| 5 | 3.36 | 3.42 | 0.06 | 3.26 | -0.10 |
| 6a | 1.20 | 1.26 | 0.06 | 1.15 | -0.05 |
| 6b | 2.02 | 1.94 | -0.08 | 1.98 | -0.04 |
| 7 | 3.82 | 3.77 | -0.05 | 3.76 | -0.06 |
| 8a | 1.22 | 1.22 | 0.00 | 1.27 | 0.05 |
| 8b | 1.87 | 1.84 | -0.03 | 1.75 | -0.12 |
| 9 | 3.32 | 3.33 | 0.01 | 3.16 | -0.16 |
| 10a | 1.21 | 1.27 | 0.06 | 1.14 | -0.07 |
| 10b | 1.51 | 1.69 | 0.18 | 1.52 | 0.01 |
| 11 | 2.37 | 2.44 | 0.07 | 2.48 | 0.11 |
| 12 | 5.45 | 5.61 | 0.16 | 5.32 | -0.13 |
| 13 | 6.28 | 6.22 | -0.06 | 6.10 | -0.18 |
| 14 | 6.05 | 6.01 | -0.04 | 6.00 | -0.05 |
| 15 | 5.28 | 5.27 | -0.01 | 5.20 | -0.08 |
| 16a | 1.88 | 2.14 | 0.26 | 2.08 | 0.20 |
| 16b | 2.28 | 2.29 | 0.01 | 2.25 | -0.03 |
| 17 | 3.98 | 4.03 | 0.05 | 3.99 | 0.01 |
| 18 | 2.52 | 2.43 | -0.09 | 2.46 | -0.06 |
| 19a | 1.17 | 1.28 | 0.11 | 1.26 | 0.09 |
| 19b | 2.01 | 2.04 | 0.03 | 2.09 | 0.08 |
| 20 | 3.63 | 3.71 | 0.08 | 3.74 | 0.11 |
| 21 | 3.42 | 3.45 | 0.03 | 3.46 | 0.04 |
| 22a | 1.46 | 1.54 | 0.08 | 1.55 | 0.09 |
| 22b | 1.76 | 1.77 | 0.01 | 1.88 | 0.12 |
| 23 | 5.23 | 5.24 | 0.01 | 5.23 | 0.00 |
| 24a | 3.61 | 3.65 | 0.04 | 3.65 | 0.04 |
| 24b | 3.81 | 3.78 | -0.03 | 3.79 | -0.02 |
| 25 | 0.85 | 1.00 | 0.15 | 0.98 | 0.13 |
| 26 | 1.03 | 0.98 | -0.05 | 0.98 | -0.05 |
| 1' | 5.02 | 5.02 | 0.00 | 4.99 | -0.03 |
| 2' | 3.40 | 3.40 | 0.00 | 3.38 | -0.02 |
| 3' | 3.68 | 3.69 | 0.01 | 3.68 | 0.00 |
| 4' | 3.34 | 3.34 | 0.00 | 3.33 | -0.01 |
| 5' | 3.62 | 3.63 | 0.01 | 3.61 | -0.01 |
| 6' | 1.27 | 1.28 | 0.01 | 1.26 | -0.01 |
| 7' | 3.45 | 3.46 | 0.01 | 3.44 | -0.01 |

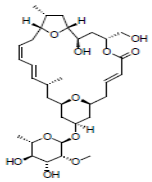
*Table 8.4*: Comparison of the $^{13}C$ NMR chemical shifts of **124** and 11-*epi*-**124** (150 MHz, $CDCl_3$)with the data of the natural product (Lit.[141]; 175 MHz, $CDCl_3$).

| atom n° | δ (Lit.) /ppm | δ(124) /ppm | Δδ (124–Lit.) | δ(11-*epi*-**124**) /ppm | Δδ (11-*epi*-**124**–Lit) |
|---|---|---|---|---|---|
| 1 | 167.5 | 167.3 | -0.2 | 166.8 | -0.7 |
| 2 | 123.1 | 123.1 | 0.0 | 123.6 | 0.5 |
| 3 | 147.1 | 146.3 | -0.8 | 146.1 | -1.0 |
| 4 | 38.8 | 38.5 | -0.3 | 39.5 | 0.7 |
| 5 | 73.9 | 73.4 | -0.5 | 73.9 | 0.0 |
| 6 | 37.6 | 36.7 | -0.9 | 38.2 | 0.6 |
| 7 | 73.1 | 72.8 | -0.3 | 72.7 | -0.4 |
| 8 | 39.7 | 39.3 | -0.4 | 39.2 | -0.5 |
| 9 | 72.5 | 73.1 | 0.6 | 73.2 | 0.7 |
| 10 | 43.1 | 42.9 | -0.2 | 43.5 | 0.4 |
| 11 | 34.2 | 32.8 | **-1.4** | 34.1 | -0.1 |
| 12 | 141.5 | 140.9 | -0.6 | 141.3 | -0.2 |
| 13 | 123.9 | 123.8 | -0.1 | 124.9 | 1.0 |
| 14 | 131.3 | 130.5 | -0.8 | 130.6 | -0.7 |
| 15 | 126.9 | 126.5 | -0.4 | 126.2 | -0.7 |
| 16 | 31.1 | 31.2 | 0.1 | 31.0 | -0.1 |
| 17 | 81.0 | 81.3 | 0.3 | 81.8 | 0.8 |
| 18 | 37.4 | 37.1 | -0.3 | 36.9 | -0.5 |
| 19 | 36.8 | 36.0 | -0.8 | 36.4 | -0.4 |
| 20 | 83.2 | 82.7 | -0.5 | 82.1 | -1.1 |
| 21 | 73.0 | 73.4 | 0.4 | 73.3 | 0.3 |
| 22 | 34.1 | 34.1 | 0.0 | 34.7 | 0.6 |
| 23 | 72.3 | 72.5 | 0.2 | 74.0 | 1.7 |
| 24 | 66.1 | 65.7 | -0.4 | 65.7 | -0.4 |
| 25 | 18.3 | 20.1 | **1.8** | 22.0 | 3.7 |
| 26 | 14.5 | 14.7 | 0.2 | 14.9 | 0.4 |
| 1' | 94.2 | 94.0 | -0.2 | 94.1 | -0.1 |
| 2' | 80.8 | 80.9 | 0.1 | 80.9 | 0.1 |
| 3' | 71.7 | 71.7 | 0.0 | 71.6 | -0.1 |
| 4' | 74.3 | 74.2 | -0.1 | 74.2 | -0.1 |
| 5' | 68.1 | 68.2 | 0.1 | 68.2 | 0.1 |
| 6' | 17.7 | 17.7 | 0.0 | 17.7 | 0.0 |
| 7' | 59.1 | 59.2 | 0.1 | 59.1 | 0.0 |


synthetic **219**
(CDCl3, 600 MHz)
7.24
6.97
6.28
6.06
6.01
5.45
5.28
5.23
5.02
3.98
3.82
3.81
3.68
3.63
3.62
3.61
3.46
3.42
3.40
3.36
3.34
3.32
2.58
2.53
2.39
2.37
2.36
2.28
2.25
2.02
2.01
1.88
1.87
1.76
1.54
1.51
1.46
1.27
1.22
1.21
1.20
1.17
1.03
0.85
natural product
(CDCl3, 700 MHz)
synthetic (11-*epi*)-**219**
(CDCl3, 600 MHz)
ppm

synthetic **219**
($CDCl_3$, 150 MHz)



natural mandelalide A
($CDCl_3$, 175 MHz)




synthetic (11-*epi*)-**219**
($CDCl_3$, 150 MHz)

