Concise Total Synthesis of Enigmazole A

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Studies Towards the Total Synthesis of Rhizoxin D

Dissertation

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"Concise Total Synthesis of Enigmazole A"

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Die praktischen Arbeiten entstanden teilweise in Zusammenarbeit mit Dr. Teresa de Haro und Chris Hartding (Enigmazole) sowie Felix Ungeheuer und Christian Wille (Rhizoxin). Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesen Mitarbeitern alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

1. Berichterstatter: Herr Prof. Dr. Alois Fürstner

2. Berichterstatter: Herr Prof. Dr. Martin Hiersemann

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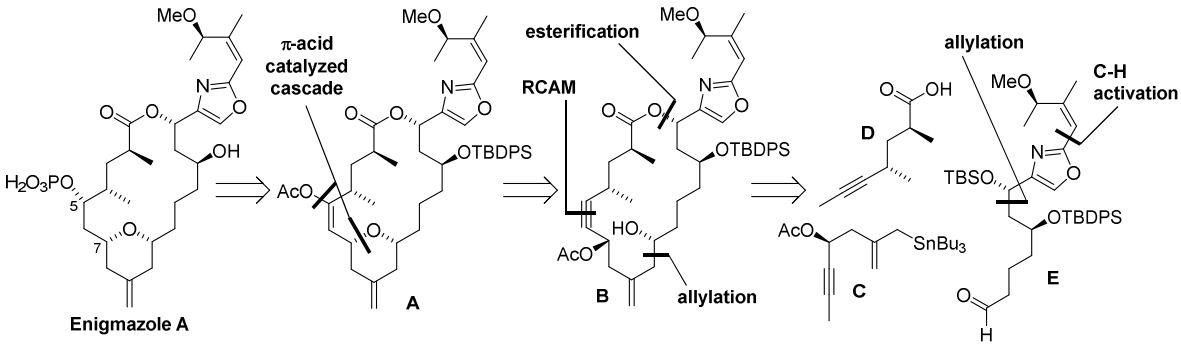
Abstract

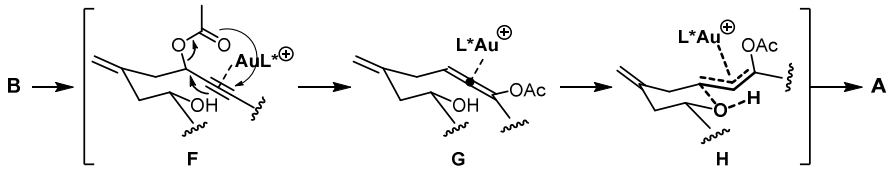
Enigmazole A and its congeners, isolated form the sponge *Cinachyrella enigmatica*, are the first known phosphorylated macrolides of marine origin. Their structure features an 18-membered macrocycle which is decorated with a highly functionalized disubstituted oxazole and a phosphate ester, rarely found in natural polyketides. The macrolactone includes seven stereogenic centers and an embedded *syn*-2,6-disubstituted tetrahydropyran ring with an *exo*-methylene group. Enigmazole A shows cytotoxic activity against numerous cancer cell lines at significant concentrations. Structural siblings of it interfere selectively with mutant c-Kit signaling which is an important target for cancer treatment. The differentiation is found in less than 0.03% of tested natural products. This exceptional structure and the rare pharmacological activity make enigmazole A an attractive target for total synthesis.



Scheme 1: *Retrosynthetic analysis of enigmazole A.*

A concise and convergent synthesis of this natural product was envisioned featuring a sequence of a ring closing alkyne metathesis (RCAM) and a post-metathesis functionalization by a nobel metal-catalyzed rearrangement with subsequent hydroalkoxylation.

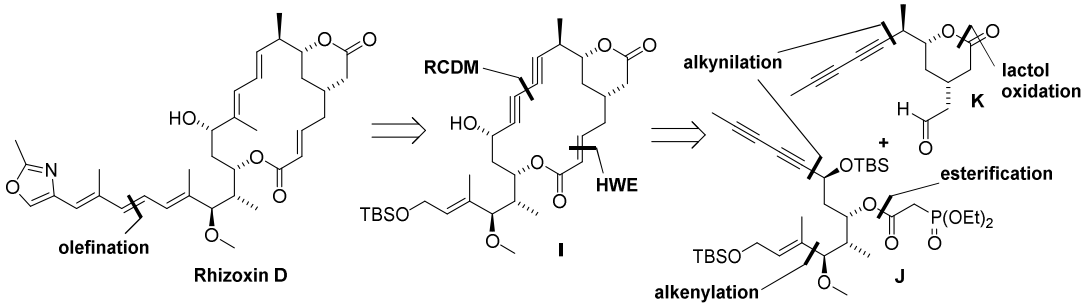
The required fragment **E** was accessed in 11 steps from a commercial oxazole precursor by a palladium-catalyzed C–H activation and a Keck allylation reaction. Enantioselective allylation of aldehyde **E** and stannane **C** (5 steps) and subsequent Yamaguchi esterification with acid **D** (8 steps) afforded the metathesis precursor. Smooth RCAM created the 18-membered macrocycle in excellent yields.



Scheme 2: *Illustration of the π-acid catalyzed cascade reaction.*

A gold-catalyzed [3,3]-sigmatropic rearrangement of the propargylic acetate (**F**) alongside the alkyne followed by a transannular hydroalkoxylation (**H**) of allene **G** gave exclusively the desired *syn*-tetrahydropyran ring **A** in excellent yields. The use of a chiral gold catalyst was mandatory in this transformation to obtain a diastereomerically matched system with the substrate **B**. Finally, enigmazole A was obtained after standard manipulations.

Rhizoxin D was isolated from an endosymbiotic bacterium of the genus *Burkholderia* which causes the rice seedling blight disease. Its unprecedented structure exhibits a strained 16-membered macrocycle containing three (*E*)-olefins, a δ-lactone and a highly unsaturated sidechain which is terminated with an oxazole heterocycle. The selective cytotoxicity of rhizoxin D and its derivatives against cancer cell lines led to clinical trials as potential drug candidate. This high pharmacological potency and the strained structure drew attention to several research groups to pursue syntheses of this molecule.



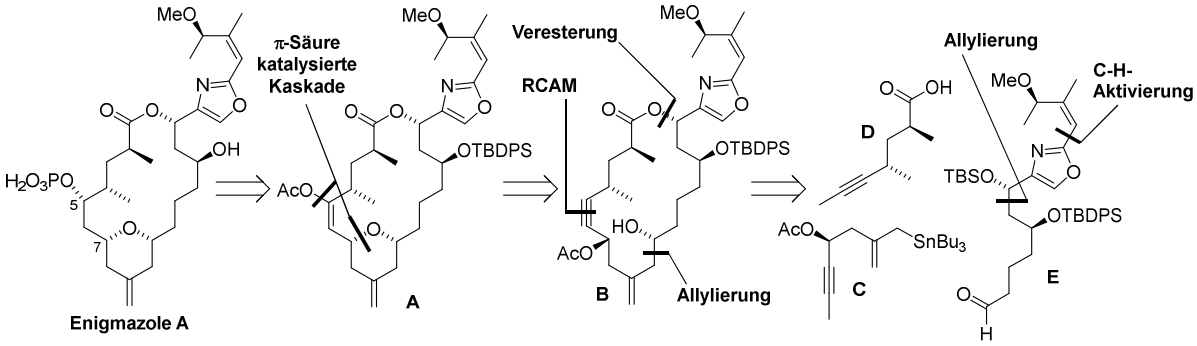
Scheme 3: *Retrosynthetic analysis of rhizoxin D.*

The designed synthesis featured two key transformations: a ring-closing diyne metathesis (RCDM) and a substrate-directed ruthenium-catalyzed hydrostannation of a 1,3-diyne to create the embedded 1,3-(*E*,*E*)-diene.

For this strategy fragment **K** (6 steps) was prepared by an oxidation of thermodynamically resolved lactols. Fragment **J** (11 steps) was accessible by a challenging alkenylation and an esterification. The 1,3-diynes in both molecules were installed by alkynylation reactions with 1,3-pentadiyne. Horner–Wadsworth–Emmons coupling (HWE) of fragments **J** and **K** gave the metathesis precursor, which underwent RCDM to obtain macrocycle **I** in moderate yields. Further investigations on the final steps of the total synthesis of rhizoxin D are ongoing.

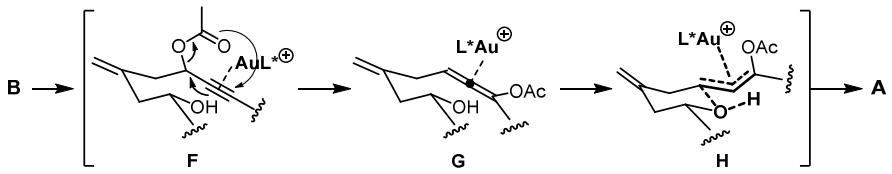
Zusammenfassung

Enigmazole A gehört zu einer Familie von Naturstoffen, die aus dem Schwamm *Cinachyrella enigmatica* isoliert wurden. Sie sind die ersten bekannten phosphorylierten Makrolaktone maritimen Ursprungs. Der 18-gliedrige Makrozyklus enthält unter anderem sieben Stereozentren, einen *syn*-2,6-disubstituierten Tetrahydropyranring mit einer *exo*-Methylengruppe und eine Seitenkette mit einem hoch funktionalisierten Oxazol Heterozyklus. Enigmazole zeigen bereits bei niedrigen Konzentrationen eine sehr hohe Zytotoxizität gegen eine Vielzahl von Krebszelllinien. Darüber hinaus zeigen strukturverwandte Verbindungen aus dieser Familie eine selektive Interaktion mit mutierten c-Kit Proteinen, welche ein bedeutendes Ziel bei der Therapie von Krebs sind. Weniger als 0,03% von fast 135 000 getesteten Naturstoffen zeigen diese Unterscheidung zwischen gesunden und mutierten c-Kits.



Schema 1: *Retrosynthetische Analyse von Enigmazole A.*

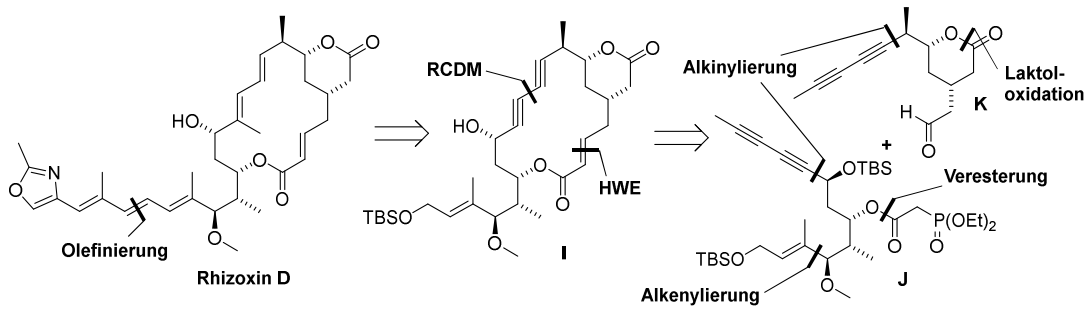
Eine effiziente Synthese von Enigmazole A wurde realisiert durch die Kombination aus Ringschlussmetathese (RCAM) und anschließender Funktionalisierung der entstandenen Dreifachbindung durch eine Gold-katalysierte Umlagerung gefolgt von einer Hydroalkoxylierung.
Das Fragment **E** wurde u.a. durch eine Palladium-katalysierte C-H-Aktivierung und eine Keck-Allylierung ausgehend von einem Oxazol Heterozyklus in 11 Stufen hergestellt. Mittels enantioselektiver Allylierung zwischen Aldehyd **E** und dem Stannan **C** (5 Stufen) und darauf folgender Yamaguchi-Veresterung mit **D** (8 Stufen) konnte der Metathesevorläufer hergestellt werden. Eine RCAM schloss den 18-gliedrigen Makrozyklus in sehr guten Ausbeuten.



Schema 2: *Vorgeschlagener Mechanismus der π-Säure-katalysierten Kaskadenreaktion.*

Eine Gold-katalysierte [3,3]-sigmatrope Umlagerung des propargylischen Acetats (**F**) entlang der Dreifachbindung, gefolgt von einer transannularen Hydroalkoxylierung (**H**) des Allens **G** lieferte ausschließlich den gewünschten *syn*-Tetrahydropyranring **A** in sehr guter Ausbeute. Für diese Reaktion war die Wahl eines chiralen Goldkatalysators unerlässlich, um ein passendes Diastereomerenpaar von Katalysator und Startmaterial zu erhalten. Von **A** ausgehend konnte schließlich Enigmazole A durch Standardmodifikationen hergestellt werden.

Rhizoxin D wurde aus einem endosymbiontischen Bakterium der Gattung *Burkholderia* isoliert, welches die wirtschaftlich bedeutsame Reiskeimlingsfäule auslöst. Es besteht aus einem spannungsreichen 16-gliedrigen Makrozyklus mit drei (*E*)-Olefinen, einem δ-Lakton und einer ungesättigten Seitenkette, die mit einem Oxazol endet. Wegen der selektiven Zytotoxizität der Vertreter dieser Naturstofffamilie wurden klinische Studien mit ihnen als Krebstherapeutika durchgeführt.



SchemA 3: *Retrosynthetische Analyse von Rhizoxin D.*

Die geplante Syntheseroute enthält zwei Schlüsselschritte: eine Ringschluss-Diin-Metathese (RCDM) und eine substratgesteuerte Ruthenium-katalysierte Hydrostannylierung eines 1,3-Diins, zur Darstellung des 1,3-(*E,E*)-Diens.

Zu diesem Zwecke wurden die Fragmente **J** (11 Stufen) und **K** (6 Stufen) durch eine Horner–Wadsworth–Emmons Kupplung (HWE) zum Metathesevorläufer kombiniert. In beiden Fragmenten wurden die Diin-Motive durch Alkenylierungsreaktionen mit 1,3-Pentydiin hergestellt. Durch RCDM konnte der geschlossene Makrozyklus **I** in akzeptablen Ausbeuten hergestellt werden. Derzeit laufen weitere Optimierungsversuche in unserer Gruppe, um die Totalsynthese von Rhizoxin D zeitnah abzuschließen.

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1. Introduction:

1.1. Total Synthesis

In my opinion, the beauty of total synthesis is the never ending competition of laboratory synthesis with Mother Nature. Nature is able to synthesize remarkable and intricate molecules and synthetic chemists have been trying to emulate this ever evolving process, which occurred over millions of years.

The current state-of-the-art in total synthesis is the culmination of the past 200 years of developments in organic synthesis.[1] The first total synthesis was performed by Wöhler in 1828, who synthesized urea from cyanic acid and ammonia.[2] Even though one could argue that the preparation of urea is not a total synthesis, it proved the principle that organic molecules are accessible from inorganic material without the attendance of living organisms. In the ensuing 100 years, relatively simple – but fundamentally important – chemicals like acetic acid (1845)[3], fructose (1886)[4] or camphor (1903)[5] were prepared in multistep syntheses. Modern targets for total synthesis are increasingly complex as shown by a selection of recently completed natural products (Figure 1.1).

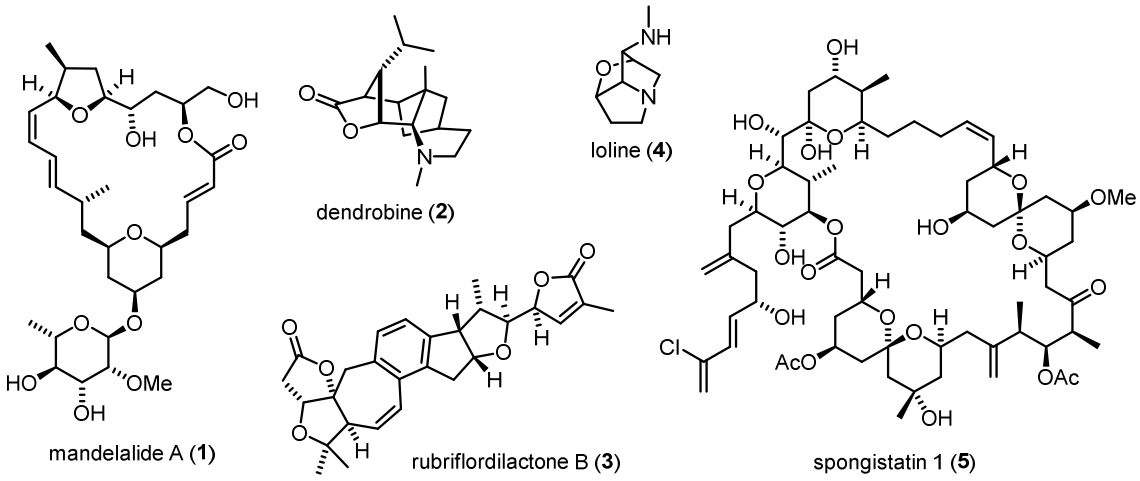


Figure 1.1: *Examples of recently synthesized natural products: mandelalide A[6], rubriflordilactone B[7], loline[8], dendrobine[9] and spongistatin 1[10].*

Natural product chemistry should be seen as an evolving, interdisciplinary science with its constituent parts being, *inter alia*, biology, computational chemistry, pharmacology, and, in particular, organic synthesis. Although the target natural products have become more challenging and the techniques of organic synthesis have improved, the three main objectives of total synthesis remain unchanged:

1) the investigation and understanding of chemical reactions,
2) the preparation (and derivatization) of molecules which are not easily accessible from natural sources, and
3) the structural elucidation of natural products.[1]

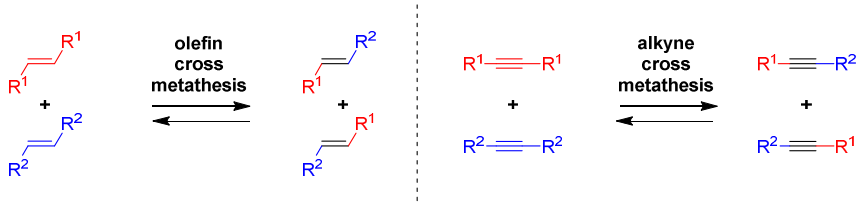
The complex structures of natural products, having numerous functional groups and stereocenters in a unique architecture, offer a tremendous challenge to chemists, especially in terms of selectivity. Therefore, total synthesis can serve as the ultimate setting for the testing and improvement of new methodologies. Furthermore, despite modern analytical methods, structural misassignments of natural products are still regularly published and total synthesis remains the ultimate tool to confirm or reassign the most complex structures.[6a, 11] In addition to these core aims, modern organic synthesis also strives to face up to environmental and social challenges.[12] Concepts such as atom economy[13] and interfacing with medicine have truly changed our understanding of organic synthesis.[1]

One of the most important contributions of total synthesis to society is the development of new therapeutics for a range of diseases including bacterial infections, dementia and cancer.[14] Once a molecule with promising therapeutic properties is discovered in nature, total synthesis can be employed to afford usable quantities for bioactivity studies. Furthermore, by divergent synthesis, libraries of non-natural congeners can be created.[15]

Macrocyclic compounds are among the most desirable to medicinal chemists due to their ring architecture.[16] They can exhibit a higher potency as well as a higher selectivity in drug-protein-interactions by the structural preorganization compared to less conformationally rigid molecules.
The synthesis of macrocyclic compounds, however, is challenging for both enthalpic (ring strain) and entropic (loss of conformational degrees of freedom) reasons.[17] One method for macrocyclization that made rapid progress over the last two decades is ring-closing alkyne metathesis. This methodology is the central theme of this thesis.

1.2. Ring-Closing Alkyne Metathesis

Over the past 50 years, olefin metathesis (Scheme 1.1) has become one of the most powerful C–C bond forming reactions, owing to its high chemoselectivity, reliability and the commercial availability of a broad range of transition metal catalysts which show excellent stability and a high level of functional group tolerance.[18] The immense impact of this methodology has been recognized by the scientific community with the award of the Nobel Prize in Chemistry in 2005 to Chauvin, Grubbs and Schrock "for the development of the metathesis method in organic chemistry".[19]



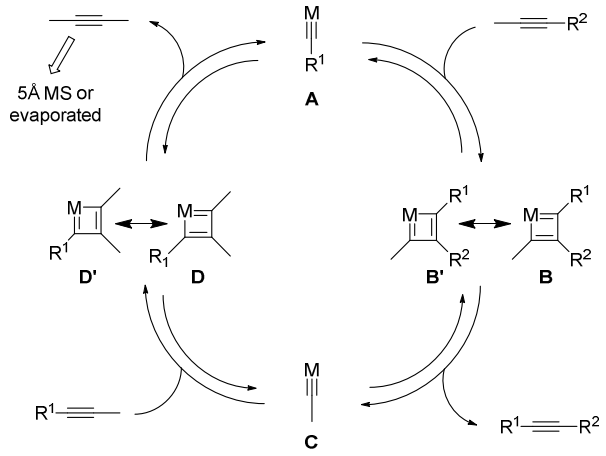
Scheme 1.1: *Illustration of olefin and alkyne metathesis.*

Olefin and alkyne metathesis (Scheme 1.1) are powerful tools in total synthesis, owing to the redox neutral rearrangements of unsaturated C–C bonds with the potential for further functionalization of the installed bonds through redox reactions, hydroelementation or π-acid catalysis (Chapter **1.3**). Alkyne metathesis, which gained popularity by the work of Fürstner *et al.*,[20] offers great potential for building structural complexity. Alkynes allow access not only to the same motifs accessible by olefin metathesis, such as olefins and alkanes, but also to new and different structures, such as heterocycles and carbonyl derivatives.

The first example of alkyne metathesis was reported in 1968 by Pennella *et al.* (Figure **1.2**).[21] They observed that WO_3 on silica catalyzes the scrambling of 2-pentyne into 2-butyne and 3-hexyne at 200-450 °C. Six years later, Mortreux and Blanchard utilized a mixture of $[Mo(CO)_6]$ and resorcinol to metathesize aromatic alkynes at 160 °C in homogeneous solution. The molybdenum likely forms *in situ* some kind of alkylidyne species with phenolate ligands.[22] However, the competing polymerization of the starting materials with Pennella's tungsten catalyst and the harsh reaction conditions (temperatures far above 150 °C) in both of these systems limited the application of metathesis at this time.[23]

The generally accepted mechanism for alkyne metathesis (Scheme 1.2) was first proposed by Katz and McGinnis[24] in 1975, only one year after the discovery of the Mortreux[22] catalyst. Their proposal was analogous to the Chauvin cycle[25] for olefin metathesis. Schrock *et al.* subsequently

studied the properties of high-valent alkylidyne complexes and isolated catalytically active metallacyclobutadiene species (**B** and **D**), giving support to this mechanism.[26]



Scheme 1.2: *Generally accepted mechanism of alkyne metathesis for two methyl capped alkynes.*

According to the mechanism, a metal alkylidyne species **A** reacts with the alkyne substrate in a formal [2+2] cycloaddition forming metallacyclobutadiene **B**. Cycloreversion of its resonance **B'** releases the product R^1-C≡C-R^2 and generates alkylidyne **C**. This species undergoes another [2+2] cycloaddition and cycloreversion with the second substrate, releasing butyne as a byproduct, and regenerating alkylidyne **A**. Since all cycloadditions and cycloreversions are in equilibrium, removing the butyne from the catalytic cycle, either by absorption with molecular sieves or by evaporation, ensures that the reaction is driven towards the desired product. High-valent alkylidyne complexes of molybdenum, rhenium and tungsten have all been shown to follow this cycle.[26c]

In 1981, the first well-defined alkyne metathesis catalyst **6** was developed by Schrock *et al*.[26a, 26b] and this tungsten neopentylidyne still serves as a benchmark catalyst decades later.[27] The bulky alkoxide ligands impede dimerization of the complex via oxygen bridges and subsequent decomposition. The scope is however limited because of the high Lewis acidity of the tungsten center, which does not tolerate coordinating groups like amines or carboxylates.[20] In contrast to the high metathetic activity of **6**, the molybdenum analogue [(*t*BuO)$_3$Mo ≡ CCMe$_3$] showed essentially no catalytic activity.[28]

The trisamido molybdenum complex **7**, originally designed by Cummins for the stoichiometric cleavage of nitrogen,[29] finally ended the "tungsten age" of metathesis catalysts. Complex **7** reacts with dichloromethane to form *in situ* a catalytically active complex which, due to its lower Lewis acidity, tolerates a much broader variety of functional/coordinating groups. Therefore this

catalytic system was the catalyst of choice in the Fürstner group for over ten years. Nevertheless, the broad applicability of this catalyst still suffered from its high sensitivity toward oxygen, nitrogen and moisture.

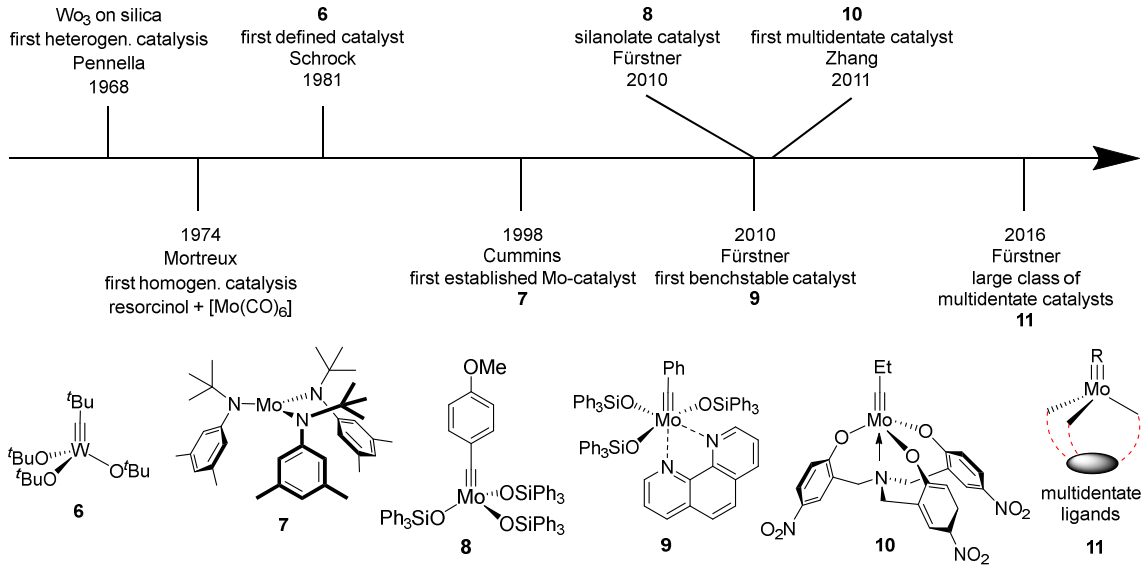


Figure 1.2: *The historic timeline of the development of alkyne metathesis catalysts.*

In 2010, Fürstner *et al.* developed a silanolate ligated molybdenum catalyst **8**, which extended the scope of alkyne metathesis to highly functionalized, sensitive and elaborate substrates under mild conditions.[30] The combination of the high-valent molybdenum center and three arylsilanolates ensures a balance of stability and activity. Furthermore, catalyst **8** could be rendered air stable by complexation with heterocycles like 1,10-phenanthroline (**9**) or pyridine. This development made metathesis user-friendly and the catalysts commercially distributable.[31] The bench-stable precatalysts are converted *in situ* into active species **8** by treatment with manganese(II) or zinc(II) chloride. Only in the cases of extremely sterically demanding alkynes or of molecules with several protic functionalities do the silanolate catalysts **8-9** show poor catalytic activity or lead to polymerization in the case of small substrates.[32]

With such challenging substrates, better results can be achieved with multidentate ligated molybdenum catalysts, which take advantage of the chelate effect. Zhang *et al.*[33] as well as Fürstner *et al.*[34] developed ligand systems allowing transformations beyond the scope of catalyst **8**. In these cases, the active species is formed *in situ* upon addition of precatalyst **12** to one of the ligands **13-15** (Figure 1.3). However, despite significant experimentation, the exact structure of the catalytically relevant alkylidyne remains unknown.

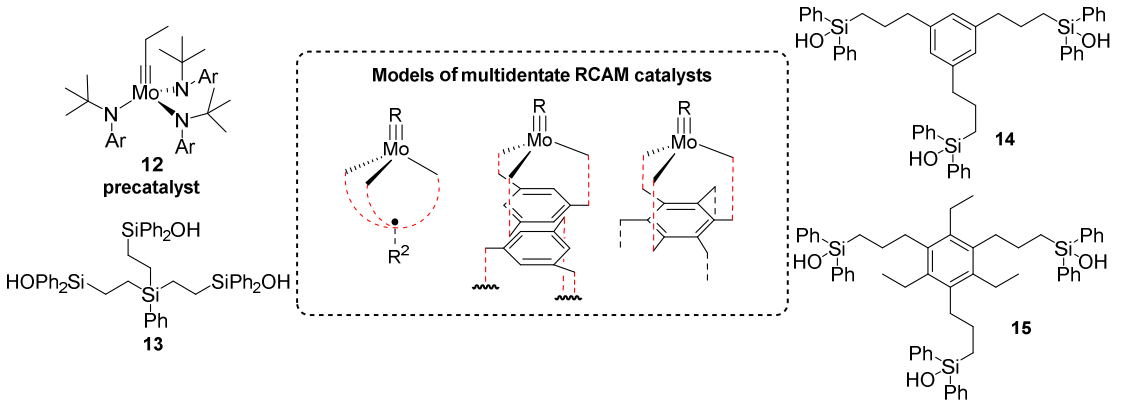


Figure 1.3: *Structure of multidentate RCAM catalysts designed by our group.*

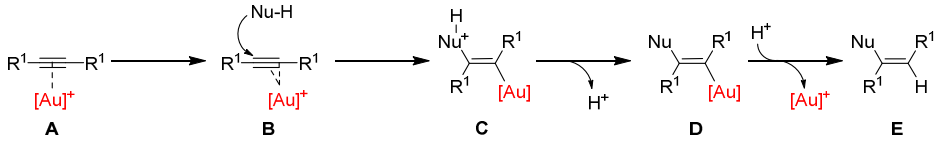
Although, the potential of alkyne metathesis was explored by numerous groups since the development of Schrock's catalyst in 1981, it was only in 1998 that Fürstner *et al.* showed the power of intramolecular alkyne metathesis to create macrocycles.[35] The ability to form macrocycles containing triple bonds sparked a resurgence of interest in alkyne metathesis. Furthermore, the substrate scope was recently extended to enynes and 1,3-diynes, leading to multiple sites for functionalization in the products formed.[36] The value of RCAM has already been shown in the syntheses of a variety of natural products,[20, 37] and is always closely related to the post-metathesis functionalization of the triple bond.

1.3. Post-Metathesis Transformations

To realize the full potential of ring closing alkyne metathesis in the synthesis of natural products, further transformation of the created triple bond is of primary importance. In the Fürstner group, a broad repertoire of possible transformations has been developed for this purpose. Among the most successful ones are, *inter alia*, *trans*-selective hydrogenation[38], π-acid catalysis[39], and selective hydrostannation[40], the latter two having special significance for this thesis.

π-Acid catalysis describes any transformation in which a Lewis-acid[41] (LA) activates an unsaturated C–C bond which then reacts with a nucleophile either in an intra- or intermolecular fashion, giving access to various motifs. According to the theory of hard and soft acids and bases (HSAB) by Pearson,[42] LAs and Lewis bases (LB) can be categorized by their polarizability. For example, hard LAs are less polarizable (higher electronegativity) than soft ones. This categorization allows general predictions on the affinity and reactivity of LA/LB to be made (hard LAs form stronger interactions with hard LBs). In order to activate a soft LB, such as an alkyne, a soft LA is required. Platinum(II) and gold(I) are especially suited to this task, and their applications have made π-acid catalysis to one of the most rapidly growing disciplines of catalysis.[39]

The high nuclear charge of these noble metals causes a contraction of the s-orbitals which strongly shield the outer 5d and 4f-orbitals.[43] These orbitals are therefore diffuse in nature and give these metal cations their soft LA properties. Interaction of these soft LAs with alkynes results in the formation of π-complexes (**A**, Scheme 1.3). Activation of the π-system (as described by the Dewar-Chatt-Duncanson model[44]) enables a nucleophile to attack with anti-selectivity (**B**) under mild conditions. Slippage of the gold along the π-system affords intermediate **C** which, after proton transfer and proto-deauration, releases the product **E** and regenerates the catalytic species.

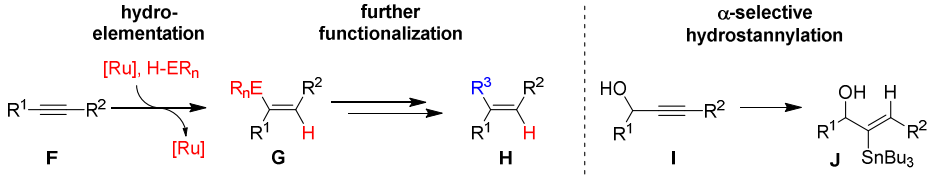


Scheme 1.3: *Illustration of π-acid catalysis for alkyne and gold(I).*

π-Acid catalysis with gold (or other metals) provides the possibility to use alkynes in a broad variety of transformations, such as nucleophile additions, (cyclo-) isomerizations and cycloadditions. Of particular importance is the ability to form new (hetero-) cycles or extend existing ones, making π-acid catalysis a very powerful method in total synthesis.

Another method for the functionalization of alkynes is hydroelementation which refers to the addition of H–ER_n (E = Sn, B, Si etc.) across double or triple bonds. Classical hydroelementation reactions, such as hydroborations,[45] traditionally occur in a *syn*-fashion, limiting their versatility. In 2001, Trost *et al.* reported the ruthenium-catalyzed *trans*-hydrosilylation of alkynes, which extended the synthetic scope immensely.[46] Due to the high interest of our group in alkyne functionalizations, we have investigated such *trans*-selective hydroelementations. Recent results include the development of the *trans*-selective ruthenium-catalyzed hydroelementation of alkynes with boranes[47] or stannanes.[40] Catalyzed hydrostannation reactions, in particular, render (*E*)-olefins accessible by a hydrostannation and subsequent destannation sequences, tolerating a broad scope of functional groups including motifs which would not survive established "non-catalyzed" hydrostannation protocols (relying on Lewis acids or free-radicals). Furthermore, hydroelementation reactions provide a handle for additional functionalizations of the resulting alkenyl metal species. For example, the combination of hydroelementation (**F** → **G**, Scheme 1.4) with cross coupling (**G** → **H**) allows for the synthesis of tri-substituted olefins.

In addition, a cooperative effect between the Ru-catalyst and a protic functionality in an unsymmetric alkyne ensures region-control of the hydrostannation (Scheme 1.4). The presence of a hydroxy directing group (**I**), for example, results in very high α–regioselectivity in favor of product **J**. In this work, we will rely on this remarkable selectivity and will showcase its usefulness in the late stages of the synthesis of a natural product.



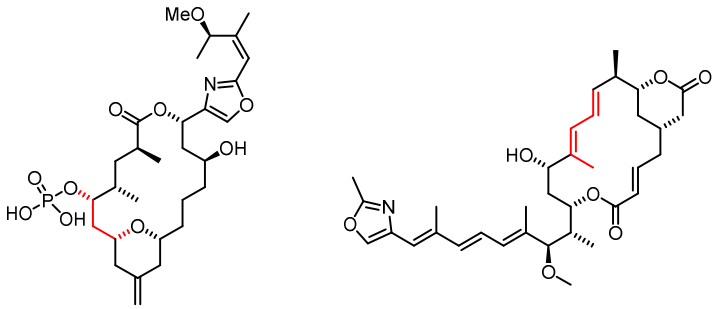
Scheme 1.4: *Illustration of hydroelementation reactions on alkynes.*

2. Aim of this Thesis

After developing the latest generation of alkyne metathesis catalysts and demonstrating their utility in several total syntheses, post-metathesis functionalization became a major interest in the Fürstner group. Novel and reliable methodologies for alkyne functionalization would allow access to additional chemical motifs and enhance the importance of RCAM in organic synthesis. This thesis is focused on the investigation of new strategies for the functionalization of alkynes and their applications in two natural product syntheses (Figure 2.1).

First, an unprecedented metal-catalyzed [3,3]-sigmatropic rearrangement/transannular hydroalkoxylation cascade is described, giving access to a *syn*-tetrahydropyran from a propargylic acetate in a single step. This new methodology is applied, as the post-metathesis transformation, in the total synthesis of enigmazole A (**16**).

Second, the combination of two recently reported methodologies from the Fürstner group, ring closing diyne metathesis and α-selective *trans*-hydrostannation, enabled access to macrocyclic, trisubstituted 1,3-(*E,E*)-dienes in an elegant and concise manner. Rhizoxin D (**17**) was identified as a suitable target for this sequence of reactions.



Enigmazole A (16) **Rhizoxin D (17)**

Figure 2.1: *Structures of the targeted natural products. The functionalized alkynes are highlighted in red.*

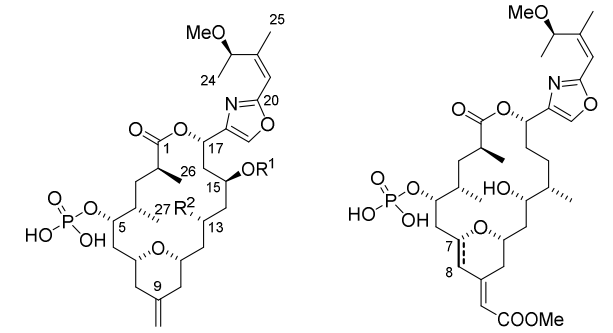
Furthermore, the applied methodologies would grant divergence to efficiently synthesize unnatural, structural derivatives of **16** and **17**. These derivatives could contribute to pharmacological studies and, as a consequence, help to discover new lead structures for anti-cancer therapeutics.

3. Total Synthesis of Enigmazole A

3.1. Introduction

3.1.1. Isolation and Structure

Enigmazole A (**16**) and its congeners, 15-*O*-methylenigmazole A (**18**) and 13-hydroxy-*O*-methylenigmazole A (**19**), have been isolated from the marine sponge *Cinachyrella enigmatica* in 2010 (Figure 3.1) and represent the first phosphorylated macrolides of marine origin.[48] *C. enigmatica* was collected in 1998 in Papua New Guinea as part of the marine collection program of the U.S. National Cancer Institute. In addition to the aforementioned natural products, another member of the family, *i.e.* enigmazole B (**20**), was reported in two dissertations, which however disagree on the saturation between carbon C7 and C8 (Scheme 3.1).[49]



Enigmazole A R^1 = H R^2 = H (16)
R^1 = Me R^2 = H **18**
R^1 = Me R^2 = OH **19**

Enigmazole B (20)

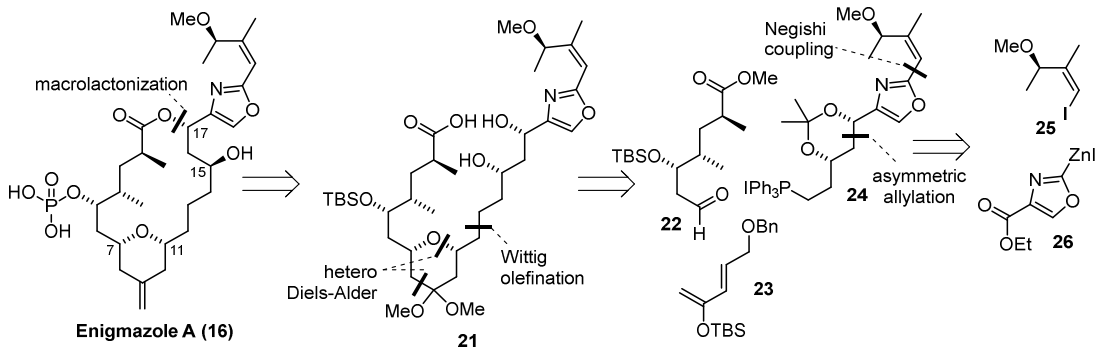
Figure 3.1: *Structures of the enigmazole family.*

Alongside the 18-membered macrocyclic ring, **16**–**18** feature an embedded 2,6-disubstituted 4-methylenetetrahydropyran ring and a densely functionalized 2,4-disubstituted oxazole sidechain attached at C17. In addition, **16**–**18** present a phosphate ester at C5, a rare feature found in only a few polyketide natural products.[50] The structure of enigmazole A (**16**) was elucidated by derivatization, degradation experiments and intensive 1D and 2D NMR analyses which revealed the absolute configuration of the eight stereogenic centers. Molecular modeling studies were in agreement with the stereochemistry assignments. The first total synthesis by Molinski *et al.* [51] published back-to-back with the isolation paper confirmed the absolute stereochemistry.

3.1.2. Literature Review

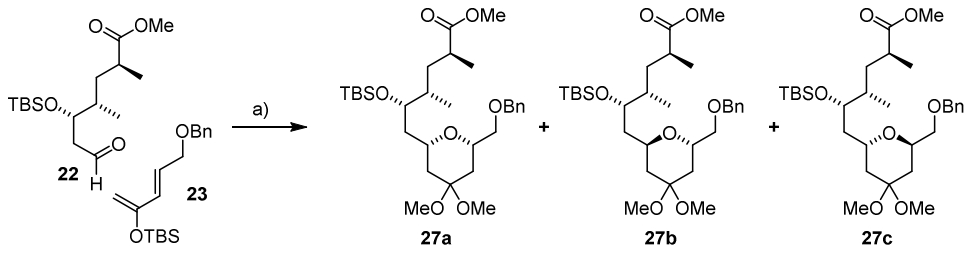
Total Synthesis by the Molinski group 2010

The first total synthesis of enigmazole A (**16**) was reported by Molinski *et al.* in 2010.[51] As shown in the retrosynthetic analysis (Scheme 3.1), a macrolactonization of **21** was envisioned as the ring closing event. The key intermediate **21** was prepared by a hetero Diels-Alder reaction between **22** and **23**, constructing the *syn*-tetrahydropyran ring, followed by Wittig olefination with **24**. Fragment **24** was accessed by two-directional heterocycle extension by (i) Negishi cross coupling of oxazole **26** with iodide **25** and (ii) subsequent asymmetric allylation. The hetero Diels-Alder reaction and the macrolactonization proved to be particularly challenging and required detailed investigations.



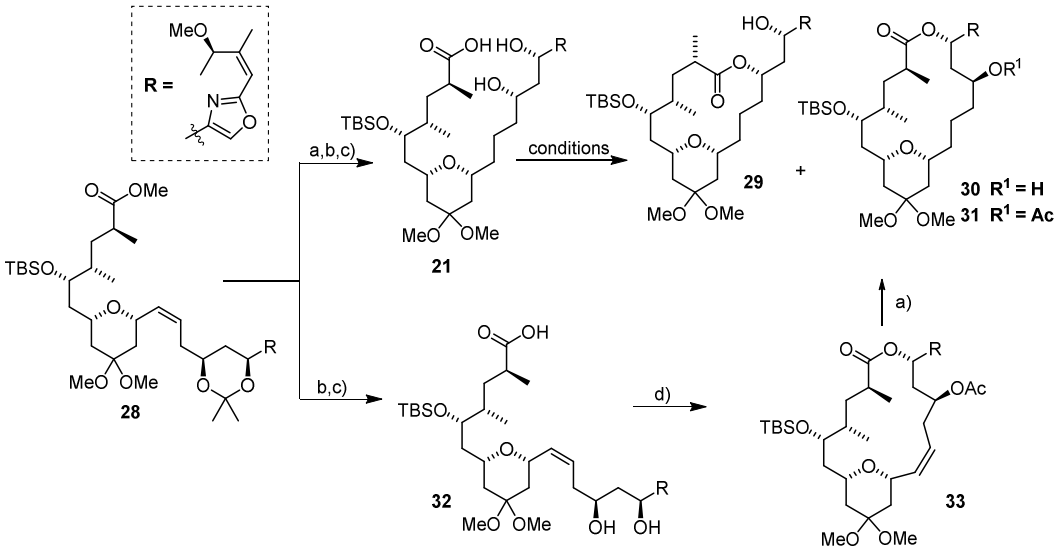
Scheme 3.1: *Retrosynthetic analysis of Molinski's synthesis of enigmazole (**16**).*

To achieve stereocontrol of the hetero Diels-Alder reaction between **22** and **23**, a range of chiral Lewis acids was screened. However all attempts at reagent-controlled stereoselectivity proved to be unsuccessful and did not afford the desired diastereomer **27a** (Scheme 3.2). Instead, achiral Lewis acid catalysis afforded **27** in good yield (81%) but as a mixture of three diastereomers. Gratifyingly, this substrate-control afforded **27a** as the major product (*d.r.* >3:1) which could be separated from the minor isomers.



Scheme 3.2: *Hetero Diels-Alder reaction of fragments **22** and **23**: Conditions: a) $BF_3{\cdot}OEt_2$, (cat.), DCM, −78 °C, then $CH(OMe)_3$, MeOH, CSA, −78 °C → rt, 81%.*

After deprotection and oxidation of **27a**, the Wittig olefination of the corresponding aldehyde and **24** gave fragment **28** (Scheme 3.3). A sequence of protecting group manipulations and hydrogenation of the (*Z)*-olefin gave access to compound **21**. Attempts at regioselective macrolactonization of **21** to obtain **30** using various conditions were low yielding and gave the undesired 16-memebered macrocycle **29** as the major product (best conditions: **29**:**30** = 3:1 and only 31% yield). Molinski *et al.* suspected that **29** was kinetically and thermodynamically favored over **30**.



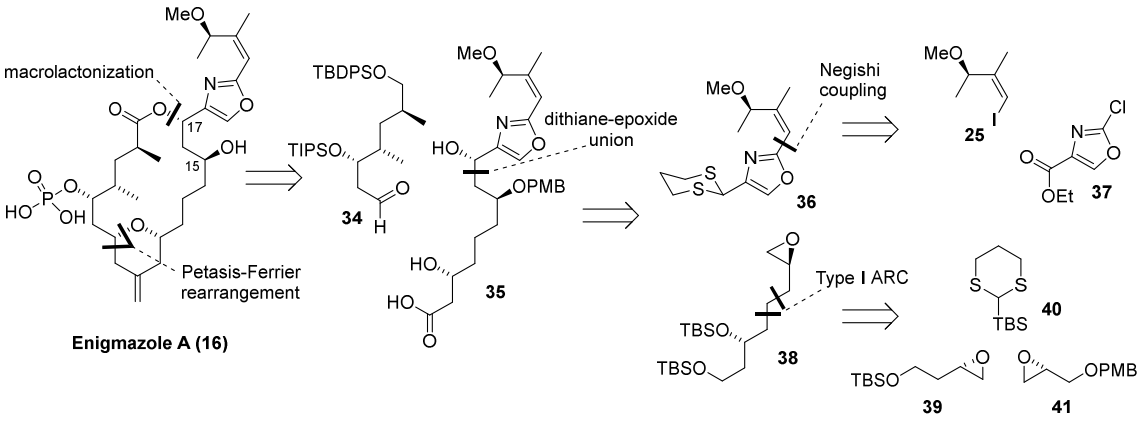
Scheme 3.3: *Molinski's optimization of the Keck macrolactonization. Conditions: a) $(PPh_3)_3RhCl$ (cat.), H_2, THF/t-BuOH (1:1), 50 °C, 83% (**21**), 70% (**31**); b) LiOH, MeOH/H_2O, 80 °C; c) CSA (cat.), MeOH, rt, quant. over 2 steps (**21**); d) (i) DCC, DMAP, DMAP·HCl, $CHCl_3$, reflux, then (ii) AcOH, MeOH, 35% over 3 steps (**33**).*

To overcome this regioselectivity issue, the order of hydrogenation–macrocyclization was reversed. Precursor **32**, still bearing the (*Z*)-olefin, allowed for selective macrocyclization under Keck conditions to form the 18-membered ring **33**, which was acetylated *in situ* to prevent further ring contraction. Hydrogenation of **33** afforded the desired macrocycle **31**, containing all of the stereocenters of enigmazole A (**16**). Standard transformations and protecting group manipulations ultimately gave access to the natural product **16** in 24 steps (LLS) with an overall yield of 0.16%.

Total Synthesis by the Smith group 2015

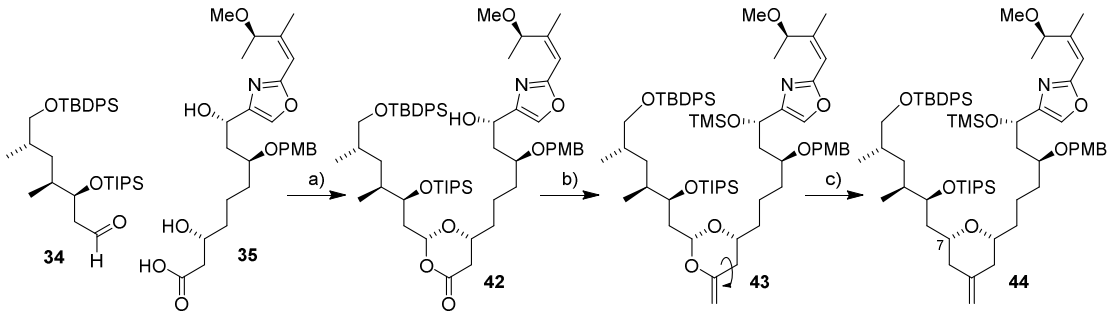
Independent from the work described in this thesis, Smith *et al.* reported a total synthesis of enigmazole A (**16**) featuring a distinct strategy.[52] As shown in the retrosynthetic analysis (Scheme 3.4), macrolactonization, similar to that in Molinski's synthesis, was employed to generate the 18-membered macrolactone in excellent yield (89%). The choice of orthogonal

protecting groups at the C15 and C17 hydroxy groups prevented the formation of the undesired 16-membered macrolactone in this step. The key motif, the *syn*-tetrahydropyran, was formed in a three-stage sequence including Petasis-Ferrier rearrangement, employing fragments **34** and **35**. The main fragment **35** was accessible from dithiane **36** and epoxide **38**. Dithiane **36** was prepared by Negishi coupling, and **38** arose from a multicomponent Type I Anion Relay Chemistry, previously developed by the Smith group.[53]



Scheme 3.4: *Retrosynthetic analysis of Smith's synthesis of enigmazole A (**16**).*

The approach by Smith to construct the *syn*-tetrahydropyran is particular convergent, as seven of the eight stereocenters were already installed in the two fragments **34** and **35**. Acetalization connected these two building blocks forming dioxanone **42** (Scheme 3.5). After microwave accelerated Petasis olefination, **43** was used in the Ferrier carbocyclization affording a tetrahydropyranone, which was directly transformed to the *exo*-methylene-tetrahydropyran to prevent the retro-Michael fragmentation. The stereochemical configuration at C7 was retained, giving exclusively **44**. Straightforward transformations of **44** finally afforded enigmazole A (**16**) in 22 steps (LLS) with an overall yield of 4.4%.



Scheme 3.5: *The Petasis olefination/Ferrier carbocyclization sequence. Conditions: a) (i) **35**, HMDS, THF, 40–45 °C, then (ii) **34**, TMSOTf, H_2O (cat.), DCM, −78 °C, 95%, d.r. >20:1; b) Cp_2TiMe_2, 2,6-lutidine (cat.), toluene/THF, MW 100 °C, 87%; c) Me_2AlCl, DCM, −78 °C, 30 sec., then $Ph_3P{=}CH_2$, 84%, d.r. >20:1.*

3.1.3. Bioactivity

Enigmazole A (**16**) was found to be the most cytotoxic component of the *Cinachyrella enigmatica* extracts, and therefore it was tested in the NCI 60-cell antitumor assay.[48] It showed significant cytotoxic activity against 60 human tumor cell lines (IG_{50} value of 1.7 µM), but no specificity among the cell lines. Therefore, further analysis to identify the molecular target or certain cytotoxic pathways for its activity could not be performed.[54] Because of structural similarity to calyculin A, which is known to be a potent serine/threonine protein phosphatase inhibitor,[55] enigmazole A (**16**) was also tested against a panel of 16 different protein phosphatase enzymes including PPT1 and PPT2A.[56] It showed no activity at concentrations ≤40 µg/mL, thereby indicating that its cytotoxic effect is not related to the inhibition of phosphatases. Furthermore, enigmazole A (**16**) was screened in an assay with 70 different protein kinases to rule the possibility out that it interferes in the cellular phosphorylation dynamics by blocking the addition of phosphate groups to proteins. Once again the molecule was inactive at concentrations ≤40 µg/mL. Proteins controlling the function of cellular signal transduction pathways are often regulated by their phosphorylation state and disruption of these functions can result in inhibited growth or cell death. The phosphate group present in **16** could potentially interfere with those pathways. However, despite extensive tests Gustafson *et al.* could not find any evidence to support this hypothesis.[48]

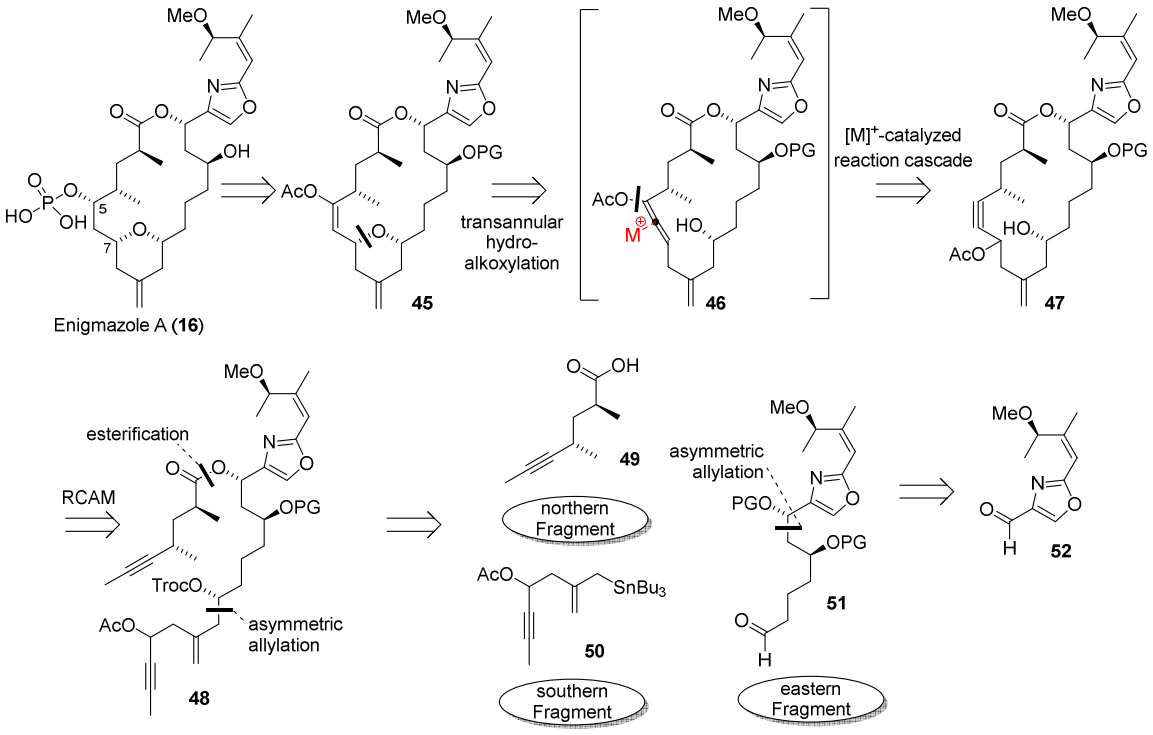
The most important observation was made in an assay for the inhibition of the receptor tyrosine kinase protein (c-Kit).[57] This receptor is an evolutionary highly conserved transmembrane glycoprotein with tyrosine kinase activity. The receptor shares structural homology with platelet-derived growth factor receptor (PDGFR) and macrophage colony-stimulating-factor receptor (CSF-1). c-Kit signaling plays a very important role in the regulation of the red blood cell production, lymphocyte proliferation, mast cell development and function, melanin and gamete formation.[57] It subsequently regulates gene expression and the proliferation, differentiation, growth and survival of hematopoietic cells.[57] Mutations of c-Kit have been associated with several cancers, for example systemic mastocytosis, acute myelogenous leukemia and gastrointestinal stromal cell tumors.[58] The relevance of this target is confirmed by established kinase inhibitors like imatinib (Gleevec/Glivec©), which targets the c-Kit receptor, among others.[59] While the enigmazoles **16**, **18** and **19** showed no differentiation between wild-type and mutant c-Kit, several advanced chromatographic fractions also isolated from *C. enigmatica* selectively inhibited cells expressing the mutant c-Kit.[48] This phenotypic effect is rarely observed. Only 32 out of 134631

tested natural product extracts produced the desired differentiation.[48, 60] Analysis of the tested fractions referred the activity to structural siblings of enigmazole A (**16**). Gustafson *et al.* planned to communicate the structural and biological characterization of these compounds in subsequent work,[48] but these results already showed the importance of the enigmazole scaffold as a potential lead-structure for anti-cancer drugs.