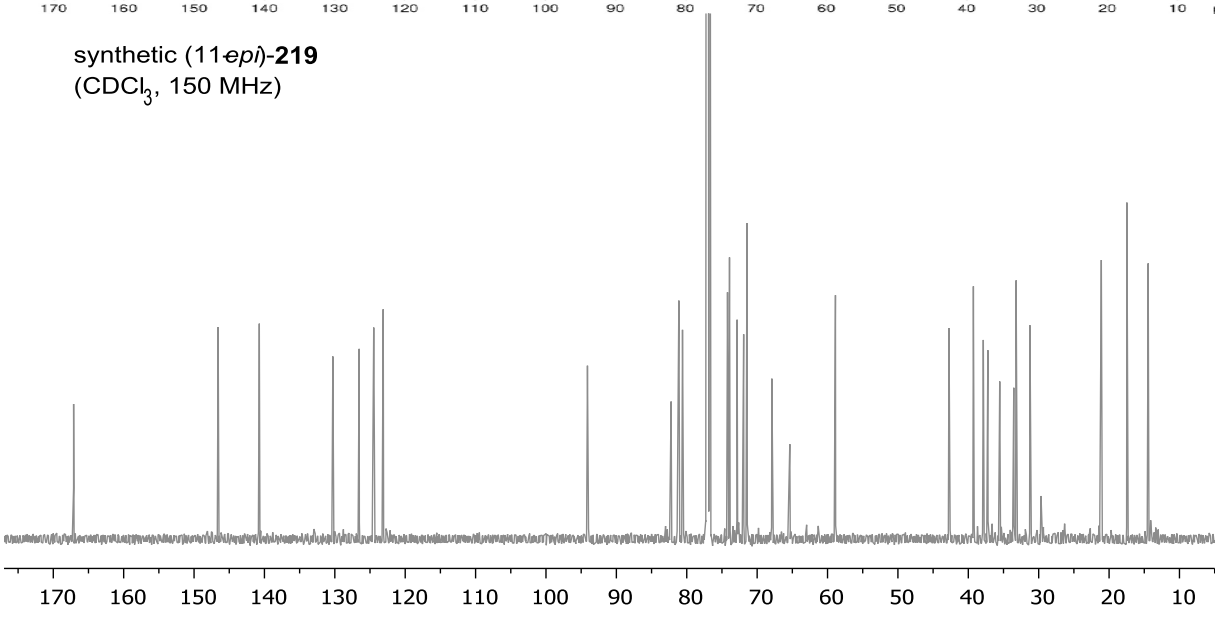


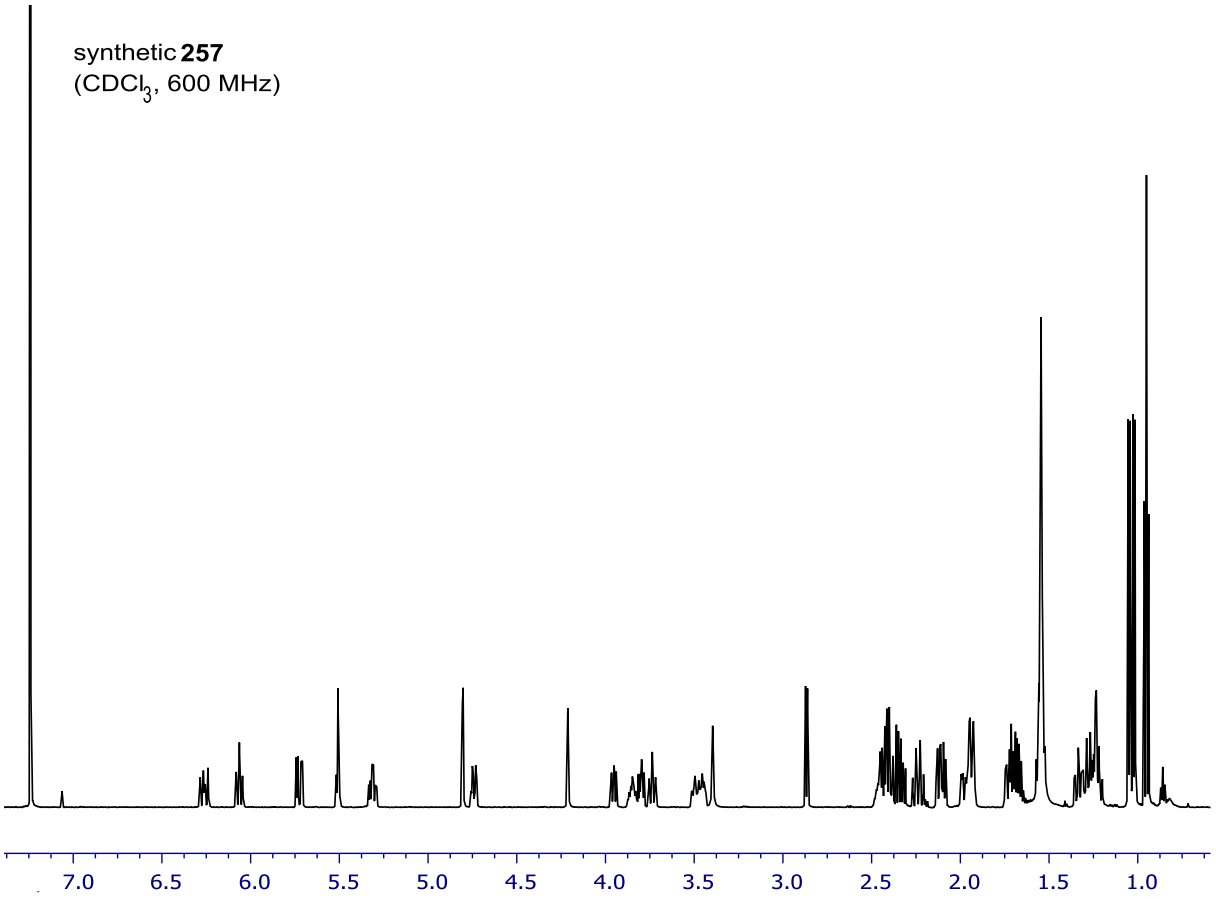
*Table 8.5*: Comparison of the $^{1}$H NMR chemical shifts of **219** and 11-*epi*-**219** (600 MHz, $CDCl_3$) with the data of the natural product (Lit.[141]; 700 MHz, $CDCl_3$).

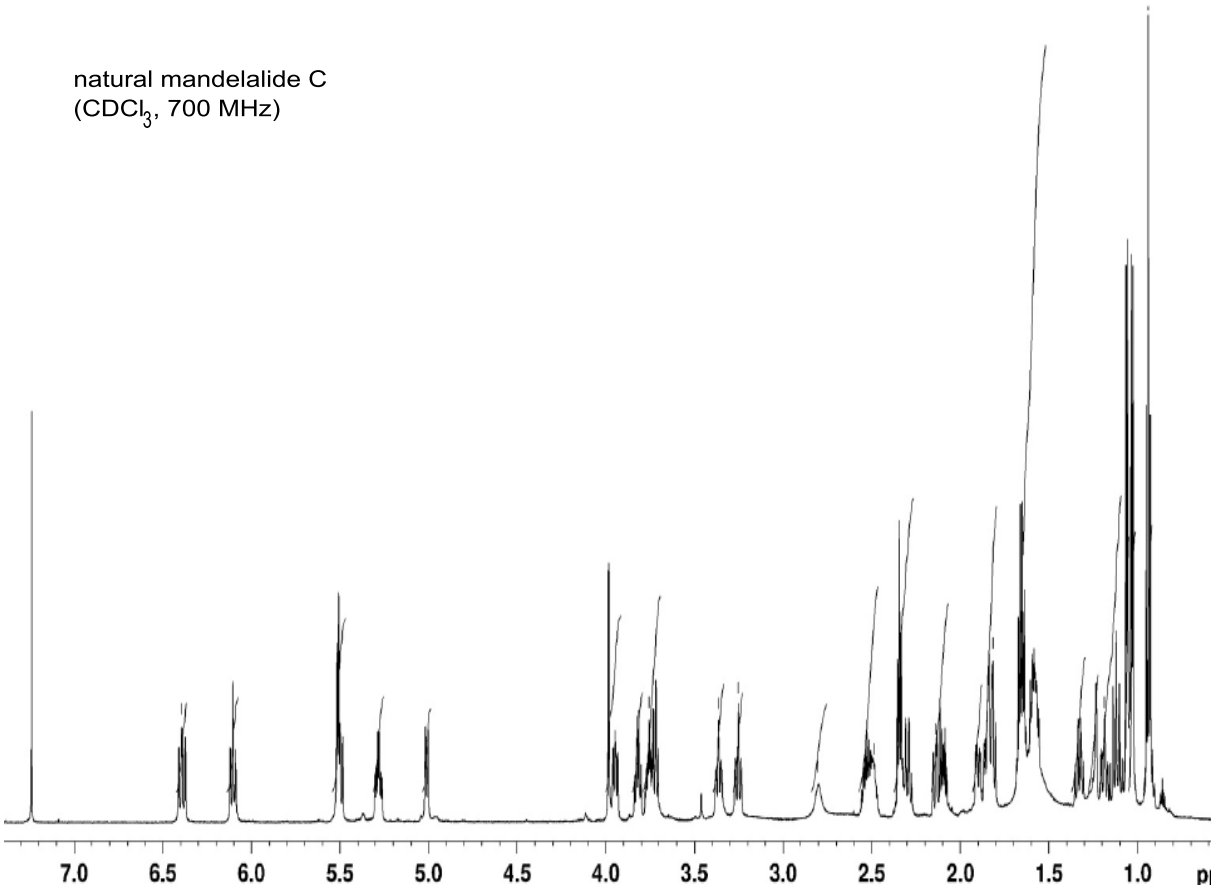
| atom n° | δ (Lit.) /ppm | δ(219) /ppm | Δδ (219–Lit.) | δ(11-*epi*-**219**) /ppm | Δδ (11-*epi*-**219**–Lit.) |
|---|---|---|---|---|---|
| 1 | - | - | - | - | - |
| 2 | 6.01 | 6.01 | 0.00 | 5.93 | -0.08 |
| 3 | 6.97 | 6.96 | -0.01 | 6.98 | 0.01 |
| 4a | 2.36 | 2.36 | 0.00 | 2.31 | -0.05 |
| 4b | 2.39 | 2.39 | 0.00 | 2.42 | 0.03 |
| 5 | 3.36 | 3.37 | 0.01 | 3.3 | -0.06 |
| 6a | 1.20 | 1.20 | 0.00 | 1.17 | -0.03 |
| 6b | 2.02 | 2.02 | 0.00 | 2.00 | -0.02 |
| 7 | 3.82 | 3.82 | 0.00 | 3.75 | -0.07 |
| 8a | 1.22 | 1.22 | 0.00 | 1.23 | 0.01 |
| 8b | 1.87 | 1.87 | 0.00 | 1.82 | -0.05 |
| 9 | 3.32 | 3.31 | -0.01 | 3.27 | -0.05 |
| 10a | 1.21 | 1.21 | 0.00 | 1.37 | 0.16 |
| 10b | 1.51 | 1.52 | 0.01 | 1.49 | -0.02 |
| 11 | 2.37 | 2.37 | 0.00 | 2.45 | 0.08 |
| 12 | 5.45 | 5.44 | -0.01 | 5.6 | 0.15 |
| 13 | 6.28 | 6.27 | -0.01 | 6.2 | -0.08 |
| 14 | 6.05 | 6.05 | 0.00 | 6.00 | -0.05 |
| 15 | 5.28 | 5.28 | 0.00 | 5.28 | 0.00 |
| 16a | 1.88 | 1.88 | 0.00 | 2.21 | 0.33 |
| 16b | 2.28 | 2.25 | -0.03 | 2.2 | -0.08 |
| 17 | 3.98 | 3.98 | 0.00 | 4.01 | 0.03 |
| 18 | 2.52 | 2.52 | 0.00 | 2.44 | -0.08 |
| 19a | 1.17 | 1.17 | 0.00 | 1.28 | 0.11 |
| 19b | 2.01 | 2.01 | 0.00 | 2.00 | -0.01 |
| 20 | 3.63 | 3.63 | 0.00 | 3.73 | 0.10 |
| 21 | 3.42 | 3.42 | 0.00 | 3.76 | 0.34 |
| 22a | 1.46 | 1.46 | 0.00 | 1.53 | 0.07 |
| 22b | 1.76 | 1.76 | 0.00 | 1.83 | 0.07 |
| 23 | 5.23 | 5.23 | 0.00 | 5.17 | -0.06 |
| 24a | 3.61 | 3.61 | 0.00 | 3.67 | 0.06 |
| 24b | 3.81 | 3.79 | -0.02 | 3.78 | -0.03 |
| 25 | 0.85 | 0.85 | 0.00 | 1.00 | 0.15 |
| 26 | 1.03 | 1.02 | -0.01 | 0.98 | -0.05 |
| 1' | 5.02 | 5.02 | 0.00 | 5.00 | -0.02 |
| 2' | 3.40 | 3.40 | 0.00 | 3.38 | -0.02 |
| 3' | 3.68 | 3.68 | 0.00 | 3.69 | 0.01 |
| 4' | 3.34 | 3.34 | 0.00 | 3.33 | -0.01 |
| 5' | 3.62 | 3.62 | 0.00 | 3.61 | -0.01 |
| 6' | 1.27 | 1.26 | -0.01 | 1.26 | -0.01 |
| 7' | 3.45 | 3.45 | 0.00 | 3.45 | 0.00 |