3.2. Retrosynthetic Analysis of Enigmazole A

Our group envisioned a concise and flexible route for the total synthesis of enigmazole A (**16**) by applying in-house developed RCAM and π-acid catalysis (Scheme 3.6). Our idea was to approach the tetrahydropyran ring and the C5/C7 oxygen pattern via a noble metal-catalyzed [3,3]-sigmatropic rearrangement of the acetate group present in the key intermediate **47**. The formed allene **46** could be engaged in a transannular hydroalkoxylation with the same catalyst, thereby forming compound **45**. This cascade could place all atoms in position and deliver the enol acetate at C5 as a handle for the installation of the phosphate ester. The chemo- and stereoselectivity of this cascade is crucial to the success of this route. A synthetical equivalent could be obtained by a stepwise approach via enone formation followed by an oxa-Michael addition.[61]

Macrocycle **47** could be derived from diyne **48** by RCAM. The open macrocycle **48** could be accessed by allylation of the southern fragment **50** with the eastern fragment **51** and subsequent esterification with the northern fragment **49**. The eastern fragment **51** could be prepared by an allylation reaction performed on literature known oxazole **52**.

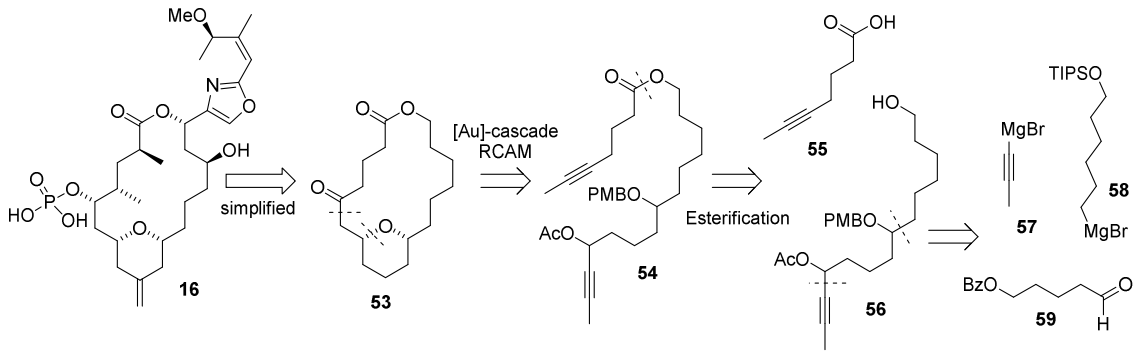


Scheme 3.6: *Retrosynthetic analysis of enigmazole A (**16**).*

3.3. Model System

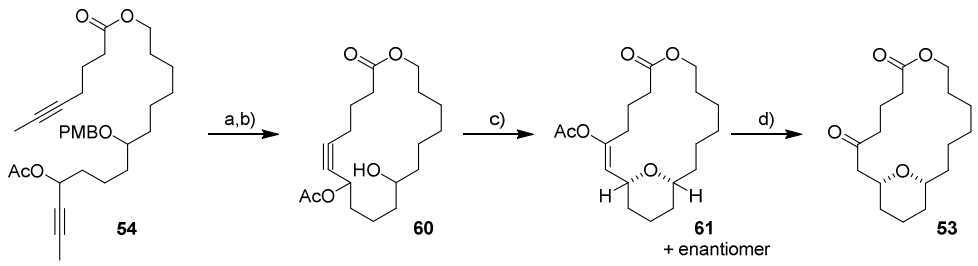
Prior to the total synthesis, our group studied the key steps on the simplified model substrate **53**. This compound was prepared by Dr. de Haro in 2013.[62]

The key intermediate **54** was obtained by an esterification of **55** and **56** (Scheme 3.7). The main fragment **56** was prepared by the combination of fragments **57**-**59** via two Grignard additions.



Scheme 3.7: *Retrosynthesis of model substrate **53.***

RCAM of **54** afforded **53** in very good yields using molybdenum alkylidyne complex **8** under standard in-house conditions (Scheme 3.8). Both the propargylic acetate and the PMB protecting group were tolerated in the metathesis reaction. Upon oxidative cleavage of the PMB protecting group, compound **60** was obtained. As initially envisioned, treatment of **60** with catalytic amount of $Ph_3PAuNTf_2$ triggered a [3,3]-sigmatropic rearrangement; subsequent transannular hydroalkoxylation afforded the embedded 2,6-disubstituted tetrahydropyran **61** in excellent yield as a single diastereoisomer. Saponification of the acetate group gave the model substrate **53**.

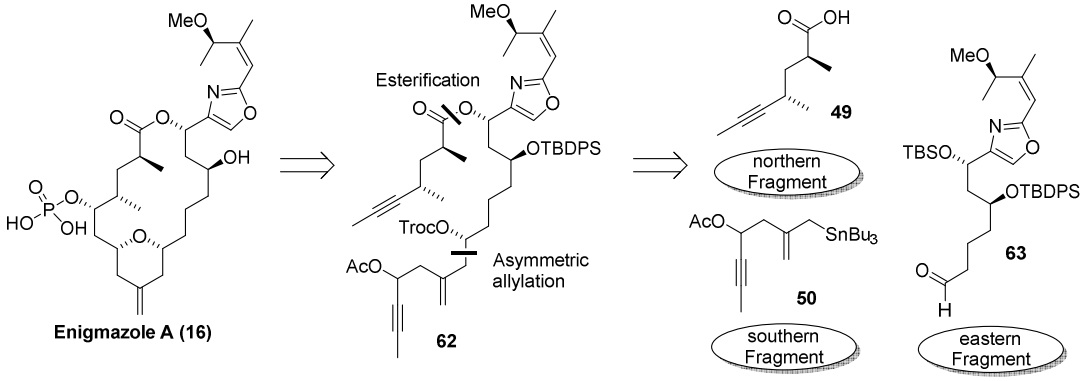


Scheme 3.8: *RCAM and gold catalyzed cascade for the model substrate. Conditions: a) complex **8** (cat.), 5Å MS, toluene, 80 °C, 95%; b) DDQ, DCM/phosphate buffer pH 7 1:1, rt, 98%; c) $Ph_3PAuNTf_2$ (cat.), DCM, rt, 95%; d) in situ addition to c: K_2CO_3, MeOH, rt, 78% (over two steps).*

The NMR analysis and X-ray diffraction confirmed the diequatorial substitution of the tetrahydropyran moiety of **53** ensuring the validity of this model for the total synthesis of enigmazole A (**16**). Encouraged by this model study we proceeded towards the forward synthesis of **16**.

3.4. Synthesis of Enigmazole A

Preceding experiments and results performed by Dr. Teresa de Haro made it possible to directly start into this project with the synthesis of advanced intermediates. Detailed and comprehensive analysis of already established steps allowed access to bigger scales and ensured more material for the investigation of the key steps. The forward synthesis started with the preparation of fragments **49, 50** and **63**. The eastern fragment **63** was part of the longest linear sequence.

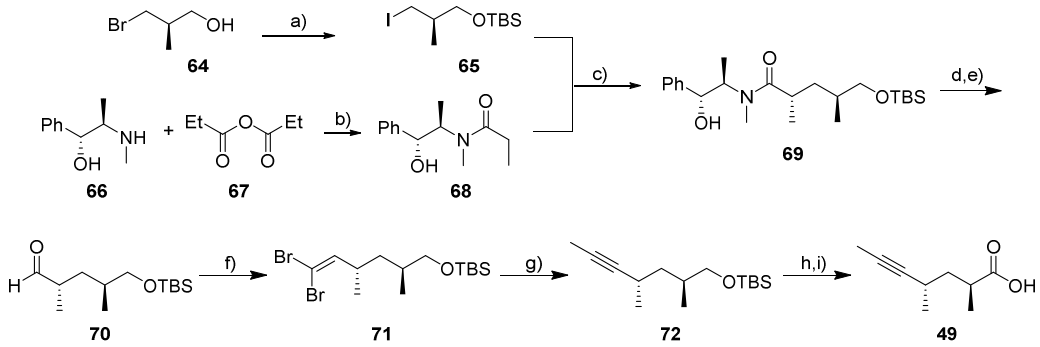


Scheme 3.9: *Retrosynthesis of Enigmazole A (**16**) showing key fragments **49**, **50** and **63**.*

3.4.1. Synthesis of the Northern Fragment

Access to northern fragment **49** was achieved in a straightforward synthesis (Scheme 3.10), starting with a selective asymmetric alkylation of the pseudo-ephedrine derived propionamide **68** with iodide **65,** mediated by lithium diisopropylamide in presence of lithium chloride. Product **69** was obtained in excellent yield and in very high diastereoselectivity (*d.r.* = 96:4; determined at the stage of aldehyde **70**). The well-established methodology of Myers[63] guaranteed reliable access to this route on a multigram scale. Reductive cleavage of the auxiliary gave an primary alcohol as already described before by Panek[64] and subsequent mild ruthenium-catalyzed Ley-Griffith oxidation[65] afforded the literature known aldehyde **70**.[66] This aldehyde was transferred in an alkylative Corey-Fuchs reaction[67] to the end-capped alkyne **72**. The desired product was only isolated when zinc powder was added to the reaction mixture. In the absence of zinc powder the *in situ* generated triphenylphosphine dibromide substituted the silylated alcohol by a bromide.[68] Desilylation and subsequent oxidation afforded the northern fragment **49**.[69] In this oxidation, 4-methylmorpholine *N*-oxide was beneficial by *(i)* stabilizing the aldehyde hydrate intermediate, and *(ii)* recycling the active ruthenium(VIII) catalyst as co-oxidant. Under these conditions, **49** was obtained in excellent yield (92%) without epimerization in the α-position. Alternative oxidative

conditions[70] were not met with success. In summary, **49** was obtained in 8 steps with an overall yield of 37% from commercially available materials.



Scheme 3.10: *Synthesis of northern fragment **49**. Conditions: a) (i)NaI, acetone, reflux; (ii) TBS-Cl, imidazole, DCM, 0 °C, 85% (over two steps); b) Et_3N, DCM, rt, 75%; c) LDA, LiCl, THF, −78°C →rt, 98%; d.r. = 96:4; d) LDA, then $BH_3{\cdot}NH_3$, THF, 0 °C → rt, 89%; e) TPAP (cat.), NMO, 4 Å MS., DCM, 88%; f) CBr_4, PPh_3, Zn, DCM, 74%; g) n-BuLi, then MeI, −78 °C → rt, 97%; h) TBAF, THF, 96%; i) TPAP (cat.), NMO·H_2O, ACN, 92%.*

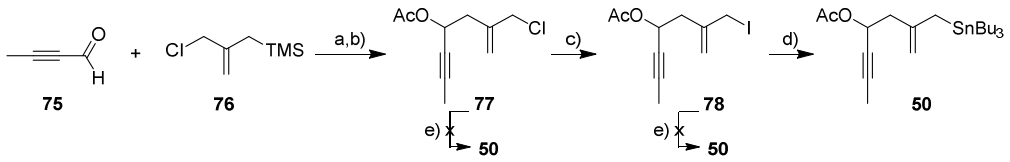
3.4.2. Synthesis of the Southern Fragment

Racemic synthesis:

Synthesis of the southern fragment **50** was originally planned in a racemic fashion. Due to the formation of allene **46** after the [3,3]-sigmatropic rearrangement, the stereochemistry of the migrating acetate group should not influence the stereochemical outcome (discussed in Section **3.4.5**). This hypothesis was further confirmed by studies on the model substrate (Chapter **3.3**).

The synthesis of **50** started from commercially available 2-butynol, which was oxidized to 2-butynal (**75**) (Scheme 3.11). Several oxidation agents were screened, but the best results (67% yield) were obtained by conducting a TEMPO catalyzed biphasic oxidation, employing *N*-chlorosuccinimide as oxidant and tetrabutylammonium chloride as phase transfer agent.[71] The main problems were the purification and handling of **75** due to the volatility and instability. Freshly distilled fractions changed their color from colorless to pink within a few minutes which we associated with decomposition. Despite the color change, **75** could be used in the next step without significant decrease in yield. The lifetime of aldehyde **75** could be extended to several months if stored under argon at −80 °C. Boron trifluoride diethyl etherate promoted allylation of 2-butynal (**75**) with (2-chloromethyl)allyl trimethylsilane (**76**), and subsequent acetylation of the

racemic secondary alcohol gave access to chloride **77**. Halogen exchange under Finkelstein conditions[72] gave **78**, which could be converted into allyltin building block **50** by a $Pd_2(dba)_3$ catalyzed coupling with bis(tributyltin).[73] Attempts to introduce the tributyltin fragment by nucleophilic substitution of the allyl halogens using tributylstannyllithium resulted in decomposition of the starting material. In conclusion, the racemic southern fragment **50** was successfully synthetized in 5 steps and 30% overall yield from 2-butynol. Other approaches for the synthesis of **50**, which were investigated by Dr. de Haro, were unsuccessful.[74]



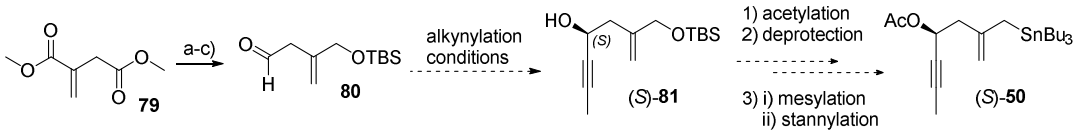
Scheme 3.11: *Racemic synthesis of southern fragment **50**. Conditions: a) $BF_3{\cdot}OEt_2$,then **76**, DCM, −60°C, 60%; b) Ac_2O, Et_3N, DMAP (cat.), DCM, rt, quant.; c) NaI, acetone, 70 °C, 95%; d) $(SnBu_3)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$ (cat.), degassed THF, 55°C, 78%; e) n-BuLi, $HSnBu_3$, THF, −78°C, 60%.*

The pivalic ester analogue of **50** was prepared following the route outlined above to provide a migrating group other than the acetate in the [3,3]-sigmatropic rearrangements. The different steric and electronic properties of the pivalate might have an influence on the rearrangement and its stereoselectivity.

Enantioselective synthesis:

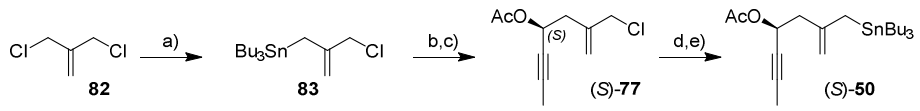
The absolute configuration of the acetate group in molecule **50** turned out to be essential in the key-step cascade (see Chapter **3.4.5**). Therefore, access to the enantiopure building blocks (*R*) and (*S*)-**50** was needed. Due to prior knowledge in our group concerning alkynylation reactions, (*R*)/(*S*)-**50** should be accessed by this methodology (Scheme 3.12). Aldehyde **80** was prepared in a straightforward route starting from dimethyl itaconate (**79**). Diisobutylaluminum hydride reduction[75] afforded the corresponding diol. Subsequent mono-TBS protection[76] and oxidation gave desired aldehyde **80**, setting the stage for the asymmetric alkynylation reaction. Carreira conditions, which are known to give poor yields and enantioselectivities with unsaturated substrates,[77] led to an isomerization of **80** to the α,β-unsaturated aldehyde, which did not undergo further reaction. A more positive outcome was obtained by using the Pu conditions.[78] This method includes pre-formation of the alkynyl-zinc species by refluxing diethyl zinc and propyne, followed by the titanium-catalyzed addition to aldehyde **80** in presence of 1,1'-bi-2-naphthol (BINOL) as chiral ligand. However, under the standard conditions, the yields were not

reproducible probably due to the volatility of propyne which caused inconsistent formation of the propynyl-zinc species. Operating under various propyne pressures did not improve the outcome. While (*R*)-**81** could be obtained in 60% yield and *e.e.* ≥88%, (*S*)-**81** was obtained in only 28% yield and an unsatisfactory *e.e. of* ≤22%. The absolute configuration was determined by Mosher ester analysis[79] of **81**. A racemic reference was prepared by the addition of propynyl lithium to aldehyde **80**. Overall, the stereoselective alkynylation of **80** proved to be unsuccessful.



Scheme 3.12: *Enantioselective approach using alkynylation. Conditions: a) Dibal-H, THF, 0°C → rt, 98%; b) NaH, THF, −78°C, then TBS-Cl, −30 °C, 38%; c) DMP, DCM, rt, 86%.*

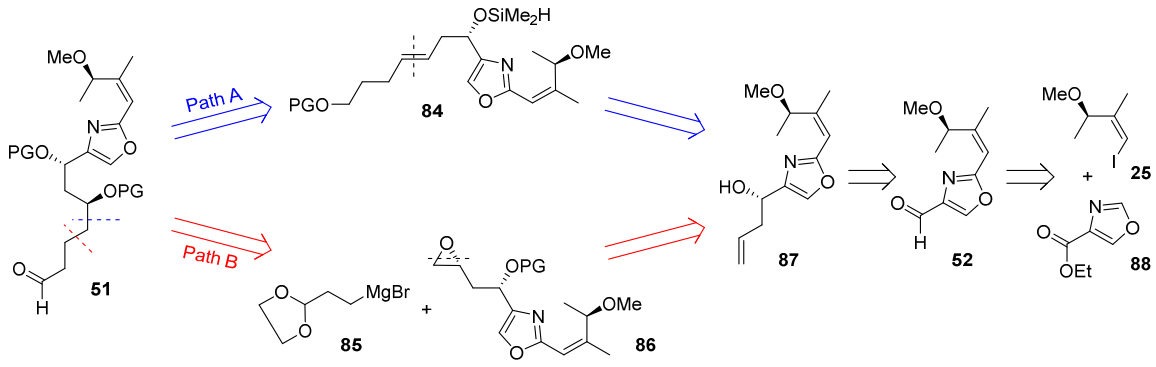
In parallel, another approach was examined to access the enantiopure southern fragment **50** starting from the symmetric 3-chloro-2-(chloromethyl)prop-1-ene (**82**) (Scheme 3.13). Selective monostannylation afforded **83**,[80] which was subjected to a Keck allylation[81] with 2-butynal (**75**) to undergo clean conversion to secondary alcohol (*S*)-**77** in good yield (84%) and enantiomeric selectivity (*e.e.* ≥95%). The absolute configuration was determined by Mosher ester analysis[79] showing that (*S*)-BINOL afforded (*S*)-**77** and (*R*)-BINOL the (*R*)-enantiomer. It is noteworthy to mention that good results were only obtained with freshly distilled titanium isopropoxide and molecular sieves, which were oven dried over several days at 120 °C.[82] Molecular sieves which were activated over 24 h at 200 °C and 10^{-3} mbar (standard procedure for the RCAM) completely inactivated the allylation reaction. Interactions with the titanium catalyst, the isopropoxide-ligands and the molecular sieves might be the reason for this observation. Transformations alike to the racemic route afforded desired (*R*) and (*S*)-enantiomer of **50** over 5 steps and 25% overall yield on a multigram scale.



Scheme 3.13: *Enantioselective approach using Keck allylation. Conditions: a) LDA, Bu_3SnH, THF, −78°C, 49%; b) $(iPrO)_4Ti$ (cat.), (S)-BINAP (cat.), 4 Å MS, DCM, reflux, then **75**, rt, then **83**, −78°C, 84%, e.e. ≥95%; c) Ac_2O, Et_3N, DMAP (cat.), DCM, rt, 93%; c) NaI, acetone, 70 °C, 88%; d) $(SnBu_3)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$ (cat.), degassed THF, 55°C, 73%.*

3.4.3. Synthesis of the Eastern Fragment

The eastern fragment **51** represents the first part of the longest linear sequence and two possible pathways, A and B, were envisioned for the synthesis of this fragment in our group (Scheme 3.14). Initial studies on these possible routes were performed by Dr. de Haro and the reported results on pathway A are based on her work.



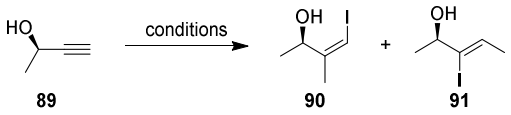
Scheme 3.14: *Retrosynthetic analysis of the eastern fragment* ***51****.*

Pathway A focused on an olefin cross-metathesis to form intermediate **84**, which would afford the 1,3-*syn*-diol motif of **51** via an intramolecular hydrosilylation reaction. The challenge of this pathway would be the stereoselectivity of this hydrosilylation and the selective, orthogonal protection of the two resulting secondary alcohols. In pathway B, the 1,3-diols would be obtained by an addition Grignard reagent **85** to epoxide **86**. Both pathways converge in substrate **87**, which could derive from aldehyde **52**, already reported in the total synthesis by Molinski.[51] We envisioned a shortcut to the previous reported route including a disassembly of **52** into ethyl 4-oxazole carboxylate (**88**) and alkenyl iodide **25**.

The first milestone of the route was the access to key intermediate **52** in an efficient and elegant manner. Extension of Ma's methodology on Cu(I)-catalyzed regioselective *anti*-carbometallations[83] to methylmagnesium reagents followed by an iodine quench gave in one step the literature known allylic alcohol **90**.[51] Optimization reactions, involving screening of several Grignard reagents and solvents gave high regioselectivities (Table 3.1). Allylic alcohol **90** was obtained in good yield only by employing methylmagnesium bromide in a mixture of THF/toluene 3:1 (Entry **1**-**3**). Toluene showed slightly better regioselectivities compared to benzene (Entry **3**+**4**). Nevertheless, the biggest drawback in this reaction was the high excess of reagent (7 equiv of Grignard reagent and iodine) which was necessary to reach full conversion and good selectivity

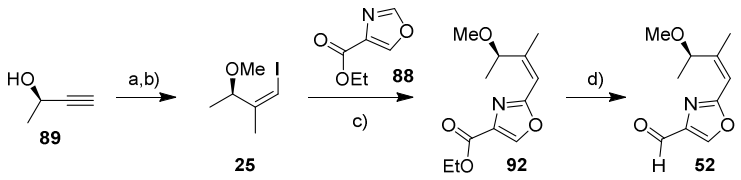
(Entry **4**-**6**). Ultimately, this approach afforded **90** from commercially available (*R*)-(+)-3-butyn-2-ol (**89**) on multigram scale in only one step and 74% yield. So far **90** was accessible in three steps with an overall yield of 19 %.[51]

Table 3.1: *Optimization of the carbomagnesiation of butyn-2-ol terminated by an iodine quench.*



entry	MeMgX	MeMgX & I_2 (equiv)	CuI (equiv)	solvent	regioselec. (90:91)	yield (%)
1	Br, 3 M in Et_2O	7	1	benzene	40:60	n.d.
2	Cl, 3 M in THF	7	1	benzene	100:0	56
3	Br, 1.4 M in THF/ toluene 3:1	7	1	benzene	90:10	90
4	Br, 1.4 M in THF/ toluene 3:1	7	1	toluene	93:1	73-98
5	Br, 1.4 M in THF/ toluene 3:1	3.5	0.5	toluene	80:20	20
6	Br, 1.4 M in THF/ toluene 3:1	3.5	1	toluene	80:20	n.d.

Subsequent *O*-methylation of **90** using methyl iodide and sodium hydride[51] gave alkenyl iodide **25**, which was coupled in a palladium-catalyzed C–H activation reaction with the commercially available ethyl 4-oxazole carboxylate (**88**) (Scheme 3.15).[84] To the best of our knowledge, this is the first time that a C–H activation of an oxazole has been applied in total synthesis. Diisobutylaluminium hydride reduction of the ethyl ester at low temperatures gave key intermediate **52** in good yield (80%).[51]

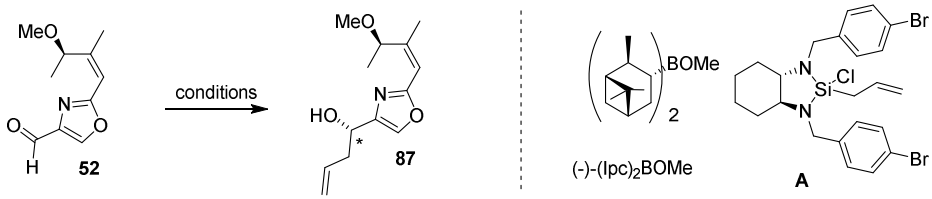


Scheme 3.15: *Synthesis of key intermediate **52**. Conditions: a) (i) MeMgBr, CuI, toluene, −78 °C → rt; (ii) I_2, THF, −40 °C → rt, 74%; b) MeI, NaH, imidazole (cat.), THF, −40 °C → rt, 64%; c) $Pd(OAc)_2$ (cat.), 2-(dicyclohexylphosphino)-biphenyl (cat.), Cs_2CO_3, 1,4-dioxane, 110 °C, 74%; d) Dibal-H, DCM, −90 °C, 80%.*

Despite literature precedence on asymmetric allylation reactions in total synthesis[85] and particularly involving oxazoles,[86] we faced difficulties in obtaining good yield and selectivity for the allylation reaction of aldehyde **52**. Several allylation conditions such as Maruoka[87] and Leighton[88] (Entry **1+2**) were screened (Table 3.2), but gave either poor yield and almost no

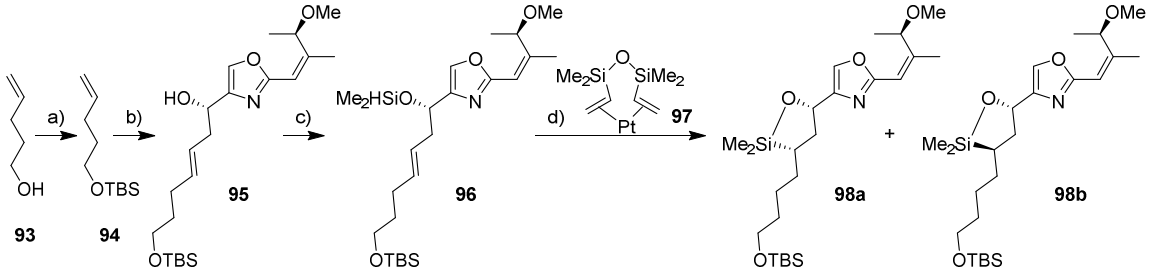
stereoselectivity. Applying Krische[89] conditions to either the aldehyde **52** or the corresponding alcohol gave the desired product **87** in good enantioselectivity, but only low yield (Entry **3**). The Brown[90] and Keck[81, 91] protocols finally showed very good yield and selectivity (Entry **4**+**5**). Due to the slightly higher *d.r*. the Keck allylation was chosen in the final route. Again, it is noteworthy to mention, that the allylation only proceeded with freshly distilled titanium isopropoxide and molecular sieves, which were oven dried over several days at 120 °C.[82] The enantiomeric ratio of the obtained allylic alcohol **87** was determined by subsequent Mosher ester analysis.[79]

Table 3.2: *Screening of different allylation conditions.*



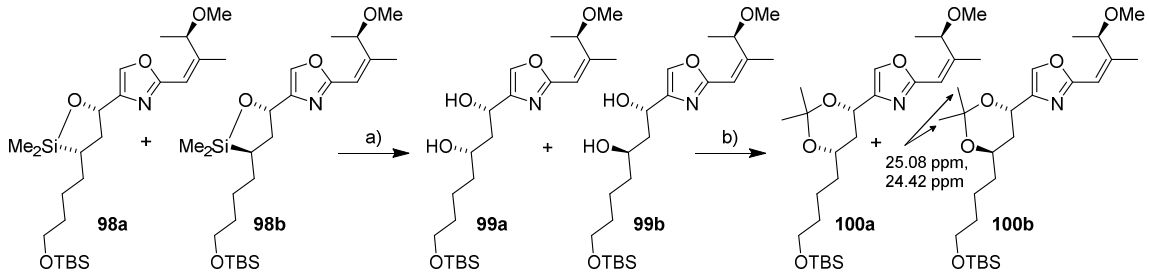
entry	reaction conditions	yield (%)	*d.r.*
1	**Maruoka allylation**: bidentate-Ti(IV)-(*S*)-BINOL (10 mol %), allyl tributyltin, DCM, -15 ºC to 0 ºC, 18 h	42 (84 brsm)	53:47
2	**Leighton allylation: A** (100 mol%), DCM, -10 ºC, 20 h	0	0
3	**Krische allylation:** Allyl acetate (10 equiv), $Ir(Cod)Cl_2$ (2.5 mol %), (*S*)-BINAP (5 mol %), Cs_2CO_3 (20 mol%), *m*-nitrobenzoic acid (10 mol %), *i*PrOH (200 mol %), THF, 100 ºC, 20 h	40	95:5
4	**Brown allylation:** (-)-$(Ipc)_2$BOMe, allylmagnesium bromide, Et_2O, -100 ºC, 1.5 h	96	93:7
5	**Keck allylation:** $Ti(OiPr)_4$ (10 mol%), (*S*)-BINOL (10 mol %), allyl tributyltin, 4Å MS, DCM, -20 ºC, 96 h	95-99	>95:5

With the common intermediate **87** in hand, pathway A was first investigated (Scheme 3.16). The two building blocks **94** and **87** were coupled via a cross metathesis using Hoveyda-Grubbs 2nd generation catalyst.[92] Inspired by a report by Roush,[93] who synthesized *syn,syn*- and *syn-anti*-1,3,5-triols by intramolecular hydrosilylation of pent-3-en-1,5-diols catalyzed by Karstedt's catalyst,[94] alcohol **95** was transformed into dimethylsilyl ether **96**, which gave siloxanes **98a** and **98b** under the described conditions. The best diastereomeric ratio was 71:29.



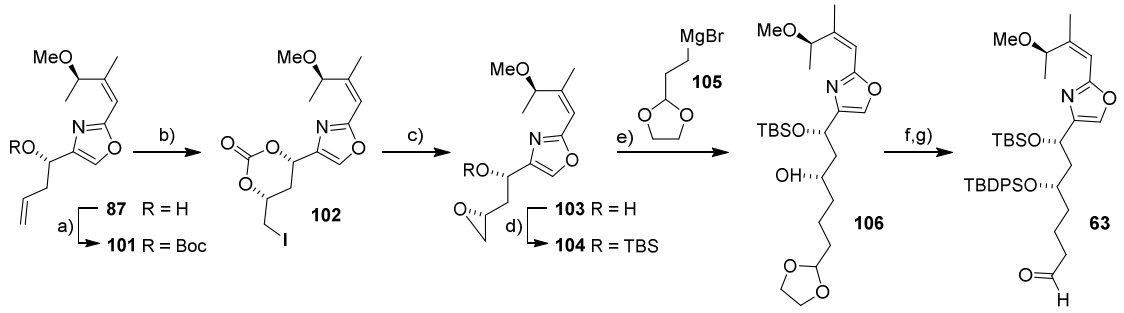
Scheme 3.16: *Forward synthesis of pathway A. Conditions: a) TBS-Cl, imidazole, DMAP (cat.), DCM, rt, quant.; b)* ***87****, Hoveyda-Grubbs 2nd (cat.), DCM, rt, 59%; c) (HMe2Si)2NH, neat, rt, quant.; d)* ***97*** *(cat.), toluene, −78°C → 0°C, yield n.d..*

To assign the absolute stereochemistry, acetonides **100a** and **100b** were prepared from the silylethers **98** via the corresponding diols **99a** and **99b** (Scheme 3.17). However, ^{13}C NMR analysis following Rychnovsky´s protocol[93, 95] revealed 1,3-*anti* configuration for the major diastereomer **100b**. These results implied that the silylation of compound **96** is not directed intramolecularly by the hydroxy-silyl-ether as suggested by Roush[93], but rather by the oxazole moiety coordinating the palladium(0) species to favor the *anti*-1,3-diol. For detailed information on this pathway, see Dr. de Haro's research summary.[74]



Scheme 3.17: *Analysis of the absolute configuration of* ***98****. Conditions: a) KHCO3, H2O2, THF/MeOH 1:1, rt, 76% (over 3 steps); b) 2,2-dimethoxypropane, PPTS (cat.), DCM, rt, yield n.d..*

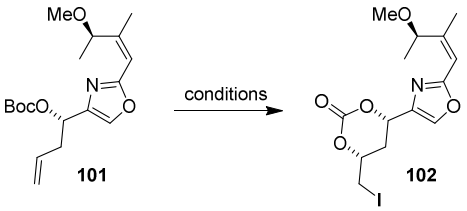
Because of the unsatisfying stereoselectivity in pathway A (29:71 for desired **98a**), the alternative route B was investigated to get access to the eastern fragment **51** (Scheme 3.14). Route B used the same allylic alcohol **87** as a starting point, however, instead of chain extension as described above, the *syn*-diol should be installed first. A regio- and stereoselective iodo-cyclization reaction turned out to be an efficient way to rearrange Boc-protected compound **101** to carbonate **102** (Scheme 3.18).



Scheme 3.18: *Forward synthesis of eastern fragment* ***63*** *following pathway B. Conditions: a) $(Boc)_2O$, DMAP (cat.), ACN, rt, 92%; b) IBr, toluene, −78 °C, 54–73%; c) K_2CO_3, MeOH, rt, 79% (d.r. >95:5); d) TBS-Cl, imidazole, DMAP (cat.), DCM, rt, 98%; e)* ***105****, CuI (cat.), THF, −78 °C → −40 °C, 92%; f) TBDPS-OTf, 2,6-lutidine, DCM, 0 °C, 88%; g) TMS-OTf, 2,4,6-trimethylpyridine, DCM, rt, 97%.*

Different electrophilic iodine sources, such as *N*-iodosuccinimide (NIS)[96], iodine[97] and iodine monobromide[98], were screened (Table 3.3, Entry **1-3**) and best results were obtained by employing a 1 M solution of iodine monobromide in dichloromethane at −90 °C. These conditions afforded **102** in good yield (≥70%) and excellent diastereoselectivity (≥95:5). The reaction times were kept short and the temperatures below −78 °C in order to prevent product decomposition. Lower temperatures had no positive influence on the outcome (Entry **3** vs **5**). The yield was however not reproducible on multigram scales for unknown reasons (Entry **5**). While regio- and stereoselectivity remained constant, the yield dropped from 70% to 54% on scales employing >300 mg (**101**). Iodine monobromide concentrations below 1 M resulted in incomplete consumption of starting material **101** which could be reisolated, giving moderate yield (59%) but no decomposition of **101** or **102** (99% brsm) (Entry **4**).

Table 3.3: *Optimization of the iodo-lactonization reaction.*

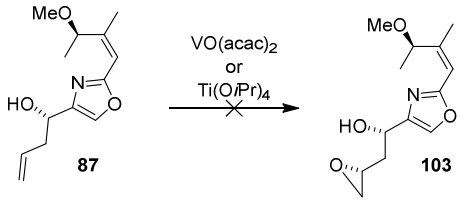


entry	Iodine source (equiv.)	Conditions	Conversion (%)[a]	d.r.	isolated yield (%)
1	NIS (10)	ACN, –40 → 0 °C, 12h	7	>98:2	n.d.
2	I_2 (3)	ACN, –20 °C, 12h	69	77:23	n.d.
3	1 M IBr (3)	Toluene, –90 °C, <1 h	98	>95:5	73-76
4	0.1 M IBr (3)	Toluene, –90 °C, <1 h	60	>95:5	59 (99 brsm)
5	1 M IBr (3)	Toluene, –78 °C, <1 h	100	>95:5	54 / 73[b]

[a] determined by NMR; [b] 54% on 4 g scale, 73% on 200 mg.

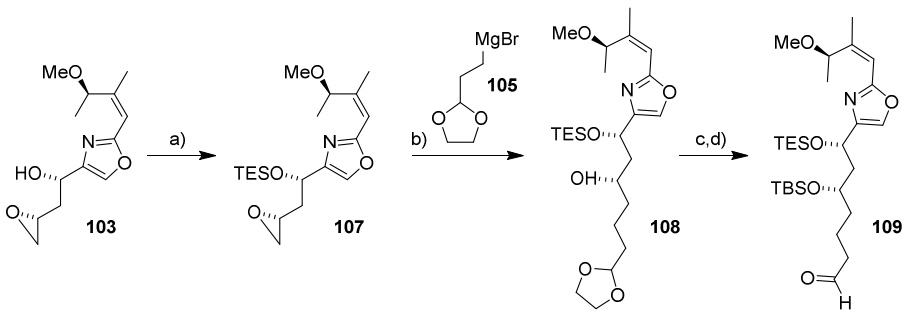
The resulting iodide **102** was treated with potassium carbonate in methanol to cleave the cyclic carbonate and immediately close the terminal oxirane ring (**103**, Scheme 3.18). The iodo-cyclization and methanolysis could also be performed in one-pot but with much lower yield (<40%).

Inspired by a report of Berkessel, we saw a potential shortcut by applying the methodology of stereoselective epoxidation of olefins.[99] The direct *syn*-epoxidation of homoallylic alcohol **87** was tried employing vanadium and titanium catalyst systems (Scheme 3.19).[100] Initial attempts already showed that the starting material **87** was too sensitive, resulting in complete degradation.



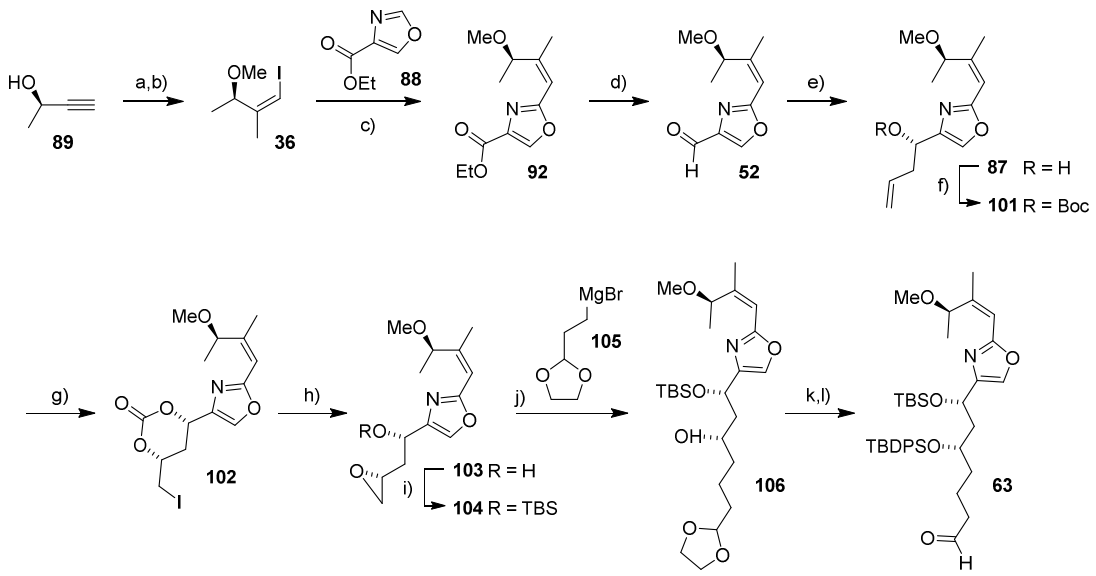
Scheme 3.19: *Direct syn-epoxication of homoallylic alcohol **87** using vanadium or titanium catalyst systems.*

After TBS protection of secondary alcohol **103**, **104** was prepared for the final carbon chain elongation (Scheme 3.18). Therefore, epoxide **104** was opened in a copper-catalyzed addition of functionalized Grignard reagent **105**, giving the desired product **106** regioselectively in very good yield (92%).[101] Grignard reagent **105** was prepared from the commercially available bromide precursor via a modified procedure described by Forbes.[102] At this stage the stereoselectivity of the 1,3-*syn*-diol motif was determined by acetonide formation, as described before, after desilylation of **106**. The ^{1}H NMR shifts of the methyl signals of the acetonide (19 and 30 ppm) confirmed the *syn*-stereochemistry of the 1,3-diol motif. Standard TBDPS-protection and cleavage of the acetal afforded eastern fragment **63**. Aware of the problems which might occur on using such a stable TBDPS-protecting group, the TES/TBS-analogue **109** was synthesized following the same route (Scheme 3.20).



Scheme 3.20: *Synthesis of eastern fragment **109** with alternative silyl protecting groups. Conditions: a) TES-Cl, imidazole, DMAP (cat.), DCM, rt, 93%; b) **105**, CuI (cat.), THF, −78 °C → −40 °C, 77%; c) TBS-Cl, imidazole, DMAP (cat.), DCM, rt, 74%; d) TMSOTf, 2,4,6-trimethylpyridine, DCM, rt, 93%.*

Overall, we were able to prepare the eastern fragment **63** (and its sibling **109**) from commercially available (*R*)-(+)-3-butyn-2-ol (**89**) in 12 steps with an overall yield of 11.2% (and 7.2% respectively) (Scheme 3.21). In the case of the TBS/TBDPS-fragment **63**, all reactions were performed on a multigram scale (≥5 mmol). Due to this robust and scalable route, investigations on the combination of the three fragments and the key steps could be performed as described in the next chapter.

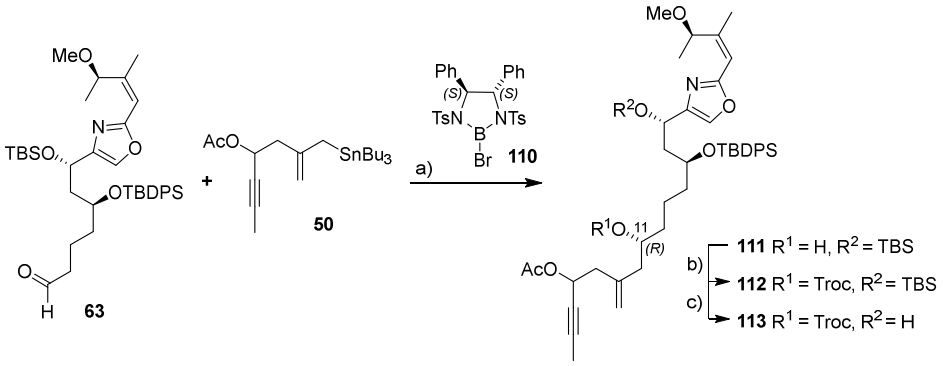


Scheme 3.21: *Synthesis of eastern fragment **63**. Conditions: a) (i) MeMgBr, CuI, toluene, −78 °C → rt; (ii) I_2, THF, −40 °C → rt, 74%; b) MeI, NaH, imidazole (cat.), THF, −40 °C → rt, 64%; c) $Pd(OAc)_2$ (cat.), 2-(dicyclohexylphosphino)-biphenyl (cat.), Cs_2CO_3, 1,4-dioxane, 110 °C, 74%; d) Dibal-H, DCM, −90 °C, 80%; e) $Ti(OiPr)_4$ (cat.), (S)-BINOL (cat.), allyl tributyltin, 4 Å MS, DCM, −20 °C, 98%; f) $(Boc)_2O$, DMAP (cat.), ACN, rt, 92%; g) IBr, toluene, −78 °C, 54–73%; h) K_2CO_3, MeOH, rt, 79% (d.r.>95:5); i) TBS-Cl, imidazole, DMAP (cat.), DCM, rt, 98%; j) **105**, CuI (cat.), THF, −78 °C → −40 °C, 92%; k) TBDPSOTf, 2,6-lutidine, DCM, 0 °C, 88%; l) TMSOTf, 2,4,6-trimethylpyridine, DCM, rt, 97%.*

3.4.4. Combination of the Fragments and RCAM

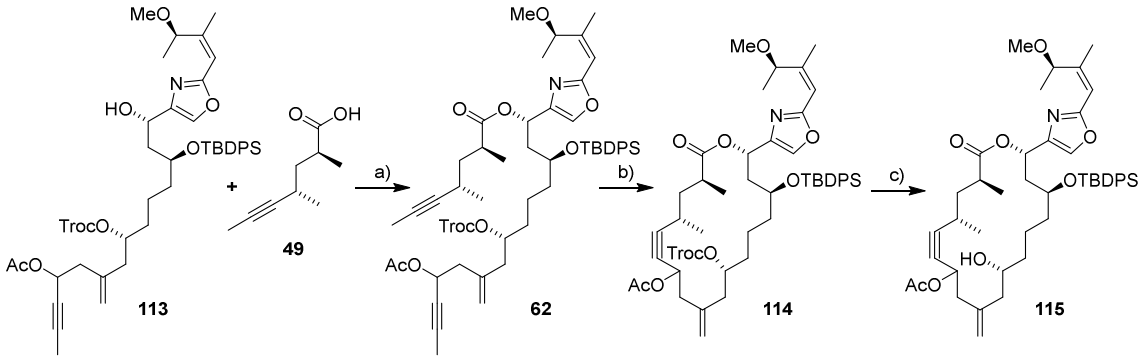
With access to the three fragments, **49**, **50** and **63**, on reliable and multigram scale syntheses, their assembly was investigated. Coupling of aldehyde **63** and stannane **50** was envisioned via an asymmetric allylation reaction. The best results were obtained by applying the conditions described by Corey *et al.* using chiral diaminoborane **110** (Scheme 3.22).[103] The reaction proceeds via the *in situ* formation of the boron species **110**, followed by a boron-stannane exchange prior to stereoselective allylation of aldehyde **63**. Very good yield (95%) and selectivity (≥10:1) of the desired (11*R*)-epimer **111** was achieved in spite of the fragile characteristics of the propargyl acetate motif in **50** that could easily eliminate to give a conjugated π-system. For derivatization purposes and mechanistic insight into the [3,3]-sigmatropic rearrangement, the corresponding

(11*S*)-epimer of **111** was prepared following the same conditions and (*R,R*)-**110** in comparable yield. The stereochemical outcome of each isomer was confirmed by Mosher ester analysis[79] and was in full agreement with Corey's observations. One advantage of this methodology was the commercial availability of the (*R,R*) or (*S,S*)-1,2-diamino-1,2-diphenylethane ligands, which could be fully recovered after the workup.



Scheme 3.22: *Coupling of eastern **63** and southern fragment **50** by enantioselective allylation. Conditions: a) (S)-**110**, DCM, −78°C, 95% (d.r. > 10:1); b) TrocCl, DMAP (cat), pyridine, DCM, 0 °C → rt, quant.; c) camphorsulfonic acid (cat.), DCM/MeOH (3:1), 0 °C → rt, 61% (98% brsm).*

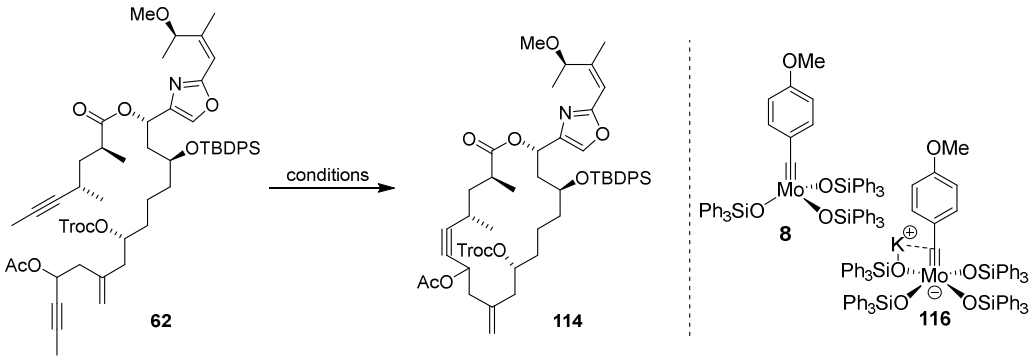
Standard PMB-protection of secondary alcohol **111** was unsuccessful, despite intensive attempts.[74] Much better results were obtained by 2,2,2-trichlorethoxycarbonyl (Troc) protection which was equally orthogonal to the silyl esters in **111**. Selective TBS deprotection of **112** afforded **113**. To suppress the cleavage of the acetate ester in **112** during the reaction, the progress was monitored by TLC and the reaction was stopped as soon as the undesired cleavage was observed. Starting material **112** and the desired product **113** were isolated without major loss of material via secondary side reactions (61%, 98% brsm). Subsequent Yamaguchi esterification with the northern fragment **49**,[104] as already elaborated in our group before,[105] gave the metathesis precursor **62** in quantitative yield (Scheme 3.23). The corresponding TES-analogue of **62** was also prepared by following the same route, but not used further due to the success employing the TBDPS-protected substrate **62**.



Scheme 3.23: *Combination of the last fragment and closing of the macrocycle by RCAM. Conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, then **113**, DMAP, toluene, 0 °C, quant.; b) **8** (cat.), 4Å + 5Å MS, toluene, 79%; c) Zn, HOAc, ultrasonication, 93%.*

With **62** in hand, we started the screening of conditions for RCAM (Table 3.4), which would already set the complete carbon framework of enigmazole A (**16**). Initial attempts were similar to those described in the model system (Chapter **3.3**) using the neutral catalyst **8** at elevated temperatures giving only moderate yield (40-60%) (Entry **1-2**).[62] Due to the complete consumption of **62** after 2 h, the temperature was lowered, resulting in an increase of yield (>70%) (Entry **3**). Decreasing of catalyst loading from initial 50 mol% to 10 mol% resulted in incomplete conversion. In these cases more catalyst had to be added to achieve complete consumption of starting material, leading to longer reaction times, but to comparable yield (70-80%) (Entry **4**). In all experiments a quite fast decomposition of catalyst **8** was observed indicated by color change of the reaction mixture and loss of activity. Initially, experiments employing the more stable ate-complex **116** showed complete conversion of diyne **62**, but gave only moderate yield (57%) (Entry **5**). The actual break through was achieved by decreasing the reaction time to less than 60 min (Entry **6**). Under these conditions, catalyst loadings between 16-18 mol% showed complete consumption of **62** and very good yield (85-90%). The reliability of this step allowed a metathesis on 1.7 g scale with 79% isolated yield of **116** (Entry **7**).

Table 3.4: *Screening of ring closing alkyne metathesis conditions.*



entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Isolated yield (%)
1	**8** (50)	120	2	56
2	**8** (54)	80	2	42
3	**8** (53)	21	3	70-80
4	**8** (3×10)[a]	21	60	76
5	**116** (25)	21	24	57
6	**116** (18)	21	0.75	87[b]
7	**116** (30)	21	0.50	79[c]

*[a] after every 24 h additional 10 mol% of catalyst **8** were added; [b] 51 mg scale; [c] 1.7 g scale.*

In summary, the RCAM of this specific molecule (**62**) worked in a reliable and reproducible manner with catalyst loadings between 25-30 mol% at room temperature and reaction times of less than 1 h. Complete conversions were also obtained with lower catalyst loadings of 16-18 mol%, but the low catalyst loading made the reaction very sensitive to moisture or impurities in the starting material. The addition of catalyst in several portions over time, e.g. 3 × 10 mol%, adding up to 30 mol%, gave worse results than the addition of only one batch. This effect and the short reaction times could be explained by the inhibition of the catalytic cycle by free silanol ligands due to catalyst decomposition. During these experiments, we never observed noteworthy amounts of dimer formed by metathesis of **62** with itself (head/head or head/tail). Nevertheless, the lower yield at extended reaction times might indicate that **114** underwent decomposition or polymerization under metathesis conditions.

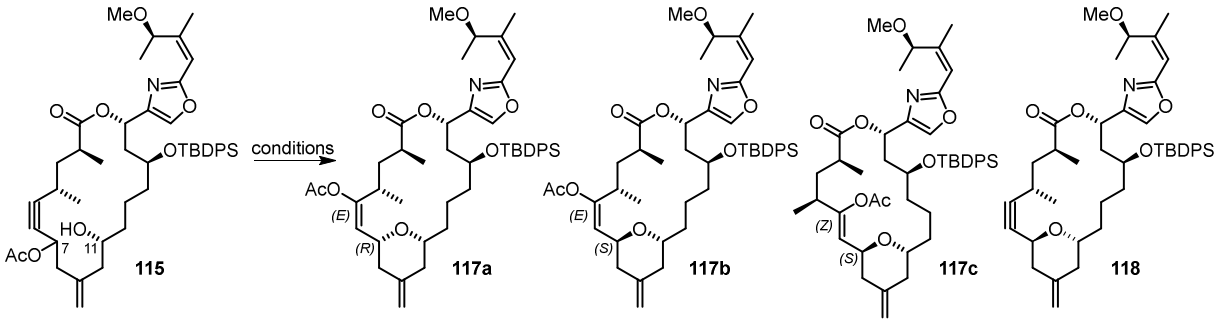
To set the stage for the gold-catalyzed cascade, the Troc-ester **114** had to be cleaved to allow the hydroxy group to participate in the transannular attack. This standard deprotection, however, proved to be unexpectedly challenging. Literature known procedures applying zinc in acetic acid always led to incomplete conversions and disappointing yield (<40%).[106] Intensive screenings on

reaction parameters, such as the mesh sizes of zinc dust and additives, finally provided an extremely efficient ultra-sound accelerated method giving ≥95% yield (Scheme 3.23). To this end, **114** was treated with high excess of zinc dust (10 mesh, Sigma Aldrich) and sonicated for 30-45 min. The inorganic salts were filtered off and the crude mixture was concentrated. Aqueous workup, as originally reported in the literature, led to partial decomposition. Other conditions, *e.g.* saponification with potassium carbonate in methanol, led to transesterification (methoxy carbonyl ester instead of trichloroethoxy) or to decomposition. It is noteworthy that this was the first reaction of the entire route which was not performed on a gram scale (510 mg largest scale).