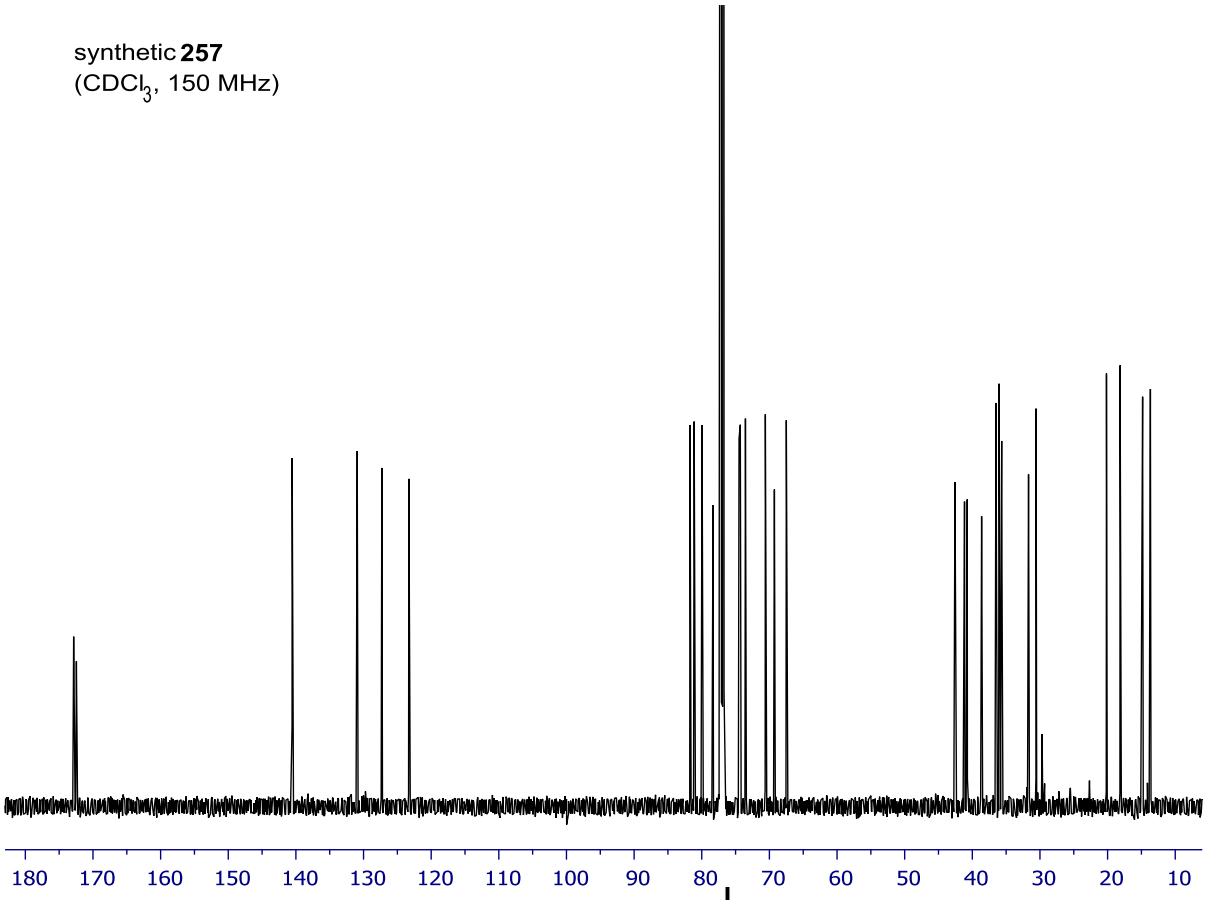
*Table 8.6*: Comparison of the $^{13}C$ NMR chemical shifts of **219** and 11-*epi*-**219** (150 MHz, $CDCl_3$) with the data of the natural product (Lit.[141]; 175 MHz, $CDCl_3$).

| atom n° | δ (Lit.) /ppm | δ(219) /ppm | Δδ (219–Lit.) | δ(11-*epi*-**219**) /ppm | Δδ (11-*epi*-**219**–Lit.) |
|---|---|---|---|---|---|
| 1 | 167.5 | 167.4 | -0.1 | 167.4 | -0.1 |
| 2 | 123.1 | 123.1 | 0.0 | 123.4 | 0.3 |
| 3 | 147.1 | 147.1 | 0.0 | 146.8 | -0.3 |
| 4 | 38.8 | 38.8 | 0.0 | 39.5 | 0.7 |
| 5 | 73.9 | 73.9 | 0.0 | 74.2 | 0.3 |
| 6 | 37.6 | 37.6 | 0.0 | 37.5 | -0.1 |
| 7 | 73.1 | 73.1 | 0.0 | 73.1 | 0.0 |
| 8 | 39.7 | 39.7 | 0.0 | 39.5 | -0.2 |
| 9 | 72.5 | 72.5 | 0.0 | 72.9 | 0.4 |
| 10 | 43.1 | 43.1 | 0.0 | 43 | -0.1 |
| 11 | 34.2 | 34.2 | 0.0 | 33.5 | -0.7 |
| 12 | 141.5 | 141.5 | 0.0 | 141 | -0.5 |
| 13 | 123.9 | 123.9 | 0.0 | 124.7 | 0.8 |
| 14 | 131.3 | 131.3 | 0.0 | 130.5 | -0.8 |
| 15 | 126.9 | 126.9 | 0.0 | 126.8 | -0.1 |
| 16 | 31.1 | 31.1 | 0.0 | 31.5 | 0.4 |
| 17 | 81.0 | 81 | 0.0 | 80.9 | -0.1 |
| 18 | 37.4 | 37.4 | -0.1 | 37.5 | 0.1 |
| 19 | 36.8 | 36.8 | 0.0 | 35.8 | -1.0 |
| 20 | 83.2 | 83.2 | 0.0 | 82.5 | -0.7 |
| 21 | 73.0 | 73.1 | -0.1 | 73.1 | 0.1 |
| 22 | 34.1 | 34.1 | 0.0 | 33.8 | -0.3 |
| 23 | 72.3 | 72.3 | 0.0 | 72.2 | -0.1 |
| 24 | 66.1 | 66.1 | 0.0 | 65.6 | -0.5 |
| 25 | 18.3 | 18.3 | 0.0 | 21.4 | 3.1 |
| 26 | 14.5 | 14.5 | 0.0 | 14.7 | 0.2 |
| 1' | 94.2 | 94.2 | 0.0 | 94.3 | 0.1 |
| 2' | 80.8 | 80.8 | 0.0 | 80.8 | 0.0 |
| 3' | 71.7 | 71.7 | 0.0 | 71.7 | 0.0 |
| 4' | 74.3 | 74.3 | 0.0 | 74.4 | 0.1 |
| 5' | 68.1 | 68.1 | 0.0 | 68.1 | 0.0 |
| 6' | 17.7 | 17.7 | 0.0 | 17.8 | 0.1 |
| 7' | 59.1 | 59.1 | 0.0 | 59.1 | 0.0 |