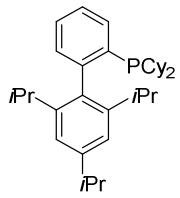
3.4.5. Key Step: The Gold-catalyzed Cascade Reaction

With the carbon framework of enigmazole A (**16**) all set in key intermediate **115**, we proceeded to investigate the cascade reaction featuring a [3,3]-sigmatropic rearrangement followed by transannular hydroalkoxylation, generating the tetrahydropyran motif present in **117** (Table 3.5). Due to the preliminary studies on the model substrate, initial reaction conditions were already established.[62] Nevertheless, the exact same reaction conditions gave exclusively decomposition of the starting material **115** (Entry **1**), forcing intensive investigations on different catalyst systems. Substrate **115** was exposed to several gold catalysts, with varying ligands and counter ions, as well as to other metals known to trigger [3,3]-rearrangements, such as platinum (Entry **2**-**8**).[107] Only in a few cases the experiments showed traces of the desired product **117**, which could only be detected by MS analysis (Entry **2-3**). Driven by these first indications, further attempts of using gold(I)-species with hexafluoroantimonate(V) or tosylate counter ions led to the isolation of two byproducts referred by NMR analysis as structure **117c** and **118** (Entry **9**). Unfortunately, the tetrahydropyran rings showed an *anti*-configuration for both products. The first promising results were obtained with the NHC-ligand IPr **120** giving the desired product **117a** and its isomer **117b** albeit in low yield (38%) and selectivity (*d.r.* = 2:3).

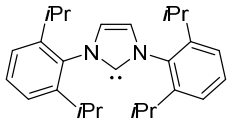
Table 3.5: *Brief summary of the catalysts screening for the reaction cascade giving the tetrahydropyran ring.*



entry	Catalyst	Temp. (°C)	Solvent	Results
1	$Ph_3PAuNTf_2$	65	DCM	decomp.
2	AuCl	70	DCM	mixture[a]
3	$AuCl_3$	70	DCM	mixture[a]
4	$XPhosAuNTf_2$	65	DCM	**115,** decomp.
5	$IPrAuNTf_2$	21	DCM	rec. **115**
6	$PtCl_2$	80	toluene	rec. **115**
7	$Cy_3PAuNTf_2$	21	DCE	decomp.[a]
8	$Me_3PAuNTf_2$	0	DCE	decomp.[a]
9	$AuSbF_6$ or OTs	60	DCE	**117c + 118**
10	$AuSbF_6$ or OTs	60	ACN	rec. **115**
11	IPrAuOTs	40	DCE	**117a/b 2:3 (38%)**



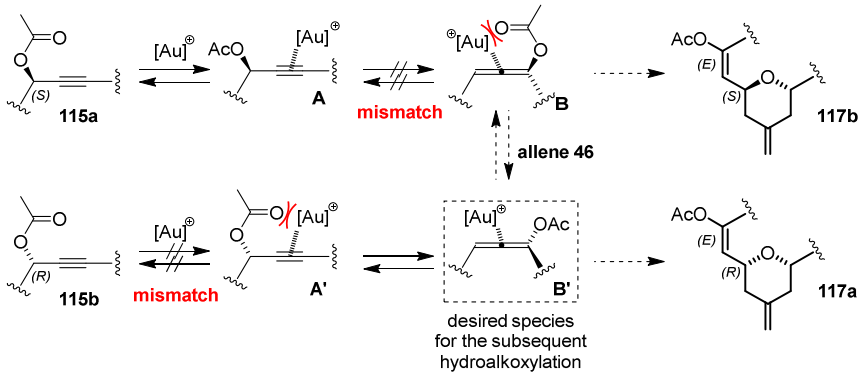
XPhos **119**



IPr **120**

*[a] MS analysis revealing traces of **117** in a complex mixture of starting material **115** and undefined byproducts.*

With reference compounds **117a-c** in hand, this transformation could be followed by HPLC-MS. Interestingly, a clear difference in the consumption of the two epimers of **115** (undefined stereocenter at C7) was observed in all experiments. These observations led to the hypothesis, that exclusively one of the two possible π-complexes **A** and **A'** (Scheme 3.24) is formed (here **A**) which does not undergo the [3,3]-sigmatropic rearrangement due to steric and/or electronic reasons. Therefore, we could not expect the desired intermediate **B'** to be formed. This might be a result of the complex and rigid macrocyclic structure of **115**.



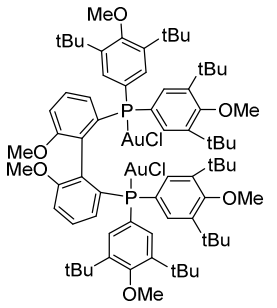
Scheme 3.24: *Models of the π-complexes of the gold catalyst and substrate* ***115*** *affecting the reaction outcome.*

In addition, allene **46**, which would be formed by the [3,3]-sigmatropic rearrangement, was never observed, supporting the hypothesis that already the early stage of coordination might be interfered. Side product **118**, obtained by S_N2-type elimination of the acetate group by the C11-OH, suggested close proximity of these two groups. Consequently, the cascade might be initiated by this hydroxy group, but only if the correct stereochemical configuration of the π-complex (**B'**) would allow that.

To underline our hypothesis, chiral gold catalysts were screened to find a matching substrate/catalyst pair, which could introduce the right stereochemical environment in **115** (and **46**) for the reaction cascade to occur (Table 3.6). Indeed, conditions using binuclear precatalyst **121** (DTBM-MeO-Biphep-$(AuCl)_2$) developed by the Toste group,[108] showed moderate yield and enhanced selectivity in favor of **117a** (Entry **3-4**). Especially gratifying was the beneficial influence of the ligand chirality on the diastereomeric ratio of **117a** and **117b**. Other similar chiral catalysts only gave traces of **117** or complex mixtures (Entry **1-2**). To confirm that the chirality of the ligand and not the different electronics influenced the outcome, several similar substituted triphenyl phosphines were tested (Entry **5-7**). None of them showed similar stereoselectivity or reactivity compared to precatalyst **121**; yet, it must be considered, that these catalysts did not feature the binuclear gold-center. Optimizations on the solvent and counter ion finally gave the desired *syn*-tetrahydropyran **117a** in 55% yield and a diastereomeric ratio of 4:1 (**117a**/**b**) (Entry **8-9**). Despite the improved results in these experiments, HPLC-MS still indicated, that only one of the two diastereomers of **115** afforded the desired product **117a**, while the other diastereomer mainly reacted to a variety of unidentified byproducts.

Table 3.6: *Optimization of the gold-catalyzed reaction cascade using chiral catalysts.*

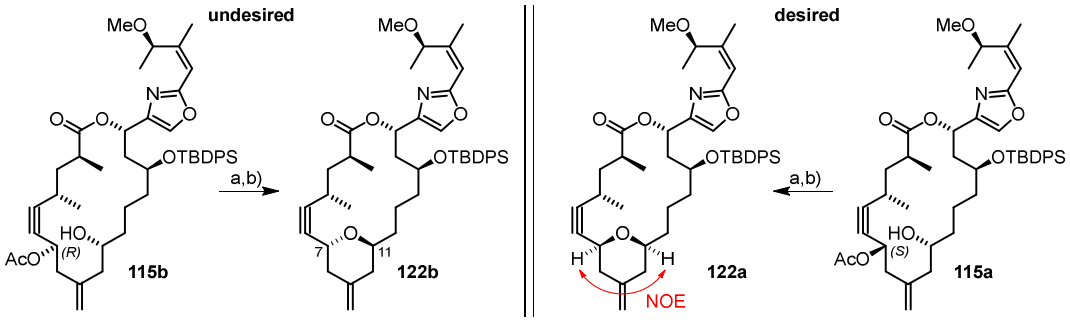
entry	Catalyst	Solvent	*d.r.* 117a/117b	Results
1	(*S*)-BINAP-AuSbF$_6$	DCE	-	mixture[a]
2	(*R*)-DTB-MeO-Biphep-(AuOTs)$_2$	DCE	1:1	sm + products[a]
3	(*R*)-DTBM-MeO-Biphep-(AuOTs)$_2$	DCE	2:3	60% yield
4	(*S*)-DTBM-MeO-Biphep-(AuOTs)$_2$	DCE	3:2	61% yield
5	(4-OMe-Ph)$_3$PAuOTf	DCE	1:1	sm + product traces[a]
6	(3,5-Me-4-OMe-Ph)$_3$PAuOTf	DCE	-	no reactivity
7	(2,6-OMe-Ph)$_3$PAuOTf	DCE	-	no reactivity
8	(*S*)-DTBM-MeO-Biphep-(AuSbF$_6$)$_2$	DCE	3:2	43%, large scale
9	(*S*)-DTBM-MeO-Biphep-(AuSbF$_6$)$_2$	DCM	4:1	55%, large scale



DTBM-MeO-Biphep-(AuOTs)$_2$
121

[a] in case of bad d.r. the products were not isolated. sm = starting material ***115****.*

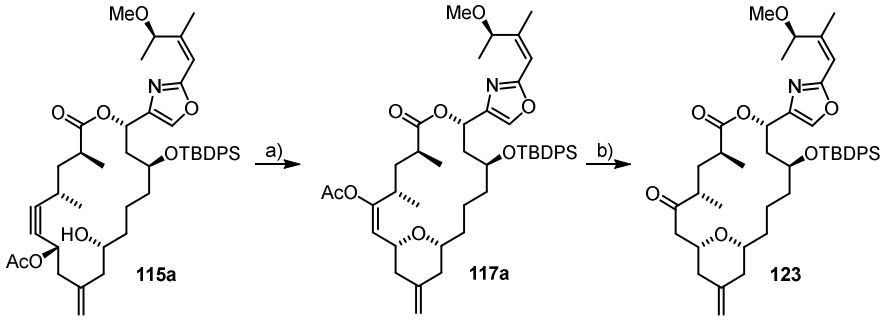
To further improve the reaction outcome, the two diastereomers of **115** were separated by preparative LC giving two enantiopure compounds **115a** and **115b** with unknown absolute configuration at C7 (Scheme 3.25). To determine the absolute stereochemistry, the tetrahydropyran ring was closed by an intramolecular S_N2 substitution of the prior mesylated C11-hydroxy group with C7-OH. NMR analysis of the two six membered rings **122a** and **122b** revealed their configuration and allowed the conclusion to be drawn regarding the configuration of **115a**/**b**. Comparison of the HPLC retention times, obtained in the previous experiments, confirmed the (*S*)-isomer **115a** as the diastereomer reacting selectively to **117a**. Aware of the absolute configuration, the desired diastereomer **115a** was prepared by the previously described route employing the (*S*)-southern fragment **50** (described in Section **3.4.2**).



Scheme 3.25: *Determination of the absolute configuration of* ***115*** *by chemical transformation. Conditions: a) TEA, MsCl, DCM, 21 °C; b) K_2CO_3, MeOH/DCM 1:1, rt, yields not determined.*

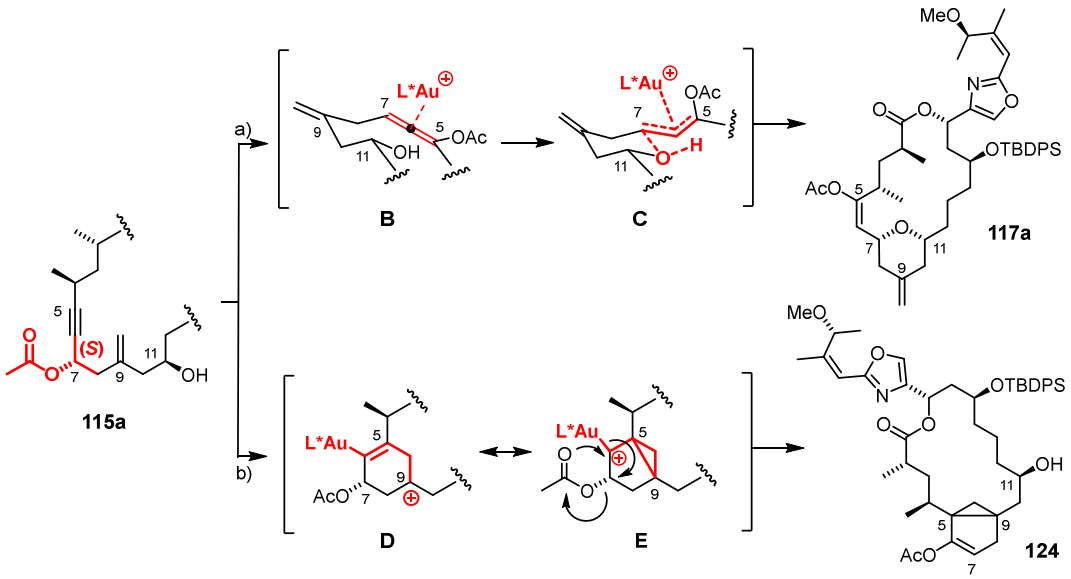
The matching pair of catalyst (*R*)-**121** and enantiopure starting material **115a** ultimately afforded selectively the desired product **117a** in excellent yield (91%) and subsequent basic saponification

afforded ketone **123** (Scheme 3.26). The configuration of **117a** can be explained by the attack occurring exclusively from the site distal to the acetate at the allene (transition state **B**, Scheme 3.27). Considering a pseudo-chair-like transition state **C,** the six-membered ring should be favored over an eight-membered ring setting the *syn*-configuration at the tetrahydropyran.



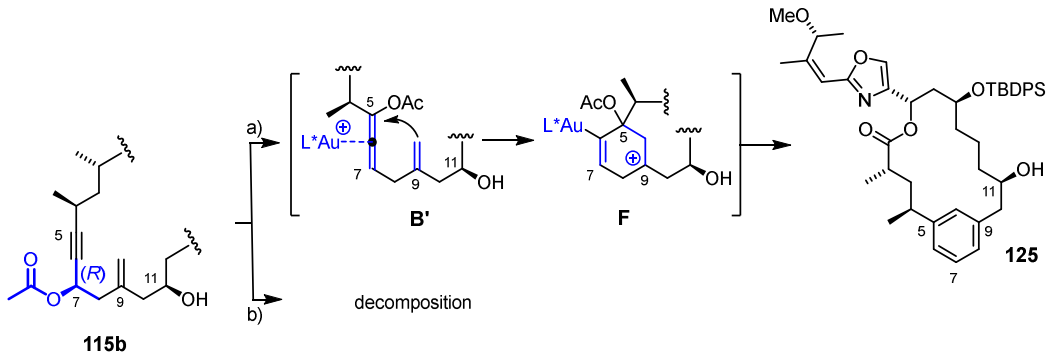
Scheme 3.26: *Gold cascade with the optimized conditions. Conditions: a) (R)-**121** (cat.), $AgSbF_6$ (cat.), DCM, rt, 91%; b) K_2CO_3, MeOH, 95%.*

The hypothesis of a mismatch of catalyst and substrate, as suspected from HPLC-MS analysis, had still to be confirmed. Indeed, the mismatch pair, (*S*)-catalyst **121** and (*S*)-substrate **115b**, afforded the desired product **117a** in only 50-70% yield, but gave in addition the unexpected tricycle **124** which was unmistakably assigned by NMR analysis (Scheme 3.27). The stereochemistry at the cyclopropane ring could not be elucidated. Apparently, upon activation of the alkyne by the gold catalyst, the C10 *exo*-methylene group reacts as a nucleophile and forms intermediate **D**, which undergoes cyclopropanation to **E**. Cycloisomerization involving the gold species, well known in π-acid catalysis,[109] gives finally **124**.



Scheme 3.27: *Intermediates of the gold cascade with the (S)-diastereomer **115a**. Conditions: a) (R)-catalyst **121** (cat.), $AgSbF_6$ (cat.), DCM, rt, 91%; b) (S)-catalyst **121** (cat.), $AgSbF_6$ (cat.), DCM, rt, 50-70% (**117a**) + 20-30% (**124**).*

An even stronger example of mismatch between the substrate and the catalyst was shown in the case of the (*R*)-isomer **115b**. The combination of **115b** and precatalyst (*S*)-**121** resulted in complete degradation of the starting material (Scheme 3.28). The other enantiomer of the catalyst, (*R*)-**121**, gave only traces of desired product **117a** (10-20%) and a second, aromatic side product **125** in acceptable yield (approx. 50%). A possible reaction mechanism initiated by the [3,3]-sigmatropic rearrangement could first proceed via allene **B'** (C5-epimer to **B**). In this environment, the attack of the *exo*-methylene is favored over the attack of C11-OH giving transition state **F** and after aromatization compound **125**. Indeed, similar reactions were reported in the literature before.[110]



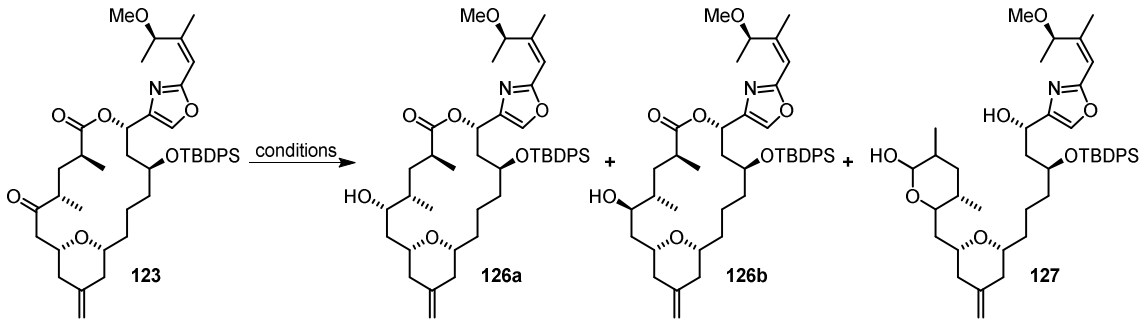
Scheme 3.28: *Intermediate of the gold cascade with (R)-diastereomer **115b**. Conditions: a) (R)-catalyst **121** (cat.), $AgSbF_6$ (cat.), DCM, rt, 50% (**125**) + 10-20% (**117a**); b) (S)-catalyst **121** (cat.), $AgSbF_6$ (cat.), DCM, rt, decomposition only.*

Collectively, those results demonstrate the important role of stereochemical matching between catalyst and substrate. The big difference in the reactivity of the two diastereomers **B** and **B'** of **46** has to be seen in the context of literature showing that [3,3]-sigmatropic rearrangements of propargylic esters are reversible and the corresponding allenes prone to racemization.[108] While methodological studies and the model substrate had shown the desired results, the real substrate is the perfect example for the influence of intricate details in total synthesis. The combination of strain, bulk and electronics makes each reaction unique – especially with such elaborated intermediates.

3.4.6. Completion of the Total Synthesis

To complete the total synthesis, last adjustments were missing including the installation of the phosphate ester and global deprotection. In order to install the phosphate ester at C5, ketone **123** had to be stereo-selectively reduced. Initial screenings on several reagent-controlled methods, including CBS-catalysts [111] or BINAP/BINOL derived catalysts[112], did not afford any desired product **126** (Table 3.7, Entry **1**-**3**). Substrate-control by L- or K-selectride provided first amounts of **126** but also lactol **127** as major byproduct (Entry **4**). Better selectivities for the desired epimer **126a** were achieved with sodium borohydride (Entry **5**). Variations of boron salt, temperature, solvent or additives did not improve the selectivity (*d.r.* ≤2:1) (Entry **6**-**8**). In contrast, the undesired epimer **126b** could be prepared with a selectivity of 95:5 using lithium tri-*tert*-butoxyaluminum hydride (Entry **9**). The two diastereomers **126** were easily separable by flash chromatography and could be isolated in 60% and 30% yield; the undesired epimer **126b** already representing a potential candidate for library synthesis.

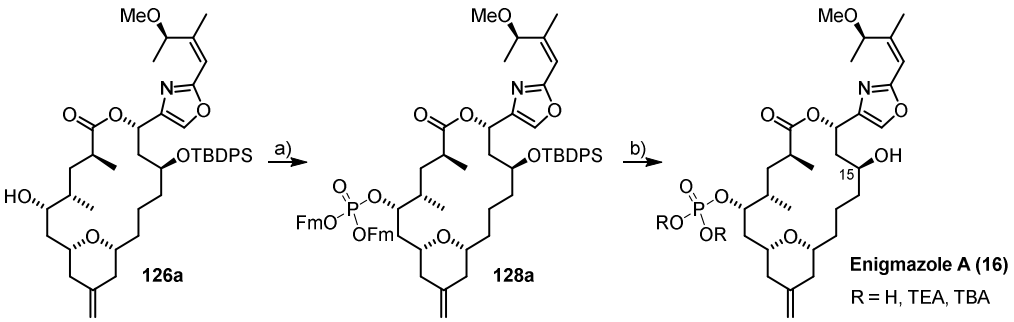
Table 3.7: *Optimization of the stereoselective reduction of ketone* ***123****.*



entry	Conditions	*d.r.* 126a/126b	Results
1	CBS[a]	-	no reaction
2	(*R*)/(*S*)-BINAP-$RuCl_2$	-	90% **123** + sp
3	(*S*)-BINAL	-	decomp.
4	L/K-selectride	-	**126b** + **127**
5	$NaBH_4$ in MeOH, –40 °C	2:1	62% **126a** + 33% **126b**
6	KBH_4 / $Zn(BH_4)_2$	<1:1	**126** + sp
7	$NaBH_4$, $CeCl_3$ in MeOH, –40 °C	1:2	**126b** favored
8	$NaBH_4$ in *i*PropOH / EtOH, –40 °C	<1:1	**126b** favored
9	(*t*BuO)$_3$LiAlH, THF, 0 °C	5:95	selectively **126b**

[a] Corey-Bakshi-Shibata reductions performed with different boranes. sm = ***123****; sp = unidentified side products.*

Phosphorylation of **126a** gave access to protected enigmazole **128a**,[51] but the global deprotection step posed some unexpected challenges. Under basic or acidic conditions the 18-membered macrocycle tended to undergo ring contraction by trans-esterification with the deprotected C15-OH. Furthermore, most fluoride sources, such as caesium fluoride, ammonium fluoride, selectfluor or TASF, left the silyl ether untouched. Only tetra-*n*-butylammonium fluoride (TBAF) gave, beside the described transesterification, traces of **16**. Ultimately, the best yields were obtained by using a high excess of TBAF (50 equiv), which had to be buffered by acidic acid (75 equiv) to prevent ring contraction. Other reagent/buffer ratios resulted in either transesterification to the undesired 16-membered ring or recovered starting material. Slight heating to 40 °C was essential to accelerate the cleavage, which still needed 12-14 days under the described conditions. Ultimately, enigmazole A (**16**) was isolated in 82% yield. The counter ion of the phosphate ester could be adjusted by ion exchange with the help of HPLC chromatography or an ion exchange resin, furnishing the free acid, the triethylammonium, or the tetrabutylammonium salt of **16**.

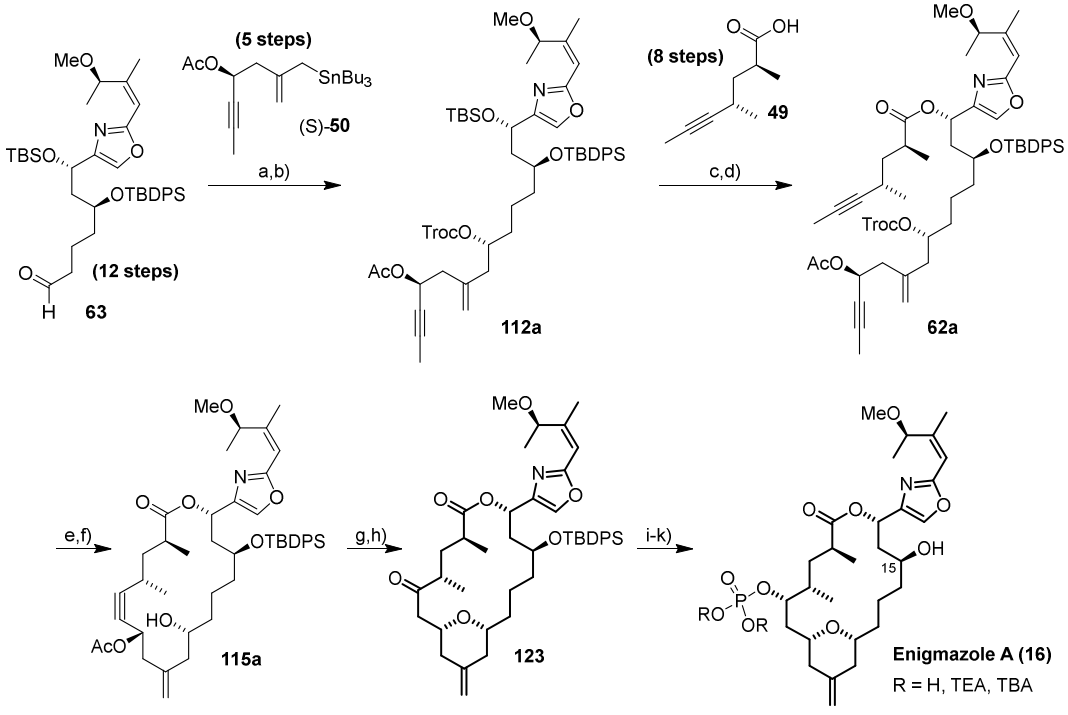


Scheme 3.29: *Phosphorylation and global deprotection in the total synthesis of Enigmazole A. Conditions: a) (i) $(FmO)_2PNiPr_2$, tetrazole, ACN; (ii) aq. H_2O_2, 0 °C, quant.; b) TBAF/HOAc 1:1.5, THF, 40 °C, 14d, 82%.*

All analytical data were in full agreement with those reported in the literature[48, 51]. Acquired NMR data of the different salts are compared in Table 6.1 and 6.2.

3.4.7. Summary

Overall, the total synthesis of enigmazole A (**16**) presented herein is robust, scalable and concise allowing access to the natural product in 23 steps (LLS) with an overall yield of 3.3% (Scheme 3.30). The two key steps of this total synthesis are (i) the RCAM of the highly functionalized substrate **62** giving the desired macrocycle **115** on a multigram scale in excellent yield and (ii) a new and unprecedented post-metathesis functionalization to access the *syn*-tetrahydropyran ring **123**. This gold-catalyzed rearrangement/transannular hydroalkoxylation cascade is a noteworthy example of a complex catalyst/substrate chirality interaction. Experiments on the substrate/catalyst combinations revealed several reaction mechanisms leading to different cyclic byproducts **115a/b**, **124**, and **125**. Further structural derivatization of **16** (as described in the next chapter) by exloring the possibilitis of the reported methodologies could contribute to insights on the biological activity of enigmazole A (**16**).



Scheme 3.30: *Fragment combination and final synthesis of enigmazole A (**16**). Conditions: a) (S)-**50**, (S)-**110**, DCM, −78°C, 95% (d.r. > 10:1); b) TrocCl, DMAP (cat), pyridine, DCM, 0 °C → rt, quant.; c) camphorsulfonic acid (cat.), DCM/MeOH (3:1), 0 °C → rt, 61% (98% brsm); d) 2,4,6-trichlorobenzoyl chloride, Et_3N, then **112a**, DMAP, toluene, 0 °C, quant.; e) **116** (cat.), 4Å + 5Å MS, toluene, 79%; f) Zn, HOAc, ultrasonication, 93%; g) (R)-**121** (cat.), $AgSbF_6$ (cat.), DCM, rt, 91%; h) K_2CO_3, MeOH, 95%; i) NaBH4, MeOH, −40°C, 62%; j) (i) $(FmO)_2PNiPr_2$, tetrazole, ACN; (ii) aq. H_2O_2, 0 °C, quant.; k) TBAF/HOAc 1:1.5, THF, 40 °C, 14d, 82%.*

3.4.8. Outlook: Derivatization and SAR

The limited availability of the enigmazoles (**16**, **17**-**20**) from natural sources and their potent bioactivity make them attractive synthetic targets for structural derivatization. The syntheses of structural siblings could give valuable insight into their structure-activity-relationship, and therefore contribute to the development of new lead structures for anti-cancer drugs. Taking the performed synthetic route of enigmazole A (**16**) into account, we envisioned modifications on the four structural motifs highlighted in Figure 3.2. These motifs are interesting targets for two reasons, (i) they cover most of the functional groups of **16** and (ii) they are readily accessible by the previously described route.

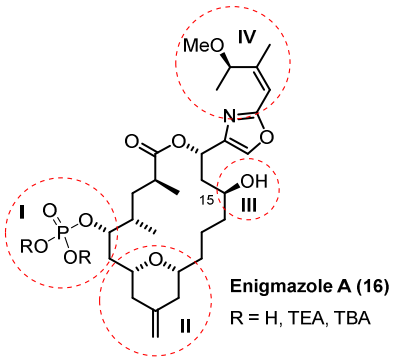
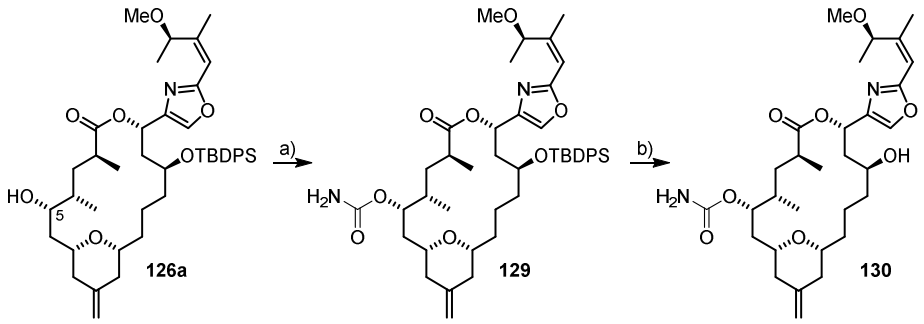


Figure 3.2: *Targets for the derivatization of enigmazole A (**16**).*

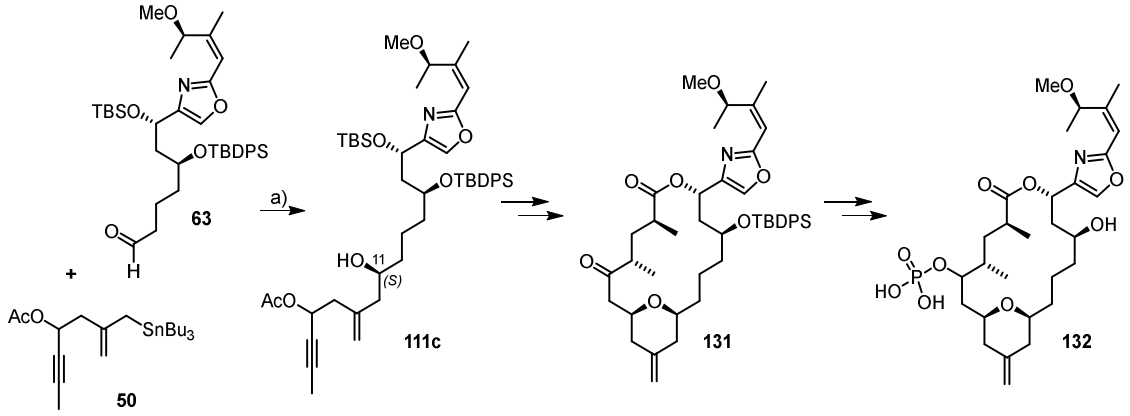
(I) We embarked on the synthesis of a carbamate at C5 in place of the phosphate ester as they have similar electronic character. In analogy to the previously reported route, carbamate **130a** was prepared from the corresponding alcohol **126a** as a first synthetic congener of **16** (Scheme 3.31).[113]



Scheme 3.31: *Synthesis of C5-carbamate **130.** Conditions: a) (i) trichloroacetyl isocyanate, DCM, 0 °C; (ii) rinsed over neutral Al_2O_3; b) TBAF, AcOH, THF, 40 °C, 14 d, 70% (over two steps).*

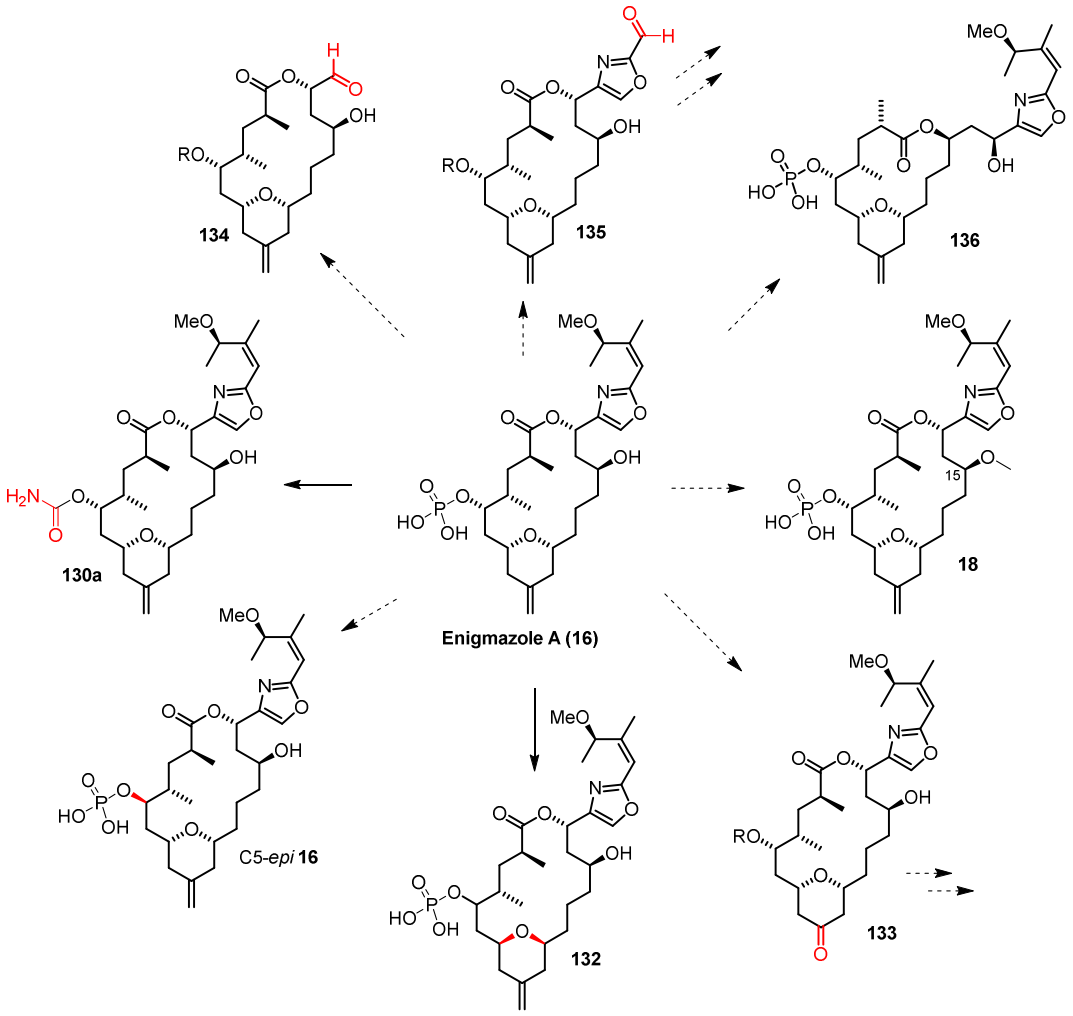
(II) Epimers at C5 and C7 were already formed along the way to the completion of **16**, and C7/11 diastereomer was accessible through a minor variation. The C11-epimer of **111**, for example, was prepared via enantioselective allylation of aldehyde **63** with **50** in the presence of (*R*)-**110**

(Scheme 3.22). With compound **111c** in hand, we moved on to prepare (7*S*,11*S*)-enigmazole A (**132**). All steps were performed under similar conditions as described in the total synthesis of enigmazole A (**16**) and gave comparable yields. The [3,3]-sigmatropic rearrangement showed the same catalyst/substrate chirality match/mismatch. Use of achiral gold catalysts gave poor yields (<10%) and mainly the *anti*-tetrahydropyran. Under the same catalyst system with (*S*)-**121**, **115c** converted to the desired product **117d** in 75% yield and a *d.r.* ≥95%. In contrast, diastereomer **115d** gave undfined mixtures with the screened catalyst. Interestingly, the reduction of **131** with sodium borohydride gave exclusively a single diastereomer in excellent yield. The stereochemistry at C5 could not be assigned unambiguously due to the small amounts of isolated material. Standard transformations finally afforded the streochemical-sibling **132**.



Scheme 3.32: *Synthesis (7S,11S)-enigmazole A (**132**). Conditions: a) (R)-**110**, DCM, −78°C, 95% (d.r. >10:1).*

(III) Future derivatives would consider the C15 hydroxy group. For example, methylation of this group could give the naturally occurring sibling **18**. Further investigations are ongoing in our group. (IV) The modification of the oxazole side chain remains a challenge. Since this heterocycle is carried along the entire route, its modification should be made at a late stage. One possibility could be the oxidative cleavage of the olefins in the oxazole side chain, which would give access to substrates such as **134** and **135** (Scheme 3.33). Similar substrates featuring *exo*-methylene groups and/or oxazoles are known to react selectively under different oxidative conditions.[51, 114] Unfortunately, initial attempts on this transformation resulted in the decomposition of the starting material **126**. Particularly, oxidative cleavage of the *exo*-methylene[115] could give the crucial precursor **133** for the synthesis of enigmazole B (**20**).



Scheme 3.33: *Possible modifications of enigmazole A (**16**) creating a unique compound library.*

4. Total Synthesis of Rhizoxin D

4.1. Introduction

4.1.1. Isolation

Rhizoxin (**140**), the first representative of a large family of polyketide macrolides (**17** and **141**-**148**, Figure 4.1 and 4.2), was isolated from the plant pathogenic fungi of *Rhizopus* sp. by Iwasaki and co-workers in 1984.[116] The Iwasaki group investigated the origin of the rice seedling blight disease and found that swelling was caused not by pathogens inside the seedling root, but by the metabolites of *Rhizopus,* such as **140**, which were absorbed into the bed soil. In particular, the fungus *Rhizopus chinensis* was found to cause the major loss of seedlings and was therefore used as the source for isolating **140**.

Structurally, rhizoxin (**140**) exhibits eleven stereogenic centers, two epoxides, a δ-lactone annulated to a 16-membered macrocyclic lactone and a triene side-chain, which is terminated with an oxazole heterocycle. The di-desepoxy congener, rhizoxin D (**17**), which is the putative biosynthetic precursor of rhizoxin (**140**), was isolated shortly afterwards from the same fungus.[117] The structures were determined by extensive NMR analysis, X-ray diffraction and degradation studies.[118]

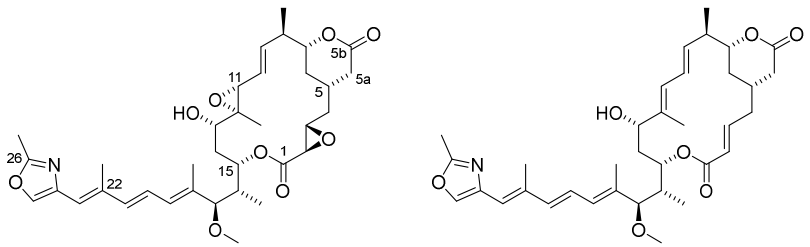


Figure 4.1: *Structures of the rhizoxin (**140**) and rhizoxin D (**17**).*

In 2005, Partida-Martinez and Hertweck showed that rhizoxin (**140**) is biosynthesized not by the fungi of *Rhizopus* themselves, but by endosymbiotic bacteria of the genus *Burkholderia*.[119] The proof of principle was based on the three "Koch postulates" in classical microbiology. Upon antibiotic treatment of *Rhizopus*, a symbiont-free *Rhizopus* strain could be isolated, which did not show any rhizoxin (**140**) production. On the other hand, the isolated and incubated *Burkholderia* strain produced **140** and its congeners in pure culture. Interestingly, the isolated symbiont lost its ability to synthesize rhizoxin (**140**) over time, hinting at a more complex chemical signaling in the

fungal–bacterial symbiosis to trigger and/or maintain rhizoxin (**140**) biosynthesis. After re-introduction of the bacteria to the fungus, the reestablished endosymbiotic relationship enabled the production of rhizoxin (**140**) again. With this work, Partida-Martinez and Hertweck showed a remarkably complex relationship that extends the pathogenic fungus–plantae interaction to a third player, a bacterium, which holds major implications in crop protection.

4.1.2. Bioactivity

At concentrations lower than 10 ng/mL, rhizoxin (**140**) induces an abnormal swelling of rice seedlings known as rice blight, which is an economically costly agricultural disease.[116a] Biological studies showed that rhizoxin (**140**) has a potent activity (≥0.1 µg/mL) against a variety of phytopathogenic fungi, but shows only little activity against bacteria. Further investigations revealed the remarkable *in vitro* and *in vivo* potency against human and murine tumor cells (L1210, K562 or P388 leukemia and B16 melanoma) including vincristine- and Adriamycin-resistant sublines (Table 4.1).[120] **140** was found to be less toxic and more potent than vincristine (Oncovin), a top-of-the-line chemotherapy agent, rendering rhizoxin (**140**) an effective antitumor drug candidate for clinical trials.[121]

Table 4.1: *Cytotoxicity of rhizoxin (**140**) and vincristine in mouse and tumor cell lines sensitive and resistant to vincristine and Adriamycin.*[120a]

Cell line / Compound	IC_{50} (nM)				
	P388	P388/VCR	P388/ADM	K562	K562/VCR
Rhizoxin	0.91	3.84	4.13	0.51	1.28
Vincristine	2.10	32.4	54.0	2.68	56.3

Due to the physical characteristics of the swelling of rice seedlings, it was already assumed in a very early stage of research that rhizoxin inhibits the cell division. Indeed, rhizoxin binds at the β-tubulin of many eukaryotic cells causing inhibition of tubulin polymerization.[122] This disruption of microtubule formation prevents the formation of the mitotic spindle and inhibits cell division leading to cell death.[123] Binding studies revealed that rhizoxins have their own distinct binding site, which may overlap with the binding site of the vinca alkaloids, also affecting their binding to proteins.[122]

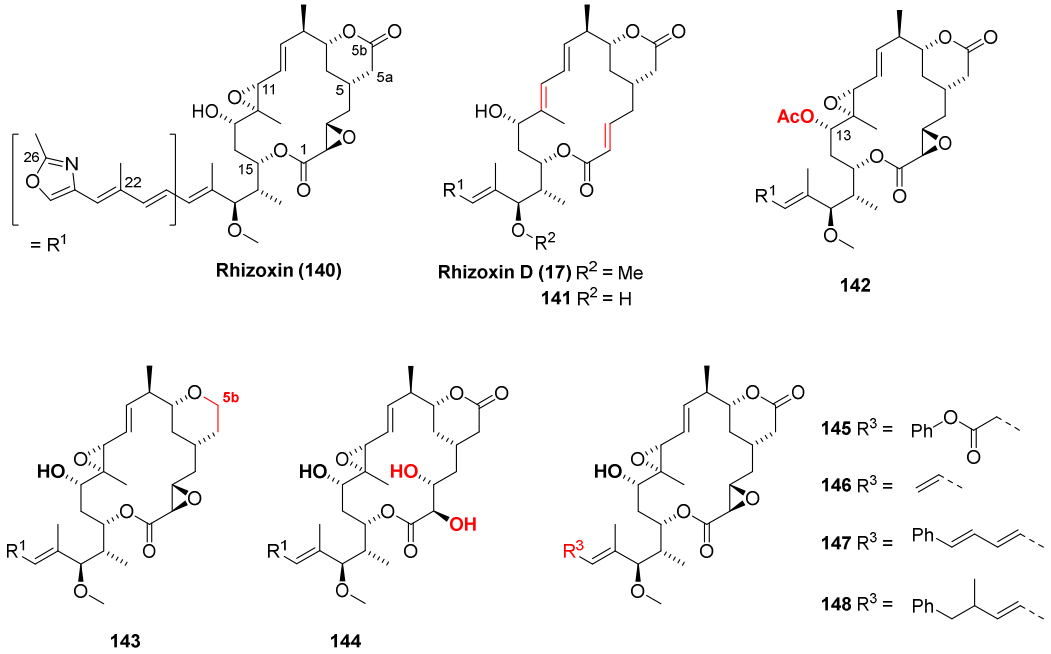


Figure 4.2 *Structures of rhizoxin (**140**) and its analogues.*

The promising biological activities of rhizoxin (**140**) prompted detailed investigations of structure-activity relationship (SAR).[116b, 124] Biologically essential parts of the rhizoxin structure are the free hydroxy group at C13, the δ-lactone spanning C5-7, and the methyl group at C8.[125] Acetylation of the hydroxy group (**142**) or removal of the carbonyl of the δ-lactone (**143**) resulted in loss of activity (Table 4.2). It was found that these oxygen functionalities (plus the carbonyl at C1) form hydrogen bonds to the active site of β-tubulin.[126] The epoxide functionalities at C2-3 and C11-12 could be replaced by double bonds (**17** and **141**) without significant influence on the activity. In contrast, hydrolytic opening of the epoxides had detrimental effects (**144**), presumably due to conformational changes in the 16-membered macrocycle.[123] Compared to the macrocyclic core modifications at the oxazole side-chain were better tolerated and had less effect on the activity. Thereby, derivatizations at the end of the chain C22-26 (**146**-**148**) had the smallest influence.

Table 4.2: *Activity of rhizoxin (**140**) and derivatives on cytotoxicity (P388) and tubulin polymerization.[123, 125] n.a. = no activity.*

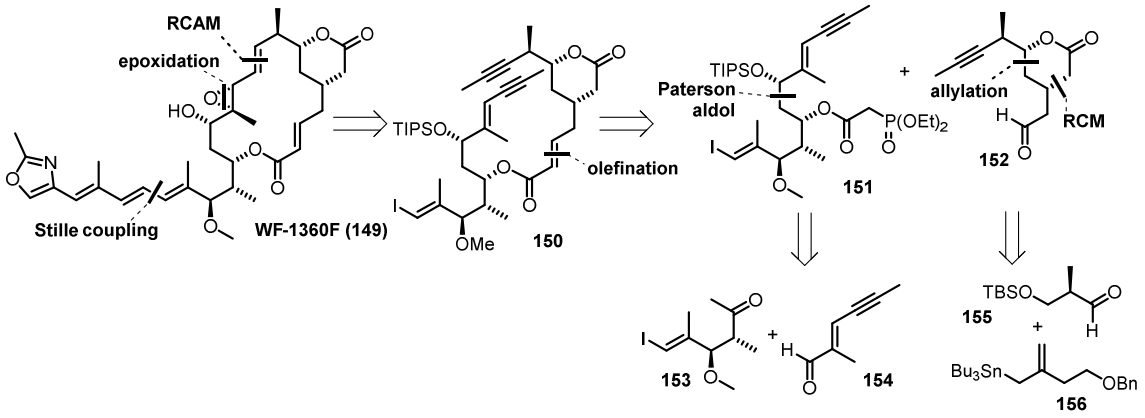
Activity / Substance	**140**	**17**	**141**	**142**	**143**	**144**	**145**	**146**	**147**	**148**
P388 (IC_{50} µM)	0.00043	-	-	-	n.a.	-	12.4	0.063	0.005	0.17
Tubulin polymeriz.	3.4	5.0	7.0	>20	>50	50	35	3.8	3.8	7.4

Phase I and II clinical trials of rhizoxin (**140**) and its derivatives were carried out in the USA, Japan and Europe. However, **140** did not show sufficient *in vivo* results or major therapeutic advantages compared to other chemotherapeutic agents.[127] Therefore, the trials led to no further approvals.

4.1.3. Literature Review

The rhizoxin family attracted several groups to pursue syntheses of these natural products due to their bioactivity and structure. Detailed reviews of previous syntheses can be found in the literature;[116b, 128] only the most recent synthesis by Altmann *et al.* in 2013 is discussed briefly because the ring closing event featured a RCAM.[129]

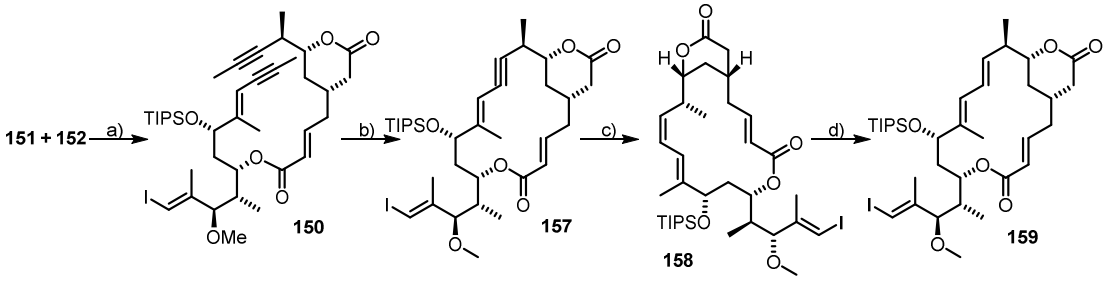
Originally, the synthesis relied on olefin metathesis to close the macrocycle. This strategy proved unsuccessful in spite of extensive efforts. Ultimately, the retrosynthetic analysis focused on a modified approach employing a RCAM (Scheme 4.1). The desired product **149** could be obtained by the hydroxy-directed epoxidation of rhizoxin D (**17**), its desepoxy congener, after RCAM of **150** and subsequent Stille coupling to install the sidechain. Key intermediate **150** would be obtained by a HWE olefination between the two fragments **151** and **152**, which would be accessed by a Paterson aldol reaction between **153** and **154**, asymmetric allylation reaction and ring closing olefin metathesis (RCM) of **155** and **156**.



Scheme 4.1: *Retrosynthetic analysis of WF-1360F (**149**) by the Altmann group.*

The two fragments **151** (8 steps) and **152** (16 steps) were prepared following straightforward routes and joined by HWE olefination (Scheme 4.2). The subsequent RCAM of **150** required high temperatures and long reaction times to afford the desired macrocycle **157** in good yield (69%). However, the reduction of enyne **157** to the desired 1,3-(*E,E*)-diene motif **159** proved to be challenging. *trans*-Selective hydrogenation or hydroelementation attempts were unsuccessful or

gave poor yields and *E/Z*-selectivities. The conjugated diene **159** was accessed in a step wise procedure through conversion of **157** into (*Z*)-olefin **158** and subsequent isomerization of the olefin in good yield (65% over two steps) and in excellent *E/Z* ratio (20:1). The coupling of **159** and the sidechain followed by global deprotection afforded rhizoxin D (**17**); a hydroxy-directed epoxidation of **17** gave WF-1360F (**149**).

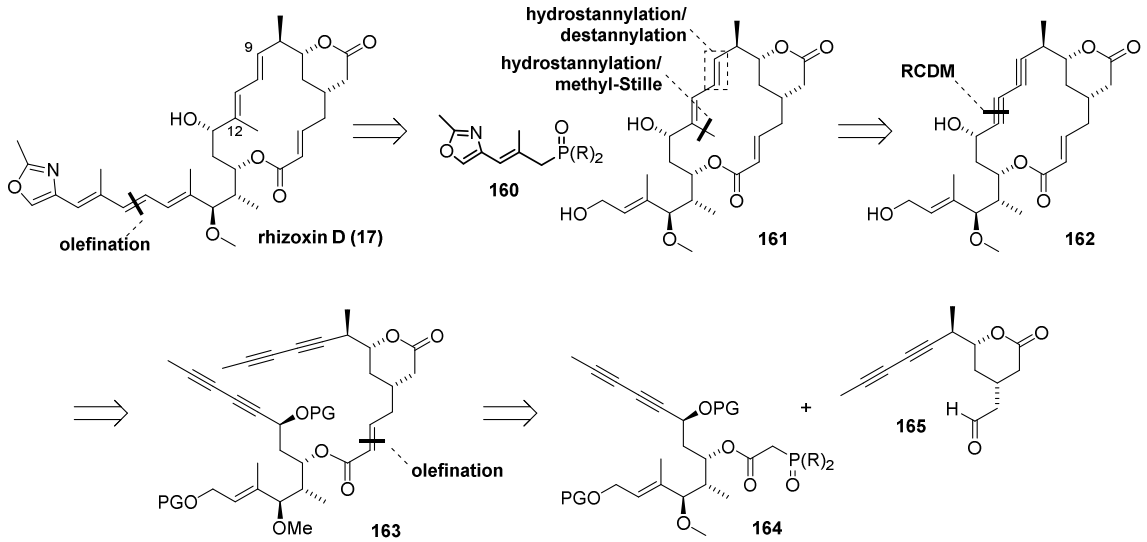


Scheme 4.2: *RCAM applied by the group of Altmann to synthesize WF-1360F (**149**). Conditions: a) LiCl, DBU, THF/ACN 3:1, 0 °C → rt, 81%; b) **9** (cat.), $MnCl_2$, toluene, 5 Å MS, 125 °C, 69%; c) (i) $[Co_2(CO)_8]$, DCM, rt; (ii) 1-ethylpiperidine hypophosphite, benzene, reflux, 74% over 3 cycles; d) AIBN, PhSH, benzene, reflux, 88%, E/Z = 20:1.*

In conclusion, Altmann *et al.* showed a convergent synthesis of two members of the rhizoxin family. It is worth noting the unsuccessful attempts in employing olefin metathesis for ring macrocyclization event and the problems with the 1,3-(*E,E*)-diene motif, showing the challenge of constructing the strained 16-membered macrocycle.

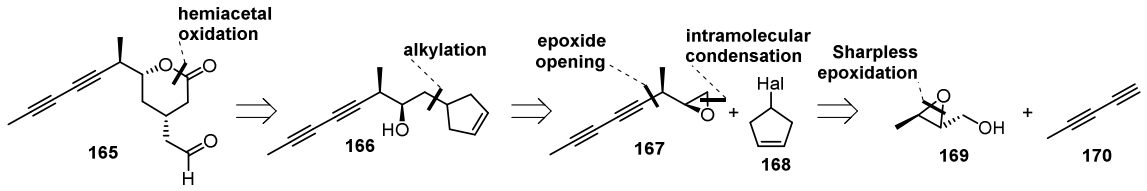
4.2. Retrosynthetic Analysis and Preliminary Studies

Our group envisioned a retrosynthetic analysis of rhizoxin D (**17**) via RCDM, which would construct a versatile diyne motif (Scheme 4.3). This motif would allow downstream modifications between C9 to C12 which may give access to a broad variety of family members and their analogues. The synthesis should not only extend the understanding and application of our own methodology, but further provide new insights in the structure-activity relationship of the rhizoxin core.



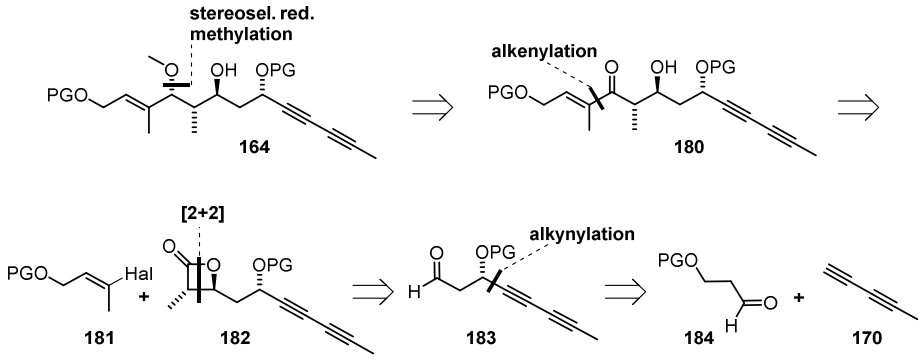
Scheme 4.3: *Retrosynthesis of Rhizoxin D (**17**) showing the two key fragments **164** and **165**. PG = protecting group, R = aryl or alkoxy.*

Retrosynthetically, we envisioned that **17** could be prepared by previously reported olefination between sidechain **160** and key intermediate **161**.[130] The (*E,E*)-diene in **161** would be installed in four steps: first, a sequence of regioselective hydrostannation and methyl-Stille coupling to provide the trisubstituted olefin, followed by a second sequence of hydrostannation/destannylation completing the desired diene. This sequence was already verified on a simple test substrate described later in this section. Macrolactone **162** would be obtained by a RCDM of tetrayne precursor **163**. This compound could be prepared via an olefination reaction between phosphonate **164** and aldehyde **165**.



Scheme 4.4: *Retrosynthetic analysis of the eastern fragment **165**.*

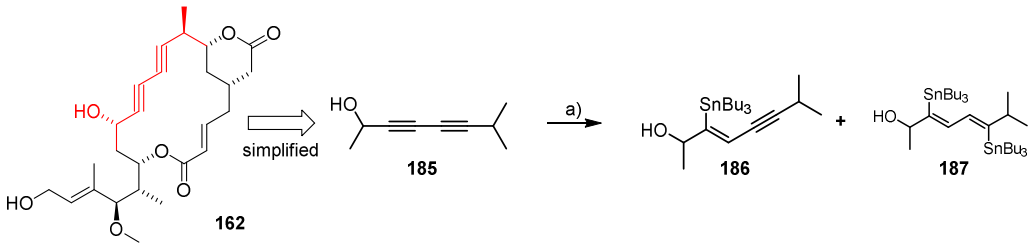
The eastern fragment **165** could be prepared by an oxidation of the thermodynamically favored hemiacetal derived from an oxidative cleavage of cyclopentene **166**. Cyclopentene **168** was planned to undergo regioselective alkylation of epoxide **167**. **167** could be accessed via an intramolecular condensation reaction of the diol obtained by nucleophilic addition of 1,3-pentadiyne (**170**) to known epoxide **169**.[131]



Scheme 4.5: *Retrosynthetic analysis of the western fragment* ***164****.*

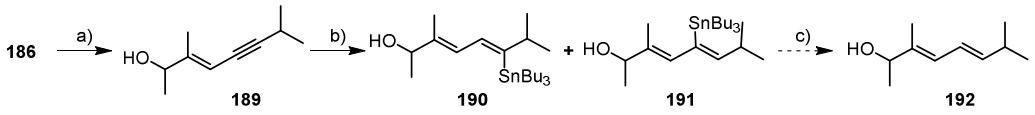
The western fragment **164** could be made by methylation of the alcohol, derived from a directed anti-selective reduction of ketone **180** (Scheme 4.5). This ketone could be obtained via alkenylation of β-lactone **182** or any pre-activated derivative (e.g. an ester or Weinreb amide) with alkenyl halide **181**. Lactone **182** would be prepared by *trans*-selective and asymmetric [2+2] cyclocondensation[132] of aldehyde **183** with propionyl bromide or by a tandem Mukaiyama aldol-lactonization[133] with a thiopyridylsilylketene acetal. Aldehyde **183** could be accessed by an enantioselective alkynylation of aldehyde **184** with 1,3-pentadiyne (**170**), followed by protection and oxidation state adjustments.

Preliminary studies on the transformation of the 1,3-diyne motif into a (*E,E*)-diene were conducted by Felix Ungeheuer, who demonstrated that the scope of classical RCAM could be extended to 1,3-diynes.[36, 128] To verify the regioselectivity of *trans*-hydrostannations on 1,3-diynes, the very much simplified test system **185** was used (Scheme 4.6). In this system, the hydrostannation[40] was highly regioselective for the α-position yielding product **186** in 74% yield. Unfortunately, bis-stannation was also observed leading to side product **187** in 20% yield.



Scheme 4.6: *Trans-selective hydrostannation of 1,3-diynes. Conditions: a) [Cp*RuCl$_4$]$_n$ (cat.), Bu$_3$SnH, deg. DCM, rt, 74%* ***186*** *and 20%* ***187****.*

Subsequent methyl-Stille coupling of stannane **186** afforded the desired trisubstituted olefin **189** in very good yield (92%) (Scheme 4.7). A second hydrostannation reaction on enyne **189,** using the same conditions as before, afforded a mixture of diastereomers **190**/**191** (10:1) which could be transferred into the desired product **192** by destannylation. In the light of these positive results combined with the concise retrosynthetic analysis, we embarked in the forward synthesis of rhizoxin D (**17**).

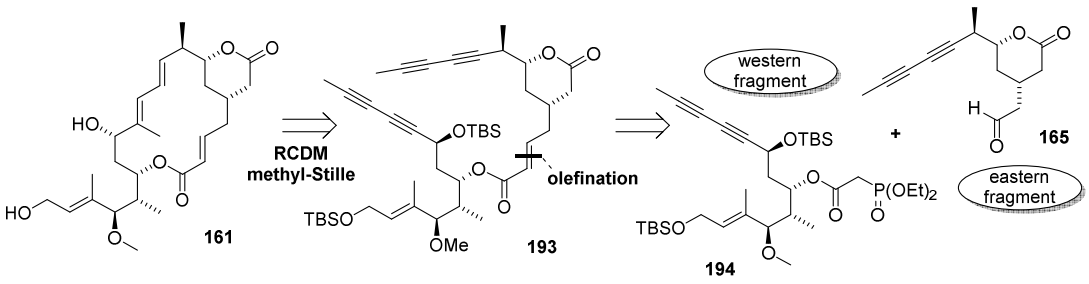


Scheme 4.7: *Final transformation of the 1,3-diyne motif into (E,E)-1,3-diene. Conditions: a) [Pd(PPh$_3$)$_4$] (cat.), [Ph$_2$PO$_2$][NBu$_4$], CuTc, MeI, DMF, 92%; b) [Cp*RuCl$_4$]$_n$ (cat.), Bu$_3$SnH, deg. DCM, rt, 89%; c) destannylation (not performed).*[128]

4.3. Synthesis of Rhizoxin D

The studies towards the total synthesis of rhizoxin D (**17**) performed by Felix Ungeheuer promised a feasible approach to this molecule.[128] Remaining tasks were reproducing the explored reactions on larger scale, the optimization of several challenging transformations, and the investigation on the final key steps to complete the total synthesis of rhizoxin D (**17**). The key milestone of the project was to obtain intermediate **161**, an analogue of a former total synthesis,[134] which could be accessed via RCDM and hydrostannation reactions developed in our group (Scheme 4.8). The corresponding tetrayne precursor **193** could be disconnected into the two main fragments, **194** and **165**.

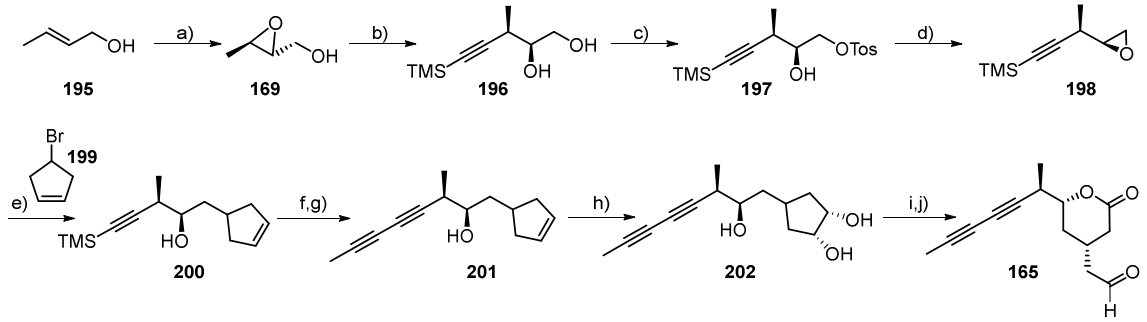
The main focus of this chapter is to discuss the synthesis of the eastern fragment **165** along with optimization on the synthesis of **194** and the combination of the two fragments. The western fragment **194** was previously reported by Felix Ungeheuer and details can be found in his thesis.[128]



Scheme 4.8 *Retrosynthesis of rhizoxin D (**17**) showing key fragments **194** and **165.***

4.3.1. Synthesis of the Eastern Fragment

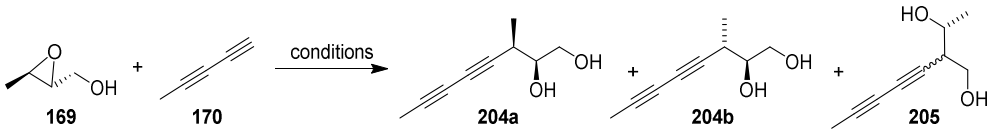
A previous route to the eastern fragment **165** pursued by our group is shown in Scheme 4.9.[128] However, due to subsequent experience gained on the preparation and handling of 1,3-pentadiyne (**170**), which is part of the synthesis of western fragment **194** (Section **4.3.2**), we envisioned a shortcut and optimization of the route.



Scheme 4.9: *Original synthesis of the eastern fragment* ***165****.*[128] *Conditions: a) (-)-DIPT, $Ti(OiPr)_4$, TBHP, 3 Å MS, DCM, −20 °C to rt, 78%; b) TMS-acetylene, n-BuLi, toluene, −78 °C then Et_2AlCl, 0 °C then* ***169****, 95%; c) Tos-Cl, Bu_2SnO, Et_3N, DCM, rt, 75%; d) DBU, DCM, rt, 85%; e) Mg, Et_2O, then CuI, THF, −40 °C, 68%; f) NBS, $AgNO_3$ (cat.), acetone, rt; g) propyne, CuCl, $NH_2OH{\cdot}HCl$, aq. $BuNH_2$ (30% in water), 60% (over two steps); h) OsO_4 (cat), NMO, acetone/H_2O (2:1), 70% (d.r. = 7.7:1); i) $NaIO_4$ (10% on SiO_2), DCM, rt; j) PIDA, TEMPO (cat.), $Yb(OTf)_3$ (cat.), DCM, rt, 76% (over two steps).*

The second generation synthesis started with the same epoxide **169** which was obtained by an asymmetric Sharpless epoxidation[135] of *trans*-crotyl alcohol (**195**) as previously described in the literature.[131] As the preparation of TMS-alkyne **196** required the installation of the diyne functionality at a later stage, we planned to add diyne **170** directly to epoxide **169**. Diyne **170** was prepared from 1,4-dichloro-2-butyne by a base-induced elimination reaction quenched with methyl iodine.[136] Unfortunately, the previously described conditions to make TMS-alkyne **196** (>95% yield, one isomer)[137] gave very poor selectivities when **170** was used as pre-nucleophile to afford desired diyne **204a** (Table 4.3, Entry **1**). In addition to the poor selectivity we observed several side products, which were the corresponding diastereomer **204b** and the 1,3-diol **205**. Variations of the conditions did not improve the yields (Entry **2**).[138] Also, prior deprotonation of the alcohol using *n*-butyllithium gave the same ratio of product and side products (Entry **3**). A positive influence on the selectivity was observed after increasing the reaction time of the diynyl-lithium species and diethyl aluminum chloride, probably allowing for complete transmetalation (Entry **4**). The best yields and selectivities were obtained by using dichloromethane as solvent, giving **204a** in 95% isolated yield on a multi gram scale with very good regio- and diastereoselectivity (Entry **5**). This observation was in agreement with the findings in a publication by Oshima,[139] showing that use of less polar solvents, such as hexane or dichloromethane, increases the regioselectivity for the desired β-addition. However, literature suggests that this effect is highly substrate dependent.[140]

Table 4.3: *Optimization of the alkynylation reaction.*

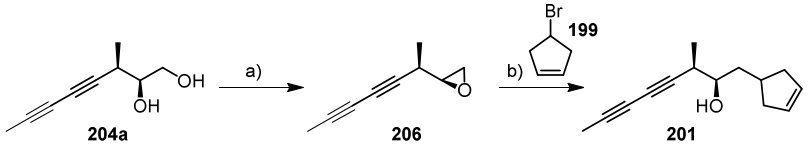


169 **170** **204a** **204b** **205**

entry	Diyne (equiv)	*n*-BuLi (equiv)	Et_2AlCl (equiv)	Additives (equiv)	solvent	Ratio (pd:sp)	isolated yield[a] (%)
1	3.0	2.6	2.6		toluene	75:25	90
2	1.5	1.2	1.2		toluene	60:40	n.d.
3	2.2	2.0	2.0	*n*-BuLi[b]	toluene	77:23	n.d.
4	2.2	2.0	2.0	[c]	toluene	89:11	n.d.
5	2.2	2.0	2.0		DCM	95:5	95

*[a] mixture of isomers; [b] the epoxide was deprotonated with n-BuLi (1 equiv) before adding it to the reaction mixture; [c] epoxide **169** was added after 2 h. pd = product **204a**, sp = side products **204b** and **205**.*
*General experimental procedure: n-BuLi was added to a solution of diyne **170** in toluene at −78°C. After 30 min the reaction mixture was warmed up to 0 °C, before Et_2AlCl was added. After 30 min, a solution of the epoxide **169** in toluene was added still at 0 °C. Stirring of the reaction mixture was continued over night at ambient temperature.*

A separation of regioisomers **204** and **205** was not possible at this stage, but the mixture could be directly used in the next reactions in which only the desired regioisomer **204** could form epoxide **206** after chemoselective tosylation and treatment with DBU (Scheme 4.10). Copper-catalyzed epoxide opening at the primary position using the Grignard reagent derived from 4-bromocyclopent-1-en (**199**) gave compound **201** as well as trace amounts of the corresponding hydrolysis product **204**. The 4-bromocyclopent-1-en (**199**) was accessible from commercially available cyclopent-3-en-1-ol in one step on large scale and excellent yield.[141] The critical step in this reaction was the formation of the Grignard reagent derived from **199**. Only magnesium turnings which were activated by the addition of catalytic amounts of 1,2-dibromo-ethane reacted with bromide **199**. A reaction set at 1 M concentration gave the best results. Curiously, no reaction was observed between the corresponding iodide and magnesium. Attempted lithium/halogen exchange with *t*-butyllithium resulted in complex mixtures.

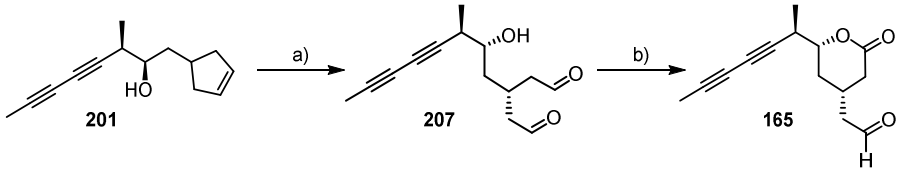


204a **206** **201**

Scheme 4.10: *Synthesis of cyclopentene **201**. Conditions: a) i) Tos-Cl, Bu_2SnO (cat.), Et_3N, DCM; ii) DBU, 72% (stepwise 97% and 86%); b) Mg, **199**, Et_2O, rt, then CuI, −40 °C, then **206**, 86%.*

The δ-lactone was installed by an oxidative cleavage of cyclopentene **201** (Scheme 4.11). Direct ozonolysis of **201** and subsequent ytterbium-catalyzed oxidation[142] of **207** afforded **165** in only

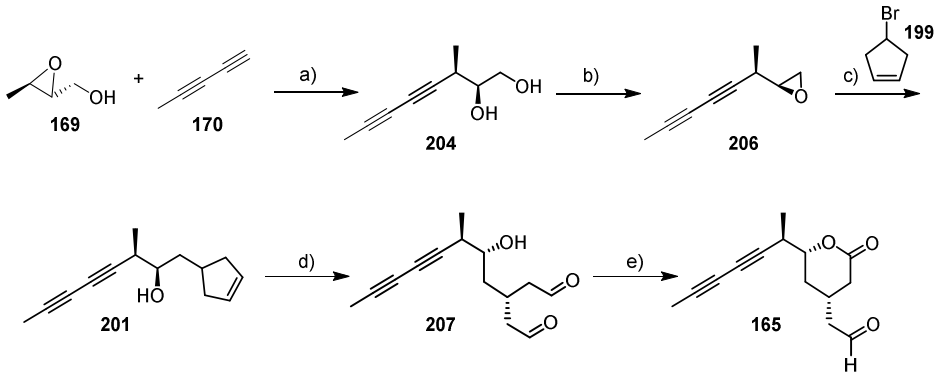
two steps and excellent yield (81% over two steps). Other oxidizing agents, like TPAP[65] or PCC[143], showed similar results; however it was always necessary to purify and oxidize dialdehyde **207** immediately to obtain reasonable yields above 30%.



Scheme 4.11: *Synthesis of the eastern fragment **165**. Conditions: a) O_3, DCM, −78 °C, then PPh_3, 88%; b) PIDA, TEMPO (cat.), $Yb(OTf)_3$ (cat.), DCM, 92%.*

Both aldehydes **207** and **165** were very unstable, probably due to polymerization (even at −25°C), explaining the broad range of yield (30-90%) in the oxidations of **207**. Consequently, the storage times were kept short and these aldehydes were directly used in the next reactions.

In summary, the eastern fragment **165** was accessed in 6 steps from the commercially available (2*E*)-but-2-en-1-ol (**195**) with an overall yield of up to 43% (Scheme 4.12). All steps were scalable and reliable.



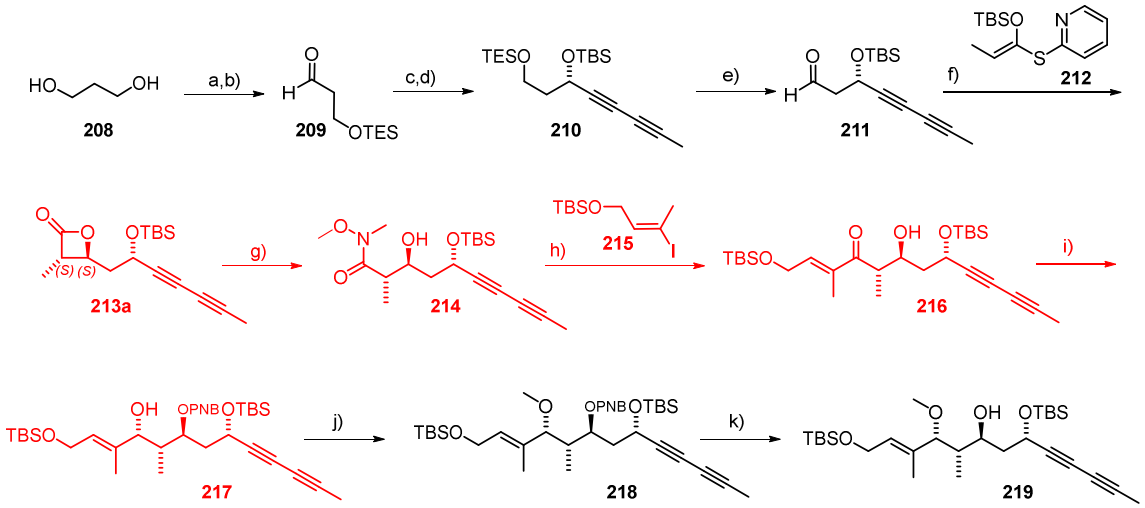
Scheme 4.12: *Final synthesis of the eastern fragment **165**. Conditions: a) n-BuLi, Et_2AlCl, then **169**, DCM, −78°C → 0 °C, 95%; b) i) Tos-Cl, Bu_2SnO (cat.), Et_3N, DCM; ii) DBU, 72% (stepwise: 97% and 86%); c) Mg, **199**, Et_2O, rt, then CuI, −40 °C, then **206**, 86%; d) O_3, DCM, −78 °C, then PPh_3, 88%; e) PIDA, TEMPO (cat.), $Yb(OTf)_3$ (cat.), DCM, 92%.*

4.3.2. Synthesis of the Western Fragment

The western fragment **194** displayed the longest linear sequence in the proposed total synthesis of rhizoxin D (**17**). Felix Ungeheuer proposed a synthetic route to this fragment and provided preliminary results (Scheme 4.13).[128]

However, the red-highlighted steps remain challenging. In particular, the coupling of the alkenyl sidechain **215** with β-lactone **213** required further investigations which will be discussed below.

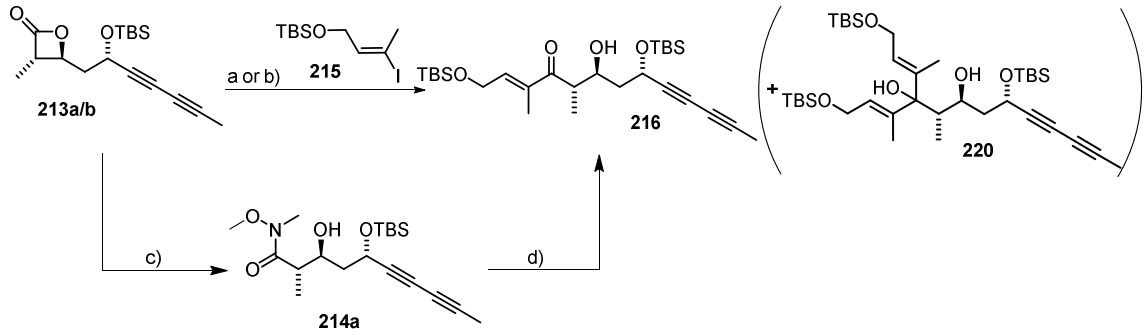
This β-lactone was used as a mixture of inseparable diastereomers (*S,S*)-**213a** and (*R,R*)-**213b** (*d.r.* = 5:1).



Scheme 4.13: *Original synthesis of the western fragment **219** by Felix Ungeheuer.[128] Conditions: a) TES-Cl, Et_3N, DMAP (cat.), DCM, 87%; b) SO_3·Py, Et_3N, DMSO/DCM (1:1), 0 °C to rt, 85%; c) **170**, Me_2Zn, (R,R)-ProPhenol, Ph_3P=O, toluene, 0 °C, 84%; d) TBS-Cl, imidazole, DCM, 87%; e) $(ClCO)_2$, DMSO, , −78 °C to −30 °C, 1 h then −78 °C, Et_3N, 76%; f) **212**, $ZnCl_2$, DCM, 62% (d.r. = 5:1); g) MeNH(OMe), $AlMe_3$, DCM, 0 °C, 78%; h) **215**, t-BuLi, THF, −78 °C, 15 min, then $CeCl_3$·2LiCl, 30 min, then **214**, −78 °C, THF, 45 min, 38% (96% brsm); i) SmI_2, p-nitrobenzaldehyde, THF, −10 °C, 70%; j) $(CH_3)_3OBF_4$, 1,8-bis-(dimethylamino)naphthalin, DCM, 69% (77% brsm.); k) K_2CO_3, MeOH/THF 1:1, 71%.*

Initial efforts in our group on the direct alkenylation of β-lactone **213** using the alkenyl-lithium species formed by a lithium-iodine exchange with *t*-butyl lithium and alkenyl iodine **215** gave very poor yields and resulted in epimerization at the α-stereocenter next to the lactone (Scheme 4.14). Epimerization for similar additions were already reported in the literature and did not come unexpected.[144] Transmetalation of the lithium species to a less Brønsted basic organocerium analogue prevented this epimerization. Treatment of the lithium species with anhydrous cerium(III) chloride gave a deep orange solution of an organocerium species, which was only stable at low temperatures (≤−60 °C). Addition of this solution to lactone **213** gave the desired product **216** in yields around 20% along with recovered starting material **213**, as well as the double addition product **220**. Further experiments varying concentration, temperature, reaction time and equivalents of reagents could not increase the yield above 30%. It is noteworthy that the best results were obtained when the lithium-cerium exchange was performed over several hours (≥2 h) at −78 °C with an excess amount of cerium(III) chloride. Shorter reaction times resulted in epimerization of the α-stereogenic center, suggesting that the transmetalation was not completed. Using a solution of $CeCl_3$·2LiCl in tetrahydrofuran as described by Knochel[145] improved the yield and reproducibility due to the increased solubility of cerium chloride in the reaction medium. Under those conditions we never observed byproduct **220**. To further explore the

reactivity of substrate **213**, we tested it in simple reactions, utilizing vinylmagnesium bromide as nucleophile (with and without copper(I) iodide). Although these transformations were very well described in the literature,[146] low conversion was observed even at elevated temperatures, and starting material **213** could be re-isolated. This indicates very low reactivity of this substrate towards nucleophilic additions in general.



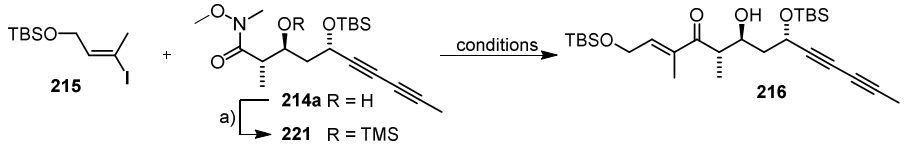
Scheme 4.14: *Initial attempts for the preparation of unsaturated ketone **216**. Conditions: a) **215**, t-BuLi, Et_2O/pentane, −90 °C, then **213**, −78 °C, 20 min, 24%; b) **215**, t-BuLi, Et_2O/pentane, −78 °C, then $CeCl_3$, 1 h, then **213**, −78 , 1 h, 20%; c)* $CH_3NH(OCH_3)$, $AlMe_3$, DCM, 0 °C, 78% (**213**, 11%); *d) **215**, t-BuLi, THF, −78 °C, 15 min, then $CeCl_3$·2LiCl, 30 min, then **214a**, −78 °C, THF, 45 min, 38% (96% brsm).*

To achieve better reactivity, we planned to transfer β-lactone **213** into another carbonyl derivative. Alkenylation reactions of similar Weinreb amides, for example, were very well described in the literature.[147] The transformation of **213** into Weinreb amide **214** proceeded with good yields (70-90%) on up to 2.4 g scale.[148] At this stage, diastereomers **214a** and **214b** could be separated by flash chromatography and we proceeded with **214a**.

Initial attempts on the alkenylation of Weinreb amide **214a** with alkenyl iodide **215** in our group are shown in Table 4.4 (Entry **1-4**).[128] Best results (Entry **4**) were obtained using similar conditions as described for the direct alkenylation of β-lactone **213** (see above). The reaction yields were between 30% and 40% in favor of the desired product **216** (50-60% brsm **214**). Full conversion was not observed even when 5 equivalents of the alkenyl-cerium species were employed. When we applied the improved conditions taken from the direct alkenylation procedure, ensuring complete transmetalation by stirring the organolithium species and the $CeCl_3$·2LiCl solution for 3 h, yields decreased dramatically and complex reaction mixtures were observed. Taking these results into account, we modified the procedure by direct addition of the organolithium species of **215** to a solution of Weinreb amide **214a** and $CeCl_3$·2LiCl at −78 °C without initial metal exchange. This modification afforded **216** in better yield up to 60% (Entry **5**). The results might indicate that both reactions proceeded via different pathways. While the alkenylation of β-lactone **213** proceeded by addition of an organocerium species to the lactone, the alkenylation of Weinreb amide **214** is only

promoted by cerium(III), allowing the lithium species to attack the carbon center. This would also explain why **214** did not react with Grignard reagents, such as methylmagnesium bromide or vinylmagnesium bromide, without further activation, even though similar Weinreb amides are very well known to react under these conditions.[149]

Table 4.4: *Screening of conditions for the synthesis of ketone **216**. Entry 1-4 show results of Felix Ungeheuer.[128] Conditions: a) TMS-Cl, TEA, DMAP (cat.), 0 °C → rt, DCM, quant.*



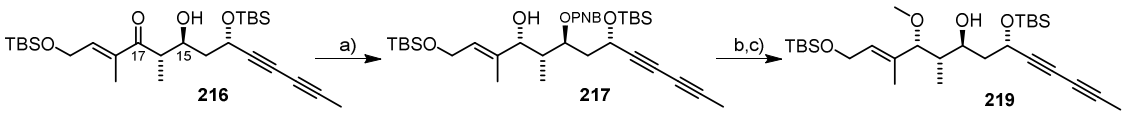
entry	R	Conditions	isolated yield (%)
1	H	**215,** *t*-BuLi, –78 °C then **214**, –78 °C [a]	24
2	H	**215,** *t*-BuLi, –78 °C then **214**[b], –78 °C [a]	16
3	H	**215,** *t*-BuLi, –78 °C then $MgBr_2 \cdot (OEt)_2$, then **214,** –78 °C to 0 °C [a]	traces
4	H	**215,** *t*-BuLi, –78 °C then $CeCl_3 \cdot 2LiCl$, then **214**, –78 °C [a]	38 (96 brsm)
5	H	**215** (5.0 equiv), *t*-BuLi (9.5 equiv), –78 °C then $CeCl_3 \cdot 2LiCl$ (4.9 equiv) and **214** (1 equiv), –78 °C [c]	50-60 (60-70 brsm)
6	TES	**215** (2.0 equiv), *t*-BuLi (4.0 equiv), –78 °C, added to $CeCl_3 \cdot 2LiCl$ (2.0 equiv) and TES-**214** (1 equiv), –78 °C [c]	45[d]
7	TMS	**215** (2.5 equiv), *t*-BuLi (5.0 equiv), –78 °C, added to $CeCl_3 \cdot 2LiCl$ (2.0 equiv) and **221** (1 equiv), –78 °C; CSA, 0°C, 5 min [e]	83

*[a] Li/I exchange was conducted in Et_2O for 20 min at −78 °C, (then transmetalation,) Weinreb amide was added as a solution in THF to the alkenyl reagent dropwise; [b] alcohol **214a** was prior deprotonated with 0.6 eq. of n-BuLi at −78 °C and stirred for 15 min; [c] Li/I exchange was conducted in Et_2O for 30 min at −78 °C, Li-alkenyl was added to a solution of Weinreb amide and $CeCl_3$ dropwise at −78 °C; [d] two steps: yield of alkenylation 91%, TES deprotection 50%; [e] Li/I exchange was conducted in THF for 30 min at −78 °C, Li-alkenyl was added to a solution of Weinreb amide and $CeCl_3$ dropwise at −78 °C; crude product dissolved in DCM/MeOH 5:1 and treated with CSA.*

Ultimately, the best results for this transformation were obtained when the hydroxyl group in Weinreb amide **214** was protected as TES or TMS silyl ethers (Entry **6** and **7**) which were obtained in excellent yields (91% and quant). To ensure substrate stability under reaction conditions, we first used the more stable TES-ether of **214a** in the alkenylation reaction which afforded excellent yields of the TES-protected-**216** (>90%) (Entry **6**). The deprotection of the TES-ether under acidic conditions was unselective, due to the primary TBS ether in substrate **214**, affording only 50% of the desired product **216**. To overcome this problem the more labile TMS-ether **221** was used for the alkenylation reaction with similar success. Subsequent TMS-deprotection (without loss of the TBS group) afforded **216** in 83% yield over three steps (protection, alkenylation, and deprotection). The reaction was also performed in one-pot, which afforded lower yields. In this case, the Weinreb amide **214** was protected *in situ* by using *n*-butyllithium and trimethylsilyl

chloride (1 equivalent each), followed by the alkenylation and final deprotection during the aqueous workup (1 N hydrochloric acid).

After the alkenylation reaction, a methylated hydroxy group at position C17 had to be installed in **216**. An intramolecular Evans–Tishchenko reaction[150] set the desired absolute configuration and protected the directing hydroxy group at C15 in one step (Scheme 4.15). The best results were obtained by using catalytic amounts of freshly prepared samarium(II) iodide and 3 equivalents of *p*-nitrobenzaldehyde in degassed solvent (freeze-pump-thaw method). Interestingly, use of more than 3 equivalents of benzaldehyde led to an unprecedented protection of both hydroxy groups (C15/17) probably due to a disproportionation of the aldehyde by a Cannizzaro-type mechanism.

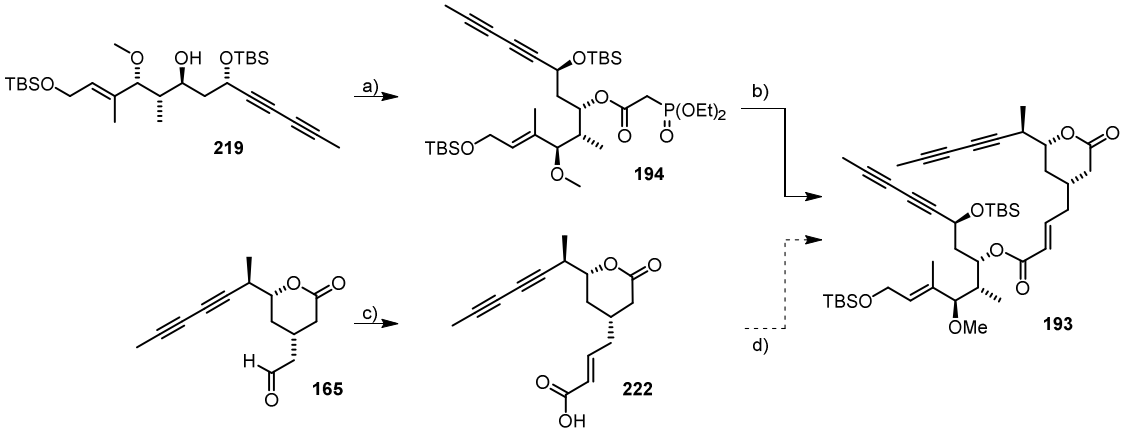


Scheme 4.15: *Final steps of the synthesis of the eastern fragment **219**. Conditions: a) SmI_2 (cat.), p-nitrobenzaldehyde, deg. THF, −25 °C, 85%; b) $(CH_3)_3OBF_4$, 1,8-bis-(dimethylamino)naphthalin, DCM, 78% (83% brsm); c) K_2CO_3, MeOH/THF 1:1, 78%.*

Subsequent methylation of desired product **217** and PNB deprotection[128] afforded the western fragment **219** in 11-13 steps and an overall yield of 3.3-4.1%. The longer route including the TMS-protection-deprotection sequence gave the better overall yield.

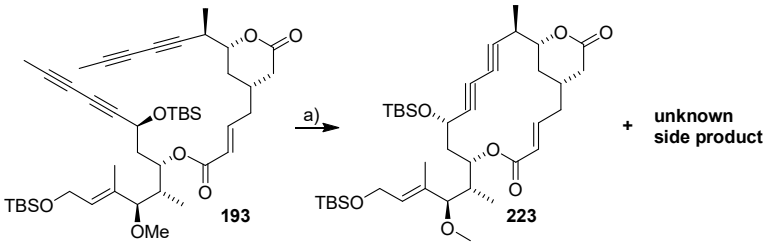
4.3.3. Combination of the Fragments and Outlook

With the two building blocks in hand, we proposed two different routes for the combination of fragment **219** and **165** (Scheme 4.16). The first route was based on the transformation of western fragment **219** to Horner-Wadsworth-Emmons (HWE) precursor **194** used in the previous synthesis of rhizoxin.[129] Reaction of this phosphonate with aldehyde **165** gave desired product **193** in good yield (77%). The second route included esterification of acid **222** and western fragment **219**. The acid was obtained in one step from eastern fragment **165** by a HWE reaction. First attempts to couple both building blocks via an esterification failed.[128] Further investigations will be performed at a later stage to differentiate this total synthesis from previously reported ones and to make use of the more stable acid **222** rather than aldehyde **165**.



Scheme 4.16: *Strategies for the combination of fragment **219** and **165**. Conditions: a) EDC·HCl, diethylphosphonoacetic acid, 3 Å MS, DMAP (cat.), DCM, rt, 85%; b) **165**, LiCl, DBU, ACN, rt, 77% (91% brsm); c) $Zn(OTf)_2$, DBU, TMEDA, diethylphosphonoacetic acid, THF, rt, 73% (E:Z = 10:1); d) **219**, esterification conditions.*

Up to this step, the optimized route made tetrayne **193** available in reliable yields and provided considerable amounts to investigate the key steps: ring closing diyne metathesis and functionalization of the diyne motif. The RCDM of **193** has already been demonstrated by Felix Ungeheuer, albeit in moderate yield and on very small scale (Scheme 4.17).[128]



Scheme 4.17: *RCDM of tetra-yne **193** giving desired product **223** and a unknown side product. Conditions: a) **8** (cat.), 4 Å and 5 Å MS, toluene, <50%.*

Since there is room for further improvement, we moved on to monitor the reaction by HPLC-MS. To our surprise, we observed, in parallel to the consumption of **193**, the formation of two products (Figure 4.3). HPLC-MS analysis indicated that the two newly formed products are the desired monomer **223** and a second unknown byproduct. In addition, the poor combined yield of the two products (<50%) suggested formation of polymer or decomposition of the substrate/products under the reaction conditions. Preparative LC allowed separation of the two compounds and the structure of **223** was confirmed by NMR and MS analysis. The structure of the second product could not be assigned unambiguously, but NMR analysis revealed its close structural relationship to **223**. Surprisingly, MS analysis suggested either a monomeric or dimeric triyne-containing macrocycle, which was so far never observed in RCDM.

HPLC-MS analysis showed the consumption of the unknown byproduct after the addition of more catalyst **8** to yield either polymerization or decomposition products with no traces of **223** observed. Ultimately, the best yield of **223** (30-50%) was obtained by RCDM at ambient temperature with 4 Å and 5 Å molecular sieves and portion wise addition of catalyst **8** (2 × 15 mol%). These conditions gave exclusively the desired product **223**.

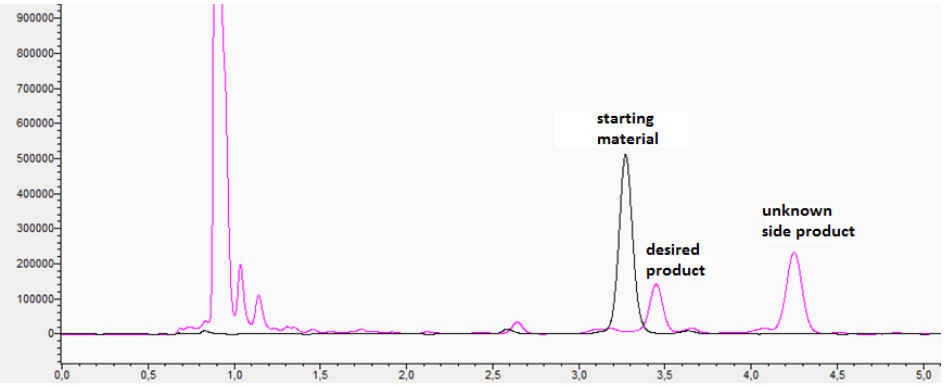
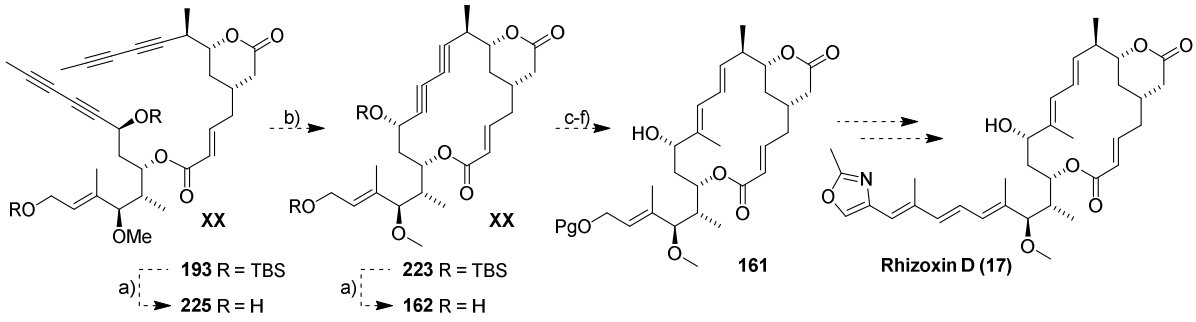


Figure 4.3: *HPLC trace of the RCDM. Black starting material, purple reaction mixture after 1 h.*

Further experiments on the optimization of the RCDM are currently in progress in our group. From previous studies, we know that varying the reaction temperature and concentration can have profound impact on the overall outcome.[32] In addition, our group has recently developed a variety of new ring closing alkyne metathesis catalysts **12**-**15**[34] which will be investigated in this specific transformation.

An alternative route would involve modifying the starting material **193** by removing the TBS protecting groups prior to metathesis to give unprotected propargylic alcohol **225** (Scheme 4.18). The removal of the sterically demanding TBS groups could change the conformation of the starting material and of the macrocyle and therefore lead to improved yields. We are expecting to be able to overcome the selectivity issues and continue the total synthesis of rhizoxin D (**17**).



Scheme 4.18: *Final steps to the total synthesis of rhizoxin D (**17**). Conditions: a) TBS deprotection; b) RCDM; c) hydrostannation; d) methyl-Stille coupling; e) hydrostannation; f) destannylation.*

In conclusion, we were able to access the open tetrayne **193** in only 13-15 steps and 4.1-5.6% overall yield. All reactions up to this important key intermediate gave high yields and were carried out on workable scales (>100 mg). The last missing transformations for completion of the total synthesis of rhizoxin D (**17**) would include hydroxy-directed hydrostannation reactions to install the methylated-(*E,E*)-diene and the attachment of the literature known sidechain **160**.

5. Summary and Conclusion

Almost 20 years after the first ring closing alkyne metathesis (RCAM) was performed in the Fürstner group, it has established its important role for organic synthesis.[20] Improvements over the years in catalyst structure and reaction protocols have expanded the scope of RCAM, including employment in several complex total syntheses.[6b, 105] In combination with post-metathesis alkyne functionalizations, RCAM has become an important tool to construct macrocyclic frameworks.

This thesis explored the scope of RCAM and applications of state-of-the-art alkyne functionalization methods in the context of synthesizing two natural products, enigmazole A (**16**) and rhizoxin D (**17**) (Figure 5.1). Both natural products belong to families with rare structural motifs and selective anti-cancer activities.

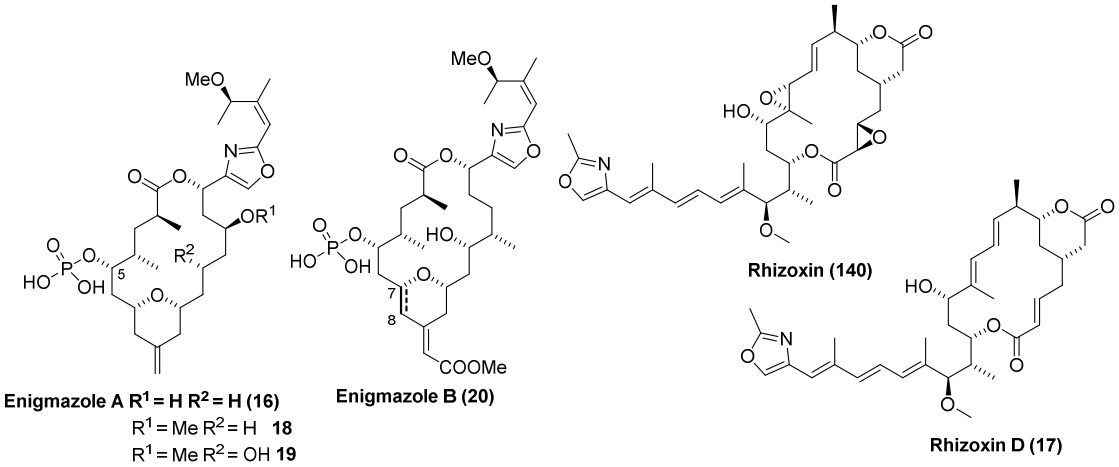
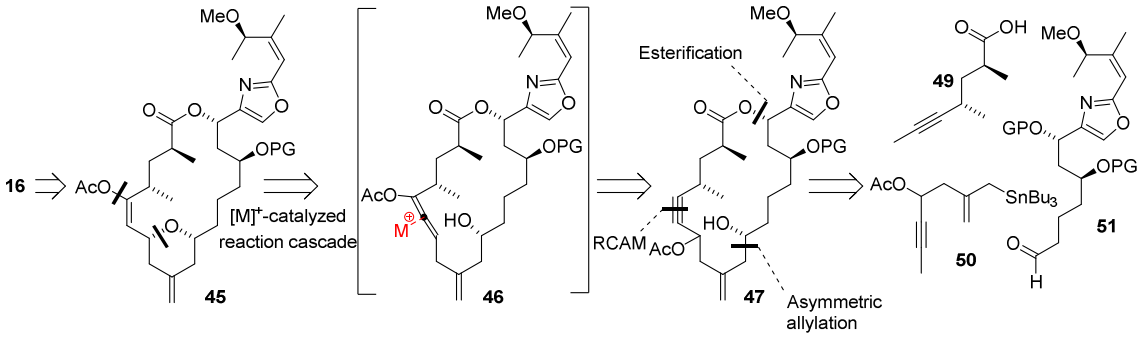


Figure 5.1: *Enigmazole and rhizoxin natural product families.*

In 2010, **enigmazole A** (**16**) and its congeners were isolated from the marine sponge *Cinachyrella enigmatica,* which was collected in Papua New Guinea as part of a marine collection program of the U.S. National Cancer Institute. These polyketide natural products represent the first phosphorylated macrolides of marine origin and show interesting structural features.[48] The 18-membered macrocyclic ring contains seven stereogenic centers, a phosphate ester, an embedded *syn*-tetrahydropyran ring, and a functionalized oxazole sidechain. Enigmazole A (**16**), in particular, showed significant cytotoxic activity in the NCI 60-cell antitumor assay (IG_{50} = 1.7 µM). Noteworthy is the selective differentiation of wild-type and mutant receptor tyrosine kinase c-Kit with structural analogues of enigmazole A (**16**), which is an important target in cancer therapy. This differentiation is found in less than 0.03% of 135.000 tested natural products.[48] The

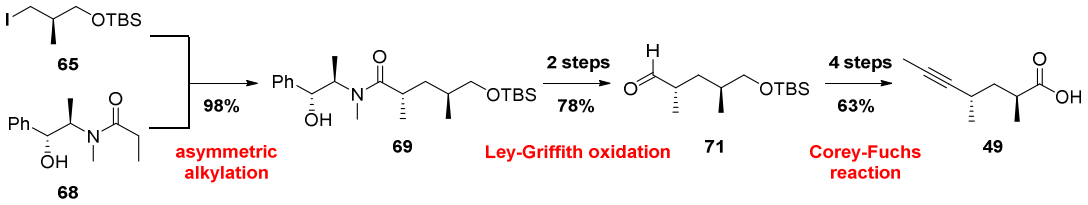
intriguing biological activity and the challenging structure prompted us to pursue the synthesis of enigmazole A (**16**).

The envisioned retrosynthetic analysis contained two key transformations, (i) a noble metal catalyzed [3,3]-sigmatropic rearrangement with subsequent hydroalkoxylation and (ii) a RCAM (Scheme 5.1). The sigmatropic rearrangement could form the *syn*-tetrahydropyran ring in key intermediate **45** via intramolecular hydroalkoxylation of allene **46**, which would be derived from macrocycle **47**. **47** could be formed by an asymmetric allylation, an esterification, and a RCAM of three fragments **49**-**51**.



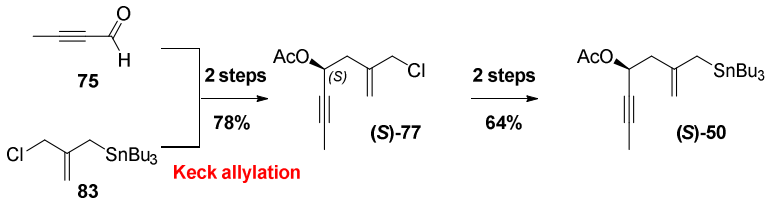
Scheme 5.1: *Retrosynthetic analysis of enigmazole A (**16**).*

Synthesis of northern fragment **49** began with Myers asymmetric alkylation[63] between **65** and **68** giving amide **69** in excellent yield (98%) and selectivity (*d.r.* = 96:4) (Scheme 5.2). Reductive cleavage of the auxiliary and Ley-Griffith oxidation[64-65] afforded aldehyde **71**. Corey-Fuchs reaction[67] installed the methyl-capped alkyne, and subsequent desilylation and TPAP-catalyzed oxidation[69] afforded acid **49** in 8 steps and 37% overall yield.



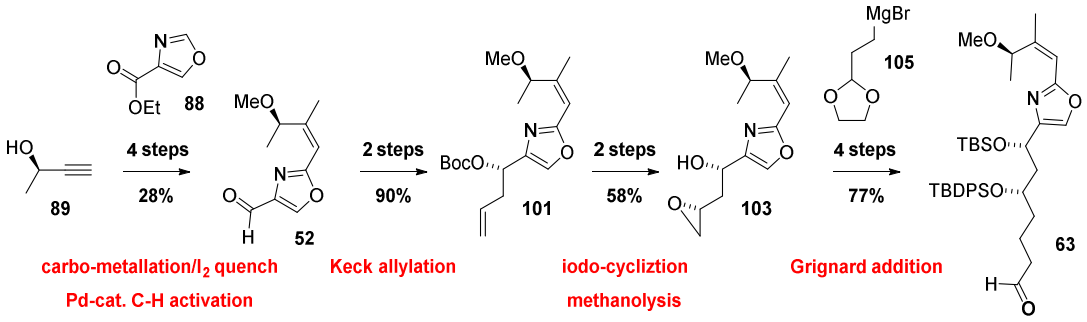
Scheme 5.2: *Synthesis of the northern fragment **49**.*

The synthesis of southern fragment **50** involved Keck allylation[81] of but-2-ynal (**75**) with stannane **83** to form (*S*)-**77** after acetylation in excellent stereoselectivity (*e.e.* ≥95%) (Scheme 5.3). Finkelstein reaction and palladium-catalyzed stannation[73] of the allyl iodide afforded the desired fragment (*S*)-**50** in 5 steps and 25% overall yield.



Scheme 5.3: *Synthesis of the southern fragment (S)-**50**.*

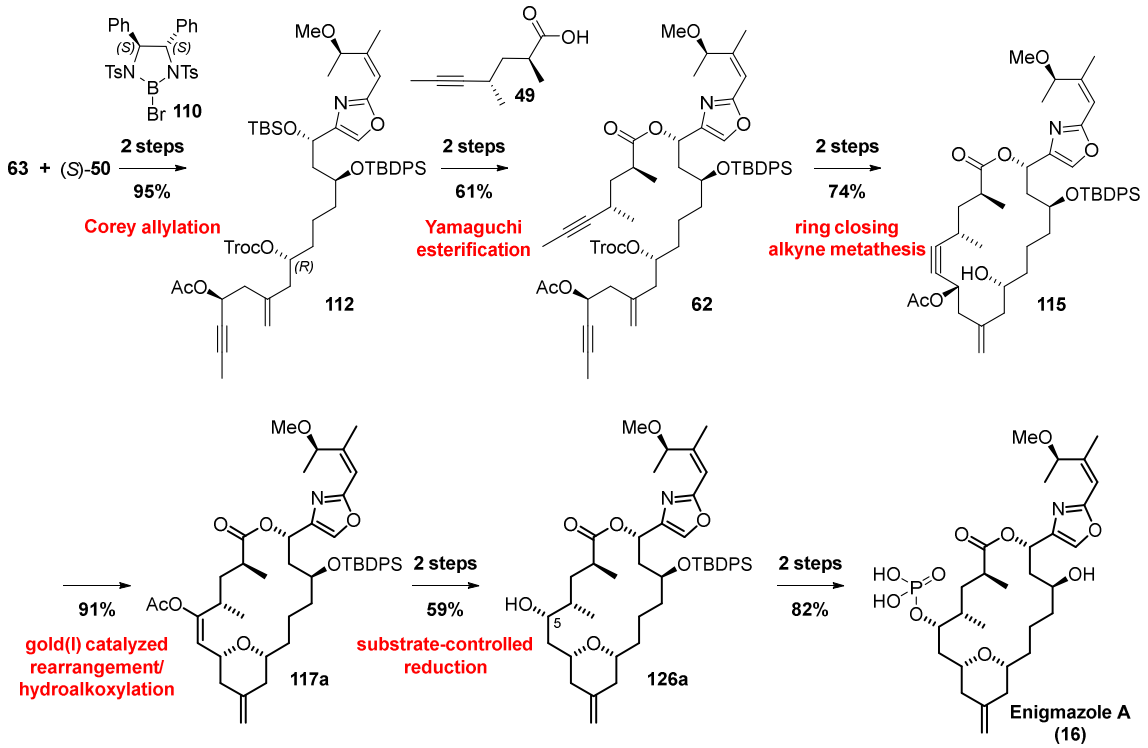
The eastern fragment **63** represents beginning of the longest linear sequence and was prepared starting from commercially available (*R*)-(+)-3-butyn-2-ol (**89**) (Scheme 5.4). A *trans*-carbomagnesiation of **89** and iodine quench gave access to an alkenyl iodide,[83] which was coupled to ethyl 4-oxazole carboxylate (**88**) via palladium-catalyzed C–H activation reaction to afford aldehyde **52**.[84] The four steps sequence including *inter alia* a highly stereoselective Keck allylation[81] (*d.r.* >95:5) of **52**, followed by a regio- and stereoselective iodo-cyclization (*d.r.* >95:5) afforded **103**. Regioselective, copper-catalyzed epoxide opening at **103** with Grignard reagent **105** and standard protecting group manipulations gave building block **63** in 12 steps and overall yield of 11.2%. The route allowed preparation of **63** in multigram quantities.



Scheme 5.4: *Synthesis of the eastern fragment **63**.*

With robust and scalable routes for all fragments, their assembly was investigated (Scheme 5.5). Enantioselective Corey allylation[103] between aldehyde **63** and stannane **50** gave **112** in good stereoselectivity (*d.r.* >10:1) and excellent yield (95%). Standard protecting group manipulations and Yamaguchi esterification[104] with acid **49** afforded metathesis precursor **62**. Due to the high density of coordinating functionalities in **62**, RCAM required unusually high catalyst loading (30 mol%) to achieve complete conversion.[30] Nevertheless, the metathesis reaction was successfully performed on 1.7 g scale with 79% yield. [3,3]-Sigmatropic rearrangement of **115** with subsequent transannular attack of the hydroxy group afforded product **117a** in 91% yield. The rearrangement, which is a noteworthy example of a complex catalyst/substrate chirality interaction, required the use of a chiral binuclear gold(I)-catalyst (for details see Section **3.4.5**). Saponification of **117a** and substrate-controlled reduction of the ketone afforded **126a** in 62%

yield (and C5-epimer **126b** in 33%). Phosphorylation[51] and global deprotection gave enigmazole A (**16**) in 23 steps (LLS) with an overall yield of up to 3.3%.