## 8.4 Comparison of synthetic 2,3-*epi*-mandelalide C with the natural product.




synthetic **257**
($CDCl_3$, 150 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

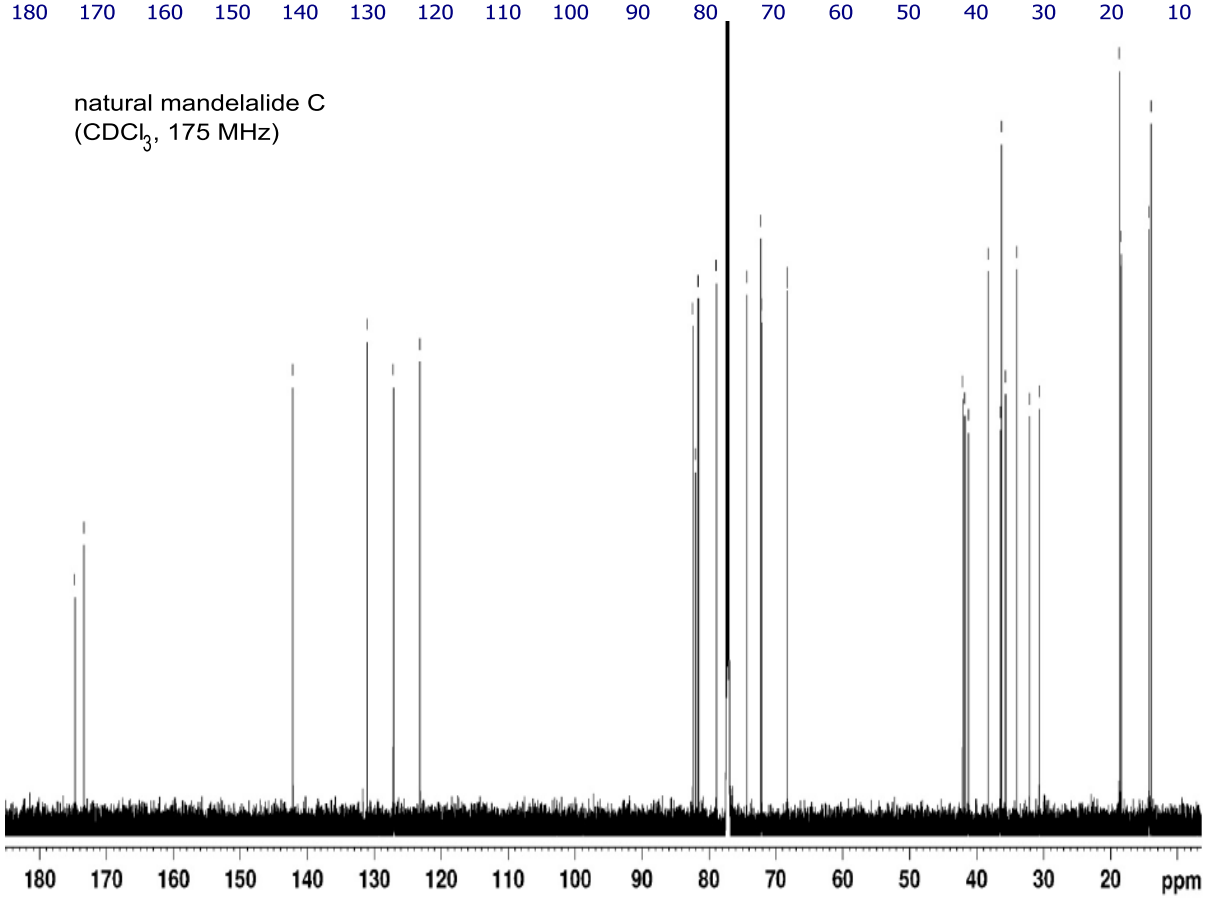
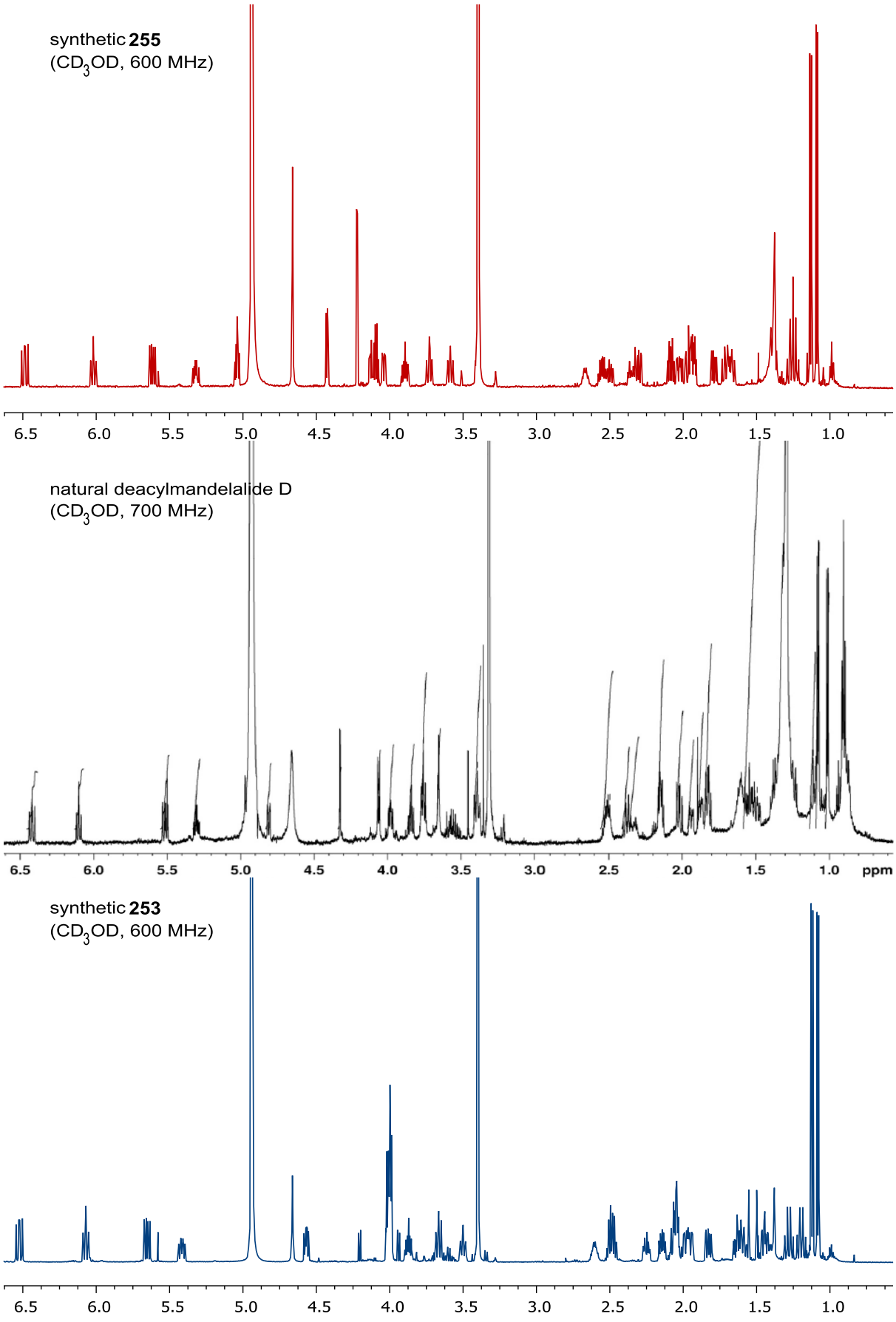
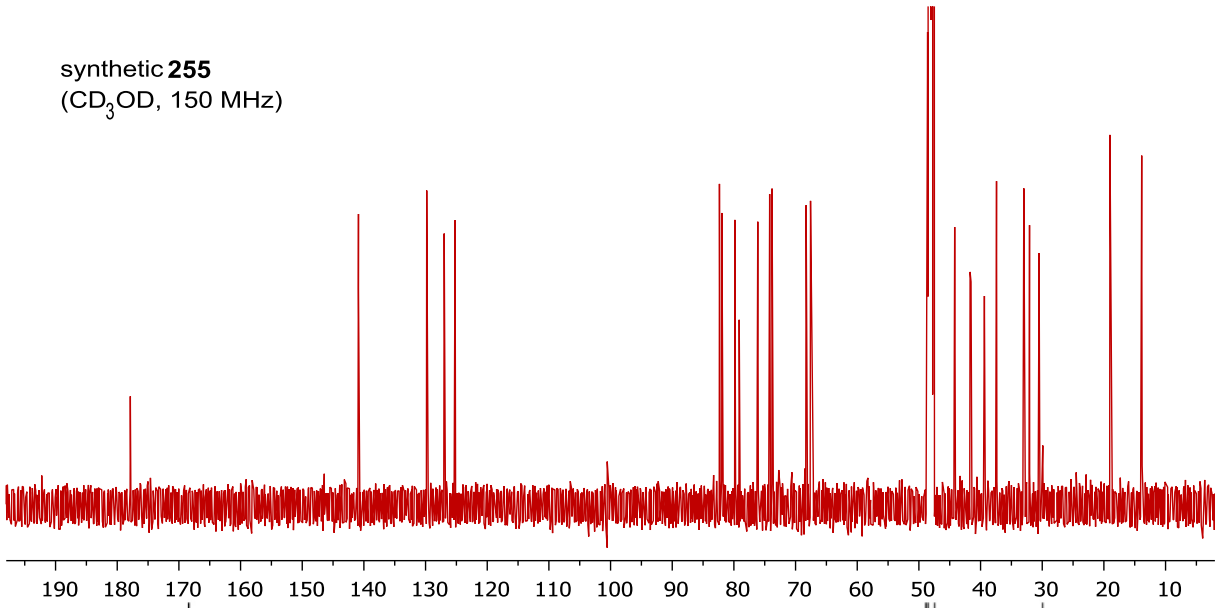