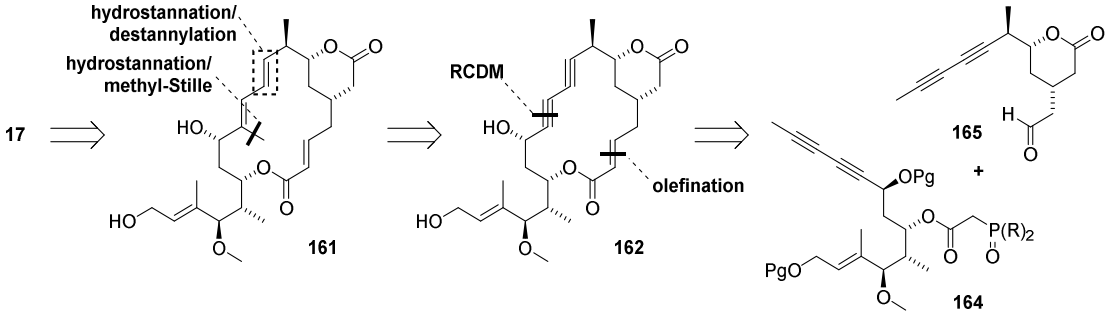


Scheme 5.5: *Fragment coupling and completion of the total synthesis of enigmazole A (**16**).*

In 1984, **rhizoxin** (**140**) was first isolated by Iwasaki *et al.* during the investigations on the rice seedling blight disease.[116a] Several congeners were also isolated, including rhizoxin D (**17**), the biosynthetic di-desepoxy precursor of rhizoxin (**140**).[117] **17** features an unprecedented 16-membered macrocyclic ring containing three (*E*)-olefins, a δ-lactone, and a highly unsaturated, oxazole terminated sidechain. The high potency of the rhizoxins against human and murine tumor cells led to high interest in the synthetic community. Several members of the rhizoxin family were synthesized but the 1,3-diene motif was rarely modified, which makes it an interesting target for further SAR studies. The recently reported metathesis of 1,3-diynes could give access to derivatives at this particular position in the molecule.[36]

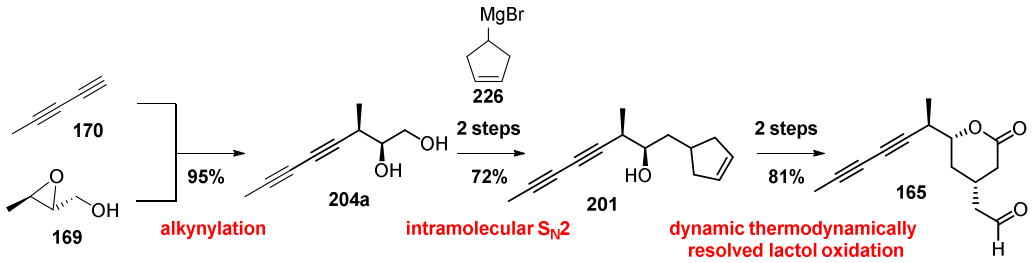
Our group[128] envisioned a convergent synthetic route towards rhizoxin D (**17**), which would allow late stage modifications of the 1,3-diyne motif via combinations of hydrostannation and cross-coupling or destannylation reactions. The key intermediate towards the synthesis of rhizoxin D (**17**) could be **161**. A sequence of hydroelementation reactions would provide 1,3-(*E,E*)-

diene motif of **161** from 1,3-diyne **162** (Scheme 5.6). **162** could be prepared by olefination of two building blocks **164** and **165** and subsequent ring closing diyne metathesis (RCDM).



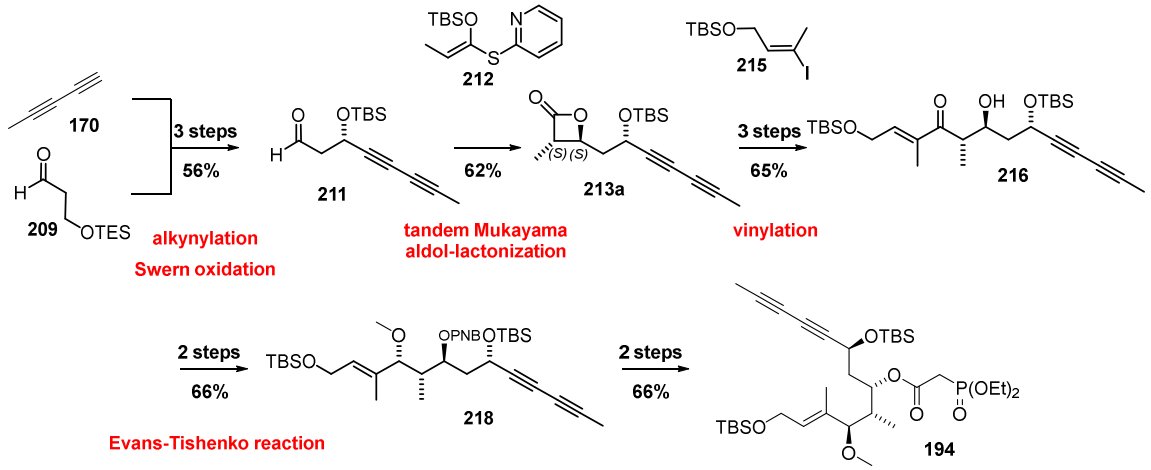
Scheme 5.6: *Retrosynthetic analysis of rhizoxin D (**17**).*

The synthesis of the eastern fragment **165** started with a regio- and stereoselective alkynylation of epoxide **169** (95%, single isomer) (Scheme 5.7). The obtained diol **204a** was turned into an epoxide, which was then opened by the Grignard reagent **226** to afford **201**. Ozonolysis of cyclopentene **201** and oxidation of the lactol gave **165** in 6 steps and overall yield of 43%.



Scheme 5.7: *Synthesis of the eastern fragment **165**.*

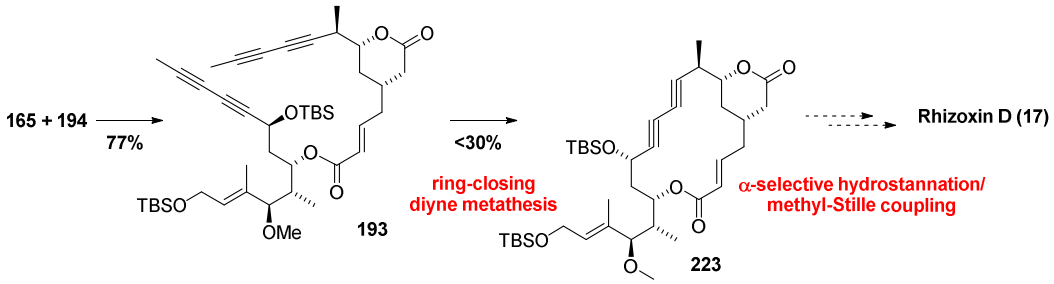
The route to the western fragment **194** started from aldehyde **209** and 1,3-alkyne **170**. Asymmetric alkynylation under Trost conditions[151] and modified Swern oxidation[152] afforded **211**. β-Lactone **213a** was prepared by a tandem Mukayama aldol-lactonization reaction.[133a] Alkenylation of **213a** with alkenyl iodide **215** was achieved after first transforming **213a** into the corresponding Weinreb amide. An Evans-Tishenko reaction[150] set the missing stereocenter and ultimately afforded fragment **194** in 13 steps and overall yield of 7.1%.



Scheme 5.8: *Synthesis of the western fragment* ***194.***

The coupling of fragment **165** and **194** was achieved by HWE olefination (Scheme 5.9). So far, RCDM of tetrayne **193** afforded the desired macrocycle **223** in less than 50% yield. We were able to observe byproduct formation and (probably) polymerization, which could be overcome in the future by optimizations on the reaction parameters, such as temperature, concentration, and catalyst.

Nevertheless, we were able to access precursor **193** in only 13-15 steps and up to 2.7% overall yield. All reactions gave high yields and could be performed on at least >100 mg scales. Further optimization of the RCDM is currently ongoing. Once macrocylce **223** can be accessed, the subsequent α-selective hydrostannation/methyl-Stille sequence would give access to the 1,3-(*E,E*)-diene motif. Further progress on this synthesis will be reported in due course.



Scheme 5.9: *Key steps of the synthesis towards rhizoxin D (**17**).*

In this thesis, the successful total synthesis of enigmazole A (**16**) was achieved and the key intermediate **193** towards rhizoxin D (**17**) was prepared. The benefit of ring closing alkyne metathesis was demonstrated on a highly functionalized substrate in a late stage during the synthesis of enigmazole A (**16**). This metathesis was reliable on a multigram scale unprecedented

for such a complex substrate. The densely functionalized macrocycle and the oxazole heterocyclic sidechain had no major impact on the stability of the Fürstner metathesis catalysts. Post-metathesis functionalization of the obtained alkyne by π-acid catalysis afforded a *syn*-tetrahydropyran ring and revealed an interesting catalyst/substrate chirality match/mismatch case. Furthermore, the recently reported ring-closing diyne metathesis was applied in the synthesis towards rhizoxin D (**17**) and gave promising preliminary results. Further investigations are necessary to optimize the yield and finish the total synthesis of rhizoxin D (**17**). Due to the concise syntheses presented in this thesis, new derivatives of enigmazole A (**16**) and rhizoxin D (**17**) could be obtained in the future, which may provide pharmacological insights on new cancer therapeutics.

6. Experimental Procedures:

6.1. General Experimental Details

All reactions were carried out under Argon in flame-dried glassware using anhydrous solvents, unless water was used as solvent or it is otherwise noted. The solvents were purified by distillation over the drying agents indicated and were transferred under argon: tetrahydrofuran, diethyl ether (Mg/anthracene), dichloromethane, hexane, pentane, toluene (Na/K), methanol (Mg, stored over 3 Å MS), ethanol (3 Å MS), ethyl acetate (P_2O_5, filtered through dry Al_2O_3, stored over 4 Å MS); dioxane, DMF, acetonitrile, triethyl amine and pyridine were dried by an adsorbtion solvent purification system based on molecular sieves. Titanium(IV) isopropoxide, 1,8-diazabicycloundec-7-ene, TMS-Cl (CaH_2) and *i*Pr_2NEt (CaH_2) were distilled over the drying agents indicated under argon prior to use. *p*-Nitrobenzaldehyde was freshly recrystallized from ethanol prior to use. Unless stated otherwise, all commercially available compounds (ABCR, Acros, Aldrich, Alfa Aesar, Fluka, Oakwood, STREM, TCI) were used as received. Conditions for the synthesis of each compound are described in the experimental below. The gold catalysts were prepared following the procedure reported herein for the example of **121.** The samarium(II) iodide solution was prepared from a reaction of samarium metal and iodine by modifying Imamoto's procedure.[153] The complexes **8** and **116** were prepared according to cited protocol within the department of Prof. Fürstner.[31]

Thin layer chromatography (TLC): Macherey-Nagel precoated plates (POLYGRAM® SIL/UV254); Flash chromatography: Merck silica gel 60 (40–63 μm) with predistilled or HPLC grade solvents. TLC plates were visualized by exposure to an aqueous solution of potassium permanganate or ethanolic solution of vanillin followed by heating with a heat gun.

NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δC ≡ 77.2 ppm; residual $CHCl_3$ in $CDCl_3$: δH ≡ 7.26 ppm; CD_3OD: δC ≡ 49.0 ppm; residual CHD_2OD: δH ≡ 3.31 ppm). Important key fragments or complex byproducts were analyzed by the NMR department of our institute, especially by Frau Gabor.

IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers (ν) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T

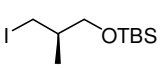
magnet) or Mat 95 (Finnigan). Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin-Elmer Model 343 or an A-KRÜSS Optronic Model P8000-t polarimeter.

LC-MS analyses were conducted with a LC-MS2020 instrument from Shimadzu (pumps LC-20 AD, autosampler SIL-20AC, column oven CTO-20AC, diode array detector SPD-M20A, controller CBM-20A, ESI detector and software LCMS-solution) with an ZORBAX Eclipse Plus C18 1.8 µm, 3.0 or 4.6 mm ID × 50 mm (Agilent). A binary gradient of acetonitrile or methanol in water or aq. triethylammonium acetate (TEAA) buffer (10 mmol. pH 8) was used at a flow rates of 0.5 (3.0 mm ID) or 0.8 (4.6 mm ID) mL/min. The oven temperature was kept at 35 °C and a detection wave length of 254 nm was used. Preparative LC was conducted on a LC-20A prominence system (pumps LC-20AP, column oven CTO-20AC, diode array detector SPD-M20A, fraction collector FRC-10A, controller CBM-20A and software LC-solution) from Shimadzu.

6.2. Enigmazole A

6.2.1. The Northern Fragment

(*R*)-*tert*-Butyl(3-iodo-2-methylpropoxy)dimethylsilane (65)[154]

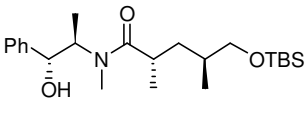


Sodium iodide (20.0 g, 133 mmol, 4.00 equiv) was added to a solution of the (*R*)-3-bromo-2-methylpropan-1-ol (5.00 g, 32.6 mmol, 1 equiv) in anh. acetone (60 mL). The mixture was refluxed for 18 h at 70 °C. Water (20 mL) was added and acetone was removed under reduced pressure. The resulting mixture was extracted with dichloromethane (2 x 30 mL) and washed with aq. sat. ammonium thiosulfate solution (2 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude material was directly used in the next step.

Imidazole (2.40 g, 35.8 mmol, 1.10 equiv) and TBS-Cl (5.40 g, 35.8 mmol, 1.10 equiv) were added at 0 °C to a solution of (*R*)-3-iodo-2-methylpropan-1-ol (6.30 g, 32.6 mmol, 1.00 equiv) in anh. dichloromethane (100 mL). The reaction mixture was stirred for 3 h at 0 °C, before it was filtered through a plug of celite, which was rinsed with pentane (50 mL). The filtrate was concentrated under reduced pressure and the residue was suspended in pentane (10 mL) and filtered again. The concentrated filtrate was purified by flash chromatography (pure hexane) to give the desired product **65** (8.54 g, 27.2 mmol, 85%).

$[\alpha]_D^{20}$ = −10.5 (c = 4.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.52 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.39 (dd, *J* = 10.1, 6.7 Hz, 1H), 3.30 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.24 (dd, *J* = 9.6, 5.4 Hz, 1H), 1.67–1.59 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.060 (s, 3H), 0.059 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 66.9, 37.6, 26.1, 18.5, 17.5, 13.9, -5.1 (2C); **IR** (film): ν = 2955, 2929, 2894, 2857, 1470, 1475, 1419, 1386, 1361, 1329, 1251, 1197, 1181, 1136, 1098, 1065, 1035, 1006, 937, 835, 773 cm^{-1}; **MS** (EI) *m/z* (%): 257 (100); **HRMS** (CI): *m/z*: calcd. for $C_{10}H_{24}OISi$ [M^++H]: 315.0641, found: 315.0642.

(2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-2,4-trimethylpentanamide (69)[64]

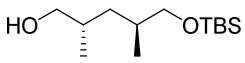


n-BuLi (1.6 M in hexanes, 48.8 mL, 78.1 mmol, 1.70 equiv) was added dropwise at −78 °C to a stirred suspension of flame-dried lithium chloride (12.8 g, 308 mmol, 13.5 equiv) and diisopropylamine (11.8 mL, 84.0 mmol, 3.70 equiv) in anh. tetrahydrofuran (48 mL). The reaction mixture was warmed to

0 °C for 5 min and then recooled to −78 °C. A solution of (*R*,*R*)-(−)-pseudoephedrine propionamide (8.00 g, 36.9 mmol, 1.60 equiv) in anh. tetrahydrofuran (102 mL) was added dropwise via cannula and the reaction mixture was stirred for 1 h at −78 °C, 30 min at 0 °C and 5 min at 23 °C. Then, a solution of (*R*)-*tert*-butyl(3-iodo-2-methylpropoxy) dimethylsilane **65** (7.20 g, 22.8 mmol, 1 equiv) in anh. tetrahydrofuran (10 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 22 h at 23 °C. The reaction was quenched by the addition of aq. sat. ammonium chloride solution (100 mL), the layers were separated and the aq. layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 3:1) to afford **69** (9.10 g, 22.3 mmol, 98%) (mixture of rotamers 3:1).

$[\alpha]_D^{20}$ = −53.0 (c = 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) (major rotamer): δ = 7.35–7.29 (m, 5H), 3.60 (t, *J* = 7.2 Hz, 1H), 4.42 (bs, 1H), 3.39 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.31 (dd, *J* = 9.7, 6.1 Hz, 1H), 2.85 (s, 3H), 2.71 (q, *J* = 7.0 Hz, 1H), 1.74 (oct, *J* = 6.5 Hz, 1H), 1.41–1.37 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.020 (s, 3H), 0.018 (s, 3H) (OH signal is missing); **^{13}C NMR** (100 MHz, $CDCl_3$) (Major rotamer): δ = 179.5, 142.8, 128.4 (2C), 127.7, 126.5 (2C), 76.7, 68.5 (2C), 37.6, 34.6, 33.7, 26.1 (3C), 18.6, 17.4, 17.1, 14.6, −5.2 (2C) (due to overlapping one carbon is missing); **IR** (film): ν = 3374, 2955, 2930, 2857, 1620, 1471, 1461, 1408, 1251, 1087, 835, 774, 701 cm^{-1}; **MS** (EI) *m*/*z* (%): 392 (3), 350 (56), 300 (16), 243 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{23}H_{41}NO_3SiNa$ [*M*+Na^+]: 430.2747, found: 430.2751.

(2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (73)[155]



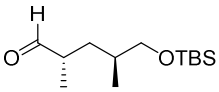
n-BuLi (1.6 M in hexanes, 55.8 mL, 89.2 mmol, 4.00 equiv) was slowly added over 15 min to a stirred suspension of diisopropylamine (13.3 mL, 95.5 mmol, 4.25 equiv) in anh. tetrahydrofuran (92 mL) at −78 °C. The solution was stirred at this temperature for 10 min and another 10 min at 0 °C before borane-ammonia complex (90%, 3.10 g, 100 mmol, 4.50 equiv) was added. The solution was stirred for 15 min at 0 °C, was allowed to warm to 23 °C and stirring was continued for additional 15 min. Then, the reaction mixture was cooled to 0 °C and a solution of amide **69** (9.00 g, 22.3 mmol, 1 equiv) in anh. tetrahydrofuran (160 mL) was added over 15 min. The reaction mixture was warmed to 23 °C and stirred for an additional 2 h. After cooling to 0 °C, excess reagent was quenched by the addition of aq. sat. ammonium chloride solution (150 mL). The aq. layer was extracted with methyl *tert*-butyl ether (3 × 100 mL) and the combined organic layers were washed with brine (30 mL), dried over sodium

sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to obtain **73** (4.90 g, 17.9 mmol, 89%).

$[\alpha]_D^{20}$ = −24.7 (c = 1.59, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.5–3.42 (m, 2H), 3.40 (dd, *J* = 6.3, 1.8 Hz, 2H), 1.78–1.67 (m, 2H), 1.47 (t, *J* = 5.9 Hz, 1H), 1.21 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 1.12 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 0.89 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.04 (s, 6H). (OH signal is missing); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 69.3, 69.2, 37.0, 33.3, 33.1, 26.2 (3C), 18.5, 16.8, 16.7, −5.1 (2C); **IR** (film): ν = 3375, 2954, 2929, 2857, 1620, 1471, 1454, 1405, 1095, 1050, 836, 774, 701 cm^{-1}; **MS** (EI) *m*/*z* (%): 215 (1), 189 (1), 55 (100); **HRMS** (CI): *m*/*z*: calcd. for $C_{13}H_{31}NO_2Si$ [*M*+H^+]: 247.2093, found: 247.2094.

((2*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (70)[156]

A solution of *N*-methylmorpholine-*N*-oxide monohydrate (1.41 g, 10.4 mmol, 1.30 equiv) and

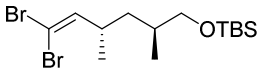


powdered molecular sieves (4 Å, 4 g) in anh. dichloromethane (66 mL) was stirred for 10 min. Then, a solution of the alcohol **73** (2.00 g, 8.1 mmol, 1 equiv) in anh. dichloromethane (32 mL) followed by tetra-*N*-propylammonium perruthenate (140 mg, 0.39 mmol, 5 mol%) was added to the reaction mixture and stirring was continued for 30 min. The resulting mixture was filtered through a plug of Celite which was carefully rinsed with dichloromethane (50 mL). The filtrate was evaporated and the crude product was purified by a quick flash chromatography (hexane/ethyl acetate 5:1) to yield **70** (1.72 g, 7.0 mmol, 88%), which was immediately used in the next reaction. The obtained characterization data were in full agreement with those reported in the literature.[66]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (d, J = 2.0 Hz, 1H), 3.43 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.39 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.45–2.36 (m, 1H), 1.71–1.63 (m, 1H), 1.47 (ddd, *J* = 13.7, 8.3, 6.0 Hz, 1H), 1.39 (ddd, *J* = 13.7, 8.3, 5.7 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.01 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 205.3, 68.2, 44.2, 34.0, 33.3, 26.0 (3C), 18.3, 16.6, 13.5, −5.3 (2C).

***tert*-Butyl(((2*S*,4*S*)-6,6-dibromo-2,4-dimethylhex-5-en-1-yl)oxy)dimethylsilane (71)**

Zinc powder (835 mg, 12.8 mmol, 1.95 equiv) followed by triphenylphosphine (3.43 g, 13.1 mmol,



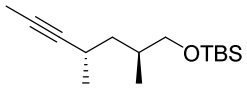
2.00 equiv) was added to a solution of tetrabromomethane (4.34 g, 13.1 mmol, 2.00 equiv) in anh. dichloromethane (70 mL) at 23 °C. After 18 h, a solution of aldehyde **70** (1.60 g, 6.54 mmol, 1 equiv) in anh. dichloromethane (20 mL) was

slowly added at 23 °C and stirring was continued for 5 h. The reaction mixture was poured into a beaker containing hexane and the resulting precipitates were filtered off. Evaporation of the filtrate and purification of the crude product by flash chromatography (hexane/ethyl acetate 5:1) gave **71** (1.93 g, 4.82 mmol, 74%).

$[\alpha]_D^{20}$ = +4.20 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.19 (d, J = 8.9 Hz, 1H), 3.44 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.40 (dd, *J* = 9.8, 5.9 Hz, 1H), 2.56–2.48 (m, 1H), 1.69–1.53 (m, 1H), 1.42 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.12 (dt, *J* = 14.7, 7.3 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.9, 87.2, 67.8, 39.6, 36.2, 33.6, 26.2 (3C), 19.4, 18.5, 17.4, −5.1 (2C); **IR** (film): ν = 2956, 2929, 2827, 1471, 1461, 1251, 1095, 1080, 1006, 836, 774, 667 cm^{-1}; **MS** (EI) *m*/*z* (%): 343 (45), 107 (100); **HRMS** (CI): *m*/*z*: calcd. for $C_{14}H_{29}OBr_2Si$ [*M*+H^+]: 399.0354, found: 399.0351.

tert-Butyl(((2*S*,4*S*)-2,4-dimethylhept-5-yn-1-yl)oxy)dimethylsilane (72)

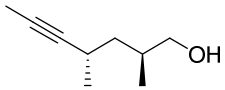
n-BuLi (1.6 M in hexanes, 6.93 mL, 11.1 mmol, 2.30 equiv) was added to a solution of the dibromo-olefin **71** (1.93 g, 4.82 mmol, 1 equiv) in anh. tetrahydrofuran (18 mL) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and for 1 h at 23 °C. Then, methyl iodide (0.810 mL, 13.0 mmol, 2.70 equiv) was added. After 2.5 h, excess reagent was quenched by the addition of aq. sat. ammonium chloride solution (20 mL). The layers were separated and the aq. layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (pure hexane grading to hexane/ethyl acetate 10:1) to obtain **72** (1.19 g, 4.66 mmol, 97%, *d.r.* ≥95:5).



$[\alpha]_D^{20}$ = +24.7 (c = 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.48 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.39 (dd, *J* = 9.7, 6.2 Hz, 1H), 2.48–2.39 (m, 1H), 1.48–1.76 (m, 1H), 1.78 (d, *J* = 2.4 Hz, 3H), 1.41 (ddd, *J* = 13,4, 7.1, 6.7 Hz, 1H), 1.23 (ddd, *J* = 14,7, 8.7, 6.6 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 84.4, 75.5, 67.7, 41.2, 33.8, 26.1 (3C), 23.9, 21.8, 18.5, 17.6, 3.7, −5.2, −5.1; **IR** (film): ν = 2956, 2929, 2857, 1471, 1388, 1361, 1251, 1092, 1019, 1006, 939, 835, 773, 666 cm^{-1}; **MS** (EI) *m*/*z* (%): 197 (13), 75 (100); **HRMS** (CI): *m*/*z*: calcd. for $C_{15}H_{31}OSi$ [*M*+H^+]: 255.2144, found: 255.2145.

(2*S*,4*S*)-2,4-Dimethylhept-5-yn-1-ol (74)

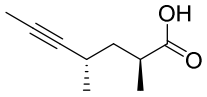
Tetrabutylammonium fluoride solution (1 M in tetrahydrofuran, 8.17 mL, 8.17 mmol, 2.00 equiv) was added to a solution of the alkyne **72** (1.04 g, 4.09 mmol, 1 equiv) in tetrahydrofuran (6.0 mL) at 23 °C. The reaction mixture was stirred at this temperature for 18 h. The excess reagent was quenched by the addition of aq. sat. ammonium chloride solution (5 mL) and extracted with methyl *tert*-butyl ether (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to yield **74** as a colorless liquid (550 mg, 3.92 mmol, 96%, *d.r.* ≥95:5).



$[\alpha]_D^{20}$ = +24.4 (c = 1.04, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.53 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.49–2.42 (m, 1H), 1.84 (oct, *J* = 6.5 Hz, 1H), 1.75 (d, *J* = 2.5 Hz, 3H), 1.72 (bs, 1H), 1.39 (ddd, *J* = 13,4, 7.2, 6.1, 1H), 1.30 (ddd, *J* = 14,9, 8.6, 6.2, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 84.1, 75.9, 67.7, 41.1, 33.7, 23.6, 21.7, 17.4, 3.6; **IR** (film): ν = 3323, 2960, 2921, 2873, 1453, 1375, 1043, 999, 977, 943, 757, 667 cm^{-1}; **MS** (EI) *m*/*z* (%): 67 (100), 31 (14); **HRMS** (CI): *m*/*z*: calcd. for $C_9H_{17}O$ [*M*+H^+]: 141.1279, found: 141.1277.

(2*S*,4*S*)-2,4-Dimethylhept-5-ynoic acid (49)

Tetra-*N*-propylammonium perruthenate (96.5 mg, 275 µmol, 10 mol%) was added to a solution of *N*-methylmorpholine-*N*-oxide monohydrate (3.22 g, 27.5 mmol, 10.0 equiv) and alcohol **74** (385 mg, 2.75 mmol, 1 equiv) in acetonitrile (5.6 mL). After stirring for 45 min at 23 °C, the resulting mixture was filtered through a pad of Celite, which was carefully rinsed with ethyl acetate (10 mL). The filtrate was evaporated and the remaining crude product was purified by flash chromatography (hexane/ethyl acetate 8:1) to give northern fragment **49** (391 mg, 2.54 mmol, 92%, *d.r.* ≥95:5).

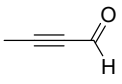


$[\alpha]_D^{20}$ = +108.2 (c = 0.55, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.82–2.73 (m, 1H), 2.52–2.43 (m, 1H), 1.78 (ddd, *J* = 14,8, 9.8, 4.8 Hz, 1H), 1. 77 (d, *J* = 2.33 Hz, 3H), 1.13 (ddd, *J* = 14,8, 10.4, 4.5 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H) (^{1}H signal from the acid is not observed); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 182.9, 82.9, 76.7, 41.2, 37.9, 24.6, 21.9, 18.2, 3.67; **IR** (film): ν = 3100, 2972, 2921, 1706, 1456, 1377, 1248, 945 cm^{-1}; **MS** (EI) *m*/*z* (%): 154 (1), 109 (26), 98 (100), 74 (37), 45 (7); **HRMS** (EI): *m*/*z*: calcd. for $C_9H_{14}O_2$ [M^+]: 154.0993, found: 154.0994.

6.2.2. The Southern Fragment

Racemic Route

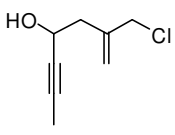
2-Butynal (75)[71b]



Tetrabutylammonium chloride (3.97 g, 14.3 mmol, 0.10 equiv) and 2,2,6,6-tetramethyl-1-piperidinyloxy (2.23 g, 14.3 mmol, 0.10 equiv) were added to a solution of 2-butin-1-ol (10.0 g, 143 mmol, 1 equiv) in a biphasic mixture of dichloromethane (200 mL) and aq. buffer solution (100 mL 0.5 M sodium hydrogen carbonate and 100 mL 0.05 M aq. potassium carbonate solution). *N*-Chlorosuccinimide (30.5 g, 228 mmol, 1.60 equiv) was added in several big portions causing a slight exotherm and an evolution of gas, which was discharged by passing the gas stream through a wash bottle containing aq. sodium hydroxide solution (1 M). After 17 h, the layers were separated and the aq. layer was extracted with dichloromethane (4 × 75 mL). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. The filtrate was purified by distillation (25 °C, ≤ 150 mbar, Vigreux column, the collection flask cooled to −78 °C) to obtain **75** (60 % in dichloromethane, 10.9 g, 96.1 mmol, 67%) as a colorless solution. The compound is very sensitive and was kept under argon at −78 °C (decomposition commences with appearance of pink coloration). The analytical data were in full agreement with those reported in the literature.[71a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (q, *J* = 1.0 Hz, 1H), 2.07 (d, *J* = 0.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =177.3, 95.1, 81.1, 4.46.

2-(Chloromethyl)hept-1-en-5-yn-4-ol (226)

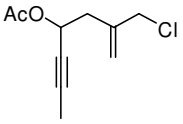


Boron trifluoride diethyl etherate (2.91 mL, 23.6 mmol, 2.00 equiv) was added to a stirred solution of 2-butynal (803 mg, 11.8 mmol, 1 equiv) in dichloromethane (25 mL) at −60 °C followed by the addition of 2-(chloromethyl)allyl-trimethylsilane (3.20 mL, 17.7 mmol 1.50 equiv). The reaction mixture was stirred for 1.5 h at this temperature. Then, the crude product was diluted with diethyl ether (20 mL) before sat. aq. sodium hydrogen carbonate solution (20 mL) was added and the reaction mixture was warmed to 23 °C. The organic layer was separated and the aq. layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with sat. aq. ammonium chloride solution (10%, 20 mL), with brine (20 mL), dried over sodium sulfate and evaporated under reduced

pressure (20 °C, ≥400 mbar). The crude product was purified by flash chromatography (pentane/diethyl ether 15:1) to give the secondary alcohol **226** (1.61 g, 7.10 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (s, 1H), 5.13 (s, 1H), 4.54–4.50 (m, 1H), 4.13 (s, 2H), 2.58 (d, *J* = 6.7 Hz, 2H), 1.84 (d, *J* = 1.8 Hz, 3H), 1.75 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 141.2, 118.3, 81.9, 79.8, 61.4, 48.5, 41.8, 3.72; **IR** (film): ν = 3367, 2919, 2930, 1646, 1437, 1258, 1136, 1113, 1006, 913, 851, 749 cm^{-1}; **MS** (EI) *m*/*z* (%): 123 (1.51), 90 (3.34), 69 (100); **HRMS** (CI): *m*/*z*: calcd. for $C_8H_{15}NO$ [M^++NH_4]: 176.0842, found: 176.0840.

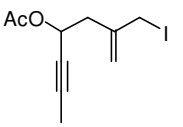
2-(Chloromethyl)hept-1-en-5-yn-4-yl acetate (77)



Triethylamine (707 µL, 5.04 mmol, 2.00 equiv) and acetic anhydride (357 µL, 3.78 mmol, 1.50 equiv) were subsequently added to a solution of 4-dimethylaminopyridine (30.7 mg, 0.25 mmol, 10 mol%) and propargylic alcohol **226** (400 mg, 2.52 mmol, 1 equiv) in dichloromethane (25 mL). The reaction mixture was stirred at 23 °C for 2 h, before the solvent was removed under reduced pressure (23 °C, ≥300 mbar). The crude product was purified by flash chromatography (pentane/diethyl ether 20:1) to yield **77** as a colorless oil (528 mg, 2.51 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51–5.48 (m, 1H), 5.25 (s, 1H), 5.08 (s, 1H), 4.10 (d, *J* = 11.8 Hz, 1H), 4.08 (d, *J* = 11.8 Hz, 1H), 2.66 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.59 (dd, *J* = 14.5, 6.9 Hz, 1H), 2.06 (s, 3H), 1.83 (dd, *J* = 1.9, 1.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 140.3, 118.6, 82.7, 76.3, 62.9, 48.2, 38.8, 21.2, 3.7; **IR** (film): ν = 2930, 2923, 1739, 1647, 1437, 1371, 1230, 1160, 1020, 989, 914, 752 cm^{-1}; **MS** (ESI) *m*/*z* (%): 222.59 (100) (M^++Na); **HRMS** (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2ClNa$ [M^++Na]: 223.0496, found: 223.0494.

2-(Iodomethyl)hept-1-en-5-yn-4-yl acetate (78)



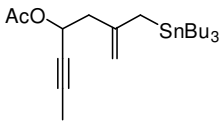
Allyl cholride **77** (500 mg, 2.50 mmol, 1 equiv) was added to a solution of sodium iodide (500 mg, 3.35 mmol, 1.50 equiv) in acetone (3 mL). The reaction mixture was heated to 70 °C for 18 h before it was cooled to 23 °C. Sat. aq. sodium thiosulfate solution (2 mL) was added to the reaction mixture, the layers were separated and the aq. phase was extracted with diethyl ether (2 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate and evaporated under reduced pressure (23 °C,

≥400 mbar). The remaining crude product was purified by flash chromatography (pentane/diethyl ether 10:1) to afford **78** (707 mg, 2.42 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50–5.49 (m, 1H), 5.35 (d, *J* = 0.8 Hz,1H), 5.01 (d, *J* = 0.8 Hz, 1H), 4.01 (dd, *J* = 9.6, 0.4 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 2.71 (ddd, *J* = 14.4, 6.1, 0.8 Hz, 1H), 2.63 (ddd, *J* = 14.4, 7.1, 0.8 Hz, 1H), 2.06 (s, 3H), 1.83 (d, *J* = 2.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 141.8, 117.7, 82.7, 76.3, 62.9, 39.8, 21.2, 10.4, 3.8; **IR** (film): ν = 2956, 2920,1739, 1636, 1431, 1371, 1230, 1157, 1020, 986, 914 cm^{-1}; **MS** (EI) *m*/*z* (%): 232 (72.05), 123 (47.29), 105 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2INa$ [M^++Na]: 314.9852, found: 314.9852.

2-((Tributylstannyl)methyl)hept-1-en-5-yn-4-yl acetate (50)

Bis(tributyltin) (1.70 mL, 3.30 mmol, 1.50 equiv) was added to a solution of the allyl iodine **78**

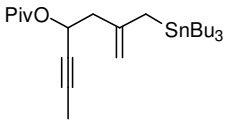


(650 mg, 2.20 mmol, 1 equiv) in tetrahydrofuran (2.6 mL) followed by the addition of tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (114 mg, 0.11 mmol, 5 mol%). The reaction mixture was flushed with Argon for 25 min, before it was heated to 55 °C for 3 h. The reaction mixture was cooled to 23 °C and treated with sat. aq. sodium hydrogen carbonate solution (2 mL) and extracted with diethyl ether (2 × 3 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography (hexane + 2% triethylamine) with silica gel which was previously washed with hexane containing 5% triethylamine to give **50** (700 mg, 1.54 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (t, *J* = 7.2 Hz, 1H), 4.62 (s, 1H), 4.53 (s, 1H), 2.35 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.31 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.06 (s, 3H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.8 (s, 2H), 1.45 (quint, *J* = 7.2 Hz, 6H), 1.30 (sext, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.7 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.5, 144.6, 108.4, 82.2, 77.1, 63.3, 44.0, 29.3, 27.5, 21.3, 19.1, 13.9, 9.6, 3.9; **IR** (film): ν = 2956, 2923, 2853, 2872, 2742, 1629, 1464, 1371, 1230, 1018, 961, 866 cm^{-1}; **MS** (EI) *m*/*z* (%): 456 (1.62), 399 (12.85), 179 (100), 57 (4.91), 43 (29.47); **HRMS** (ESI): *m*/*z*: calcd. for $C_{22}H_{40}O_2SnNa$ [M^++Na]: 479.1956, found: 479.1954.

2-((Tributylstannyl)methyl)hept-1-en-5-yn-4-yl pivalate (227)

Bis(tributyltin) (1.30 mL, 2.56 mmol, 1.50 equiv) was added to a solution of allyl iodine **78b** (85% in diethyl ether, 671 mg, 1.71 mmol, 1 equiv) in tetrahydrofuran (2 mL) followed by tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (78.1 mg, 85.3 µmol, 5 mol%). The reaction mixture was flushed with Argon for 25 min, before it was stirred at 55 °C for 4 h. The reaction mixture was cooled to 23 °C and treated with sat. aq. sodium hydrogen carbonate solution (10 mL) and extracted with diethyl ether (2 × 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The remaining crude product was purified by flash chromatography (hexane + 2% triethylamine) with silica gel which was previously washed with hexane containing 5% triethylamine to give **227** (490 mg, 0.99 mmol, 58%).

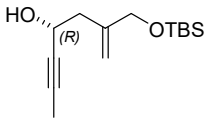


^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38 (ddq, *J* = 8.0, 6.1, 2.1 Hz, 1H), 4.58-4.41 (m, 2H), 2.38–2.20 (m, 2H), 1.76 (d, *J* = 2.1 Hz, 3H), 1.48–1.31 (m, 6H), 1.22 (dq, *J* = 14.5, 7.2 Hz, 6H), 1.12 (s, 9H), 0.82 (t, *J* = 7.3 Hz, 9H), 0.81–0.77 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 177.6, 144.6, 108.5, 81.4, 62.8, 44.0, 38.9, 29.2 ($J_{H\text{-}Sn}$ = 10.0 Hz), 27.5, 27.2, 19.0, 13.8, 9.6 ($J_{H\text{-}Sn}$ = 151.3 Hz), 3.8; **IR** (film): ν = 2957, 2923, 2872, 2854, 1734, 1462, 1280, 1147, 867 cm^{-1}; **HRMS** (ESI): *m/z*: calcd. for $C_{25}H_{46}O_2SnNa$ [*M*+Na^+]: 521.2411, found: 521.2417.

Enantioselective Route

(*R*)-2-(((tert-Butyldimethylsilyl)oxy)methyl)hept-1-en-5-yn-4-ol ((*R*)-81)[78]

In a pressure tube, liquefied propyne (approx. 0.5 mL) was added to a solution of diethylzinc (15% in toluene, 252 µL, 0.280 mmol, 4.00 equiv) in anh. toluene (0.5 mL). After heating the closed system for 1 h to 110 °C, the reaction mixture was cooled to 23 °C and the vessel was carefully opened. (*S*)-(−)-1,1′-Bi(2-naphthol) (8.01 mg, 28.0 µmol, 40 mol%), anh. diethyl ether (4 mL) and titanium(IV) isopropoxide (20.7 µL, 70.0 µmol, 1.00 equiv) were successively added to the reaction mixture and stirring was continued. After 1 h, aldehyde **80** (15.0 mg, 0.700 mmol, 1 equiv) was added and the reaction mixture was stirred for 20 h. The excess reagent was quenched by the addition of sat. aq. ammonium chloride solution (10 mL) and the layers were separated. The aq. layer was extracted with methyl *tert*-butyl ether (3 × 25 mL). The combined organic layers were washed with sat. aq. sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The crude product

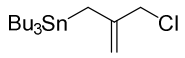


as purified by flash chromatography (hexane/ethyl acetate 20:1 grading to 10:1) to afford (*R*)-**81** (10.6 mg, 0.042 mmol, 60%, *e.e.* ≥88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.07 (q, *J* = 1.6 Hz, 1H), 4.93–4.91 (m, 1H), 4.37 (dtq, *J* = 6.9, 4.4, 2.1 Hz, 1H), 4.11–3.97 (m, 2H), 2.97 (d, *J* = 4.9 Hz, 1H), 2.49–2.28 (m, 2H), 1.75 (d, *J* = 2.1 Hz, 3H), 0.82 (d, *J* = 3.4 Hz, 9H), 0.00 (d, *J* = 1.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.2, 114.2, 80.1, 79.3, 66.0, 60.9, 42.0, 25.1 (3C), 17.6, 2.9, −6.1 (2C).

Tributyl(2-(chloromethyl)allyl)stannane (83)[80]

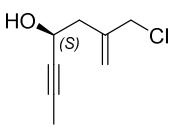
A solution of diisopropylamine (4.00 mL, 28.5 mmol, 1.10 equiv) in anh. tetrahydrofuran (60 mL) was cooled to 0 °C and treated dropwise with *n*-butyllithium (1.6 M in hexanes, 16.2 mL, 25.9 mmol, 1.00 equiv). After 5 min, tributyltin hydride (6.28 mL, 23.3 mmol, 0.90 equiv) was added and stirring was continued for 15 min at 0 °C. This solution was added dropwise over 1 h to a solution of 3-chloro-2-chloromethyl-1-propene (3.00 mL, 25.9 mmol, 1 equiv) in anh. pentane (100 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C before the excess reagent was quenched by the addition of water (100 mL). The reaction mixture was diluted with a mixture of hexane/ethyl acetate (10:1, 240 mL), the layers were separated and the organic layer was washed with sat. aq. sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (pure hexane) to yield **83** (4.78 g, 12.6 mmol, 49%) as a colorless liquid. The spectral data were in full agreement with those reported in the literature.[157]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (dt, *J* = 1.3, 0.7 Hz, $J_{H\text{-}Sn}$ = 17.3 Hz, 1H), 4.71 (dt, *J* = 1.3, 0.7 Hz, $J_{H\text{-}Sn}$ = 17.9 Hz, 1H), 3.96 (d, *J* = 0.9 Hz, $J_{H\text{-}Sn}$ = 5.8 Hz, 2H) 1.89 (d, *J* = 0.9 Hz, $J_{H\text{-}Sn}$ = 57.9 Hz, 2H), 1.60–1.36 (m, 6H), 1.36–1.22 (m, 6H), 0.95–0.79 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 145.8 ($J_{H\text{-}Sn}$ = 39.0 Hz), 110.0 ($J_{H\text{-}Sn}$ = 36.4 Hz), 50.4 ($J_{H\text{-}Sn}$ = 8.6 Hz), 29.2 ($J_{H\text{-}Sn}$ = 20.1 Hz), 27.5 ($J_{H\text{-}Sn}^{117}$ = 54.0 Hz, $J_{H\text{-}Sn}^{119}$ = 56.0 Hz), 16.0 ($J_{H\text{-}Sn}^{117}$ = 221.0 Hz, $J_{H\text{-}Sn}^{119}$ = 231.3 Hz), 13.9, 9.8 ($J_{H\text{-}Sn}^{117}$ = 306.5 Hz, $J_{H\text{-}Sn}^{119}$ = 320.8 Hz); **^{119}Sn NMR** (150 MHz, $CDCl_3$) δ = −12.9.

(*S*)-2-(Chloromethyl)hept-1-en-5-yn-4-ol ((*S*)-226)[158]

Powdered molecular sieves (4 Å, 5 g, activated for 5 days at 120 °C) and titanium(IV) isopropoxide

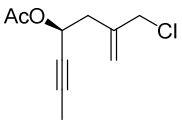


(334 µL, 1.13 mmol, 10 mol%) were added to a solution of (*S*)-(−)-1,1'-bi(2-naphthol)[a] (323 mg, 1.13 mmol, 10 mol%) in anh. dichloromethane (25 mL). The orange suspension was refluxed for 1 h at 43 °C. After cooling to 23 °C, a solution of aldehyde **75** (75% in dichloromethane, 1.02 g, 11.3 mmol, 1 equiv) in anh. dichloromethane (10 mL) was added to the reaction mixture. The mixture was cooled to −78 °C before stannane **83** (4.48 g, 13.5 mmol, 1.20 equiv) was added dropwise. After 3 d at −20 °C, excess reagent was quenched by the addition sat. aq. potassium sodium tartrate solution (50 mL). After stirring 1 h at 23 °C, the suspension was filtered through a plug of Celite which was rinsed with methyl *tert*-butyl ether (25 mL). The volume of the filtrate was reduced, the layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 4:1) to give (*S*)-**226** (1.50 g, 9.46 mmol, 84%) as a colorless liquid. The absolute configuration was determined by Mosher ester analysis.[79] The enantiomeric excess was determined after the next step by chiral HPLC.

$[\alpha]_D^{20}$ = −28.7 (c = 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.29 (s, 1H), 5.13 (s, 1H), 4.54–4.50 (m, 1H), 4.13 (s, 2H), 2.58 (d, *J* = 6.7 Hz, 2H), 1.84 (d, *J* = 1.8 Hz, 3H), 1.75 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 141.2, 118.3, 81.9, 79.8, 61.4, 48.5, 41.8, 3.7; **IR** (film): ν = 3367, 2919, 2930, 1646, 1437, 1258, 1136, 1113, 1006, 913, 851, 749 cm^{-1}; **MS** (EI) *m*/*z* (%): 123 (2), 90 (3), 69 (100); **HRMS** (CI): *m*/*z*: calcd. for $C_8H_{15}NO$ [*M*+NH_4^+]: 176.0842, found: 176.0840.

(*S*)-2-(Chloromethyl)hept-1-en-5-yn-4-yl acetate ((*S*)-77)

4-(Dimethylamino)pyridine (116 mg, 0.946 mmol, 10 mol%), triethylamine (2.64 mL, 18.9 mmol,



2.00 equiv) and acetic anhydride (1.34 mL, 14.2 mmol, 1.50 equiv) were added to a solution of alcohol (*S*)-**226** (1.50 g, 9.46 mmol, 1 equiv) in anh. dichloromethane (60 mL). After 1 h, the volume of the reaction mixture was reduced (40 °C, ≥600 mbar) and the residue was purified by flash chromatography (pentane/diethyl ether 10:1) to obtain (*S*)-**77** (1.77 g, 8.81 mmol, 93 %) as a colorless liquid. The

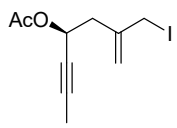
[a] The (*R*)-**226** was obtained with (*R*)-(+)-1,1'-bi(2-naphthol) in similar yields and *e.e*.

enantiomeric purity (*e.e.* ≥95%) was determined by HPLC analysis on a chiral column (150 × 4.6 mm Chiralpak IC-3, 3 µm, *n*-heptane/2-propanol 99:1 (v/v), 1.0 ml/min, 293 K).

$[\alpha]_D^{20}$ = −75.3 (c = 0.95, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.51–5.48 (ddq, *J* = 8.4 6.4, 2.2 Hz, 1H), 5.25 (d, *J* = 1.1 Hz, 1H), 5.08 (d, *J* = 1.1 Hz, 1H), 4.10 (d, *J* = 11.8 Hz, 1H), 4.08 (d, *J* = 11.8 Hz, 1H), 2.70–2.57 (m, 2H), 2.06 (s, 3H), 1.83 (d, *J* = 2.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 140.3, 118.6, 82.7, 76.3, 62.9, 48.2, 38.8, 21.2, 3.7; **IR** (film): ν = 2930, 2923, 1739, 1647, 1437, 1371, 1230, 1160, 1020, 989, 914, 752 cm^{-1}; **MS** (ESI) *m*/*z* (%): 223 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2ClNa$ [*M*+Na^+]: 223.0496, found: 223.0494.

(*S*)-2-(Iodomethyl)hept-1-en-5-yn-4-yl acetate ((*S*)-78)

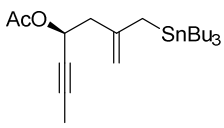
Sodium iodide (2.19 g, 14.6 mmol, 1.35 equiv) was added to a solution of chloride (*S*)-**77** (2.18 g, 10.8 mmol, 1 equiv) in acetone (15 mL) and the resulting suspension was stirred at reflux temperature for 20 h. After cooling to 23 °C, the excess reagent was quenched by the addition of sat. aq. sodium thiosulfate solution (25 mL) and the layers were separated. The aq. layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated (40 °C, ≥150 mbar). The crude product was purified by flash chromatography (pentane/diethyl ether 20:1 grading to 10:1) to yield the title compound (2.78 g, 9.52 mmol, 88%) as a pale yellow liquid.



$[\alpha]_D^{20}$ = −38.9 (c = 1.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.50–5.49 (m, 1H), 5.35 (d, *J* = 0.8 Hz, 1H), 5.01 (d, *J* = 0.8 Hz, 1H), 4.01 (dd, *J* = 9.6, 0.4 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 2.71 (ddd, *J* = 14.4, 6.1, 0.8 Hz, 1H), 2.63 (ddd, *J* = 14.4, 7.1, 0.8 Hz, 1H), 2.06 (s, 3H), 1.83 (d, *J* = 2.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 141.8, 117.7, 82.7, 76.3, 62.9, 39.8, 21.2, 10.4, 3.8; **IR** (film): ν = 2956, 2920,1739, 1636, 1431, 1371, 1230, 1157, 1020, 986, 914 cm^{-1}; **MS** (EI) *m*/*z* (%): 232 (72), 123 (47), 105 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{10}H_{13}O_2INa$ [*M*+Na^+]: 314.9852, found: 314.9852.

(*S*)-2-((Tributylstannyl)methyl)hept-1-en-5-yn-4-yl acetate ((*S*)-50)

Bis(tributyltin) (5.53 mL, 10.9 mmol, 1.50 equiv) and tris-(dibenzylidenaceton)-dipalladium(0) (110 mg, 0.120 mmol, 1.7 mol%) were added to a solution of iodide (*S*)-**78** (2.13 g, 7.29 mmol, 1 equiv) in anh. tetrahydrofuran (10 mL). Argon was bubbled through the green-black suspension for 30 min, before it was stirred



for 3 h at 55 °C. Because TLC showed unreacted starting material, more tris-(dibenzyliden aceton)-dipalladium(0) (110 mg, 0.120 mmol, 1.7 mol%) was added. Stirring at reflux temperature was continued for an additional 1.5 h before the reaction was quenched by the addition of sat. aq. sodium hydrogen carbonate solution (25 mL). The reaction mixture was filtered through a plug of Celite which was rinsed with methyl *tert*-butyl ether (2 × 25 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by repeated flash chromatography (hexane + 2% triethylamine) to separate tin impurities and to yield (*S*)-**50** (2.42 g, 7.29 mmol, 73%) as a colorless liquid.

$[\alpha]_D^{20}$ = −28.1 (c = 0.98, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.49 (t, *J* = 7.2 Hz, 1H), 4.64–4.61(m, 1H), 4.55–4.53 (m, 1H), 2.35 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.31 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.06 (s, 3H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.80 (s, 2H), 1.56–1.39 (m, 6H), 1.30 (sext, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.7 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.5, 144.6, 108.4, 82.2, 77.1, 63.3, 44.0, 29.3 ($J_{H\text{-}Sn}$ = 10.1 Hz), 27.5 ($J_{H\text{-}Sn}^{117}$ = 26.9 Hz, $J_{H\text{-}Sn}^{119}$ = 28.1 Hz), 21.3, 19.1, 13.9, 9.6 ($J_{H\text{-}Sn}^{117}$ = 151.6 Hz, $J_{H\text{-}Sn}^{119}$ = 158.7 Hz), 3.9; **IR** (film): ν = 2956, 2923, 2853, 2872, 2742, 1629, 1464, 1371, 1230, 1018, 961, 866 cm^{-1}; **MS** (EI) *m*/*z* (%): 456 (2), 399 (13), 179 (100), 57 (45), 43 (29); **HRMS** (ESI): *m*/*z*: calcd. for $C_{22}H_{40}O_2SnNa$ [*M*+Na^+]: 479.1956, found: 479.1954.

6.2.3. The Eastern Fragment

(*R*,*Z*)-4-Iodo-3-methylbut-3-en-2-ol (90)[83]

A suspension of (*R*)-(+)-3-butin-2-ol (5.96 mL, 75.6 mmol, 1 equiv) and copper(I) iodide (14.4 g, 75.6 mmol, 1.00 equiv) in anh. toluene (100 mL) was cooled to −78 °C and a solution of methyl magnesium bromide (1.4 M in tetrahydrofuran/toluene 1:3, 378 mL, 529 mmol, 7.00 equiv) was added over the course of 75 min. Once the addition was complete, the reaction mixture was allowed to warm to 23 °C and stirring was continued for 3.5 h. The mixture was then cooled to −40 °C, before a solution of iodine (134 g, 529 mmol, 7.00 equiv) in anh. tetrahydrofuran (140 mL) was slowly added via a cannula. After stirring 1.5 h at 23 °C, excess reagent was carefully quenched by the addition of sat. aq. sodium thiosulfate solution (400 mL), the layers were separated and the aq. layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated by distillation (in portions, 40 °C, ≥90 mbar, Vigreux column, the collection flask cooled to −78 °C). The residue (200 mL) was purified by flash chromatography (pentane/diethyl ether 7:1 grading to 6:1) and the product containing fractions were carefully concentrated by distillation (40 °C, ≥200 mbar) to yield **90** (93% in diethyl ether, 12.7 g, 55.7 mmol, 74%) as an orange liquid.

$[\alpha]_D^{20}$ = +12.3 (c = 2.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.89-5.88 (m, 1H), 4.77 (qd, *J* = 6.5, 2.8 Hz, 1H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.79–1.78 (m, 1H) 1.25 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 149.4, 73.7, 72.6, 20.4, 18.4; **IR** (film): ν = 3331, 2973, 2916, 16134, 1441, 1369, 1278, 1134, 1102, 1073, 1037, 1021, 975, 902, 770 cm^{-1}; **MS** (EI) *m*/*z* (%): 127 (3), 85 (69),45 (57), 43 (100); **HRMS** (EI): *m*/*z*: calcd. for C_5H_9OI [*M*]: 211.9698, found: 211.9700.