natural mandelalide C
($CDCl_3$, 175 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

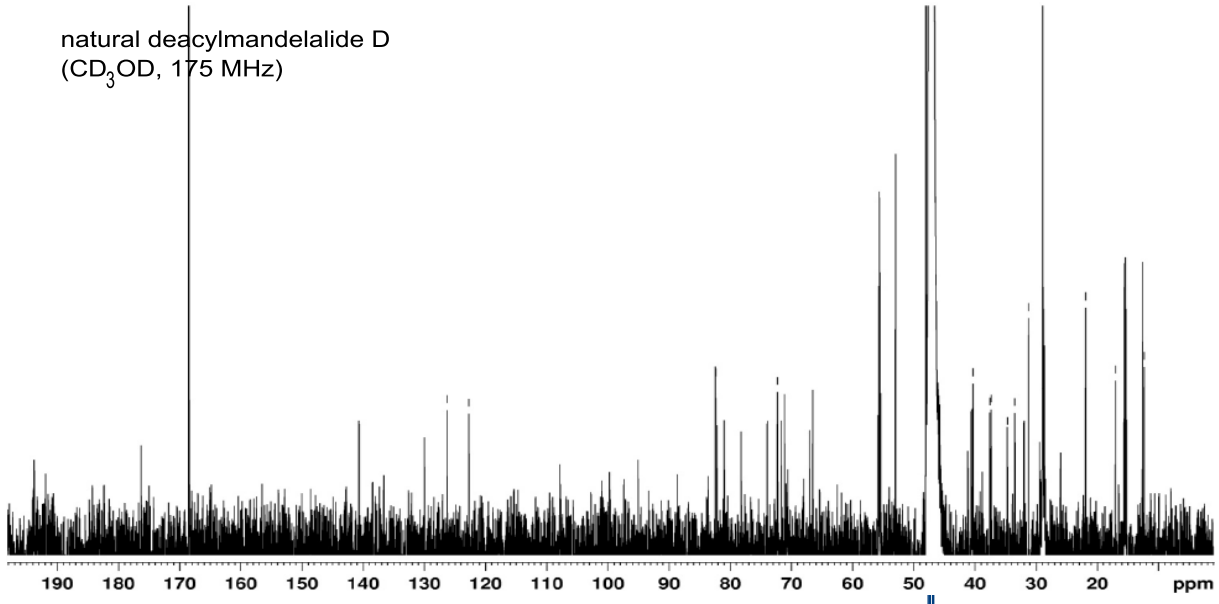
*Table 8.7*: Comparison of $^{1}H$ and $^{13}C$ NMR chemical shifts of **257** ($^{1}H$: 600 MHz, $^{13}C$: 150 MHz $CDCl_3$) with the data of the natural product (Lit.[141]; $^{1}H$: 600 MHz, $^{13}C$: 175 MHz, $CDCl_3$).

| | $^{1}H$ NMR | | | $^{13}C$ NMR | | |
|---|---|---|---|---|---|---|
| **atom n°** | **δ(Lit.) /ppm** | **δ(257) /ppm** | **Δδ (257-Lit.)** | **δ(Lit.) /ppm** | **δ(257) /ppm** | **Δδ (257-Lit.)** |
| 1 | - | - | - | 174.7 | 172.5 | 2.2 |
| 2 | - | - | - | 82.0 | 78.3 | 3.7 |
| 3 | 5.51 | 5.51 | 0.00 | 68.3 | 69.3 | -1.0 |
| 4a | 1.65 | 1.73 | -0.08 | 36.4 | 38.6 | -2.2 |
| 4b | 2.14 | 2.11 | 0.03 | | | |
| 5 | 3.25 | 3.74 | -0.49 | 72.3 | 73.5 | -1.2 |
| 6a | 1.11 | 1.23 | -0.12 | 41.2 | 41.2 | 0.0 |
| 6b | 1.86 | 1.93 | -0.07 | | | |
| 7 | 3.76 | 3.85 | -0.09 | 68.3 | 67.5 | 0.8 |
| 8a | 1.13 | 1.33 | -0.20 | 41.8 | 40.8 | 1.0 |
| 8b | 1.83 | 1.94 | -0.11 | | | |
| 9 | 3.37 | 3.50 | -0.13 | 72.3 | 74.5 | -2.2 |
| 10a | 1.19 | 1.33 | -0.14 | 42.1 | 42.6 | -0.5 |
| 10b | 1.57 | 1.71 | -0.14 | | | |
| 11 | 2.49 | 2.46 | 0.03 | 34.0 | 30.6 | 3.4 |
| 12 | 5.5 | 5.72 | -0.22 | 142.2 | 140.6 | 1.6 |
| 13 | 6.39 | 6.26 | 0.13 | 123.2 | 123.3 | -0.1 |
| 14 | 6.1 | 6.06 | 0.04 | 131.1 | 130.9 | 0.2 |
| 15 | 5.28 | 5.31 | -0.03 | 127.1 | 127.3 | -0.2 |
| 16a | 1.9 | 1.98 | -0.08 | 30.7 | 30.4 | 0.3 |
| 16b | 2.3 | 2.39 | -0.09 | | | |
| 17 | 3.95 | 3.95 | 0 | 81.6 | 81.7 | -0.1 |
| 18 | 2.53 | 2.41 | 0.12 | 38.3 | 36.5 | 1.8 |
| 19a | 1.33 | 1.54 | -0.21 | 35.7 | 35.7 | 0.0 |
| 19b | 2.1 | 2.10 | 0 | | | |
| 20 | 3.82 | 3.80 | 0.02 | 82.4 | 81.1 | 1.3 |
| 21 | 3.73 | 3.46 | 0.27 | 74.4 | 70.6 | 3.8 |
| 22a | 1.59 | 1.93 | -0.34 | 32.1 | 31.7 | 0.4 |
| 22b | 1.82 | 2.24 | -0.42 | | | |
| 23 | 5.01 | 4.74 | 0.27 | 78.9 | 80.0 | -1.1 |
| 24 | 3.98 | 4.21 | -0.23 | 72.2 | 74.3 | -2.1 |
| 25 | 1.06 | 1.05 | 0.01 | 18.4 | 20.2 | -1.8 |
| 26 | 1.03 | 1.02 | 0.01 | 14.2 | 14.8 | -0.6 |
| 27 | - | - | - | 173.4 | 172.9 | 0.5 |
| 28a | 2.34 | 2.42 | -0.08 | 36.3 | 36.0 | 0.3 |
| 28b | 2.34 | 2.33 | 0.01 | | | |
| 29 | 1.65 | 1.68 | -0.03 | 18.7 | 18.2 | 0.5 |
| 30 | 0.94 | 0.94 | 0.00 | 13.9 | 13.7 | 0.2 |

## 8.5 Comparison of synthetic deacylmandelalide D isomers 253 and 255 with the natural product.




synthetic **255**
(CD3OD, 150 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


natural deacylmandelalide D
(CD3OD, 175 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

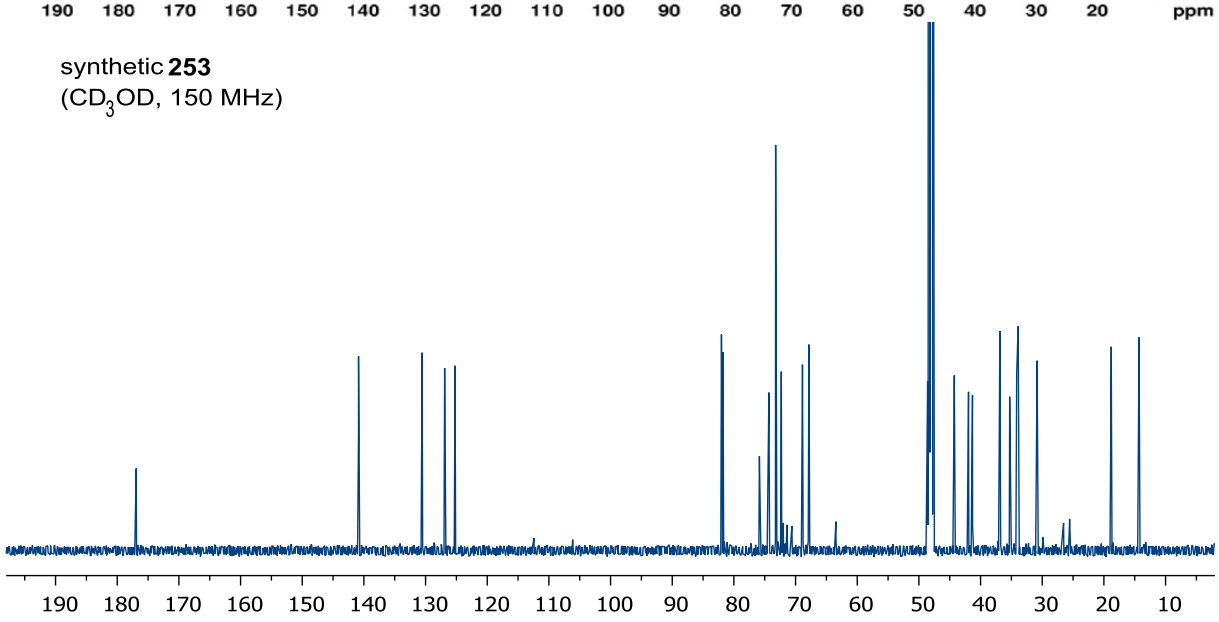

synthetic **253**
(CD3OD, 150 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