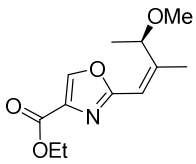
(*R*,*Z*)-1-Iodo-3-methoxy-2-methylbut-1-ene (25)[159]

A suspension of sodium hydride (2.67 g, 111 mmol, 2.00 equiv) and imidazole (379 mg, 5.57 mmol, 10 mol%) in anh. tetrahydrofuran (150 mL) was cooled to 0 °C and treated over 10 min with a solution of alcohol **90** (93% in Et_2O, 12.7 g, 55.7 mmol, 1 equiv) in anh. tetrahydrofuran (80 mL). The reaction mixture was allowed to warm to 23 °C and after 2 h, methyl iodide (31.6 g, 223 mmol, 4.00 equiv) was slowly added. After an additional 2 h, excess reagent was quenched by the addition of water (250 mL) and the aq. layer was extracted with pentane (2 × 250 mL). The combined organic layers were washed with brine (200 mL), dried over magnesium sulfate, filtered and concentrated by distillation (25 °C, ≥ 350 mbar, Vigreux column, the collection

flask cooled to −78 °C). The residue (100 mL) was purified by flash chromatography (pentane/diethyl ether 20:1) and fractions containing product were concentrated by distillation (30 °C, ≥300 mbar) to yield **25** (95% in pentane, 8.44 g, 35.5 mmol, 64%) as a pale yellow liquid. $[\alpha]_D^{20}$ = +5.30 (c = 2.55, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.03–6.02 (m, 1H), 4.26 (q, *J* = 6.5 Hz, 1H), 3.22 (s, 3H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 147.5, 80.9, 75.8, 56.4, 18.6, 18.1; **IR** (film): ν = 2978, 2928, 2820, 1613, 1441, 1369, 1339, 1279, 1205, 1144, 1114, 1094, 1064, 1030, 968, 865, 773. cm^{-1}; **MS** (EI) *m*/*z* (%): 195 (3), 127 (2), 99 (100), 31 (14); **HRMS** (EI): *m*/*z*: calcd. for $C_6H_{11}OI$ [*M*]: 225.9854, found: 225.9855.

Ethyl (*R*,*Z*)-2-(3-methoxy-2-methylbut-1-en-1-yl)oxazole-4-carboxylate (92)[159]

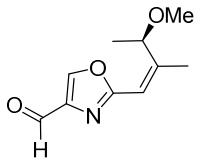
In a pressure tube, palladium(II) acetate (265 mg, 1.18 mmol, 5 mol%) was added to a suspension



of caesium carbonate (15.4 g, 47.3 mmol, 2.00 equiv), ethyl-4-oxazolcarboxylate (23.6 g, 23.6 mmol, 1 equiv), iodide **25** (95% in pentane, 8.44 g, 35.5 mmol, 1.50 equiv) and 2-(dicyclohexylphosphino)biphenyl (829 mg, 2.36 mmol, 0.10 equiv) in anh. dioxane (65 mL). The reaction mixture was stirred at 110 °C for 23 h. After cooling to 23 °C, the suspension was filtered through a plug of Celite which was rinsed with dichloromethane (50 mL). The filtrate was concentrated under reduced pressure (40 °C, ≥50 mbar) and the residue was purified by flash chromatography (hexane/ethyl acetate 20:1 grading to 4:1) to yield **92** (4.16 g, 23.6 mmol, 74%) as a colorless oil. $[\alpha]_D^{20}$ = +41.7 (c = 1.76, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 6.25 (s, 1H), 5.13 (q, *J* = 6.4 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.22 (s, 3H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.6, 161.2, 153.4, 142.9, 134.4, 112.9, 75.0, 61.4, 56.7, 19.6, 18.1, 14.5; **IR** (film): ν = 3154, 2981, 2932, 2821, 1743, 1720, 1654, 1575, 1562, 1447, 1370, 1332, 1316, 1279, 1217, 1178, 1109, 1025, 971, 947, 839, 771 cm^{-1}; **MS** (EI) *m*/*z* (%): 224 (100), 194 (7), 180 (3), 59 (9); **HRMS** (ESI): *m*/*z*: calcd. for $C_{12}H_{17}NO_4Na$ [*M*+Na^+]: 262.1049 found: 262.1051.

(*R*,*Z*)-2-(3-Methoxy-2-methylbut-1-enyl)oxazole-4-carbaldehyde (52)[159]

A solution of the oxazole **92** (4.20 g, 17.6 mmol, 1 equiv) in anh. dichloromethane (150 mL) was

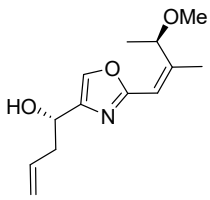


cooled to −90 °C and treated dropwise over 15 min with a diisobutylaluminium hydride solution (1 M in toluene, 35.1 mL, 35.1 mmol, 2.00 equiv). The reaction mixture was stirred at −90 °C until TLC showed complete consumption of the starting material (20 min). The excess reagent was quenched by the addition of methanol (15 mL) and sat. aq. potassium sodium tartrate solution (200 mL). The mixture was stirred for 18 h at 23 °C before the layers were separated and the aq. layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with aq. sat. sodium chloride solution (200 mL), dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 10:1) to give **52** (2.74 g, 14.0 mmol, 80%) as a pale yellow oil.

$[\alpha]_D^{20}$ = +46.8 (c = 2.18, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.93 (s, 1H), 8.16 (s, 1H), 6.23–6.22 (m, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 3.23 (s, 3H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 184.7, 161.4, 154.7, 142.9, 141.7, 112.1, 74.9, 56.7, 19.3, 18.0; **IR** (film): ν = 3144, 3085, 2979, 2932, 2822, 1698, 1652, 1563, 1447, 1393, 1381, 1326, 1290, 1206, 1149, 1113, 1096, 1069, 833, 759 cm^{-1}; **MS** (EI) *m*/*z* (%): 195 (15), 180 (100), 59 (6); **HRMS** (ESI): *m*/*z*: calcd. for $C_{10}H_{13}NO_3Na$ [*M*+Na^+]: 218.0787, found: 218.0789.

(*S*)-1-(2-((R,Z)-3-Methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)but-3-en-1-ol (87)[158]

Powdered molecular sieves (4 Å, 5 g, activated for 5 days at 120 °C) followed by titanium(IV)



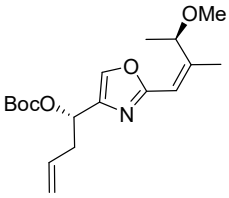
isopropoxide (411 µL, 1.39 mmol, 10 mol%) were added to a solution of (*S*)-(−)-1,1′-bi(2-naphthol) (398 mg, 1.39 mmol, 10 mol%) in anh. dichloromethane (25 mL). The orange suspension was stirred for 1 h at 43 °C. After cooling to 23 °C, a solution of aldehyde **52** (2.71 g, 13.9 mmol, 1 equiv) in anh. dichloromethane (15 mL) was added. The mixture was cooled to −78 °C before allyltributylstannane (5.25 mL, 16.9 mmol, 1.22 equiv) was added dropwise. After 3 days at −30 °C, TLC showed complete consumption of the starting material and the reaction was quenched by the addition sat. aq. sodium hydrogen carbonate solution (25 mL) and allowed to warm to 23 °C. The suspension was filtered through a plug of Celite which was rinsed with methyl *tert*-butyl ether (25 mL). The volume of the filtrate was reduced, the layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 25 mL). The combined organic layers were dried over

magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 4:1) to give **87** (3.21g, 13.5 mmol, 98 %) as a pale yellow oil. (Mosher ester analysis revealed a *d.e*. >95%).

$[\alpha]_D^{20}$ = +22.3 (c = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 6.19 (s, 1H), 5.84 (ddt, *J* = 17.2, 10.3, 7.1 Hz, 1H), 5.20–5.14 (m, 3H), 4.73 (dd, *J* = 7.3, 5.6Hz, 1H), 3.22 (s, 3H), 2.69–2.62 (m, 1H), 2.59–2.52 (m, 1H), 2.39 (br s, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.7, 151.1, 144.0, 134.0, 133.2, 118.8, 113.5, 75.0, 66.7, 56.7, 41.1, 19.4, 17.8; **IR** (film): ν = 3417, 2980, 2933, 1655, 1642, 1542, 1539, 1381, 1371, 1206, 1154, 1113, 1095, 1068, 915, 862. cm^{-1}; **MS** (EI) *m*/*z* (%): 237 (38), 222 (56), 204 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{13}H_{19}NO_3Na$ [*M*+Na^+]: 260.1257, found: 260.1257.

tert-Butyl ((*S*)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)but-3-en-1-yl) carbonate (101)

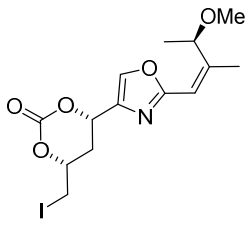
Di-*tert*-butyl dicarbonate (7.30 g, 33.5 mmol, 2.00 equiv) and 4-(dimethylamino)pyridine (1.02 g, 8.37 mmol, 0.50 equiv) were added to a solution of alcohol **87** (3.79 g, 17.7 mmol, 1 equiv) in anh. acetonitrile (150 mL). After stirring for 20 h, the mixture was concentrated and the residue was dissolved in methyl *tert*-butyl ether (100 mL) and water (100 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 10:1) to yield **101** (5.18 g, 15.4 mmol, 92%) as a yellowish oil.



$[\alpha]_D^{20}$= −8.80 (c = 0.60, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 0.4 Hz, 1H), 6.19–6.18 (m, 1H), 5.76 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.62 (t, *J* = 6.5 Hz, 1H), 5.21 (q, *J* = 6.5 Hz, 1H), 5.13 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.08–5.05 (m, 1H), 3.22 (s, 3H), 2.78 (ddt, *J* = 14.3, 6.6, 1.46 Hz, 1H), 2.71 (ddt, *J* = 14.2, 7.1, 1.2 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.47 (s, 9H), 1.31 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.6, 153.1, 151.2, 140.1, 134.9, 133.0, 118.5, 113.4, 82.6, 74.9, 71.2, 56.9, 37.8, 28.0 (3C), 19.3, 17.8; **IR** (film): ν = 2980, 2933, 2820, 1740, 1644, 1544, 1449, 1369, 1342, 1280, 1254, 1163, 1095, 1036, 973, 919, 845, 793, 762 cm^{-1}; **MS** (EI) *m*/*z* (%): 337 (15.86), 281 (18.30), 220 (57.00), 204 (100), 117 (2); **HRMS** (ESI): *m*/*z*: calcd. for $C_{18}H_{27}NO_5Na$ [*M*+Na^+]: 360.1781, found: 360.1783.

(4*R*,6*S*)-4-(Iodomethyl)-6-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-1,3-dioxan-2-one (102)[160]

A solution of olefin **101** (3.97 g, 11.8 mmol, 1 equiv) in anh. toluene (140 mL) was cooled to −78 °C

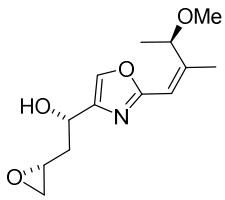


and treated dropwise with iodine monobromide (1 M in dichloromethane, 35.3 mL, 35.3 mmol, 3.00 equiv) over 40 min (it was essential to store the iodine monobromide solution at 23 °C). After complete addition, stirring was continued until TLC showed complete consumption of the starting material (10 min). The excess reagent was quenched by the addition of sat. aq. sodium hydrogen carbonate solution (100 mL) and sat. aq. sodium thiosulfate solution (100 mL). After warming to 23 °C, the layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 2:1) to yield **102** (2.58 g, 6.34 mmol, 54%[b]) as a yellowish oil.

$[\alpha]_D^{20}$ = +21.7 (c = 0.79, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 0.7 Hz, 1H), 6.19 (s, 1H), 5.50 (ddd, *J* = 11.7, 3.1, 0.7 Hz, 1H), 5.15 (q, *J* = 6.3 Hz, 1H), 4.64–4.58 (m, 1H), 3.46 (dd, *J* = 10.5, 4.4 Hz, 1H), 3.46 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.23 (s, 3H), 2.78 (dt, *J* = 14.1, 3.19 Hz, 1H), 2.15 (dt, *J* = 14.3, 11.1 Hz, 1H), 1.92 (d, *J* = 1.7 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.3, 152.7, 147.9, 138.5, 134.9, 112.9, 74.9, 73.5, 69.5, 56.7, 33.0, 19.4, 17.9, 4.9; **IR** (film): ν = 3482, 3135, 2978, 2931, 2820, 1745, 1656, 1602, 1543, 1519, 1446, 1382, 1239, 1184, 1109, 1092, 1038, 971, 854, 760 cm^{-1}; **MS** (ESI) *m*/*z* (%): 430 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{14}H_{18}NO_5INa$ [*M*+Na^+]: 430.0121, found: 430.0120.

(*S*)-1-(2-((*R*,*Z*)-3-Methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-2-((*R*)-oxiran-2-yl)ethan-1-ol (103)

A solution of iodide **102** (2.11 g, 5.18 mmol, 1 equiv) in anh. methanol (25 mL) was treated at 0 °C



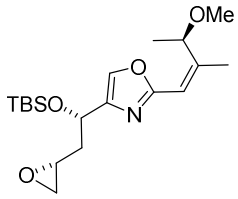
with anh. potassium carbonate (2.15 g, 15.5 mmol, 3.00 equiv). After 40 min, the reaction mixture was diluted with methyl *tert*-butyl ether (25 mL) and excess reagent was quenched by addition of sat. aq. ammonium chloride solution (50 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 1:1) to yield **103** (1.03 g, 4.07 mmol, 79%) as a colorless oil.

[b] Smaller scales of approximately 200 mg of starting material $M6 gave yields between 70-80%.

$[\alpha]_D^{20}$ = +28.0 (c = 0.30, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 6.19 (s, 1H), 5.18 (q, *J* = 6.6 Hz, 1H), 4.94 (t, *J* = 5.7 Hz, 1H), 3.22 (s, 3H), 3.17–3.09 (m, 1H) 2.80 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.72 (d, *J* = 4.3 Hz, 1H), 2.57 (dd, *J* = 5.9, 2.6 Hz, 1H), 2.27 (dt, *J* = 14.4, 4.5 Hz, 1H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.92–1.81 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.9, 151.3, 143.9, 133.4, 113.5, 75.0, 66.3, 65.8, 50.3, 47.0, 39.4, 19.4, 18.9; **IR** (film): ν = 3417, 2980, 2824, 2821, 1655, 1542, 1518, 1447, 1370, 1258, 1206, 1152, 1206, 1152, 1109, 1094, 1068, 1036, 971, 856, 753 cm^{-1}; **MS** (EI) *m*/*z* (%): 253 (13), 238 (53), 178 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{13}H_{19}NO_4Na$ [*M*+Na^+]: 276.1206, found: 276.1208.

4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-((*R*)-oxiran-2-yl)ethyl)-2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazole (104)

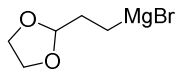
tert-Butyldimethylsilyl chloride (1.25 g, 8.29 mmol, 1.50 equiv) was added to a solution of alcohol



103 (1.40 g, 5.53 mmol, 1 equiv), imidazole (564 mg, 8.29 mmol, 1.50 equiv) and 4-(dimethylamino)-pyridine (67.5 mg, 0.553 mmol, 10mol%) in dichloromethane (5.5 mL) at 0 °C. The mixture was stirred at 23 °C until TLC showed complete consumption of the starting material (ca. 75 min). The reaction mixture was diluted with methyl *tert*-butyl ether (20 mL) and excess reagent was quenched by the addition of sat. aq. ammonium chloride solution (30 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (pure hexane grading to hexane/ethyl acetate 30:1) to give **104** (1.99 g, 5.41 mmol, 98%) as a yellow oil.

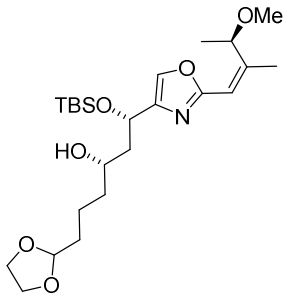
$[\alpha]_D^{20}$ = +13.2 (c = 0.44, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 0.7 Hz, 1H), 6.18 (dd, *J* = 0.7, 1.2 Hz, 1H), 5.21 (q, *J* = 6.2 Hz, 1H), 4.92 (td, *J* = 5.8, 1.1 Hz, 1H), 3.23 (s, 3H), 3.04–3.03 (m, 1H), 2.74 (t, *J* = 4.8 Hz, 1H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.11 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.93 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.3, 150.7, 145.1, 133.7, 113.5, 74.9, 67.0, 56.6, 49.4, 47.0, 40.7, 25.8 (3C), 19.2, 18.2, 17.7, −4.6, −4.8; **IR** (film): ν = 2954, 2929, 2887, 2857, 2820, 1654, 1542, 1472, 1463, 1447, 1408, 1387, 1362, 1253, 1206, 1153, 1093, 1034, 1006, 968, 938, 913, 871, 833, 811, 775, 811, 775 cm^{-1}; **MS** (EI) *m*/*z* (%): 367 (5), 336 (2), 310 (100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{19}H_{33}NO_4SiNa$ [*M*+Na^+]: 390.2071, found: 390.2067.

(2-(1,3-dioxolan-2-yl)ethyl)magnesium bromide (105) [161]



A solution of 2-(2-bromoethyl)-1,3-dioxolane (2.00 mL, 17.0 mmol, 1 equiv) in anh. tetrahydrofuran (8.5 mL) was added over 30 min to a suspension of magnesium powder (1.04 g, 42.6 mmol, 2.50 equiv) in anh. tetrahydrofuran (4.2 mL). The reaction temperature was kept by a water bath below 30 °C. After stirring 1.5 h, the mixture was filtered through a syringe filter and the flask rinsed with anh. tetrahydrofuran (2 mL) to give a yellowish solution (0.80 M in tetrahydrofuran, 16.7 mL, 13.4 mmol, 79%). The titer was determined by titration using lithium chloride and iodine.[162]

(1*S*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(1,3-dioxolan-2-yl)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)hexan-3-ol (106)



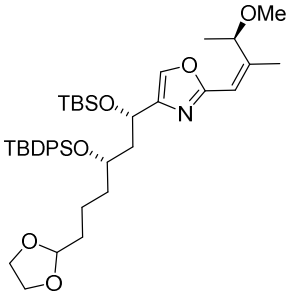
Copper(I) iodide (206 mg, 1.08 mmol, 0.20 equiv) was suspended in anh. tetrahydrofuran (30 mL) and the suspension was cooled to −78 °C before an aliquot of the freshly prepared Grignard reagent **105** (0.80 M in tetrahydrofuran, 10.2 mL, 8.12 mmol, 1.50 equiv) was added dropwise. After stirring for 5 min, a solution of epoxide **104** (1.99 g, 5.41 mmol, 1 equiv) in anh. tetrahydrofuran (30 mL) was added over 30 min. Once the addition was complete, the mixture was stirred at −40 °C for 50 min. The excess reagent was quenched by the addition of sat. aq. ammonium chloride solution (60 mL) and the mixture was allowed to warm to 23 °C. The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 60 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 5:1 grading to 2:1) to yield **106** (2.35 g, 5.00 mmol, 92%) as a yellowish oil.

$[\alpha]_D^{20}$ = −2.60 (c = 0.52, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 0.7 Hz, 1H), 6.17 (dd, *J* = 1.0, 0.7 Hz, 1H), 5.16 (q, *J* = 6.7 Hz, 1H), 4.93 (t, *J* = 6.7 Hz, 1H), 4.83 (t, *J* = 4.7 Hz, 1H), 3.97–3.3.78 (m, 5H), 3.49 (d, *J* = 2.7 Hz, 1H), 3.23 (s, 3H), 1.93 (ddd, *J* = 13.9, 9.1, 7.1 Hz, 1H), 1.59 (ddd, *J* = 13.9, 6.3, 2.7 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.68–1.43 (m, 6H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.3, 151.3, 145.4, 133.6, 113.3, 104.8, 75.0, 69.5, 68.4, 65.0 (2C), 56.7, 45.2, 37.4, 34.0, 25.9 (3C), 20.3, 19.4, 18.2, 17.8, −4.5, −4.8; **IR** (film): ν = 3487, 2950, 3930, 2859, 1655, 1543, 1462, 1253, 1096, 970, 838, 778 cm^{-1}; **MS** (ESI)

m/*z* (%): 492 (*M*+Na$^+$, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{24}H_{43}NO_6SiNa$ [*M*+Na$^+$]: 492.2751, found: 492.2751.

4-((5*S*,7*S*)-7-(3-(1,3-Dioxolan-2-yl)propyl)-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazole (228)

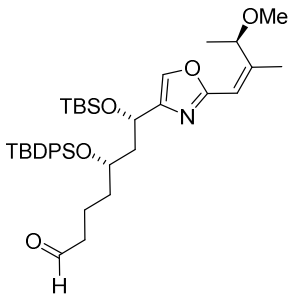
A solution of alcohol **106** (2.35 g, 5.00 mmol, 1 equiv) in anh. dichloromethane (45 mL) was cooled to 0 °C before 2,6-lutidine (1.75 mL, 15.0 mmol, 3.00 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.77 mL, 5.75 mmol, 1.15 equiv) were successively added. After stirring 20 min at 0 °C, the reaction was quenched by the addition of sat. aq. ammonium chloride solution (50 mL), the layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (2 × 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 6:1) to obtain **228** (3.11 g, 4.39 mmol, 88%) as a colorless oil.



$[\alpha]_D^{20}$ = −9.00 (c = 0.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.62 (td, *J* = 7.8, 1.3 Hz, 4H), 7.40–7.29 (m, 6H), 7.06 (s, 1H), 6.14 (s, 1H), 5.21 (q, *J* = 6.2 Hz, 1H), 4.80 (t, *J* = 6.6 Hz, 1H), 4.67 (t, *J* = 4.1 Hz, 1H), 3.90-3.77 (m, 5H), 3.17 (s, 3H), 2.01 (td, *J* = 6.8, 1.3 Hz, 2H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.48–1.38 (m, 6H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.02 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), −0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.6, 150.3, 144.9, 136.1 (2C), 136.0 (2C), 134.8, 134.6, 133.6, 129.6, 129.57, 129.55, 127.55 (2C), 127.54 (2C), 113.7, 104.7, 74.9, 70.6, 65.8, 64.9, 56.5, 44.0, 36.6, 34.0, 27.3 (3C), 26.0 (3C), 19.6, 19.3, 19.1, 18.3, 17.7, −4.3, −4.6; **IR** (film): ν = 2953, 2931, 2887, 2852, 1428, 1257, 1107, 1066, 972, 939, 837, 820, 776, 702 cm^{-1}; **MS** (ESI) *m*/*z* (%): 730 (*M*+Na$^+$, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{40}H_{61}NO_6SiNa$ [*M*+Na$^+$]: 730.3929, found: 730.3938.

(5*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-7-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)heptanal (63)

2,4,6-Trimethylpyridine (1.10 mL, 8.31 mmol, 3.00 equiv) and TMSOTf (1.00 mL, 5.54 mmol, 2.00 equiv) were added to a solution of **228** (2.21 g, 2.77 mmol, 1 equiv) in anh. dichloromethane (50 mL) at 0 °C. After stirring for 1 h at 0 °C, water (50 mL) was added to the reaction mixture and stirring was continued for 2 h at 23 °C. The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 20:1 grading to 15:1) to obtain **63** (1.78 g, 2.68 mmol, 97%) as a yellowish oil.

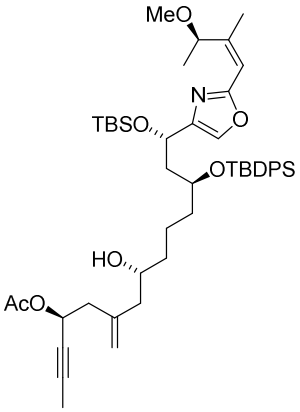


$[\alpha]_D^{20}$ = −10.4 (c = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.57 (t, *J* = 1.8 Hz, 1H), 7.64–7.60 (m, 4H), 7.42–7.30 (m, 6H), 7.11 (s, 1H), 6.15 (qd, *J* = 1.4, 0.8 Hz, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 4.79 (t, *J* = 6.5 Hz, 1H), 3.95–3.86 (m, 1H), 3.18 (s, 3H), 2.15–1.99 (m, 4H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.61–1.42 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), −0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 202.5, 160.0, 150.4, 145.0, 136.1 (2C), 136.0 (2C), 134.6, 134.4, 133.6, 129.7 (2C), 127.62 (2C), 127. 61 (2C), 113.6, 74.9, 70.1, 65.8, 56.6, 44.1, 43.8, 36.0, 27.2 (3C), 25.9 (3C), 19.6, 19.3, 18.2, 17.7, 17.2, −4.3, −4.7; **IR** (film): ν = 2953, 2930, 2891, 2857, 1727, 1655, 1589, 1544, 1472, 1462, 1428, 1388, 1361, 1252, 1205, 1078, 1068, 1005, 971, 938, 836, 777 cm^{-1}; **MS** (ESI) *m*/*z* (%): 686 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{38}H_{57}NO_5Si_2Na$ [*M*+Na^+]: 686.3667, found: 686.3664.

6.2.4. Combination of Fragments

(4*S*,8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-8-hydroxy-14-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl) oxazol-4-yl)-6-methylenetetradec-2-yn-4-yl acetate (111a)

Boron tribromide (1 M in dichloromethane, 3.39 mL, 3.39 mmol, 1.50 equiv) was added to a solution of (*S,S*)-1,2-diphenyl-1,2-ethylenediamine bis(toluenesulfonamide)[103b] (1.76 g, 3.39 mmol, 1.50 equiv) in anh. dichloromethane (40 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and for 1 h at 23 °C before all volatile materials were removed in high vacuum.



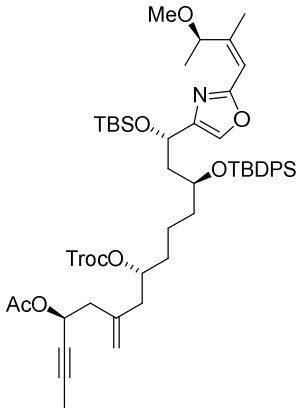
Allyl stannane (*S*)-**50** (1.80 g, 3.95 mmol, 1.75 equiv) was added to a solution of the residue in anh. dichloromethane (40 mL) at 0 °C. After stirring for 17 h at 23 °C, the reaction mixture was cooled to −78 °C and a solution of aldehyde **63** (1.50 g, 2.26 mmol, 1 equiv) in anh. dichloromethane (10 mL) was added dropwise over 5 min. The mixture was stirred for 2 h before the reaction was quenched by the addition of aq. phosphate buffer solution (pH 7, 50 mL). Water (50 mL) was introduced and the aq. phase was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over magnesium sulfate, filtered and concentrated. The residue was suspended in diethyl ether (20 mL) and the colorless solid was filtered off to recover the chiral diamine ligand. The filtrate was concentrated and the crude product purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 3:1) to give **111a** (1.79 g, 2.15 mmol, 95%, *d.r.* >10:1) as a colorless oil.

$[\alpha]_D^{20}$ = −20.9 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.62 (m, 2H), 7.59 (m, 2H), 7.37 (m, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.29 (m, 2H), 7.08 (d, *J* = 0.5 Hz, 1H), 6.14 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.45 (ddq, *J* = 7.8, 6.0, 2.2 Hz, 1H), 5.19 (qd, *J* = 6.5, 0.8 Hz, 1H), 4.95 (dt, *J* = 1.4, 1.2 Hz, 1H), 4.90 (d, *J* = 1.1 Hz, 1H), 4.81 (td, *J* = 6.7, 0.7 Hz, 1H), 3.84 (tdd, *J* = 6.2, 5.8, 5.1 Hz, 1H), 3.52 (dddt, *J* = 9.4, 7.6, 4.4, 3.2 Hz, 1H), 3.15 (s, 3H), 2.45 (ddd, *J* = 14.4, 7.8, 0.8 Hz, 1H), 2.40 (ddd, *J* = 14.4, 6.0, 0.9 Hz, 1H), 2.14 (ddd, *J* = 14.3, 3.3, 1.2 Hz, 1H), 2.03 (s, 3H), 2.01 (t, *J* = 6.7 Hz, 2H), 1.95 (ddd, *J* = 14.3, 9.4, 0.5 Hz, 1H), 1.86 (d *J* = 1.5 Hz, 3H), 1.82 (d, *J* = 2.2 Hz, 3H), 1.63 (d, *J* = 3.1 Hz, 1H), 1.47–1.46 (m, 1H), 1.38–1.37 (m, 1H), 1.32–1.31 (m, 1H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.24–1.23 (m, 1H), 1.20–1.19 (m, 1H), 1.15–1.14 (m, 1H), 1.01 (s, 9H), 0.80 (s, 9H), 0.00 (s, 3H), −0.09 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.0, 159.8, 150.1, 144.7, 141.3, 135.90 (2C), 135.87 (2C), 134.6, 134.3, 133.5, 129.5, 129.4, 127.41 (2C), 127.39 (2C), 116.1, 113.5, 82.2, 76.5, 74.7, 70.4, 68.8, 65.6, 62.8,

56.4, 44.3, 44.0, 41.6, 37.2, 36.7, 27.1 (3C), 25.8 (3C), 21.0, 20.7, 19.4, 19.2, 18.1, 17.5, 3.6, −4.5, −4.8; **IR** (film): ν = 3479, 2929, 2857, 1740, 1428, 1371, 1233, 1109, 837, 777, 703, 507 cm^{-1}; **MS** (ESI) *m*/*z* (%): 852 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{48}H_{71}NO_7Si_2Na$ [*M*+Na^+]: 852.4661, found: 852.4673.

(4*S*,8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl) oxy) tetra-dec-2-yn-4-yl acetate (112a)

2,2,2-Trichlorethoxycarbonyl chloride (0.89 mL, 6.45 mmol, 3.00 equiv) was added at 0 °C to a solution of aclohol **111a** (1.79 g, 2.15 mmol, 1 equiv), 4-(dimethylamino)pyridine (26.3 mg, 215 µmol, 0.10 equiv) and pyridine (1.04 mL, 12.9 mmol, 6.00 equiv) in anh. dichloromethane (20 mL). After stirring for 20 min at 23 °C, the excess reagent was quenched by the addition of water (20 mL). The layers were separated and the aq. layer was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to give **112a** (2.15 g, 2.14 mmol, quant.) as a colorless oil.

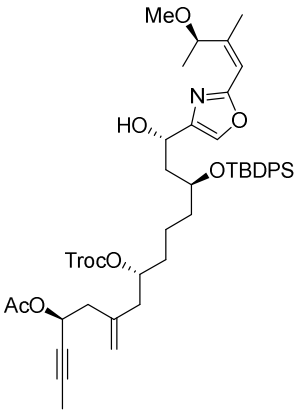


$[\alpha]_D^{20}$ = −21.0 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.61 (m, 2H), 7.59 (m, 2H), 7.38 (m, 1H), 7.37 (m, 1H), 7.32 (m, 2H), 7.30 (m, 2H), 7.08 (d, *J* = 0.6 Hz, 1H), 6.14 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.41 (tq, *J* = 6.9, 2.2 Hz, 1H), 5.18 (qd, *J* = 6.5, 0.7 Hz, 1H), 4.89 (dt, *J* = 1.3 Hz + not dissolved, 1H), 4.88 (dt, *J* = 1.3 Hz + not dissolved, 1H), 4.78 (t, *J* = 6.7 Hz, 1H), 4.75 (m, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.84 (tt, *J* = 6.2, 5.4 Hz, 1H), 3.16 (s, 3H), 2.44 (d, *J* = 6.9 Hz, 2H), 2.26 (ddd, *J* = 14.6, 8.2, 0.7 Hz, 1H), 2.22 (ddd, *J* = 14.6, 5.0, 0.9 Hz, 1H), 2.02 (s, 3H), 2.00 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.94 (dt, *J* = 13.7, 6.4 Hz, 1H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.46 (m, 1H), 1.39 (m, 1H), 1.36 (m, 1H), 1.29 (m, 2H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.24 (m, 1H), 1.01 (s, 9H), 0.79 (s, 9H), 0.00 (s, 3H), −0.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 169.9, 159.8, 153.7, 150.2, 144.8, 139.4, 135.90 (2C), 135.84 (2C), 134.5, 134.2, 133.5, 129.5 (2C), 127.44 (2C), 127.43 (2C), 117.1, 113.5, 94.6, 82.1, 77.9, 76.53, 76.50, 74.7, 70.2, 65.6, 62.7, 56.4, 44.0, 41.4, 40.9, 36.4, 34.1, 27.1 (3C), 25.8 (3C), 21.0, 20.3, 19.4, 19.2, 18.1, 17.5, 3.6, −4.5, −4.9; **IR** (film): ν = 2954, 2930, 2857,

1755, 1378, 1250, 1110, 836, 821, 704, 507 cm^{-1}; **MS** (ESI) *m*/*z* (%): 1028 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{51}H_{72}NO_9Cl_3Si_2Na$ [*M*+Na^+]: 1026.3703, found: 1026.3719.

(4*S*,8*R*,12*S*,14*S*)-12-((*tert*-Butyldiphenylsilyl)oxy)-14-hydroxy-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-2-yn-4-yl acetate (113a)

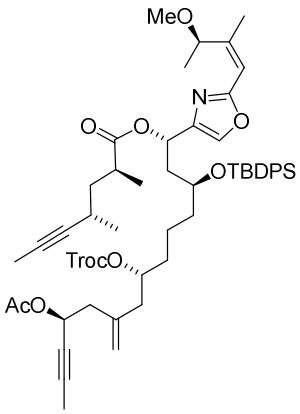
10-Camphorsulfonic acid (102 mg, 0.438 mmol, 0.10 equiv) was added to a solution of **112a** (2.20 g, 2.19 mmol, 1 equiv) in anh. dichloromethane/methanol (24 mL/8 mL). After stirring for 8 h, TLC control indicated that the acetate started to get cleaved. At this point the mixture was neutralized by the addition of aq. sat. sodium hydrogen carbonate solution (40 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 2:1) to obtain unreacted starting material (823 mg, 0.818 mmol, 37%) and the desired product **113a** (1.19 g, 1.34 mmol, 61%, 98% brsm).



$[\alpha]_D^{20}$ = −2.60 (c = 1.15, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.67 (m, 2H), 7.67 (m, 2H), 7.42 (m, 1H), 7.42 (m, 1H), 7.36 (m, 4H), 7.26 (d, *J* = 1.0 Hz, 1H), 6.15 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.40 (tq, *J* = 6.9, 2.2 Hz, 1H), 5.10 (qd, *J* = 6.5, 0.8 Hz, 1H), 4.88 (dt, *J* = 1.3, 1.1 Hz, 1H), 4.86 (dt, *J* = 1.2 Hz + not dissolved, 1H), 4.82 (dtd, *J* = 8.9, 3.8, 0.9 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.71 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.00 (tt, *J* = 7.2, 4.7 Hz, 1H), 3.18 (s, 3H), 3.06 (d, *J* = 3.8 Hz, 1H), 2.43 (dt, *J* = 6.9, 1.1 Hz, 2H), 2.25 (ddd, *J* = 14.5, 8.2, 0.6 Hz, 1H), 2.19 (ddd, *J* = 14.5, 4.8, 0.8 Hz, 1H), 2.02 (s, 3H), 1.99 (ddd, *J* = 14.2, 4.7, 3.9 Hz, 1H), 1.90 (ddd, *J* = 14.3, 8.8, 7.7 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.80 (d, *J* = 2.2 Hz, 3H), 1.45 (m, 1H), 1.33 (m, 1H), 1.31 (m, 1H) 1.27 (d, *J* = 6.5 Hz, 3H), 1.20 (m, 3H), 1.04 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 169.9, 160.4, 153.7, 150.5, 144.3, 139.3, 135.88 (2C), 135.87 (2C), 134.1, 133.5, 133.0, 129.9, 129.8, 127.7 (2C), 127.6 (2C), 117.1, 113.5, 94.6, 82.2, 77.7, 76.53, 76.46, 74.7, 72.8, 66.2, 62.7, 56.4, 42.6, 41.4, 40.9, 36.8, 33.9, 27.0 (3C), 21.0, 20.5, 19.29, 19.26, 17.6, 3.6; **IR** (film): ν = 3422, 2932, 2858, 1754, 1652, 1428, 1378, 1250, 1109, 1067, 1021, 821, 735, 704, 612, 508 cm^{-1}; **MS** (ESI) *m*/*z* (%): 914 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{45}H_{58}NO_9Cl_3SiNa$ [*M*+Na^+]: 912.2838, found: 912.2843.

(1*S*,3*S*,7*R*,11*S*)-11-Acetoxy-3-((*tert*-butyldiphenylsilyl)oxy)-1-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-9-methylene-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-12-yn-1-yl (2S,4S)-2,4-dimethylhept-5-ynoate (62a)[163]

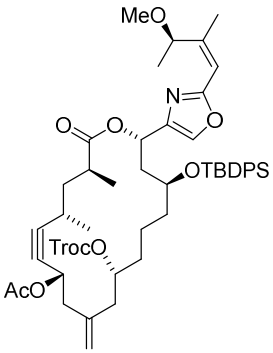
2,4,6-Trichlorobenzoyl chloride (413 µL, 2.64 mmol, 1.50 equiv) and triethylamine (368 µL, 2.64 mmol, 1.50 equiv) were added at 0 °C to a solution of acid **49** (299 mg, 1.94 mmol, 1.10 equiv) in anh. toluene (25 mL). The mixture was stirred at 23 °C for 1 h. After cooling to 0 °C, a solution of alcohol **113a** (1.57 g, 1.76 mmol, 1 equiv) in anh. toluene (20 mL) and 4-(dimethylamino)pyridine (215 mg, 1.76 mmol, 1.00 equiv) were successively added. Stirring was continued for 1 h at 23 °C before the mixture was diluted with ethyl acetate (30 mL) and the excess reagent was quenched by the addition hydrochloric acid (1 N, 80 mL). The layers were separated and the aq. layer was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 4:1) to yield **62a** (1.81 g, quant.).



$[\alpha]_D^{20}$ = −7.40 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.64–7.57 (m, 4H), 7.44–7.29 (m, 6H), 7.19 (br s, 1H), 6.17–6.14 (m, 1H), 5.94–5.85 (m, 1H), 5.44 (ddq, J = 6.6, 1.8 Hz, 1H), 5.11 (qd, J = 6.6, 0.9 Hz, 1H), 4.91 (br s, 2H), 4.83–4.74 (m, 2H), 4.68 (d, *J* = 11.9 Hz, 1H), 3.68 (dt, *J* = 11.7, 5.6 Hz, 1H), 3.15 (s, 3H), 2.68–2.56 (m, 1H), 2.47 (d, *J* = 6.9 Hz, 2H), 2.36–2.08 (m, 5H), 2.05 (s, 3H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.74 (d, *J* = 2.3 Hz, 3H), 1.67 (ddd, *J* = 14.8, 9.7, 5.1 Hz, 1H), 1.54–1.30 (m, 7H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.9, 170.1, 160.2, 153.9, 150.8, 140.1, 139.4, 136.03 (2C), 136.00 (2C), 135.2, 134.2, 134.0, 129.8 (2C), 127.6 (4C), 117.4, 113.4, 94.7, 83.0, 82.3, 77.9, 76.64, 76.57, 76.4, 74.8, 69.8, 65.7, 62.8, 56.6, 41.4, 41.2, 41.1, 39.6, 38.0, 36.4, 34.2, 27.1 (3C), 24.4, 21.8, 21.2, 20.5, 19.5, 19.3, 18.2, 17.8, 3.8, 3.7; **IR** (film): ν = 2962, 2932, 2858, 1753, 1737, 1448, 1428, 1377, 1249, 1162, 1110, 1064, 1021, 970, 821, 733, 704, 611, 507, 489 cm^{-1}; **MS** (ESI) *m*/*z* (%): 1050 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{54}H_{70}Cl_3NO_{10}SiNa$ [*M*+Na^+]: 1048.3727, found: 1048.3746.

(3*S*,5*S*,8*S*,12*R*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-18-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxo-12-(((2,2,2-trichloroethoxy)carbonyl)oxy) oxacyclo-octadec-6-yn-8-yl acetate (114a)

In a flame dried 1 L two-neck round-bottom flask, molecular sieves (4 Å, 8 g and 5 Å, 19 g) were

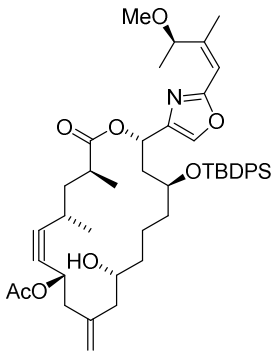


added to a solution of diyne **62a** (1.62 g, 1.57 mmol, 1 equiv) in anh. toluene (830 mL). After stirring for 1 h, alkyne metathesis catalyst[31] **116** (640 mg, 0.483 mmol, 0.31 equiv) was dissolved in an aliquot (20 mL) of the reaction mixture and the resulting solution was added. The suspension was stirred for 45 min at 23 °C before it was filtered through a plug of Celite which was rinsed with methyl *tert*-butyl ether (100 mL). The filtrate was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 4:1) to obtain **114a** (1.21 g, 1.24 mmol, 79%).

$[\alpha]_D^{20}$ = −1.50 (c = 1.02, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65-7.59 (m, 4H), 7.46-7.30 (m, 7H), 6.18-6.12 (m, 1H), 6.08 (dd, *J* = 9.3, 1.8 Hz, 1H), 5.46 (ddd, *J* = 9.0, 4.3, 1.4 Hz, 1H), 5.15 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.96 (br s, 1H), 4.94 (d, *J* = 1.1 Hz, 1H), 4.84-4.66 (m, 3H), 3.91-3.77 (m, 1H), 3.19 (s, 3H), 2.63-2.18 (m, 7H), 2.06 (s, 3H), 1.95 (ddd, *J* = 15.0, 7.1, 2.2 Hz, 1H), 1.89 (d, *J* = 1.3 Hz, 4H), 1.69-1.39 (m, 5H), 1.38-1.30 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.5, 169.9, 160.4, 153.9, 151.0, 140.9, 139.5, 135.9 (4C), 135.1, 134.11, 134.06, 129.8 (2C), 127.7 (4C), 116.9, 113.3, 94.7, 90.6, 78.2, 78.1, 76.6, 74.8, 70.2, 65.6, 63.4, 56.6, 41.9, 40.9, 40.7, 38.11, 38.09, 35.9, 34.1, 27.1 (3C), 24.1, 21.7, 21.3, 20.5, 19.4, 19.3, 17.8, 17.1; **IR** (film): ν = 2932, 2859, 1743, 1650, 1428, 1379, 1250, 1163, 1111, 1021, 821, 739, 704, 613, 570, 508 cm^{-1}; **MS** (ESI) *m*/*z* (%): 996 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{50}H_{64}Cl_3NO_{10}SiNa$ [*M*+Na^+]: 994.3257, found: 994.3274.

(3*S*,5*S*,8*S*,12*R*,16*S*,18*S*)-16-((*tert*-butyldiphenylsilyl)oxy)-12-hydroxy-18-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxooxacyclooctadec-6-yn-8-yl acetate (115a)

Zinc dust (1.55 g, 23.6 mmol, 100 equiv, Sigma-Aldrich®, < 10 µm) was added to a solution of **114a**

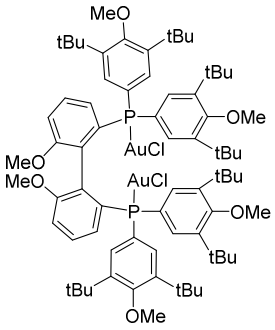


(230 mg, 0.236 mmol, 1 equiv) in neat acetic acid (12 mL). The suspension was sonicated for 15 min (if TLC showed unconsumed starting material, more zinc dust (100 equiv) was added and sonication was continued). The suspension was filtered through a plug of Celite which was rinsed with ethyl acetate (20 mL). The filtrate was diluted with toluene (10 mL) and all volatile materials were evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 2:1) to give the title compound (175 mg, 0.219 mmol, 93%).

$[\alpha]_D^{20}$ = −5.00 (c = 1.03, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.45-7.30 (m, 7H), 6.15 (dd, *J* = 1.5, 0.8 Hz, 1H), 6.06 (dd, *J* = 9.2, 1.8 Hz, 1H), 5.44 (ddd, *J* = 8.3, 4.8, 1.4 Hz, 1H), 5.15 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.99 (br s, 1H), 4.97 (br s, 1H), 3.91-3.78 (m, 1H), 3.70-3.58 (m, 1H), 3.19 (s, 3H), 2.60 (q, *J* = 6.9 Hz, 1H), 2.56-2.38 (m, 4H), 2.32 (ddd, *J* = 14.9, 9.4, 2.6 Hz, 1H), 2.05 (s, 3H), 2.04-1.94 (m, 2H), 1.89 (d, *J* = 1.2 Hz, 3H), 1.72-1.52 (m, 4H), 1.51-1.42 (m, 1H), 1.42-1.30 (m, 4H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.5, 169.8, 160.4, 150.9, 141.4, 140.9, 135.9 (4C), 134.2, 134.14, 134.13, 129.78, 129.77, 127.7 (4C), 116.8, 113.4, 90.5, 78.3, 74.8, 70.4, 68.8, 65.7, 63.7, 56.6, 45.0, 41.0, 40.6, 38.4, 38.0, 36.9, 35.9, 27.1 (3C), 24.0, 21.9, 21.3, 20.4, 19.4, 19.3, 17.8, 17.0; **IR** (film): ν = 3467, 2932, 2858, 1737, 1649, 1449, 1428, 1373, 1232, 1162, 1105, 1022, 969, 900, 856, 822, 757, 704, 612, 509, 489 cm^{-1}; **MS** (ESI) *m*/*z* (%): 820 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4223.

(*R*)- or (*S*)-DTBM-MeOH-Biphep-(AuCl)$_2$ (121)[164]

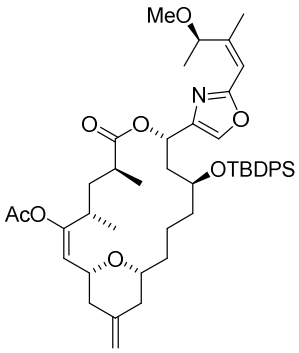
A solution of chloro(dimethylsulfide)gold(I) (56.6 mg, 192 µmol, 2.00 equiv) and the (*R*) or (*S*)-3,5-*t*Bu-4-MeO-MeO-Biphep-ligand (111 mg, 96.1 µmol, 1 equiv) in anh. dichloromethane (7 mL) was stirred for 24 h at 23 °C. The solvent was removed under a stream of argon and the colorless solid was dried in high vacuum to obtain **121** (quant.). The analytical data were in full agreement with those reported in the literature.[165]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (td, *J* = 8.1, 2.5 Hz, 2H), 7.39 (d, *J* = 13.7 Hz, 4H), 7.11 (br d, *J* = 14.0 Hz, 4H), 7.02-6.86 (m, 4H), 3.72 (s, 6H), 3.69 (s, 6H), 2.72 (s, 6H), 1.33 (s, 72H); **^{31}P NMR** (160 MHz, $CDCl_3$): δ = 21.87 (s).

(1*R*,4*S*,6*S*,9*S*,11*S*,15*R*,*E*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxabicyclo[13.3.1]nonadec-2-en-3-yl acetate (117a)

A suspension of silver hexafluoroantimonate (2.94 mg, 8.56 µmol, 0.34 equiv) and gold catalyst (*R*)-DTBM-MeOH-Biphep-(AuCl)$_2$ **121** (6.89 mg, 4.26 µmol, 0.17 equiv) in anh. dichloromethane (0.30 mL) was sonicated for 5 min. The suspension was filtered through a plug of Celite (rinsed with anh. dichloromethane 2 × 0.25 mL) into a solution of compound **115a** (20.0 mg, 25.1 µmol, 1 equiv) in anh. dichloromethane (0.5 mL). After stirring for 48 h at 23 °C, the solvent was removed by a stream of argon and the residue was purified by flash chromatography (hexane/ethyl acetate 10:1) to give **117a** (18.1 mg, 22.7 µmol, 91%) as a colorless oil and a single isomer.

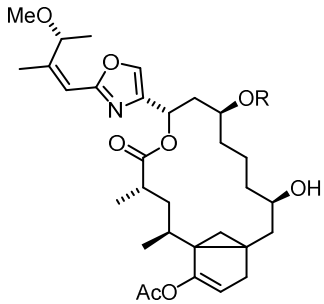


$[\alpha]_D^{20}$ = −28.9 (c = 0.98, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.70 (m, 2H), 7.64 (m, 2H), 7.40 (m, 1H), 7.37 (m, 1H), 7.34 (m, 2H), 7.32 (m, 2H), 7.15 (s, 1H), 6.08 (qd, *J* = 1.4, 1.0 Hz, 1H), 5.93 (dd, *J* = 12.4, 3.4 Hz, 1H), 5.11 (qd, *J* = 6.5, 0.7 Hz, 1H), 5.04 (d, *J* = 3.5 Hz, 1H), 4.69 (t, *J* = 1.8 Hz, 2H), 4.06 (ddd, *J* = 11.9, 3.5, 2.6 Hz, 1H), 3.74 (tdd, *J* = 10.2, 4.4, 1.8 Hz, 1H), 3.39 (tt, *J* = 11.3, 1.8 Hz, 1H), 3.14 (s, 3H), 2.57 (dqd, *J* = 8.9, 7.0, 6.0 Hz, 1H), 2.53 (dqd, *J* = 9.2, 6.9, 6.2 Hz, 1H), 2.33 (ddd, *J* = 13.9, 12.4, 4.4 Hz, 1H), 2.27 (ddd, *J* = 13.4, 2.5, 1.4 Hz, 1H), 2.09 (s, 3H), 2.08 (ddtd, *J* = 13.4, 11.9, 1.6, 0.9, 1H), 2.08 (m,1H), 1.94 (ddtd, *J* = 13.3, 11.3, 1.6, 1.0 Hz, 1H), 1.87 (ddd, *J* = 13.9, 10.1, 3.5 Hz, 1H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.83 (m, 1H), 1.72 (t, *J* = 13.1 Hz, 1H), 1.67 (m, 1H), 1.33 (m, 2H),

1.25 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.16 (dd, *J* = 9.1, 6.1 Hz, 2H), 1.03 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.0, 169.3, 160.1, 154.7, 151.0, 144.2, 141.0, 136.1 (2C), 135.9 (2C), 134.9, 133.8, 133.4, 129.7, 129.5, 127.7 (2C), 127.4 (2C), 119.9, 113.0, 109.1, 74.7, 74.6, 72.8, 71.7, 64.9, 56.5, 41.4, 40.95, 40.94, 40.0, 37.7, 34.5, 34.3, 32.8, 27.1 (3C), 22.0, 21.0, 20.0, 19.4, 19.0, 18.1, 17.6; **IR** (film): ν = 2934, 2858, 1759, 1733, 1653, 1456, 1428, 1367, 1258, 1194, 1163, 1106, 1056, 1024, 899, 821, 743, 704, 610, 511, 491, 451 cm^{-1}; **MS** (ESI) *m/z* (%): 820 (*M*+Na^+, 100); **HRMS** (ESI): *m/z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4217.

(1*S*,3*S*,6*S*,8*S*,12*R*)-8-((*tert*-Butyldiphenylsilyl)oxy)-12-hydroxy-6-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-1,3-dimethyl-4-oxo-1,2,3,4,6,7,8,9,10,11,12,13-dodecahydro-14H-13a,16a-methanocyclopenta[f][1]oxacyclopentadecin-16-yl acetate (124)

The reaction was performed analogously, using (*S*)-DTBM-MeOH-Biphep-$(AuCl)_2$ **121** (0.10 equiv) as precatalyst.

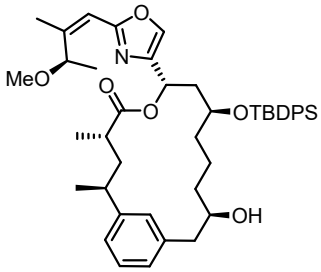


Flash chromatography (hexane/ethyl acetate 10:1) gave **117a** (50-70%) as an inseparable mixture of the *E* and *Z* isomers (approx. 4:1) and product **124** (20-30%), which analyzed as follows:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59 (m, 2H), 7.57 (m, 2H), 7.38 (m, 1H), 7.36 (m, 1H), 7.31 (m, 2H), 7.28 (m, 2H), 7.24 (s, 1H), 6.09 (qd, *J* = 1.4, 1.0 Hz, 1H), 6.07 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.13 (t, *J* = 2.5 Hz, 1H), 5.06 (qd, *J* = 6.4, 0.8 Hz, 1H), 3.86 (dddd, *J* = 8.0, 6.9, 5.7, 2.3 Hz, 1H), 3.60 (m, 1H), 3.12 (s, 3H), 2.62 (dd, *J* = 17.5, 2.7 Hz, 1H), 2.41 (dd, *J* = 17.5, 2.2 Hz, 1H), 2.39 (dqi, *J* = 7.0, 6.7 Hz,1H), 2.21 (ddd, *J* = 15.1, 9.2, 2.4 Hz, 1H), 2.10 (s, 3H), 1.91 (ddd, *J* = 15.1, 8.0, 2.5 Hz, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.78 (m, 1H), 1.72 (m, 1H) 1.66 (dd, *J* = 14.4, 3.1 Hz, 1H), 1.54 (m, 1H), 1.52 (ddd, *J* = 14.4, 10.2, 1.1, 1H), 1.45 (m, 2H), 1.42 (m, 1H), 1.39 (m, 1H), 1.35 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.21 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.04 (m, 1H), 1.02 (s, 9H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.60 (dd, *J* = 4.0, 0.8 Hz, 1H), 0.41 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 176.0, 168.3, 160.1, 153.7, 150.6, 140.4, 135.8 (2C), 135.7 (2C), 134.3, 134.2 (2C), 129.6 (2C), 127.49 (2C), 127.48 (2C), 113.2, 110.5, 74.7, 73.3, 70.7, 65.2, 56.4, 40.9, 40.5, 39.8, 38.7, 37.6, 36.8, 36.6, 36.5, 31.0, 29.6, 27.0 (3C), 24.1, 21.3, 20.7, 20.4, 19.3, 19.2, 18.1, 17.6.