*Table 8.8*: Comparison of $^{1}$H NMR chemical shifts of **253** and **255** (600 MHz, $CD_3OD$) with the data of the natural product (Lit.[141]; 700 MHz, $CD_3OD$).

| atom n° | δ (Lit.) /ppm | δ(255) /ppm | Δδ (255–Lit.) | δ(253) /ppm | Δδ (253–Lit.) |
|---|---|---|---|---|---|
| 1 | - | - | - | - | - |
| 2 | - | - | - | - | - |
| 3 | 4.06 | 4.34 | −0.28 | 3.92 | 0.14 |
| 4a | 1.56 | 1.70 | −0.14 | 1.74 | −0.18 |
| 4b | 2.02 | 1.90 | 0.12 | 1.96 | 0.06 |
| 5 | 3.39 | 3.64 | −0.25 | 3.58 | −0.19 |
| 6a | 1.11 | 1.17 | −0.06 | 1.19 | −0.08 |
| 6b | 1.88 | 1.94 | −0.06 | 1.89 | −0.01 |
| 7 | 3.76 | 3.81 | −0.05 | 3.78 | −0.02 |
| 8a | 1.08 | 1.15 | −0.07 | 1.11 | −0.03 |
| 8b | 1.83 | 1.85 | −0.02 | 1.88 | −0.05 |
| 9 | 3.39 | 3.50 | −0.11 | 3.41 | −0.02 |
| 10a | 1.23 | 1.28 | −0.05 | 1.35 | −0.12 |
| 10b | 1.49 | 1.58 | −0.09 | 1.54 | −0.05 |
| 11 | 2.49 | 2.58 | −0.09 | 2.52 | −0.03 |
| 12 | 5.51 | 5.53 | −0.02 | 5.55 | −0.04 |
| 13 | 6.42 | 6.4 | 0.02 | 6.44 | −0.02 |
| 14 | 6.1 | 5.93 | 0.17 | 5.98 | 0.12 |
| 15 | 5.3 | 5.23 | 0.07 | 5.33 | −0.03 |
| 16a | 1.94 | 2.27 | −0.33 | 2.16 | −0.22 |
| 16b | 2.38 | 2.42 | −0.04 | 2.38 | 0.00 |
| 17 | 3.98 | 4.01 | −0.03 | 3.91 | 0.07 |
| 18 | 2.52 | 2.47 | 0.05 | 2.40 | 0.12 |
| 19a | 1.37 | 1.62 | −0.25 | 1.51 | −0.14 |
| 19b | 2.14 | 2.00 | 0.14 | 2.05 | 0.09 |
| 20 | 3.84 | 4.04 | −0.20 | 3.90 | −0.06 |
| 21 | 3.75 | 3.95 | −0.20 | 3.91 | −0.16 |
| 22a | 1.52 | 1.85 | −0.33 | 1.95 | −0.43 |
| 22b | 1.81 | 2.22 | −0.41 | 1.96 | −0.15 |
| 23 | 4.81 | 4.95 | −0.14 | 4.48 | 0.33 |
| 24a | 4.32 | 4.14 | 0.18 | 3.90 | 0.42 |
| 24b | 1.01 | 1.00 | 0.01 | 0.99 | 0.02 |
| 25 | 1.08 | 1.04 | 0.04 | 1.03 | 0.05 |
| 26 | 4.06 | 4.34 | −0.28 | 3.92 | 0.14 |

*Table 8.9*: Comparison of $^{13}C$ NMR chemical shifts of **253** and **255** (150 MHz, $CD_3OD$) with the data of the natural product (Lit.[141]; 175 MHz, $CD_3OD$).

| atom n° | δ (Lit.) /ppm | δ(255) /ppm | Δδ (255–Lit.) | δ(253) /ppm | Δδ (253–Lit.) |
|---|---|---|---|---|---|
| 1 | 176.3 | 178.9 | −2.6 | 177.9 | 0.2 |
| 2 | 82.4 | 80.1 | 2.3 | 76.9 | 5.5 |
| 3 | 66.6 | 69.5 | −2.9 | 73.3 | −6.7 |
| 4 | 37.4 | 40.4 | −3.0 | 38.0 | −0.6 |
| 5 | 72.3 | 75.2 | −2.9 | 74.2 | −1.9 |
| 6 | 40.3 | 42.5 | −2.2 | 42.3 | −2.0 |
| 7 | 67.1 | 68.6 | −1.5 | 68.8 | −1.7 |
| 8 | 40.7 | 42.7 | −2.0 | 42.9 | −2.2 |
| 9 | 71.1 | 74.8 | −3.7 | 74.2 | −3.1 |
| 10 | 41.2 | 45.2 | −4.0 | 45.3 | −4.1 |
| 11 | 33.5 | 34.0 | −0.5 | 34.9 | −1.4 |
| 12 | 140.7 | 141.9 | −1.2 | 141.9 | −1.2 |
| 13 | 122.8 | 126.2 | −3.4 | 126.2 | −3.4 |
| 14 | 130.0 | 130.8 | −0.8 | 131.6 | −1.6 |
| 15 | 126.3 | 128.0 | −1.7 | 127.9 | −1.6 |
| 16 | 31.2 | 33.1 | −1.9 | 31.8 | −0.6 |
| 17 | 81.0 | 83.4 | −2.4 | 82.8 | −1.8 |
| 18 | 37.6 | 38.4 | −0.8 | 37.9 | −0.3 |
| 19 | 34.7 | 34.1 | 0.6 | 35.1 | −0.4 |
| 20 | 82.2 | 83.0 | −0.8 | 83.0 | −0.8 |
| 21 | 73.9 | 69.3 | 4.6 | 75.3 | −1.4 |
| 22 | 32.0 | 31.5 | 0.5 | 36.3 | −4.3 |
| 23 | 78.3 | 80.8 | −2.5 | 82.9 | −4.6 |
| 24 | 71.7 | 77.1 | −5.4 | 69.9 | 1.8 |
| 25 | 17.0 | 20.0 | −3.0 | 19.8 | −2.8 |
| 26 | 12.3 | 14.9 | −2.6 | 15.3 | −3.0 |