(2*S*,4*S*,7*S*,9*S*,13*R*)-9-((*tert*-Butyldiphenylsilyl)oxy)-13-hydroxy-7-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-2,4-dimethyl-6-oxa-1(1,3)-benzenacyclotetradecaphan-5-one (125)

Prepared analogously starting with **115b**[c], using (*R*)-DTBM-MeOH-Biphep-$(AuCl)_2$ **121** as the precatalyst. The crude product was purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, ACN/H_2O, 95:5, 35 °C, 20 mL/min) to give **117a** (10-20%) as an inseparable mixture of the *E* and *Z* isomer (approximately 4:1) and compound **125** (approx. 50%), which analyzed as follows:

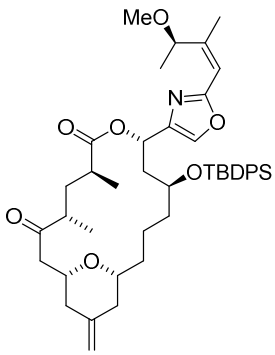


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61 (m, 2H), 7.60 (m, 2H), 7.42 (s, 1H), 7.39 (m, 1H), 7.38 (m, 1H), 7.32 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 1.7, 1H), 7.08 (ddd, *J* = 7.5, 1.3, 1.3 Hz, 1H), 7.06 (ddd, , *J* = 7.4, 2.9 Hz, 1H), 6.17 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.14 (qd, *J* = 1.4, 0.9 Hz, 1H), 5.25 (qd, *J* = 6.4, 0.5 Hz, 1H), 3.94 (dddd, *J* = 10.3, 6.5, 4.8, 1.2 Hz, 1H), 3.83 (br s, 1H), 3.19 (s, 3H), 2.89 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.81 (dd, *J* = 13.9, 2.8 Hz, 1H), 2.61 (dqd, *J* = 12.2, 7.0, 3.1 Hz, 1H), 2.56 (ddd, *J* = 15.2, 10.8, 1.2 Hz, 1H), 2.10 (dqd, *J* = 11.4, 6.9, 2.5 Hz, 1H), 1.85 (d, *J* = 1.5 Hz, 3H), 1.80 (ddd, *J* = 15.2, 6.5, 2.5 Hz, 1H), 1.74 (ddd, *J* = 13.8, 11.4, 3.1 Hz, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.44 (m, 1H), 1.42 (m, 1H), 1.34 (br s, 1H), 1.24 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 1.01 (m, 2H), 1.00 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 176.7, 160.2, 150.7, 146.4, 140.8, 135.78 (2C), 135.77 (2C), 135.4, 134.4, 134.2, 134.1, 132.3, 129.7, 129.6, 128.7, 128.0, 127.6 (2C), 127.5 (2C), 122.9, 113.2, 74.7, 71.1, 70.7, 65.3, 56.5, 45.6, 39.9, 37.4, 37.1, 36.8, 36.0, 35.6, 27.0 (3C), 22.5, 22.2, 19.3, 19.2, 18.3, 17.6.

[c] The preparation of **115b** is described in 6.2.6.

(1*R*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecane-3,7-dione (123)

Potassium carbonate (32.7 mg, 237 µmol, 3.00 equiv) was added to a solution of compound **117a**

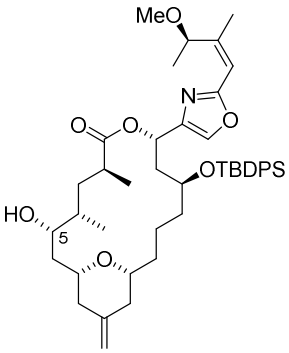


(63.0 mg, 78.9 µmol, 1 equiv) in methanol (10 mL). After stirring for 3 h at 23 °C, the reaction mixture was filtered through a plug of Celite which was rinsed with methyl *tert*-butyl ether (10 mL). The filtrate was concentrated and the residue was purified by flash chromatography (hexane/ethyl acetate 10:1) to obtain **123** (56.8 mg, 75.1 µmol, 95%) as a colorless oil.

$[\alpha]_D^{20}$ = −28.6 (c = 1.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.64 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.46–7.30 (m, 6H), 7.21 (d, *J* = 0.8 Hz, 1H), 6.12 (qd, *J* = 1.4, 0.8 Hz, 1H), 5.95 (dd, *J* = 11.4, 2.8 Hz, 1H), 5.14 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.75–4.68 (m, 2H), 3.76–3.62 (m, 1H), 3.54 (dd, *J* = 10.4 Hz, 1H), 3.39 (dd, *J* = 10.4 Hz, 1H), 3.16 (s, 3H), 2.81 (dd, *J* = 15.4, 9.9 Hz, 1H), 2.70–2.61 (m, 1H), 2.41–2.25 (m, 2H), 2.25–2.06 (m, 3H), 2.01–1.90 (m, 3H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.80–1.71 (m, 3H), 1.41–1.30 (m, 5H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 212.9, 175.0, 160.3, 151.1, 144.0, 141.1, 136.2 (2C), 136.0 (2C), 134.7, 133.8, 133.7, 129.9, 129.7, 127.8 (2C), 127.6 (2C), 113.2, 109.4, 75.2, 74.8, 74.3, 71.4, 65.0, 56.6, 48.5, 42.9, 41.4, 40.8, 40.5, 39.0, 36.0, 35.0, 33.9, 27.2 (3C), 20.8, 19.6, 19.3, 18.8, 17.8, 17.7; **IR** (film): ν = 2932, 2857, 1729, 1703, 1652, 1456, 1428, 1380, 1259, 1163, 1103, 1058, 892, 821, 804, 755, 702, 611, 509, 488 cm^{-1}; **MS** (ESI) *m*/*z* (%): 778 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{45}H_{61}NO_7SiNa$ [*M*+Na^+]: 778.4110, found: 778.4111.

(1*R*,3*S*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxy-9-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecan-7-one (126a)

Sodium borohydride (12.5 mg, 331 µmol, 5.00 equiv) was added at −40 °C to a solution of ketone



123 (50.0 mg, 66.1 µmol, 1 equiv) in anh. methanol (5 mL). After stirring for 3 h at this temperature, excess reagent was quenched by the addition of aq. phosphate buffer solution (pH 7, 10 mL) and the solution was allowed to warm to 23 °C. The aq. layer was extracted with methyl *tert*-butyl ether (3 x 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 8:1 grading to 2:1) to yield **126a** (30.8 mmol, 40.6 µmol, 61%) and **126b** (16.4 mg, 21.6 µmol, 33%) as colorless oils.

*Desired diastereomer **126a**:*

$[\alpha]_D^{20}$ = −31.4 (c = 1.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.45–7.32 (m, 6H), 7.28 (d, *J* = 0.6 Hz, 1H), 6.14–6.11 (m, 1H), 5.72 (dd, *J* = 11.9, 3.3 Hz, 1H), 5.12 (qd, *J* = 6.5, 0.9 Hz, 1H), 4.70–4.64 (m, 2H), 3.85-3.66 (m, 2H), 3.35–3.19 (m, 2H), 3.17 (s, 3H), 2.52 (dqd, *J* = 10.3, 7.0, 3.6 Hz, 1H), 2.41 (ddd, *J* = 14.0, 12.1, 3.9 Hz, 1H), 2.13 (br s, 1H), 2.09 (br s, 1H), 2.01–1.88 (m, 4H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.77–1.50 (m, 7H),1.48–1.30 (m, 4H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.8, 160.2, 151.1, 145.0, 140.8, 136.2 (2C), 136.0 (2C), 134.7, 134.3, 134.0, 129.8, 129.6, 127.8 (2C), 127.6 (2C), 113.3, 108.5, 77.2, 76.0, 75.2, 74.9, 71.2, 68.7, 65.9, 56.6, 41.9, 41.7, 41.4, 41.0, 37.9, 36.3, 35.6, 33.8, 33.6, 27.3 (3C), 21.4, 19.6, 19.2, 17.7, 16.5, 13.5; **IR** (film): ν = 3468, 2933, 2857, 1726, 1652, 1549, 1454, 1428, 1380, 1248, 1204, 1150, 1103, 1044, 1005, 976, 955, 891, 822, 756, 703, 611, 510, 488 cm^{-1}; **MS** (ESI) *m/z* (%): 780 (*M*+Na^+, 100); **HRMS** (ESI): *m/z*: calcd. for $C_{45}H_{63}NO_7SiNa$ [*M*+Na^+]: 780.4266, found: 780.4279.

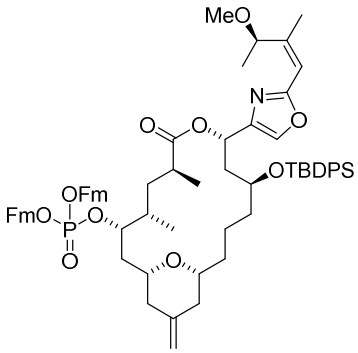
*Undesired C5-epimer **126b**:*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.66 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.46–7.33 (m, 6H), 7.25 (d, *J* = 0.6 Hz, 1H), 6.14–6.11 (m, 1H), 5.84 (dd, *J* = 11.3, 3.2 Hz, 1H), 5.10 (qd, *J* = 6.4, 0.8 Hz, 1H), 4.69 (br s, 2H), 3.8–3.75 (m, 1H), 3.57–3.24 (m, 4H), 3.17 (s, 3H), 2.92–2.81 (m, 1H), 2.32 (ddd, *J* = 14.5, 11.4, 3.4 Hz, 1H), 2.13 (br d, *J* = 13.0 Hz, 1H), 2.10 (br d, *J* = 11.9 Hz, 1H), 2.04–1.88 (m, 3H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.79–1.29 (m, 11H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H), 0.92

(d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.9, 160.3, 151.1, 144.9, 141.0, 136.1 (2C), 136.0 (2C), 134.7, 134.0 (2C), 129.8, 129.6, 127.8 (2C), 127.6 (2C), 113.3, 108.6, 76.0, 75.5, 75.2, 74.9, 71.3, 65.8, 56.6, 41.9, 41.5, 40.9, 40.4, 40.2, 39.2, 35.7, 35.0, 33.9, 27.2 (2C), 21.4, 19.6, 19.2, 18.0, 17.8, 17.2.

Bis((9H-fluoren-9-yl)methyl) ((1*R*,3*S*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-((*tert*-butyldiphenylsilyl)oxy) -9-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxa bicyclo[13.3.1]nonadecan-3-yl) phosphate (128a)[51]

A solution of tetrazole (0.45 M in acetonitrile, 264 µL, 119 µmol, 3.00 equiv) was added at 0 °C to a solution of alcohol **126a** (30.0 mg, 39.6 µmol, 1 equiv) and *i*Pr_2NP(OFm)$_2$[166] (62.9 mg, 119 µmol, 3.00 equiv) in anh. acetonitrile (0.75 mL) and anh. dichloromethane (0.75 mL). The mixture was stirred for 3 h at 23 °C, before it was cooled to 0 °C and aq. hydrogen peroxide (35% *w/w*, 115 µL, 1.19 mmol, 30.0 equiv) was added. After stirring for additional 30 min, the reaction was quenched by the addition of aq. sat. sodium hydrogen carbonate solution (5 mL). The layers were separated and the aq. layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 6:1 grading to 2:1) to afford **128a** (47.1 mg, 39.4 µmol, quant.) as a colorless solid.

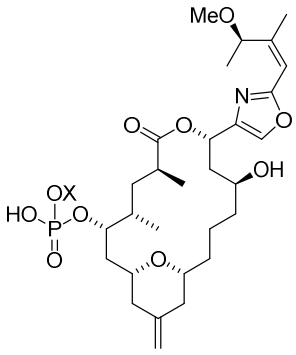


$[\alpha]_D^{20}$ = −11.1 (c = 2.35, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.69 (m, 3H), 7.63 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H),7.39–7.33 (m, 10H), 7.27 (td, *J* = 7.5, 1.0 Hz, 1H), 7.26 (td, *J* = 7.4, 1.1 Hz, 1H), 7.25 (td, *J* = 7.4, 1.1 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 7.15 (s, 1H), 6.08 (s, 1H), 5.79 (dd, *J* = 12.5, 2.9 Hz, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 4.68 (m, 2H), 4.51 (dddd, *J* = 11.6, 6.8, 4.8, 1.0 Hz, 1H), 4.23-4.14 (m, 4H), 4.10 (m, 2H), 3.59 (m, 1H), 3.23 (tt, *J* = 11.1, 2.0 Hz, 1H), 3.14 (s, 3H), 2.98 (ddd, *J* = 11.4, 9.1, 2.3 Hz, 1H), 2.55 (dqd, *J* = 12.7, 6.7, 4.0 Hz, 1H), 2.26 (ddd, *J* = 13.7, 12.5, 4.0 Hz, 1H), 2.07 (d, *J* = 13.3 Hz, 1H), 1.97 (d, *J* = 13.1 Hz, 1H), 1.84 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.84 (m, 1H), 1.83 (m, 1H), 1.82 (m, 1H), 1.80 (m, 1H), 1.64 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.63 (ddd, *J* = 12.4, 9.6, 1.6 Hz, 1H), 1.58 (m, 1H), 1.40 (m, 1H), 1.30 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.21 (m, 1H), 1.20 (m, 1H), 1.02 (s, 9H), 0.83 (td, *J* = 13.3, 3.0 Hz, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.60 (d, *J* = 6.5 Hz,

3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 174.0, 160.1, 151.0, 144.5, 143.15, 143.13, 143.12, 143.05, 141.34 (3C), 141.31, 141.2, 136.1 (2C), 135.9 (2C), 134.8, 133.6, 133.3, 129.7, 129.5, 127.90, 127.87 (2C), 127.84, 127.7 (2C), 127.4 (2C), 127.14, 127.12, 127.11, 127.07, 125.2, 125.03, 125.00 (2C), 120.09, 120.03, 120.02, 120.00, 113.0, 108.6, 78.5 (d, $J_{C\text{-}P}$ = 7.0 Hz), 74.72, 74.69, 74.3, 71.3, 69.2 (d, $J_{C\text{-}P}$ = 5.9 Hz), 68.9 (d, $J_{C\text{-}P}$ = 6.1 Hz), 64.9, 56.5, 48.0 (d, $J_{C\text{-}P}$ = 5.4 Hz), 47.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 41.7, 41.5, 41.2, 38.6, 37.9, 37.5, 35.1, 33.3, 33.2 (d, $J_{C\text{-}P}$ = 6.6 Hz), 27.1 (3C), 21.1, 19.5, 19.0, 17.6, 17.4, 13.7; **^{31}P NMR** (160 MHz, $CDCl_3$): δ = 0.00 (s); **IR** (film): ν = 3069, 2934, 2892, 2857, 1727, 1450, 1428, 1381, 1261, 1205, 1150, 1105, 1045, 1003, 988, 914, 823, 757, 740, 704, 612, 511, 494 cm^{-1}; **MS** (ESI) *m/z* (%): 1217 (*M*+Na^+, 100); **HRMS** (ESI): *m/z*: calcd. for $C_{73}H_{84}NO_{10}PSiNa$ [*M*+Na^+]: 1216.5494, found: 1216.5511.

Enigmazole A (16)

A solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 188 µL, 188 µmol, 50.0 equiv) was added to a solution of the protected enigmazole **128a** (4.50 mg, 3.77 µmol, 1 equiv) in anh. tetrahydrofuran (0.5 mL) and acetic acid (16.2 µL, 283 µmol, 75.0 equiv) and the mixture was stirred at 40 °C for 9 d. After reaching 23 °C, the solution was diluted with water (1 mL) and loaded onto a C18-cartridge (Strata® C18-U, 55 µm, 70 Å, 500 mg/6 mL). The salts were eluted with water, followed by elution of the organic fraction with methanol. The combined organic fractions were concentrated and the residue was purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, methanol/aq. TEAA pH 8.0, 70:30 grading to 100% methanol over 10 min, 35 °C, 20 mL/min) to obtain the tetrabutylammonium salt of enigmazole A (2.6 mg, 3.09 µmol, 82%) as a colorless powder after lyophilisation.



Purification by preparative LC (amount < 0.5 mg, Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, acetonitrile/aq. TEAA pH 8.0, 30:70 grading to 50:50 over 6 min, 35 °C, 20 mL/min) afforded the triethylammonium salt of enigmazole A (quant.) after lyophilisation.

The protonated form of enigmazole A was obtained by ion exchange chromatography (Adsorbex® SCX 400 mg) using methanol as eluent.

Triethylammonium salt:

$[\alpha]_D^{20}$ = −9.70 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, CD_3OD): δ = 7.70 (d, *J* = 0.7 Hz, 1H), 6.22 (dd, *J* = 1.5, 0.9 Hz, 1H), 5.96 (ddd, *J* = 12.7, 2.8, 0.5 Hz, 1H), 5.25 (qd, *J* = 6.5, 0.9 Hz, 1H), 4.72–4.69 (m, 2H), 4.46-4.41 (m, 1H), 3.62 (tdd, *J* = 10.8, 4.1, 1.8 Hz, 1H), 3.34–3.28 (m, 1H), 3.21 (s, 3H), 3.19 (q, *J* = 7.3 Hz, 6H), 3.13 (ddd, *J* = 11.0, 8.3, 2.0 Hz, 1H), 3.04-2.94 (m, 1H), 2.51 (ddd, *J* = 13.6, 12.7, 4.1 Hz, 1H), 2.22 (br d, *J* = 13.1 Hz, 1H), 2.15 (br d, *J* = 13.1 Hz, 1H), 2.10 (dd, *J* = 14.3, 4.4 Hz, 1H), 2.02–1.95 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.89–1.87 (m, 1H), 1.86–1.85 (m, 1H), 1.85–1.83 (m, 1H), 1.82–1.75 (m, 2H), 1.75–1.70 (m, 1H), 1.69–1.62 (m, 2H), 1.55 (tdt, *J* = 12.7, 13.0, 2.9 Hz, 1H), 1.45–1.38 (m, 2H), 1.31 (t, *J* = 7.3 Hz, 9H), 1.27 (d, J = 6.5 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.05–1.01 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H) (3 protic H missing); **^{13}C NMR** (150 MHz, CD_3OD): δ = 176.5, 161.9, 152.7, 146.6, 142.4, 135.9, 113.9, 108.6, 77.5, 76.2, 75.7, 75.4 (d, *J* = 6.3 Hz), 69.8, 65.7, 56.8, 47.6 (3C), 43.1, 42.6, 42.5, 40.2, 39.7, 39.4, 36.2, 34.7 (d, *J* = 6.4 Hz), 33.6, 21.8, 19.4, 18.3, 17.7, 15.0, 9.2 (3C); **^{31}P NMR** (160 MHz, $CDCl_3$): δ = 0.00 (s); **IR** (film): ν = 3402 (br), 2977, 2935, 2854, 1726, 1651, 1455, 1252, 1203, 1150, 1109, 1076, 1017, 972, 936, 896, 657, 594, 515, 497 cm^{-1}; **MS** (ESI) *m*/*z* (%): 598 (*M*−H$^-$, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{29}H_{45}NO_{10}P$ [*M*−H$^-$]: 598.2787, found: 598.2793.

Protonated phosphate ester:

^{1}H NMR (600 MHz, CD_3OD): δ = 7.70 (d, *J* = 0.6 Hz, 1H), 6.22 (qd, *J* = 1.5, 0.9 Hz, 1H), 5.96 (ddd, *J* = 12.8, 2.9, 0.6 Hz, 1H), 5.25 (qd, *J* = 6.5, 0.8 Hz, 1H), 4.73–4.70 (m, 2H), 4.51–4.42 (m, 1H), 3.61 (tdd, *J* = 10.7, 3.9, 1.4 Hz, 1H), 3.33–3.28 (m, 1H), 3.21 (s, 3H), 3.13 (ddd, *J* = 11.4, 8.3, 2.2 Hz, 1H), 3.00–2.92 (m, 1H), 2.51 (ddd, *J* = 13.6, 12.8, 4.0 Hz, 1H), 2.22 (br d, *J* = 13.0 Hz, 1H), 2.15 (br d, *J* = 12.5 Hz, 1H), 2.08 (br d, *J* = 13.4 Hz, 1H), 2.02–1.96 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.94–1.82 (m, 3H), 1.78 (ddd, *J* = 13.8, 10.9, 3.0 Hz, 1H), 1.78–1.70 (m, 2H), 1.69–1.62 (m, 2H), 1.58–1.49 (m, 1H), 1.46–1.35 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.07–1.00 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H) (2 protic H missing); **^{13}C NMR** (150 MHz, CD_3OD): δ = 176.5, 161.9, 152.7, 146.5, 142.3, 135.9, 113.9, 108.7, 77.4, 76.2, 75.9 (br), 75.8, 69.8, 65.8, 56.8, 43.1, 42.6, 42.5, 40.1, 39.7, 39.3, 36.2, 34.71 (d, *J* = 4.5 Hz), 33.6, 21.8, 19.4, 18.3, 17.7, 14.9; **^{31}P NMR** (160 MHz, $CDCl_3$): δ = 0.00 (s).

6.2.5. NMR Data of Enigmazole A

Table 6.1: *Comparison of ^{1}H NMR (CD_3OD) data of enigmazole A.*

Position	Natural product[48] protonated	Molinski Group[51] Na-salt	Fürstner Group Et_3NH-salt	Fürstner Group protonated
19	7.68, s	7.69, s	7.68, d, 0.5	7.68, d, 0.4
21	6.21, s	6.22, br s	6.21, qd, 1.4, 1.0	6.20, qd, 1.4, 1.0
17	5.95, dd, 12.8, 2.5	5.96, dd, 12.5, 2.5	5.95, ddd, 12.8, 2.8, 0.5	5.95, ddd, 12.8, 2.9, 0.4
23	5.24, q, 6.5	5.25, q, 6.3	5.24, qd, 6.5, 0.9	5.23, qd, 6.5, 0.9
28a	4.70, d, 1.5	4.71, br s	4.70, q, 2.0	4.70, q, 1.9
28b	4.69, d, 1.5	4.70, br s	4.69, q, 2.0	4.69, q, 1.9
5	4.42, m	4.43, m	4.42, dddd, 11.2, 8.8, 4.4, 1.0	4.47, m
15	3.62, dt, 11.1, 4.3	3.63, m	3.60, tdd, 10.8, 4.1, 1.8	3.60, tdd, 10.8, 4.1, 1.8
11	3.29	3.30	3.30, tt, 11.0, 2.4	3.29, tt, 11.1, 2.4
23-OMe	3.20, s	3.21, s	3.20, s	3.19, s
Et_3NH	-	-	3.17, q, 7.3	-
7	3.12, dd, 10.3, 9.8	3.13, m	3.12, ddd, 11.4, 8.6, 2.3	3.12, ddd, 11.4, 8.6, 2.0
2	2.98	2.99, m	2.98, dqd, 12.5, 6.7, 3.8	2.95, m
16a	2.50, dt, 13.2, 3.4	2.51, dt, 13.3, 3.8	2.50, ddd, 13.8, 12.8, 4.1	2.50, ddd, 13.8, 12.8, 4.1
8a	2.21, d, 12.8	2.23, d, 13.0	2.21, ddd, 13.0, 2.3, 1.2	2.20, br d, 13.2
10a	2.13, d, 12.8	2.14, d, 14.0	2.13, ddd, 13.1, 2.4, 1.2	2.13, br d, 13.2
6a	2.10, m	2.11, m	2.09, dd, 14.4, 4.4	2.07, br d, 14.4
8b	1.97, dd, 12.8, 12.3	1.98, t, 12.3	1.97, ddtd, 13.0, 11.4, 1.7, 1.0	1.97, m
25	1.89, s	1.89, d, 1.5	1.88, d, 1.6	1.88, d, 1.5
3a	1.88, m	1.89, m	1.88, m	1.87, m
6b	1.87, m	1.88, m	1.87, m	1.90, m
10b	1.84	1.86	1.85, m	1.84, m
14a	1.76	1.79	1.78, m	1.78, tt, 12.9, 1.9
16b	1.77	1.78	1.77, ddd, 13.8, 10.8, 2.9	1.77, ddd, 13.8, 10.8, 2.9
13a	1.72	1.73	1.72, m	1.72, tq, 13.0, 3.8
12a	1.64	1.66	1.65, m	1.64, dddd, 14.0, 11.2, 3.8, 2.8
4	1.62	1.63	1.64, m	1.64, m
13b	1.54, q, 12.4	1.55, q, 12.5	1.53, tdt, 13.0, 12.6, 2.9	1.52, tdt, 13.0, 12.7, 2.8
3b	1.38, t, 10.8	1.39, m	1.40, m	1.41, td, 13.2, 2.5
12b	1.37, t, 11.3	1.38, m	1.38, m	1.37, dddd, 14.0, 13.2, 3.3, 2.4
Et_3NH	-	-	1.30, t, 7.3	-
24	1.26, d, 6.4	1.27, d, 6.5	1.26, d, 6.5	1.26, d, 6.5
26	1.10, d, 6.4	1.11, d, 6.5	1.10, d, 6.7	1.10, d, 6.6
14b	1.02, td, 12.0, 3.4	1.04, dt, 12.0, 3.2	1.02, m	1.02, tdd, 12.8, 11.2, 4.1
27	0.97, d, 6.4	0.98, d, 6.5	0.97, d, 6.6	0.97, d, 6.5

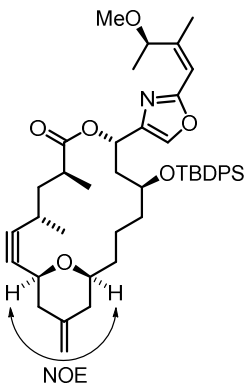
Table 6.2: *Comparison of ^{13}C NMR (CD_3OD) data of enigmazole A.*

Position	Natural product[48] protonated	Molinski Group[51] Na-salt	Fürstner Group Et_3NH-salt	Fürstner Group protonated
1	176.4	176.5	176.5	176.5
20	161.7	161.9	161.9	161.9
22	152.7	152.7	152.7	152.7
9	146.3	146.6	146.6	146.5
18	142.3	142.4	142.4	142.3
19	136.0	135.9	135.9	135.9
21	113.9	114.0	114.0	114.0
28	108.8	108.6	108.7	108.7
7	77.2	77.6	77.5	77.4
23	77.0	76.2	76.2	76.2
11	76.2	75.7	75.8	75.9
5	75.8	75.2, d, 6.1	75.4,d ,6.3	75.8, br
15	69.8	69.8	69.8	69.8
17	65.9	65.6	65.7	65.8
23-OMe	56.8	56.8	56.8	56.8
Et_3NH	-	-	47.6	-
8	43.0	43.0	43.1	43.1
16	42.6	42.7	42.7	42.6
10	42.4	42.5	42.5	42.5
6	40.1	40.1	40.2	40.1
2	39.6	39.7	39.7	39.7
3	39.3	39.3	39.4	39.3
4	36.2	34.7, d, 6.1	34.7, d, 6.4	34.7 d, 4.6
12	36.2	36.2	36.2	36.2
14	33.6	33.6	33.6	33.6
13	21.8	21.8	21.8	21.8
24	19.4	19.4	19.4	19.4
26	18.2	18.3	18.3	18.3
25	17.6	17.7	17.7	17.7
27	14.7	15.0	15.0	14.9
Et_3NH	-	-	9.2	-

6.2.6. Addenda to the Synthesis

Syn-tetrahydropyran 122a

Triethylamine (2.72 µL, 19.5 µmol, 3.00 equiv) and methanesulfonyl chloride (1.51 µL, 19.5 µmol, 3.00 equiv) were successively added to a solution of alcohol **115a** (5.20 mg, 6.50 µmol, 1 equiv) in anh dichloromethane (0.5 mL). After stirring for 30 min, the mixture was diluted with methanol (0.1 mL) and all volatile materials were removed in high vacuum.

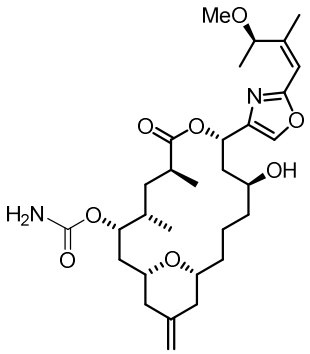


Potassium carbonate (4.50 mg, 32.6 mmol, 5.00 equiv) was added to a solution of the residue in dichloromethane/methanol (1:1, 1 mL). After stirring for 36 h, the mixture was neutralized by the addition of aq. hydrochloric acid (1 N, 1 mL) and the aq. layer was extracted with dichloromethane (4 × 3 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was purified by preperative LC (Kromasil 100-5C18 5 µm, 150 mm × 21.2 mm, 100% acetonitrile, 35 °C, 20 mL/min) to obtain the title compound (2.20 mg, 3.00 µmol, 46%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 4H), 7.48 (d, *J* = 1.1 Hz, 1H), 7.38–7.34 (m, 2H), 7.32–7.27 (m, 4H), 6.12 (dd, *J* = 1.4, 0.8 Hz, 1H), 5.84 (ddd, *J* = 5.5, 2.8, 1.1 Hz, 1H), 5.13 (qd, *J* = 6.4, 0.7 Hz, 1H), 4.73–4.69 (m, 2H), 3.97 (dt, *J* = 11.4, 2.5 Hz, 1H), 3.57 (tt, *J* = 9.6, 3.2 Hz, 1H), 3.21 (s, 3H), 3.15 (tt, *J* = 10.4, 2.5 Hz, 1H), 3.10–3.02 (m, 1H), 2.47–2.34 (m, 4H), 2.25 (t, *J* = 12.5 Hz, 1H), 2.10–1.99 (m, 2H), 1.96–1.92 (m, 1H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.81–1.69 (m, 2H), 1.50–1.43 (m, 1H), 1.40–1.30 (m, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 9H), 0.91–0.82 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 176.3, 160.2, 150.3, 143.7, 140.7, 136.07 (2C), 136.06 (2C), 134.8, 134.3, 133.8, 129.5, 129.4, 127.4 (4C), 113.6, 109.5, 88.1, 82.3, 81.3, 74.7, 71.9, 68.8, 67.7, 56.6, 41.2, 41.0, 40.9, 40.1, 38.1, 37.6, 34.7, 27.3 (3C), 25.0, 24.1, 20.9, 19.6, 19.3, 18.8, 17.8.

(1*R*,3*S*,4*S*,6*S*,9*S*,11*S*,15*R*)-11-Hydroxy-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxabicyclo[13.3.1]nonadecan-3-yl carbamate (130)

Trichloroacetyl isocyanate (6.20 mg, 33.0 µmol, 5.00 equiv) was added at 0 °C to a solution of



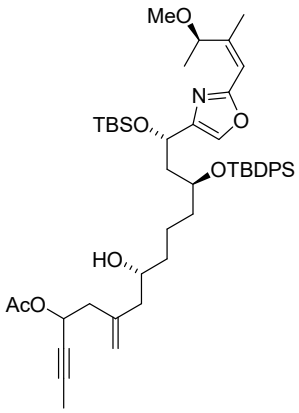
alcohol **126a** (5.00 mg, 6.60 µmol, 1 equiv) in anh. dichloromethane (1 mL). After stirring for 1.5 h at 0 °C, the mixture was directly loaded onto a plug of neutral aluminum oxide to cleave the protecting group. After 1.5 h, the crude product was carefully rinsed with ethyl acetate (10 mL) and concentrated.

The residue was dissolved in anh. THF (0.5 mL) and acetic acid (28.4 µL, 496 µmol, 75.0 equiv) before a solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 331 µL, 331 µmol, 50.0 equiv) was added. After stirring at 40 °C for 13 d, the reaction was quenched by the addition of aq. phosphate buffer solution (pH 7, 5 mL) and the aq. layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, acetonitrile/water 60:40, 35 °C, 20 mL/min) to obtain **130** (2.6 mg, 4.62 µmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 0.6 Hz, 1H), 6.17–6.15 (m, 1H), 5.98 (dd, *J* = 11.7, 3.3 Hz, 1H), 5.20–5.15 (m, 1H), 5.07 (ddd, *J* = 11.0, 4.5, 1.4 Hz, 1H), 4.70 (dt, *J* = 3.4, 1.8 Hz, 2H), 4.59 (br s, 1H), 3.72–3.63 (m, 1H), 3.39–3.30 (m, 1H), 3.26–3.22 (m, 1H), 3.22 (s, 3H), 2.85–2.72 (m, 1H), 2.51 (ddd, *J* = 13.9, 11.9, 4.2 Hz, 1H), 2.14 (dd, *J* = 29.4, 13.1 Hz, 2H), 1.99 (t, *J* = 12.6 Hz, 1H), 1.92–1.83 (m, 6H), 1.78 (t, *J* = 12.9 Hz, 1H), 1.75–1.63 (m, 6H), 1.56–1.35 (m, 4H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H) (2 protic H missing); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 174.4, 160.4, 151.2, 144.3, 140.8, 133.8, 113.0, 108.7, 75.5, 74.8, 74.4, 73.39, 73.37, 69.1, 64.7, 56.5, 41.8, 41.2, 41.1, 38.4, 38.2, 37.7, 34.9, 32.92, 32.87, 20.6, 19.1, 17.9, 17.6, 14.7; **HRMS** (ESI): *m*/*z*: calcd. for $C_{30}H_{47}N_2O_8$ [*M*+H$^+$]: 563.3327, found: 563.3331.

(8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-8-hydroxy-14-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl) oxazol-4-yl)-6-methylenetetradec-2-yn-4-yl acetate (111)

Analoguos to preparation of **111a**, the title compound was made by using boron tribromide (1 M in dichloromethane, 904 µL, 0.904 mmol, 1.50 equiv), (*S,S*)-1,2-diphenyl-1,2-ethylenediamine bis(toluenesulfon-amide)[103b] (470 mg, 0.904 mmol, 1.50 equiv), racemic allyl stannane **50** (480 mg, 1.05 mmol, 1.75 equiv), and aldehyde **63** (400 mg, 0.602 mmol, 1 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 15:1 grading to 6:1) to give **111** (517 mg, 0.592 mmol, 98%, *d.r.* >9:1[d]) as a colorless oil.

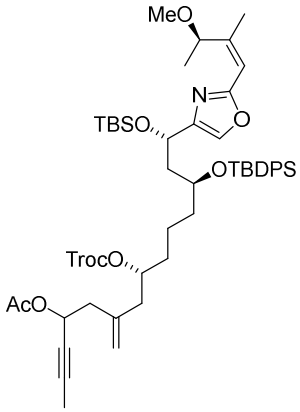


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.58 (m, 4H), 7.44–7.29 (m, 6H), 7.10 (s, 1H), 6.17 (s, 1H), 5.50–5.42 (m, 1H), 5.21 (q, *J* = 6.4 Hz, 1H), 4.98 (s, 1H), 4.93 (d, *J* = 3.3 Hz, 1H), 4.83 (t, *J* = 6.7 Hz, 1H), 3.88–3.79 (m, 1H), 3.61–3.48 (m, 1H), 3.21–3.12 (m, 3H), 2.56–2.35 (m, 2H), 2.15 (dd, J = 14.3, 3.5 Hz, 1H), 2.07 (s, 1.5H), 2.06 (s, 1.5H), 2.05–1.95 (m, 3H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.85–1.82 (m, 3H), 1.76–1.68 (m, 1H), 1.68–1.63 (m, 1H), 1.51–1.31 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H), 1.26–1.13 (m, 3H), 1.03 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), −0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.19, 170.16, 159.9, 150.2, 144.8, 141.4, 136.02, 135.99, 134.7, 134.3, 133.7, 129.59, 129.57, 127.54, 127.52, 116.4, 116.3, 113.7, 82.5, 82.3, 76.61, 76.58, 74.8, 70.5, 69.0, 68.8, 65.7, 63.2, 62.8, 56.5, 44.8, 44.4, 44.0, 41.6, 41.4, 37.3, 37.2, 36.8, 27.2, 25.9, 21.24, 21.20, 20.9, 19.5, 19.3, 18.3, 17.71, 17.65, 3.8, −4.4, −4.7 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2930, 2857, 1738, 1428, 1371, 1233, 1106, 836, 754, 702, 610, 505, 488 cm^{-1}; **HRMS** (ESI): *m/z*: calcd. for $C_{48}H_{71}NO_7Si_2Na$ [*M*+Na^+]: 852.4661, found: 852.4669.

[d] The diastereomeric ratio describes only the newly formed stereocenter; not taking the racemic sidechain into account.

(8*R*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((tert-butyldiphenylsilyl)oxy)-14-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl) oxy)tetradec-2-yn-4-yl acetate (112)

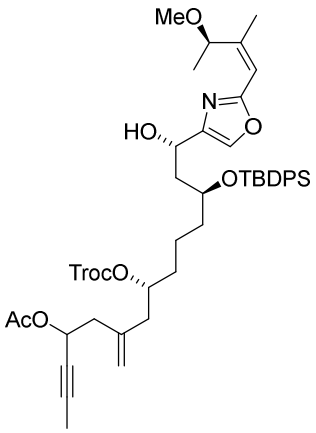
Analoguos to preparation of **112a**, the title compound was made by using **111** (492 mg, 0.592 mmol, 1 equiv), 2,2,2-trichlorethoxycarbonyl chloride (245 µL, 1.78 mmol, 3.00 equiv), 4-(dimethylamino)pyridine (7.23 mg, 59.2 µmol, 0.10 equiv) and pyridine (287 µL, 3.55 mmol, 6.00 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to give **112** (593 mg, 0.592 mmol, quant.) as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.57 (m, 4H), 7.45–7.29 (m, 6H), 7.09 (d, *J* = 1.4 Hz, 1H), 6.18–6.15 (m, 1H), 5.47–5.39 (m, 1H), 5.20 (q, *J* = 6.4 Hz, 1H), 4.93–4.88 (m, 2H), 4.83–4.72 (m, 3H), 4.71–4.64 (m, 1H), 3.89–3.80 (m, 1H), 3.18 (s, 3H), 2.48–2.44 (m, 2H), 2.36–2.18 (m, 2H), 2.05 (d, *J* = 0.7 Hz, 3H), 2.03–1.92 (m, 2H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.83 (dd, *J* = 2.1, 0.7 Hz, 3H), 1.54–1.30 (m, 6H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.03 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), −0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.4, 159.2, 153.2, 149.6, 144.1, 138.9, 138.8, 135.34, 135.29, 133.8, 133.6, 132.9, 129.0, 126.9, 116.6, 116.3, 112.9, 94.0, 81.7, 81.6, 77.5, 77.3, 75.94, 75.89, 75.8, 75.7, 74.1, 69.59, 69.56, 65.0, 62.4, 62.1, 55.9, 43.4, 40.73, 40.68, 40.4, 35.8, 35.6, 33.6, 33.5, 26.5, 25.3, 20.52, 20.50, 19.73, 19.67, 18.8, 18.7, 17.6, 17.1, 3.1, −5.1, −5.4 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2954, 2930, 2857, 1754, 1428, 1378, 1249, 1109, 836, 821, 703, 611, 507 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{51}H_{72}NO_9Cl_3Si_2Na$ [*M*+Na^+]: 1026.3703, found: 1026.3692.

(8*R*,12*S*,14*S*)-12-((*tert*-Butyldiphenylsilyl)oxy)-14-hydroxy-14-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-2-yn-4-yl acetate (113)

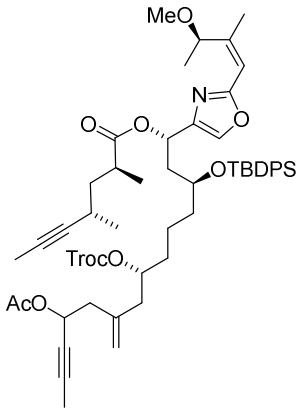
Analoguos to preparation of **113a**, the title compound was made by using **112** (592 mg, 0.589 mmol, 1 equiv) and 10-camphorsulfonic acid (27.4 mg, 0.118 mmol, 0.20 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 2:1) to give **113** (208 mg, 0.233 mmol, 40%, 74% brsm) and recovered starting material **112** (277 mg, 0.275 mmol, 47%).



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68–7.61 (m, 4H), 7.46–7.28 (m, 6H), 7.23 (s, 1H), 6.11 (s, 1H), 5.35 (tq, *J* = 6.9, 2.2 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 4.86–4.75 (m, 3H), 4.71–4.58 (m, 3H), 4.01–3.91 (m, 1H), 3.22–3.16 (m, 1H), 3.13 (s, 3H), 2.45–2.30 (m, 2H), 2.29–2.08 (m, 2H), 1.98 (d, *J* = 2.0 Hz, 3H), 1.95–1.83 (m, 2H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 (dd, *J* = 2.0, 1.1 Hz, 3H), 1.45–1.33 (m, 1H), 1.33–1.20 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.20–1.07 (m, 3H), 0.99 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.0, 160.5, 153.9, 150.6, 144.5, 139.6, 139.5, 136.0, 134.3, 133.7, 133.1, 130.0, 129.9, 127.9, 127.7, 117.2, 117.0, 113.6, 94.8, 82.4, 82.3, 78.2, 77.9, 76.6, 74.9, 72.9, 66.2, 63.1, 62.9, 56.6, 42.8, 41.6, 41.0, 37.0, 34.0, 27.2, 21.1, 20.6, 19.5, 19.4, 17.7, 3.7 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2953, 2932, 2858, 1754, 1651, 1428, 1377, 1250, 1110, 1067, 1021, 821, 737, 704, 612, 508 cm^{-1}; **HRMS** (ESI): *m/z*: calcd. for $C_{45}H_{58}NO_9Cl_3SiNa$ [*M*+Na^+]: 912.2838, found: 912.2835.

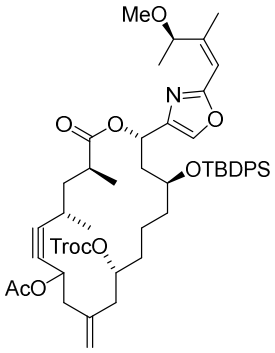
(1*S*,3*S*,7*R*)-11-Acetoxy-3-((*tert*-butyldiphenylsilyl)oxy)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-9-methylene-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-12-yn-1-yl (2*S*,4*S*)-2,4-dimethylhept-5-ynoate (62)

Analoguos to preparation of **62a**, the title compound was made by using **113** (320 mg, 0.359 mmol, 1 equiv), **49** (60.9 mg, 0.395 mmol, 1.10 equiv), triethylamine (75.1 µL, 0.539 mmol, 1.50 equiv), 2,4,6-trichlorobenzoyl chloride (84.1 µL, 0.539 mmol, 1.50 equiv) and 4-(dimethylamino)pyridine (43.9 mg, 0.395 mmol, 1.00 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 6:1) to give **62** (342 mg, 0.333 mmol, 93%) as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.58 (m, 4H), 7.43–7.31 (m, 6H), 7.19 (d, *J* = 1.6 Hz, 1H), 6.14 (s, 1H), 5.89 (t, *J* = 7.0 Hz, 1H), 5.47–5.39 (m, 1H), 5.10 (q, *J* = 6.5 Hz, 1H), 4.91 (br s, 2H), 4.82–4.73 (m, 2H), 4.68 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.72–3.63 (m, 1H), 3.14 (s, 3H), 2.67–2.56 (m, 1H), 2.52–2.41 (m, 2H), 2.39–2.07 (m, 5H), 2.05 (d, *J* = 0.7 Hz, 3H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.84–1.81 (m, 3H), 1.73 (d, *J* = 2.3 Hz, 3H), 1.66 (ddd, *J* = 14.7, 9.8, 5.1 Hz, 1H), 1.54–1.29 (m, 7H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 3.2 Hz, 3H), 1.03 (br s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.7, 169.97, 169.96, 160.1, 153.8, 150.7, 140.0, 139.5, 139.4, 135.93, 135.91, 135.1, 134.1, 133.9, 129.7, 127.6, 117.3, 117.0, 113.3, 94.7, 82.9, 82.3, 82.2, 78.0, 77.8, 76.6, 76.51, 76.46, 76.3, 74.7, 69.8, 65.6, 63.0, 62.7, 56.5, 41.34, 41.31, 41.1, 41.0, 39.5, 38.0, 36.3, 34.1, 34.0, 27.1, 24.3, 21.7, 21.11, 21.09, 20.4, 20.3, 19.4, 19.2, 18.1, 17.7, 3.7, 3.6 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2963, 2932, 2858, 1754, 1739, 1429, 1378, 1250, 1111, 1065, 821, 738, 704, 612, 507 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{54}H_{70}Cl_3NO_{10}SiNa$ [*M*+Na$^+$]: 1048.3727, found: 1048.3737.

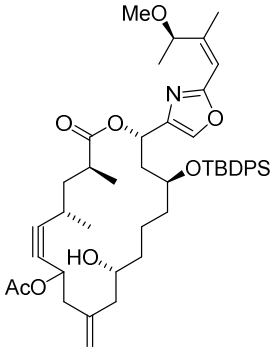
(3*S*,5*S*,12*R*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-18-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxo-12-(((2,2,2-trichloroethoxy)carbonyl)oxy) oxacyclooctadec-6-yn-8-yl acetate (114)



Analoguos to preparation of **114a**, the title compound was made by using **62** (290 mg, 0.282 mmol, 1 equiv) and alkyne metathesis catalyst **116** (74.8 mg, 56.4 µmol, 0.20 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 4:1) to give **114** (223 mg, 0.229 mmol, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.59 (m, 4H), 7.46–7.30 (m, 7H), 6.18–6.05 (m, 2H), 5.66–5.59 (m, 0.5H), 5.50–5.43 (m, 0.5H), 5.19–5.11 (m, 1H), 5.01–4.89 (m, 1H), 4.82–4.67 (m, 3H), 3.90–3.79 (m, 1H), 3.19 (d, *J* = 1.2 Hz, 3H), 2.63–2.23 (m, 7H), 2.06 (d, *J* = 4.3 Hz, 3H), 2.00–1.91 (m, 1H), 1.89 (t, *J* = 1.4 Hz, 3H), 1.60–1.38 (m, 6H), 1.36 (s, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.13–1.01 (m, 16H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.54, 175.49, 169.92, 169.87, 160.4, 153.89, 153.85, 151.0, 150.9, 141.0, 140.9, 139.5, 139.2, 135.9, 134.10, 134.06, 134.0, 129.8, 127.7, 117.9, 116.9, 113.4, 94.7, 90.9, 90.6, 78.7, 78.2, 78.05, 77.99, 76.7, 76.6, 74.78, 74.75, 70.3, 70.2, 65.6, 65.4, 63.4, 62.9, 56.6, 42.2, 41.9, 41.2, 40.9, 40.7, 38.1, 38.0, 37.9, 36.2, 35.9, 34.0, 27.1, 24.1, 22.2, 21.7, 21.29, 21.28, 20.6, 20.5, 19.4, 19.3, 17.8, 17.14, 17.07 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2932, 2859, 1741, 1428, 1378, 1247, 1162, 1110, 1067, 1021, 821, 735, 703, 612, 509, 488 cm^{-1}; **HRMS** (ESI): *m/z*: calcd. for $C_{50}H_{64}Cl_3NO_{10}SiNa$ [*M*+Na^+]: 994.3257, found: 994.3261.

(3*S*,5*S*,12*R*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-12-hydroxy-18-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxooxacyclooctadec-6-yn-8-yl acetate (115)



Analoguos to preparation of **115a**, the title compound was made by using **114** (223 mg, 0.229 mmol, 1 equiv) and zinc dust (two times 1.50 g, 22.9 mmol, 100 equiv, Sigma-Aldrich®, <10 µm). The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 2:1) to give **115** (180 mg, 0.225 mmol, 98%) as a colorless oil.

The two C7-diastereomers, **115a** and **115b**, were separated by

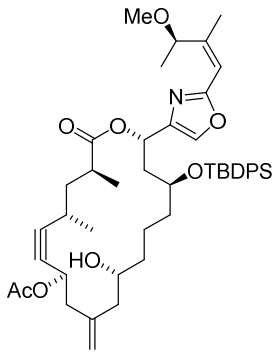
preparative LC (Kromasil 100-5C18 5 µm, 150 mm × 30.0 mm, ACN/H_2O, 90:10, 35 °C, 35 mL/min) to give **115a** (56.0 mg, 70.0 µmol, 31%) and **115b** (28.9 mg, 66.0 µmol, 29%).

*1:1 Mixture of diastereomers **115**:*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.58 (m, 4H), 7.48–7.29 (m, 7H), 6.19–6.02 (m, 2H), 5.51 (ddd, *J* = 7.2, 4.9, 2.1 Hz, 0.5H), 5.44 (ddd, *J* = 8.2, 4.7, 1.3 Hz, 0.5H), 5.15 (qd, *J* = 6.4, 2.3 Hz, 1H), 4.98 (d, *J* = 6.8 Hz, 2H), 3.93–3.79 (m, 1H), 3.71–3.59 (m, 1H), 3.19 (d, *J* = 1.2 Hz, 3H), 2.60 (q, *J* = 6.9 Hz, 1H), 2.55–2.38 (m, 4H), 2.37–2.26 (m, 1H), 2.06 (d, *J* = 6.5 Hz, 3H), 2.03–1.91 (m, 2H), 1.88 (s, 3H), 1.71–1.29 (m, 9H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.5, 175.4, 170.0, 169.8, 160.4, 160.3, 150.92, 150.85, 141.4, 141.1, 141.0, 140.9, 135.9, 134.20, 134.18, 134.1, 129.8, 127.6, 117.2, 116.7, 113.4, 113.3, 90.5, 78.3, 78.2, 74.8, 70.7, 70.4, 68.83, 68.80, 65.7, 65.5, 63.7, 63.1, 56.6, 45.1, 45.0, 41.4, 40.9, 40.6, 40.5, 38.4, 38.2, 38.1, 38.0, 36.95, 36.88, 36.2, 35.9, 27.1, 24.1, 24.0, 22.4, 21.9, 21.28, 21.26, 20.5, 20.4, 19.4, 19.3, 17.8, 17.2, 17.0 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 3493, 2932, 2858, 1738, 1428, 1373, 1233, 1164, 1109, 969, 822, 742, 704, 612, 508 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na$^+$]: 820.4215, found: 820.4214.

*Diastereomer **115b**:*

$[\alpha]_D^{20}$ = +25.0 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67-7.58 (m, 4H), 7.46-7.28 (m, 7H),

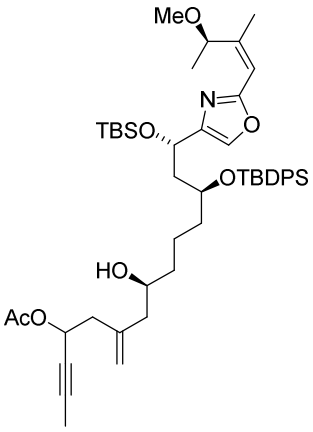


6.16-6.09 (m, 2H), 5.51 (ddd, *J* = 7.1, 4.8, 2.0 Hz, 1H), 5.16 (q, *J* = 6.4 Hz, 1H), 4.98 (br s, 1H), 4.96 (br s, 1H), 3.91-3.80 (m, 1H), 3.72-3.60 (m, 1H), 3.19 (s, 3H), 2.64-2.55 (m, 1H), 2.53-2.41 (m, 4H), 2.32 (ddd, *J* = 14.8, 9.6, 2.1 Hz, 1H), 2.12-2.03 (m, 1H), 2.07 (s, 3H), 1.94 (ddd, *J* = 15.0, 6.9, 2.1 Hz, 1H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.84-1.71 (m, 1H), 1.66-1.56 (m, 2H), 1.55-1.41 (m, 2H), 1.38-1.29 (m, 4H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.25 (br s, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.4, 170.0, 160.3, 150.8, 141.1, 141.0, 135.9, 134.2, 134.1, 129.8, 129.7, 127.6, 117.2, 113.4, 90.5, 78.2, 74.8, 70.7, 68.8, 65.5, 63.1, 56.6, 45.1, 41.4, 40.5, 38.2, 38.1, 36.9, 36.2, 27.1, 24.1, 22.4, 21.3, 20.4, 19.4, 19.3, 17.8, 17.2; **IR** (film): ν = 3478, 2931, 2858, 1739, 1648, 1451, 1428, 1373, 1233, 1164, 1109, 1026, 970, 902, 858, 822, 741, 704, 613, 509, 488 cm^{-1}; **MS** (ESI) *m*/*z* (%): 820 (*M*+Na$^+$, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na$^+$]: 820.4215, found: 820.4214.

6.2.7. (7S,11S)-Enigmazole A

(8*S*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-8-hydroxy-14-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl) oxazol-4-yl)-6-methylenetetradec-2-yn-4-yl acetate (111c)[74]

Analoguos to preparation of **111a**, the title compound was made by using boron tribromide (1 M in

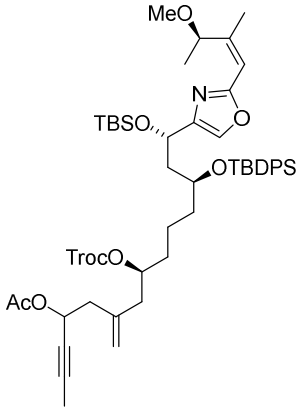


dichloromethane, 3.84 mL, 3.84 mmol, 1.50 equiv), (*R,R*)-1,2-diphenyl-1,2-ethylenediamine bis(toluenesulfon-amide)[103b] (2.00 g, 3.84 mmol, 1.50 equiv), racemic allyl stannane **50** (2.04 g, 4.48 mmol, 1.75 equiv), and aldehyde **63** (1.70 g, 2.56 mmol, 1 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 4:1) to give **111c** (2.13 g, 2.56 mmol, quant.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.61 (m, 4H), 7.41–7.29 (m, 6H), 7.10 (s, 1H), 5.48–5.43 (m, 1H), 5.20 (q, *J* = 6.2 Hz, 1H), 4.97 (s, 1H), 4.93 (s, 1H), 4.82 (t, *J* = 6.2 Hz, 1H), 3. 86 (quint, J = 5.9 Hz, 1H), 3.54 (br s, 1H), 3.18 (s, 3H), 2.50–2.38 (m, 2H), 2.17-2.12 (m, 1H), 2.05–1.97 (m, 6H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.83–1.82 (m, 3H), 1.67–1.21 (m, 8H), 1. 28 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 0.82 (s, 9H), 0.02 (s, 3H), −0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 160.0, 150.3, 145.0, 141.5, 136.14, 136.11, 134.8, 134.6, 133.7, 129.6, 127.6, 116.2, 113.7, 82.4, 82.3, 76.8, 76.7, 74.9, 70.7, 69.0, 68.8, 65.8, 63.3, 63.0, 56.6, 44.8, 44.6, 37.3, 36.8, 27.3, 26.0, 21.25, 21.21, 20.8, 19.6, 19.4, 18.3, 17.7, 3.8, −4.3, −4.6 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 3468, 2931, 2857, 1741, 1428, 1371, 1234, 1110, 837, 777, 741, 705 cm^{-1}; **MS** (ESI) *m*/*z* (%): 852 (*M*+Na^+, 100); **HRMS** (ESI): *m*/*z*: calcd. for $C_{48}H_{71}NO_7Si_2Na$ [M^++Na]: 852.4661, found: 852.4658.

(8*S*,12*S*,14*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-12-((tert-butyldiphenylsilyl)oxy)-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl) oxy)tetradec-2-yn-4-yl acetate (112c)[74]

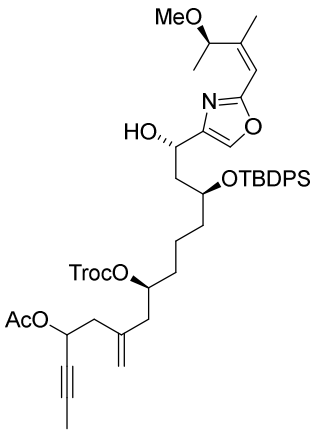
Analoguos to preparation of **112a**, the title compound was made by using **111c** (2.13 g, 2.56 mmol, 1 equiv), 2,2,2-trichlorethoxycarbonyl chloride (1.06 mL, 7.68 mmol, 3.00 equiv), 4-(dimethylamino)pyridine (31.3 mg, 0.256 mmol, 0.10 equiv) and pyridine (1.24 mL, 15.4 mmol, 6.00 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to give **112c** (2.57 g, 2.56 mmol, quant.) as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64–7.60 (m, 4H), 7.41–7.30 (m, 6H), 7.09 (s, 1H), 6.16 (s, 1H), 5.44–5.41 (m, 1H), 5.19 (q, *J* = 6.3 Hz, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 4.80–4.73 (m, 3H), 4.66 (dd, *J* = 11.8, 4.9 Hz, 1H), 3. 87–3.81 (m, 1H), 3.18 (s, 3H), 2.47–2.45 (m, 2H), 2.35–2.20 (m, 2H), 2.04–1.96 (m, 5H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.82 (d, *J* = 2.2 Hz, 3H), 1.41–1.28 (m, 6H), 1.28 (d, *J* = 7.4 Hz, 3H), 1.03 (s, 9H), 0.81 (s, 9H), 0.01 (s, 3H), −0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 160.0, 150.4, 145.0, 139.8, 139.7, 136.1, 136.0, 135.7, 134.7, 134.4, 133.7, 129.7, 127.9, 129.8, 129.7, 117.0, 113.7, 94.9, 78.2, 74.9, 70.4, 65.8, 63.2, 63.0, 56.6, 44.2, 41.5, 41.2, 36.5, 34.3, 27.3, 27.0, 26.0, 21.2, 20.2, 19.6, 19.4, 18.3, 17.7, 3.83, −4.3, −4.6 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2929, 2857, 1753, 1428, 1376, 1248 1104, 1020, 970, 938, 910, 835, 819, 777, 732, 702, 610, 571, 505, 488 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{51}H_{72}NO_9Cl_3Si_2Na$ [*M*+Na^+]: 1026.3703, found: 1026.3702.

(8*S*,12*S*,14*S*)-12-((*tert*-Butyldiphenylsilyl)oxy)-14-hydroxy-14-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-6-methylene-8-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-2-yn-4-yl acetate (113c)

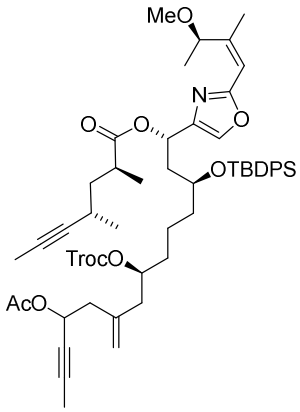
Analoguos to preparation of **113a**, the title compound was made by using **112c** (2.57 g, 2.56 mmol, 1 equiv) and 10-camphorsulfonic acid (512 mg, 0.512 mmol, 0.20 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 2:1) to give **113c** (1.18 mg, 1.32 mmol, 52%, 77% brsm) and recovered starting material **112c** (843 mg, 0.838 mmol, 33%).



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.67 (m, 4H), 7.43–7.36 (m, 6H), 7.27 (s, 1H), 6.17 (s, 1H), 5.44–5.39 (m, 1H), 5.12 (q, *J* = 6.5 Hz, 1H), 4.90 (s, 1H), 4.88 (s, 1H), 4.84–4.72 (m, 1H), 4.75–4.72 (m, 2H), 4.67 (dd, *J* = 11.8, 4.3 Hz, 1H), 4.05–4.01 (m, 1H), 3.20 (s, 3H), 3.04 (t, *J* = 3.4 Hz, 1H), 2.48–2.40 (m, 2H), 2.33–2.18 (m, 2H), 2.04 (s, 3H), 2.03–1.91 (m, 2H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.81 (d, *J* = 2.2 Hz, 3H), 1.41–1.13 (m, 6H), 1. 29 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 170.0, 160.6, 153.9, 150.7, 144.5, 139.6, 139.5, 136.1, 136.0, 134.3, 133.72, 133.73, 133.1, 130.0, 129.9, 127.9, 127.8, 117.3, 117.0, 113.6, 94.8, 82.4, 82.3, 78.0, 77.8, 76.7, 74.9, 72.91, 72.88, 66.35, 66.31, 63.1, 62.9, 56.6, 42.8, 41.5, 41.0, 36.9, 34.1, 34.0, 27.2, 21.19, 21.17, 20.5, 20.4, 19.5, 19.46, 17.8, 3.79 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 3459, 3072, 2932, 2858, 1754, 1650, 1428, 1377, 1251, 1110, 1067, 1021, 821, 737, 704, 612 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{45}H_{58}NO_9Cl_3SiNa$ [*M*+Na^+]: 912.2838, found: 912.2844.

(1*S*,3*S*,7*S*)-11-Acetoxy-3-((*tert*-butyldiphenylsilyl)oxy)-1-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-9-methylene-7-(((2,2,2-trichloroethoxy)carbonyl)oxy)tetradec-12-yn-1-yl (2*S*,4*S*)-2,4-dimethylhept-5-ynoate (62c)

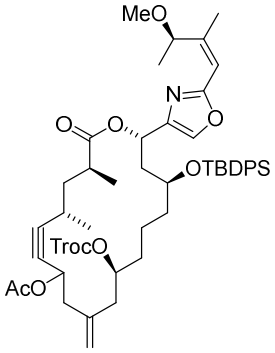
Analoguos to preparation of **62a**, the title compound was made by using **113c** (1.75 g, 1.96 mmol, 1 equiv), **49** (333 mg, 2.16 mmol, 1.10 equiv), triethylamine (410 µL, 2.95 mmol, 1.50 equiv), 2,4,6-trichlorobenzoyl chloride (460 µL, 2.95 mmol, 1.50 equiv) and 4-(dimethylamino)pyridine (240 mg, 1.96 mmol, 1.00 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 6:1) to give **62c** (1.95 g, 1.90 mmol, 97%) as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.60 (m, 4H), 7.40–7.32 (m, 6H), 7.19 (s, 0.5H), 7.19 (s, 0.5H), 6.14 (s, 1H), 5.89 (t, *J* = 6.9 Hz, 1H), 5.49–5.42 (m, 1H), 5.10 (q, *J* = 6.2 Hz, 1H), 4.92 (s, 1H), 4.91 (s, 1H), 4.79–4.74 (m, 2H), 4.67 (dd, *J* = 12.1, 4.8 Hz, 1H), 3.73–3.69 (m, 1H), 3.16 (s, 3H), 2.63–2.58 (m, 1H), 2.48–2.45 (m, 2H), 2.37–2.14 (m, 6H), 2.05 (s, 1.5H), 2.04 (s, 1.5H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.82 (d, *J* = 2.0 Hz, 3H), 1.74 (d, *J* = 2.2 Hz, 3H), 1.70–1.63 (m, 1H), 1.47–1.30 (m, 6H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.8, 170.0, 160.3, 153.9, 150.8, 140.3, 139.7, 139.5, 136.1, 136.0, 135.2, 134.3, 134.1, 129.7, 127.7, 117.3, 117.0, 113.4, 94.8, 83.1, 82.4, 82.3, 78.2, 77.9, 76.7, 76.4, 74.9, 69.9, 65.8, 63.1, 62.9, 56.6, 41.5, 41.2, 41.1, 39.6, 38.1, 36.3, 34.22, 34.17, 27.2, 24.5, 21.8, 21.18, 21.16, 20.33, 20.28, 19.5, 19.3, 18.2, 17.7, 3.8, 3.6 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 3073, 2960, 2931, 2858, 2821, 1753, 1737, 1650, 1547, 1449, 1428, 1376, 1248, 1163, 1109, 1063, 1020, 970, 911, 820, 732, 703 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{54}H_{70}Cl_3NO_{10}SiNa$ [*M*+Na^+]: 1048.3727, found: 1048.3728.

(3*S*,5*S*,12*S*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-18-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxo-12-(((2,2,2-trichloroethoxy)carbonyl)oxy) oxacyclooctadec-6-yn-8-yl acetate (114c)

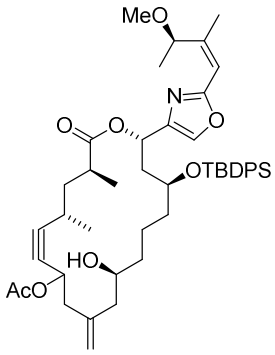
Analoguos to preparation of **114a**, the title compound was made by using **62c** (1.40 g, 1.36 mmol, 1 equiv) and alkyne metathesis catalyst **116** (406 mg, 299 µmol, 0.22 equiv). The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 6:1) to give **114c** (1.01 g, 1.03 mmol, 76%) and recovered starting material **62c** (120 mg, 0.117 mmol, 8.6%).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65–7.56 (m, 4H), 7.42–7.27 (m, 6H), 7.25 (s, 0.5H), 7.24 (s, 0.5H), 6.11 (dq, *J* = 2.2, 1.3 Hz, 1H), 6.03 (dt, *J* = 8.3, 3.6 Hz, 1H), 5.54 (ddd, *J* = 6.6, 4.7, 1.7 Hz, 1H), 5.45 (ddd, *J* = 8.4, 5.8, 2.2 Hz, 1H), 5.13 (qd, *J* = 6.5, 0.8 Hz, 1H), 5.01–4.86 (m, 3H), 4.75 (dd, *J* = 11.9, 6.3 Hz, 1H), 4.69 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.86–3.80 (m, 1H), 3.16 (s, 3H), 2.70–2.59 (m, 1H), 2.53–2.43 (m, 3H), 2.43–2.34 (m, 2H), 2.29–2.20 (m, 1H), 2.05 (s, 1.5H), 2.04–1.97 (m, 2.5H), 1.87 (d, *J* = 1.5 Hz, 1.5H), 1.86 (d, *J* = 1.6 Hz, 1.5H), 1.70–1.59 (m, 2H), 1.59–1.47 (m, 3H), 1.43–1.28 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 1.5H), 1.23 (d, *J* = 6.5 Hz, 1.5H), 1.11 (d, *J* = 7.0 Hz, 1.5H), 1.10 (d, *J* = 7.0 Hz, 1.5H), 1.04 (d, *J* = 6.9 Hz, 1.5H), 1.04 (d, *J* = 6.9 Hz, 1.5H), 1.02 (s, 4.5H), 1.01 (s, 4.5H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.6, 175.5, 169.9, 169.8, 160.4, 153.9, 153.8, 151.0, 150.9, 140.9, 139.9, 139.6, 136.0, 134.18, 134.16, 134.15, 134.13, 134.08, 133.98, 129.78, 129.77, 129.74, 127.7, 115.89, 115.86, 113.34, 113.30, 94.81, 94.79, 90.8, 90.7, 78.5, 78.3, 77.9, 77.5, 76.7, 74.84, 74.83, 70.2, 70.1, 66.10, 66.08, 63.3, 63.1, 56.6, 42.6, 41.6, 41.2, 41.0, 40.2, 39.3, 38.7, 38.5, 38.28, 38.25, 36.2, 36.1, 33.5, 33.4, 27.2, 24.4, 24.3, 21.3, 21.24, 21.21, 20.7, 20.6, 20.5, 19.4, 19.3, 17.8, 17.6 (some carbon signals of the two sets of signals expected for the two diasteroisomers are missing due to overlapping); **IR** (film): ν = 2932, 2858, 1739, 1428, 1377, 1247, 1162, 1106, 1065, 1021, 909, 820, 730, 612, 572, 507, 488 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{50}H_{64}Cl_3NO_{10}SiNa$ [*M*+Na^+]: 994.3257, found: 994.3268.

(3*S*,5*S*,12*S*,16*S*,18*S*)-16-((*tert*-Butyldiphenylsilyl)oxy)-12-hydroxy-18-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-3,5-dimethyl-10-methylene-2-oxooxacyclooctadec-6-yn-8-yl acetate (229)

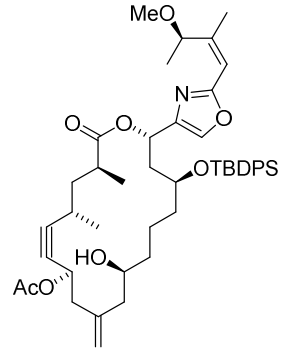
Analoguos to preparation of **115a**, the title compound was made by using **114c** (311 mg, 0.320 mmol, 1 equiv) and zinc dust (2.09 g, 31.9 mmol, 100 equiv, Sigma-Aldrich®, <10 µm). The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1) to give **229** (243 mg, 0.304 mmol, 95%) as a colorless oil.



A mixture of the two C7-diastereomers **229** (603 mg, 0.756 mmol) was separated by preparative LC (Nucleosil10-100 C18/A 10 µm, 203 mm × 48.0 mm, MeOH/H_2O, 85:15, 35 °C, 75 mL/min) to give **115c** (195 mg, 0.244 mmol, 32%) and **115d** (200 mg, 0.251 mmol, 33%) as enantiopure compounds.

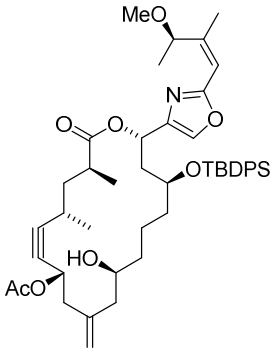
*Diastereomer **115c:***

$[\alpha]_D^{20}$ = +31.0 (c = 1.15, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 4H), 7.44–7.31 (m, 6H), 7.30 (s, 1H), 6.16–6.13 (m, 1H), 6.09 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.48 (ddd, *J* = 9.2, 5.5, 2.2 Hz, 1H), 5.16 (qd, *J* = 6.5, 0.9 Hz, 1H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.96 (d, *J* = 1.6 Hz, 1H), 3.86 (tdd, *J* = 7.5, 5.5, 2.5 Hz, 1H), 3.82 (ddt, *J* = 8.6, 4.1, 6.0 Hz, 1H), 3.19 (s, 3H), 2.66 (ddq, *J* = 9.7, 5.1, 7.0 Hz, 1H), 2.52–2.43 (m, 2H), 2.42–2.35 (m, 2H), 2.27 (ddd, *J* = 14.9, 8.9, 2.6 Hz, 1H), 2.08 (s, 3H), 2.07–2.01 (m, 2H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.72–1.64 (m, 2H), 1.56–1.49 (m, 1H), 1.43–1.34 (m, 3H), 1.34–1.28 (m, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H) (one protic H missing); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.6, 169.9, 160.3, 150.9, 141.5, 141.0, 135.98 (2C), 135.97 (2C), 134.3, 134.1, 134.0, 129.8, 129.67 (2C), 127.65 (2C), 127.7, 115.4, 113.3, 90.7, 78.4, 74.8, 70.5, 68.2, 66.1, 63.3, 56.6, 42.8, 42.6, 41.1, 38.3, 38.2, 36.4, 36.2, 27.2 (3C), 24.3, 21.3, 20.9, 20.7, 19.4, 19.3, 17.8, 17.7; **IR** (film): ν = 3479, 2930, 2857, 1737, 1450, 1428, 1373, 1231, 1162, 1105, 1066, 1022, 970, 822, 756, 703, 612, 508, 488 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4221.



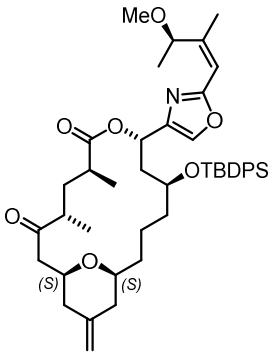
*Diastereomer **115d:***

$[\alpha]_D^{20}$ = +1.40 (c = 1.03, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.67–7.57 (m, 4H), 7.44–7.28 (m, 7H), 6.14 (s, 1H), 6.07 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.56 (t, *J* = 5.7 Hz, 1H), 5.15 (q, *J* = 6.4 Hz, 1H), 5.00 (br s, 1H), 4.96 (br s, 1H), 3.92–3.75 (m, 2H), 3.18 (s, 3H), 2.77–2.60 (m, 1H), 2.56–2.39 (m, 4H), 2.27 (ddd, *J* = 14.9, 8.6, 2.7 Hz, 1H), 2.13–2.04 (m, 2H), 2.03 (s, 2H), 1.89 (s, 3H), 1.75 – 1.49 (m, 4H), 1.46–1.30 (m, 5H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.08–1.01 (m, 12H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.3, 169.7, 160.2, 150.8, 141.5, 140.9, 135.9 (4C), 134.2, 134.1, 133.8, 129.58, 129.56, 127.5 (4C), 115.6, 113.2, 90.4, 78.3, 74.7, 70.3, 68.2, 66.0, 63.2, 56.4, 44.0, 41.3, 40.6, 38.5, 38.2, 36.2, 36.0, 27.0 (3C), 24.2, 21.1, 20.8, 20.5, 19.3, 19.1, 17.6, 17.5; **IR** (film): ν = 3478, 2931, 2858, 1739, 1451, 1428, 1373, 1233, 1164, 1109, 1026, 970, 822, 741, 704, 613, 509, 488 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{47}H_{63}NO_8SiNa$ [*M*+Na^+]: 820.4215, found: 820.4211.



(1*S*,4*S*,6*S*,9*S*,11*S*,15*S*,)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecane-3,7-dione (131)

Silver hexafluoroantimonate (7.80 mg, 22.7 µmol, 0.40 equiv) and gold catalyst (*S*)-DTBM-MeOH-Biphep-(AuCl) (*S*)-**121** (12.1 mg, 11.2 µmol, 0.20 equiv) were suspended in anh. dichloromethane (0.50 mL) and the mixture was sonicated for 10 min. The suspension was filtered through a plug of Celite (rinsing with anh. dichloromethane, 2 × 0.40 mL) into a solution of diastereomer **115c** (45.0 mg, 56.4 µmol, 1 equiv) in anh. dichloromethane (2.0 mL). After stirring for 48 h, the solvent was removed under a stream of argon and the residue was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 4:1) to give **117d** (35.0 mg, 44.0 µmol, 78%, *d.r.* ≥95:5) as a colorless oil.

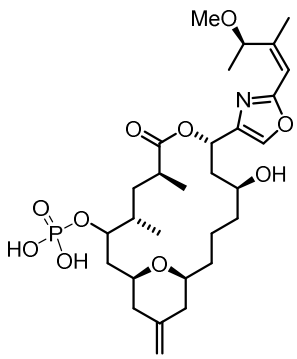


Potassium carbonate (18.2 mg, 132 µmol, 3.00 equiv) was added to a solution of **117d** in anh. dichloromethane/methanol (2:1, 6.0 mL). After stirring for 4.5 h, the mixture was filtered through a plug of silica which was rinsed with methyl *tert*-butyl ether (10 mL). The filtrate was concentrated and the residue purified by flash chromatography (hexane/ethyl acetate 10:1) to afford **131** (31.0 mg, 41.0 µmol, 94%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 2H), 7.63–7.60 (m, 2H), 7.51 (d, *J* = 0.8 Hz, 1H), 7.43–7.30 (m, 6H), 6.15 (br s, 1H), 6.00 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.18 (dq, *J* = 6.4, 0.8 Hz, 1H), 4.69 (br s, 2H), 3.81 (ddt, *J* = 7.5, 2.8, 6.4 Hz, 1H), 3.72–3.66 (m, 1H), 3.20 (s, 3H), 3.12 (ddt, *J* = 11.8, 9.7, 2.2 Hz, 1H), 2.78–2.69 (m, 1H), 2.62 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.53 (ddq, *J* = 10.1, 4.6, 6.9 Hz, 1H), 2.40 (dd, *J* = 14.5, 2.7 Hz, 1H), 2.36–2.28 (m, 1H), 2.16–2.11 (m, 2H), 2.07 (dd, *J* = 13.4, 2.3 Hz, 1H), 1.98 (ddd, *J* = 14.9, 7.6, 2.6 Hz, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.89–1.81 (m, 1H), 1.72 (ddd, *J* = 14.6, 10.3, 4.7 Hz, 1H), 1.59 (s, 1H), 1.56–1.41 (m, 4H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.27–1.24 (m, 1H), 1.23–1.16 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 213.3, 175.6, 160.2, 150.6, 144.5, 141.3, 136.01 (2C), 135.99 (2C), 134.4, 134.34, 134.26, 129.7 (2C), 127.7 (2C), 127.6 (2C), 113.5, 108.9, 78.7, 75.1, 74.8, 71.0, 65.9, 56.6, 46.0, 45.4, 41.1, 40.6, 39.1, 38.0, 37.7, 37.0, 36.4, 27.2 (3C), 21.8, 19.5, 19.3, 17.8, 17.7, 17.5; **IR** (film): ν = 2962, 2933, 2858, 1736, 1709, 1428, 1362, 1166, 1109, 704, 512 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{45}H_{61}NO_7SiNa$ [*M*+Na^+]: 778.4110, found 778.4102.

(7*S*,11*S*)-Enigmazole A (132)

Sodium borohydride (6.21 mg, 164 µmol, 4.00 equiv) was added at −5 °C to a solution of ketone



131 (31.0 mg, 41.0 µmol, 1 equiv) in anh. methanol (1.4 mL). After stirring for 2.5 h at this temperature, excess reagent was quenched by the addition of aq. phosphate buffer solution (pH 7, 5 mL) and the solution was allowed to warm to 23 °C. The aq. layer was extracted with dichloromethane (5 x 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 2:1) to yield **230** (30.8 mmol, 40.6 µmol, 61%) as a single diastereomer.

A solution of tetrazole (0.45 M in acetonitrile, 422 µL, 190 µmol, 15.0 equiv) was added at 0 °C to a solution of alcohol **230** (9.60 mg, 12.7 µmol, 1 equiv) and *i*$Pr_2NP(OFm)_2$[166] (132 mg, 253 µmol, 20.0 equiv) in anh. acetonitrile (0.25 mL) and anh. dichloromethane (0.70 mL). The mixture was stirred for 1 h at 23 °C, before it was cooled to 0 °C and aq. hydrogen peroxide (35% *w*/*w*, 246 µL, 2.53 mmol, 200 equiv) was added. After stirring for additional 15 min, the reaction was quenched by the addition of aq. sat. sodium hydrogen carbonate solution (5 mL). The layers were separated and the aq. layer was extracted with dichloromethane (5 × 3 mL). The combined

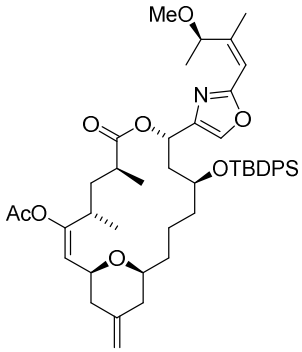
organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 1:1) and subsequent preparative LC (Kromasil 100-5C18 5µm, 150 mm × 30.0 mm, 100% acetonitrile, 35 °C, 35 mL/min) to afford fully protected (7*S*,11*S*)-enigmazole **231** (11.1 mg, 9.00 µmol, 73%).

Potassium carbonate (18.2 mg, 131 µmol, 10.0 equiv) was added to a solution of the protected enigmazole **231** (15.7 mg, 13.1 µmol, 1 equiv) in a mixture of methanol/water (10:1, 3.3 mL). After stirring at 23 °C for 18 h, the suspension was diretly loaded onto a C18-cartridge (Strata® C18-U, 55 µm, 70 Å, 500 mg/6 mL) and the salts were eluted with water, followed by elution of the organic fraction with methanol. The combined organic fractions were concentrated and the residue pufiried by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, acetonitrile/water 70:30, 35 °C, 20 mL/min) to afford **232** (8.00 mg, 9.55 µmol, 73%).

A solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 190 µL, 191 µmol, 50.0 equiv) was added to a solution of the TBDPS-protected **232** (3.20 mg, 3.80 µmol, 1 equiv) in anh. tetrahydrofuran (0.5 mL) and acetic acid (17.2 µL, 286 µmol, 75.0 equiv). After stirring at 23 °C for 3 d, the solution was diluted with water (1 mL) and loaded onto a C18-cartridge (Strata® C18-U, 55 µm, 70 Å, 500 mg/6 mL). The salts were eluted with water, followed by elution of the organic fraction with methanol. The combined organic fractions were concentrated and the residue was purified by preparative LC (Kromasil 100-5C18 5µm, 150 mm × 21.2 mm, methanol/aq. TEAA pH 8.0, 70:30 grading to 100% methanol over 10 min, 35 °C, 20 mL/min) to obtain **132** (1.00 mg, 2.00 µmol, 44%) and recovered starting material **232** (1.50 mg, 2.00 µmol, 42%).

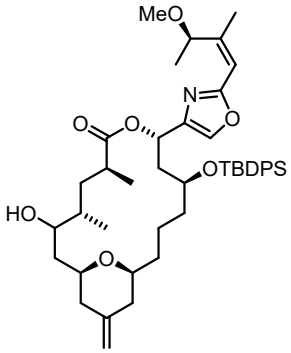
$[\alpha]_D^{20}$ = −7.00 (c = 0.10, $CHCl_3$); **^{1}H NMR** (600 MHz, MeOD): δ = 7.70 (s, 1H), 6.22 (d, *J* = 1.5 Hz, 1H), 5.95 (dd, *J* = 9.4, 2.9 Hz, 1H), 5.25 (qd, *J* = 6.5, 0.9 Hz, 1H), 4.71–4.65 (m, 2H), 4.39 (br s, 1H), 3.80 (4d, *J* = 8.5, 7.8, 5.0, 3.6 Hz, 1H), 3.55–3.48 (m, 1H), 3.30–3.27 (m, 1H),3.21 (s, 3H), 2.90–2.82 (m, 1H), 2.39 (ddd, *J* = 13.8, 9.6, 3.6 Hz, 1H), 2.25–2.18 (m, 1H), 2.15–2.13 (m, 2H), 2.08–2.01 (m, 2H), 2.00–1.93 (m, 3H), 1.89 (s, 3H), 1.86–1.75 (m, 3H), 1.75–1.68 (m, 1H), 1.60 (qui, *J* = 7.0 Hz, 2H), 1.50–1.38 (m, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H) (3 protic H missing); **^{13}C NMR** (150 MHz, MeOD): δ = 177.6, 161.8, 152.5, 147.1, 142.3, 136.1, 114.0, 108.2, 79.6, 76.6, 76.2, 74.8, 68.8, 66.6, 56.8, 49.6, 42.2, 41.9, 41.5, 40.1, 39.6, 39.1, 37.4, 36.1, 35.7, 35.6, 33.1, 30.8, 21.9, 19.5, 18.2, 17.6, 16.3, 14.4, 13.9; **IR** (film): ν = 3379, 2924, 2854, 1713, 1652, 1595, 1455, 1378, 1261, 1094, 972, 808, 759, 546 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{29}H_{45}NO_{10}P$ [*M*−H^-]: 598.2787, found: 598.2793.

(1*S*,4*S*,6*S*,9*S*,11*S*,15*S*,*E*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxabicyclo[13.3.1]nonadec-2-en-3-yl acetate (117c)



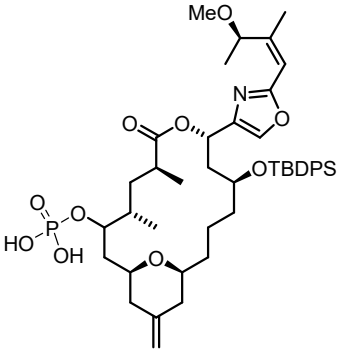
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.56 (m, 4H), 7.43–7.29 (m, 6H), 7.17 (s, 1H), 6.15–6.12 (m, 1H), 5.99 (dd, *J* = 7.0, 3.3 Hz, 1H), 5.22 (d, *J* = 7.7 Hz, 1H), 5.14 (q, *J* = 6.4 Hz, 1H), 4.94 (d, *J* = 4.2 Hz, 0H), 4.74–4.67 (m, 2H), 3.97 (ddd, *J* = 10.7, 7.7, 2.5 Hz, 1H), 3.91 (dt, *J* = 6.9, 3.4 Hz, 1H), 3.24–3.21 (m, 1H), 3.18 (s, 3H), 2.92 (dt, *J* = 9.7, 6.5 Hz, 1H), 2.62 (p, *J* = 6.4 Hz, 1H), 2.31 (dt, *J* = 13.5, 1.8 Hz, 1H), 2.22 (ddd, *J* = 15.0, 7.0, 3.3 Hz, 1H), 2.13 (s, 3H), 2.11–1.93 (m, 2H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.76 (dt, *J* = 13.9, 5.7 Hz, 1H), 1.65–1.40 (m, 4H), 1.39–1.29 (m, 2H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 3H), 1.00 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 175.7, 169.2, 160.2, 154.1, 150.6, 144.3, 140.6, 135.8 (4C), 134.3, 134.1, 133.9, 129.53, 129.50, 127.45 (2C), 127.43 (2C), 119.8, 113.3, 108.7, 77.9, 74.7, 73.6, 70.3, 65.5, 56.5, 41.3, 41.2, 38.5, 38.3, 37.4, 36.2, 36.08, 34.03, 26.9 (3C), 21.0, 20.7, 19.2, 19.1, 17.8, 17.6, 16.9.

(1*S*,4*S*,6*S*,9*S*,11*S*,15*S*)-11-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxy-9-(2-((*R*,*Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-8,19-dioxabicyclo[13.3.1]nonadecan-7-one (230)



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63–7.57 (m, 4H), 7.40–7.34 (m, 2H), 7.34–7.28 (m, 4H), 7.26 (s, 1H), 6.13 (d, *J* = 2.2 Hz, 1H), 5.90 (dd, *J* = 7.8, 4.7 Hz, 1H), 5.11 (q, *J* = 6.4 Hz, 1H), 4.65 (dq, *J* = 7.4, 2.0 Hz, 2H), 3.88 (qd, *J* = 6.4, 4.4 Hz, 1H), 3.79 (td, *J* = 6.1, 3.1 Hz, 1H), 3.29 (ddt, *J* = 11.5, 9.0, 2.7 Hz, 1H), 3.15 (s, 3H), 3.13–3.07 (m, 1H), 2.63–2.56 (m, 1H), 2.50 (br s, 1H), 2.36 (ddd, *J* = 14.5, 8.0, 4.2 Hz, 1H), 2.10 (dt, *J* = 13.3, 2.1 Hz, 1H), 2.06–1.97 (m, 3H), 1.94–1.87 (m, 1H), 1.86 (d, *J* = 1.5 Hz, 3H), 1.82 (ddd, *J* = 13.9, 9.9, 3.5 Hz, 1H), 1.76–1.68 (m, 2H), 1.68–1.52 (m, 2H), 1.46–1.30 (m, 6H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.99 (s, 9H), 0.81 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 176.2, 160.2, 150.6, 145.1, 140.7, 136.05 (2C), 136.04 (2C), 134.8, 134.5, 134.4, 129.64, 129.63, 127.6 (4C), 113.5, 108.4, 78.4, 76.6, 74.9, 70.8, 69.7, 66.1, 56.6, 41.3, 41.1, 40.3, 39.5, 37.3, 37.0, 36.0, 35.5, 33.6, 29.9, 27.2 (3C), 21.4, 19.4, 19.3, 17.7, 16.1, 14.5.

(1*S*,4*S*,6*S*,9*S*,11*S*,15*S*)-11-((*tert*-Butyldiphenylsilyl)oxy)-9-(2-((*R,Z*)-3-methoxy-2-methylbut-1-en-1-yl)oxazol-4-yl)-4,6-dimethyl-17-methylene-7-oxo-8,19-dioxabicyclo[13.3.1]nonadecan-3-yl dihydrogen phosphate (232)



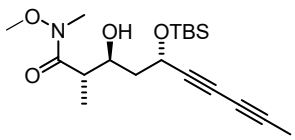
^{1}H NMR (600 MHz, MeOD): δ =7.67–7.64 (m, 2H), 7.63–7.60 (m, 2H), 7.49 (s, 1H), 7.45–7.32 (m, 6H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.97 (dd, *J* = 8.9, 3.1 Hz, 1H), 5.20 (q, *J* = 6.4 Hz, 1H), 4.68 (q, *J* = 1.9 Hz, 1H), 4.66 (q, *J* = 2.0 Hz, 1H), 4.26 (tt, *J* = 7.9, 3.8 Hz, 1H), 3.96 (ddt, *J* = 11.6, 7.9, 3.2 Hz, 1H), 3.57–3.45 (m, 1H), 3.20–3.14 (m, 1H), 3.14 (s, 3H), 2.77 (ddd, *J* = 9.8, 6.9, 5.1 Hz, 1H), 2.31 (ddd, *J* = 14.7, 8.9, 3.1 Hz, 1H), 2.21–2.16 (m, 1H), 2.10–1.89 (m, 7H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.75–1.64 (m, 2H), 1.62–1.52 (m, 2H), 1.52–1.43 (m, 2H), 1.37–1.26 (m, 1H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.22–1.18 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H) (2 protic H missing); **^{13}C NMR** (150 MHz, MeOD): δ = 177.6, 161.5, 152.3, 147.0, 142.1, 137.02 (2C), 136.96 (2C), 136.0, 135.4, 135.2, 130.9, 130.8, 128.7 (2C), 128.6 (2C), 114.1, 108.3, 79.1, 76.24, 76.15, 75.6 (d, *J* = 6.3 Hz) , 71.9, 66.4, 56.8, 49.8, 41.9, 41.9, 40.6, 40.0, 39.5, 38.9, 37.8, 36.4, 35.8 (d, *J* = 6.6 Hz), 27.6 (3C), 21.7, 20.1, 19.5, 17.7, 17.6, 16.6.

6.3. Rhizoxin D

6.3.1. The Western Fragment

(2*S*,3*S*,5*S*)-5-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethyldeca-6,8-diynamide (214a)[128]

Trimethylaluminum (2 M in toluene, 7.83 mL, 16.7 mmol, 2.00 equiv) was added dropwise over



15 min at 0 °C to a solution of freshly dried *N,O*-dimethylhydroxylamin-hydrochloride (1.56 g, 16.0 mmol, 2.05 equiv) in anh. dichloromethane (100 mL). The mixture was stirred for 30 min at 0 °C and additional 30 min at 23 °C before it was cooled to 0 °C. A solution of lactones **213a**/**b** (2.40 g, 7.83 mmol, 1 equiv) in anhydrous dichloromethane (20 mL) was added over 15 min and the cooling bath was removed. After stirred for 1 h at 23 °C, excess reagent was quenched by the addition of sat. aq. sodium potassium tartrate solution (100 mL). The mixture was stirred for 1 h until clean phase separation was observed. The aq. layer was diluted with ethyl acetate (150 mL) and the layers were separated. The aq. layer was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1) yielding the desired isomer **214a** (1.90 g, 5.17 mmol, 66%) and the undesired isomer **214b** (274 mg, 0.745 mmol, 10%).

major-isomer (**214a**)[128]

$[\alpha]_D^{20}$ = −44.6 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.77–4.68 (m, 1H), 3.90 (ddd, *J* = 8.1, 5.6, 2.6 Hz, 1H), 3.71 (s, 3H), 3.58 (d, *J* = 7.1 Hz, 1H), 3.19 (s, 3H), 2.96–2.83 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.85 (ddd, *J* = 13.9, 9.0, 2.3 Hz, 1H), 1.73 (ddd, *J* = 13.7, 10.2, 3.0 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = δ 177.1, 76.7, 76.6, 70.1, 69.3, 63.9, 61.6, 60.3, 43.9, 40.2, 31.8, 25.8(3C), 18.2, 14.8, 4.3, −4.6, −5.2; **IR** (film): ν = 2956, 2929, 2857, 1641, 1462, 1389, 1252, 1089, 996, 838, 811, 780 cm^{-1}; **MS:** *m/z* calcd for $C_{19}H_{33}NO_4SiNa$ [*M*+Na^+]: 390.2077, found 390.2071.

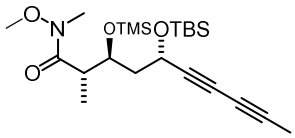
minor-isomer (**214b**)

$[\alpha]_D^{20}$ = −51.9 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.69 (t, *J* = 7.5 Hz, 1H), 3.88 (dtd, *J* = 9.3, 6.0, 3.8 Hz, 1H), 3.71 (s, 3H), 3.58 (d, *J* = 6.5 Hz, 1H), 3.20 (s, 3H), 2.98–2.90 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.89–1.83 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 177.0, 77.0, 76.0, 71.6, 70.3, 64.0, 62.3, 61.7, 44.0, 40.4, 30.4,

25.9(3C), 18.3, 14.7, 4.5, −4.4, −4.9; **IR** (film): ν = 2956, 2930, 2857, 1639, 1463, 1389, 1253, 1082, 994, 868, 836, 779 cm^{-1}; **MS:** *m*/*z* calcd for $C_{19}H_{33}NO_4SiNa$ [*M*+Na^+]: 390.2077, found 390.2071.

(2*S*,3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,2-dimethyl-3-((trimethylsilyl)oxy)deca-6,8-diynamide (221)

Freshly distilled trimethylsilyl chloride (373 µL, 2.94 mmol, 1.20 equiv) was added at 0 °C to a solution of Weinreb amide **214a** (901 mg, 2.45 mmol, 1 equiv), 4-dimethylaminopyridine (29.9 mg, 0.245 mmol, 10 mol%) and triethylamine (512 µL, 3.68 mmol, 1.50 equiv) in anh. dichloromethane (20 mL). After stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to 23 °C. After additional 2 h, excess reagent was quenched by the addition of aq. phosphate buffer solution (pH 7, 20 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to yield the title compound (1.08 g, 2.45 mmol, quant.) as a colorless liquid.



$[\alpha]_D^{20}$ = −4.90 (c = 0.65, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.59–4.52 (m, 1H), 4.11 (ddd, *J* = 7.9, 7.9, 2.6 Hz, 1H), 3.70 (s, 3H), 3.16–3.09 (m, 1H), 3.17 (s, 3H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.93–1.85 (m, 1H), 1.77 (ddd, *J* = 14.1, 8.2, 4.1 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H), 0.10 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.4, 77.0, 76.9, 70.3, 70.2, 64.0, 61.5, 59.8, 43.4, 41.8, 32.1, 26.0 (3C), 18.2, 12.5, 4.5, 0.6 (3C), −3.6, −4.3; **IR** (film): ν = 2957, 2858, 1664, 1463, 1377, 1250, 1093, 1042, 840, 778 cm^{-1}; **MS:** *m*/*z* calcd for $C_{22}H_{42}O_4Si_2$ [*M*+H^+]: 440.2647, found 440.2642.

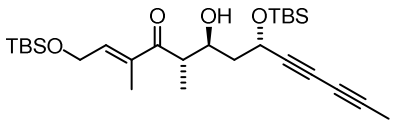
0.30 M $CeCl_3$·2LiCl solution[145]

A suspension of anh. lithium chloride (1.29 g, 0.030 mmol, 2.00 equiv) and commercially available anh. cerium(III) chloride (3.74 g, 0.015 mmol, 1 equiv) in anh. tetrahydrofuran (50 mL) was stirred for 2 d at 23 °C. The stirring was stopped to allow undissolved material to settle and molecular sieves (3 Å, pellets) were added to the colorless suspension. After 1 d, the solution was ready to be used in the following reactions.

Direct addition to the β*-lactone* ***213***[128]

(9*S*,10*S*,12*S*,*E*)-10-Hydroxy-2,2,3,3,7,9,14,14,15,15-decamethyl-12-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-6-en-8-one (216)

n-BuLi (1.6 M in hexanes, 67.3 µL, 0.108 mmol, 2.20 equiv) was added dropwise at −78 °C to a solution of alkenyl iodide **215** (30.6 mg, 98.0 µmol, 2.00 equiv) in anh. diethyl ether (500 µL). After stirring for 30 min, the solution was transferred at −78 °C via cannula into a solution of $CeCl_3$·2LiCl (0.21 M in diethyl ether, 2.00 mL, 0.425 mmol, 8.70 equiv). The colorless suspension was stirred for 2 h at −78 °C before a solution of lactone **213** (15.0 mg, 49.0 µmol, 1 equiv) in anh. diethyl ether (400 µL) was added. After stirring for 1 h, the mixture was diluted with ethyl acetate (5 mL) and excess reagent was quenched by the addition of water (10 mL). The layers were separated and the aq. layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) and subsequent preparative LC (Kromasil 100-5C18 5 µm, 150 mm × 30.0 mm, MeOH/H_2O, 90:10, 35 °C, 35 mL/min) to give the title compound (6.90 mg, 14.0 µmol, 29%)



$[\alpha]_D^{20}$ = −12.3 (c = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.67 (td, *J* = 5.1, 1.4 Hz, 1H), 4.74–4.70 (m, 1H), 4.45–4.41 (m, 2H), 4.04 (dtd, *J* = 10.2, 5.9, 2.1 Hz, 1H), 3.30 (p, *J* = 6.8 Hz, 1H), 3.23 (d, *J* = 5.9 Hz, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.83 (ddd, *J* = 14.0, 8.3, 2.2 Hz, 1H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H), 0.10 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 206.4, 143.8, 135.5, 77.0, 76.3, 70.6, 69.7, 64.0, 61.2, 60.9, 44.2, 43.1, 26.0(3C), 25.9(3C), 18.5, 18.3, 15.7, 11.7, 4.5, −4.5, −5.1, −5.1(2C); **IR** (film): ν = 2955, 2930, 2857, 1663, 1463, 1254, 1103, 1061, 1006, 836, 778 cm^{-1}; **MS:** *m*/*z* calcd for $C_{27}H_{48}O_4Si_2Na$ [*M*+Na^+]: 515.2988, found 515.2983.

Using the unprotected Weinreb amide ***214a****:*

Freshly titrated *t*-BuLi (2.18 M in pentane, 2.45 mL, 5.33 mmol, 9.80 equiv) was carefully added to anh. diethyl ether (3 mL) at −78 °C (color change to yellow). After stirring for 10 min, a solution of alkenyl iodide **215** (811 mg, 2.72 mmol, 5.00 equiv) in anh. diethyl ether (2 mL) was added dropwise over 10 min. Stirring was continued for 30 min at −78 °C. In parallel, a solution of $CeCl_3$·2LiCl (0.30 M in tetrahydrofuran, 7.25 mL, 2.18 mmol, 4.00 equiv) was added at −78 °C to a

solution of Weinreb amide **214a** (200 mg, 0.544 mmol, 1 equiv) in anh. tetrahydrofuran (3 mL). After 5 min, the organolithium-solution was added via cannula dropwise to the mixture causing a color change to deep orange. After stirring for 4 h at −78 °C, the reaction was quenched by the addition of sat. aq. ammonium chloride solution (10 mL). The mixture was allowed to warm to 23 °C, before the layers were separated and the aq. layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to give the title compound (140 mg, 0.292 mmol, 54%) and recovered starting material **214a** (37.0 mg, 0.101 mmol, 19%).

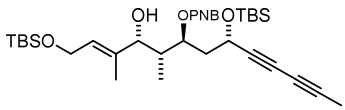
*Using the TMS-protected Weinreb amide **221**:*

Freshly titrated *t*-BuLi (2.18 M in pentane, 5.62 mL, 12.3 mmol, 5.00 equiv) was added to anh. tetrahydrofuran at −78 °C (color change to yellow). After 10 min, alkenyl iodide **215** (1.91 g, 6.13 mmol, 2.50 equiv) was added dropwise and stirring was continued for 30 min at −78 °C. In parallel, a solution of $CeCl_3 \cdot 2LiCl$ (0.30 M in tetrahydrofuran, 16.3 mL, 4.90 mmol, 2.00 equiv) was added at −78 °C to a solution of Weinreb amide **221** (1.08 g, 2.45 mmol, 1 equiv) in anh. tetrahydrofuran (25 mL). After 5 min, the solution of **215** was added via cannula dropwise to the mixture causing a color change to deep orange. After stirring for 1.5 h at −78 °C, the reaction was quenched by the addition of aq. phosphate buffer solution (pH 7, 50 mL). The mixture was allowed to warm to 23 °C before the layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated.

Camphorsulfonic acid (56.9 mg, 0.245 mmol, 10 mol%) was added at 0 °C to a solution of the residue in anh. dichloromethane (50 mL) and anh. methanol (10 mL). After stirring for 5 min, excess reagent was neutralized by the addition of aq. phosphate buffer solution (pH 7, 50 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification of the crude product by flash chromatography (hexane/ethyl acetate 20:1 grading to 10:1) afforded the desired product **216** (1.00 g, 2.02 mmol, 83%).

(5*S*,7*S*,8*R*,9*R*,*E*)-9-Hydroxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-yl 4-nitrobenzoate (217)

4-Nitrobenzaldehyde (548 mg, 3.63 mmol, 3.00 equiv) was added at −25 °C to a solution of

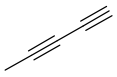


compound **216** (596 mg, 1.21 mmol, 1 equiv) in anh. tetrahydrofuran (degassed, 18 mL). After stirring for 10 min, a solution of samarium(II) iodide (0.10 M in tetrahydrofuran, 2.42 mL, 0.242 mmol, 20 mol%) was added and the mixture was stirred in the dark at −25 °C. The progress of the reaction was followed by HPLC-MS (Zorbax Eclipse Plus C18, 125 × 4.6 mm, 1.8 µm, methanol/water 95:5). After complete consumption of the starting material (approx. 3 h) sat. aq. sodium hydrogen carbonate solution (20 mL) was added. The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was diluted with hexane (10 mL) and the supernatant containing the product was carefully removed from precipitated benzaldehyde. This procedure was repeated three times. The combined organic layers were concentrated and the crude product was purified by flash chromatography to obtain **217** (635 mg, 0.986 mmol, 82%) as yellowish oil.

$[\alpha]_D^{20}$ = −7.50 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.32–8.27 (m, 2H), 8.24–8.19 (m, 2H), 5.64 (t, *J* = 6.3 Hz, 1H), 5.24 (q, *J* = 6.2 Hz, 1H), 4.44 (t, *J* = 6.5 Hz, 1H), 4.24 (qd, *J* = 13.0, 6.1 Hz, 2H), 3.93 (t, *J* = 4.4 Hz, 1H), 2.15–2.10 (m, 3H), 2.00 (d, *J* = 3.5 Hz, 1H), 1.88 (d, *J* = 0.9 Hz, 3H), 1.67–1.64 (m, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.07 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.7, 150.8, 150.1 136.4, 135.7, 131.0 (2C), 126.9, 123.7 (2C), 77.3, 76.1, 76.1, 74.5, 70.1, 63.7, 60.2, 60.1, 39.7, 39.4, 26.1 (3C), 25.9 (3C), 18.2, 13.0, 9.5, 4.4, −4.3, −5.0, −5.0, −5.2; **IR** (film): ν = 2955, 2929, 2857, 1723, 1530, 1471, 1348, 1277, 1101, 1014, 837, 779, 720 cm^{-1}; **MS:** *m*/*z* calcd for $C_{34}H_{53}NO_7Si_2Na$ [*M*+Na^+]: 666.3254, found 666.3253.

6.3.2. The Eastern Fragment

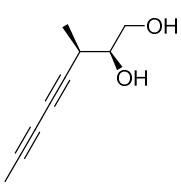
Penta-1,3-diyne (170)[136b]



Ammonia (300mL) was condensed into a 1 L three-necked-cooling flask at −78 °C equipped with a mechanical stirrer and an addition funnel. The solution was allowed to warm to −47 °C, before a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ (400 mg) was added. Small pieces of sodium (20.8 g, 905 mmol, 3.00 equiv) were added one by one, awaiting vanish of the blue color of the solution. After the sodium was completely dissolved, the 1,4-dichloro-2-butyne (29.5 mL, 302 mmol, 1 equiv) was added over 45 min.[e] The mixture became a thick suspension and stirring was continued for another 15 min at −47 °C, before methyl iodide (26.3 mL, 142 mmol, 1.40 equiv) was added over 20 min via a cannula.[f] The mixture became liquid again and stirring was continued for 15 min. The flask was attached to a cooling trap and the mixture was allowed to slowly warm to 23 °C. Undecane (150 mL) was added in several portions (cooling trap still attached). After stirring for 30 min, the mixture was poured onto ice (300 mL). The layers were separated and the aq. layer was extracted with undecane (7 × 35 mL). The combined organic layers were washed with aq. hydrochloric acid (2 N, 250 mL), dried over magnesium sulfate and filtered. The product was distilled off from the filtrate (25–50 °C, 10 mbar, long Vigreux column, the dist. bridge cooled to 0 °C and the collection flask to −78 °C) to give diyne **170** (95% in undecane, 10.3 g, 153 mmol, 51%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–1.91 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 74.3, 68.6, 64.0 (2C), 4.2.

(2*S*,3*R*)-3-Methylocta-4,6-diyne-1,2-diol (204a)



n-BuLi (1.6 M in hexanes, 44.4 mL, 71.0 mmol, 2.00 equiv) was added dropwise over 30 min at −78 °C to a solution of diyne **170** (95% in decane, 5.27 g, 78.1 mmol, 2.20 equiv) in anh. dichloromethane (200 mL). After stirring for 30 min, the mixture was warmed to 0 °C and diethylaluminium chloride (25 *wt%* in toluene, 35.7 mL, 71.0 mmol, 2.00 equiv) was added. After stirring for 3 h at 0 °C, a solution of epoxide **169**[131] (3.12 g, 35.5 mmol, 1 equiv) in anh. dichloromethane (14 mL) was added over 15 min. The reaction was left to proceed overnight at 0 °C before excess reagent was quenched by

[e] At each step the reaction was so exothermic, that the evaporation of ammonia gas could be observed. Slow addition prevented the evaporation of product.

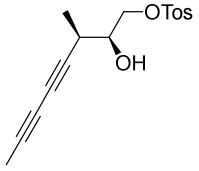
[f] The cannula was longing directly above the surface of the reaction mixture to avoid exposure of the methyl iodide to ammonia gas.

the careful addition of aq. hydrochloric acid (1.0 N, 150 mL) and sat. aq. potassium sodium tartrate solution (150 mL). The biphasic mixture was stirred for 4 h until the two layers could be separated. The aq. layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (hexane/ethyl acetate 4:1 grading to 1:1) afforded diol **204a** (5.12 g, 33.6 mmol, 95%).

$[\alpha]_D^{20}$ = +53.0 (c = 1.79, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.84 (ddd, *J* = 11.0, 6.6, 3.1 Hz, 1H), 3.69 (ddd, *J* = 11.2, 6.9, 4.6 Hz, 1H), 3.59 (dddd, *J* = 10.4, 7.2, 5.6, 3.2 Hz, 1H), 2.66 (qdq, *J* = 7.0, 7.0, 1.1 Hz, 1H), 2.41 (br s, 1H), 1.96 (br s, 1H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 74.9, 74.8 (2C), 67.9, 64.7, 64.2, 30.3, 16.8, 4.3; **IR** (film): ν = 3345, 2940, 1453, 1053, 563 cm^{-1}; **MS:** *m/z* calcd for $C_9H_{12}O_2Na$ [*M*+Na^+]: 175.0730, found 175.0730.

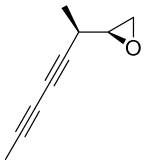
(2*S*,3*R*)-2-Hydroxy-3-methylocta-4,6-diyn-1-yl 4-methylbenzenesulfonate (203)

Dibutyltin(IV) oxide (29.3 mg, 0.118 mmol, 10 mol%) was added to a solution of diol **204a** (179 mg, 1.18 mmol, 1 equiv) in anh. dichloromethane (6 mL). After stirring for 5 min, triethylamine (180 µL, 1.30 mmol, 1.10 equiv) and 4-toluolsulfonyl chloride (246 mg, 1.30 mmol, 1.10 equiv) were added. Stirring was continued for 18 h, before the excess reagent was quenched by the addition of sat. aq. ammonium chloride solution (10 mL). The layers were separated and the aq. layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 2:1) to afford **203** (351 mg, 1.15 mmol, 97%).



$[\alpha]_D^{20}$ = +68.6 (c = 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.30 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.08 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.74–3.67 (m, 1H), 2.65–2.56 (m, 1H), 2.46 (br s, 3H), 2.22 (br s, 1H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 145.3, 132.6, 130.1 (2C), 128.2 (2C), 75.7, 75.2, 72.6, 72.2, 68.3, 64.1, 29.9, 21.9, 16.8, 4.3; **IR** (film): ν = 3528, 2980, 1598, 1358, 1190, 1175, 1096, 959, 814, 667, 555 cm^{-1}; **MS:** *m/z* calcd for $C_{16}H_{18}O_4SNa$ [*M*+Na^+]: 329.0818, found 329.0817.

(*S*)-2-((*R*)-Hepta-3,5-diyn-2-yl)oxirane (206)



1,8-Diazabicyclo[5.4.0]undec-7-ene (1.10 mL, 7.35 mmol, 2.00 equiv) was added at 0 °C to a solution of tosylate **203** (1.13 g, 3.68 mmol, 1 equiv) in anh. dichloromethane (30 mL). After complete consumption of the starting material (approx. 1 h), water (30 mL) was added, the layers were separated and the aq. layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure (40 °C, >500 mbar) to afford the title compound (426 mg, 3.18 mmol, 86%).

*Direct transformation from the diol **204a**:*

Dibutyltin(IV) oxide (425 mg, 1.71 mmol, 5 mol%) was added to a solution of diol **204a** (5.20 g, 34.2 mmol, 1 equiv) in anh. dichloromethane (175 mL). After stirring for 5 min, triethylamine (5.00 mL, 35.9 mmol, 1.05 equiv) and 4-toluolsulfonyl chloride (6.84 g, 35.9 mmol, 1.05 equiv) were added. Stirring was continued for 14 h at 23 °C, before 1,8-diazabicycloundec-7-ene (10.2 mL, 68.3 mmol, 2.00 equiv) was added. After complete consumption of the starting material (approx. 2 h), water (150 mL) was added, the layers were separated and the aq. layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure (40 °C, >500 mbar). The crude product was purified by flash chromatography (pentane/diethyl ether 10:1) to afford epoxide **206** (3.30 g, 24.6 mmol, 72%).

$[\alpha]_D^{20}$ = +59.7 (c = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.91 (ddd, *J* = 6.4, 3.8, 2.6 Hz, 1H), 2.78 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.67 (dd, *J* = 4.9, 2.5 Hz, 1H), 2.51–2.39 (m, 1H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.32 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 75.3, 74.9, 67.6, 64.1, 54.7, 46.4, 29.9, 17.7, 4.3; **IR** (film): ν = 2982, 2932, 1722, 1455, 1258, 1073, 1025, 922, 882, 828 cm^{-1}; **MS**: *m/z* calcd for $C_9H_{10}O$ [*M*]: 134.0733, found 134.0732.

4-Bromocyclopent-1-ene (199)[141]

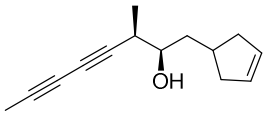
Bromine (1.60 mL, 31.2 mmol, 1.05 equiv) was added over 60 min at −30 °C to a solution of triphenylphosphine (8.19 g, 31.2 mmol, 1.05 equiv) in anh. dichloromethane (30 mL). After stirring for additional 30 min, a premixed solution of 3-cyclopenten-1-ol (2.50 g, 29.7 mmol, 1 equiv) and pyridine (2.50 mL, 29.7 mmol, 1.00 equiv) was added over 1 h at such a rate as to keep the reaction temperature below −15 °C. The mixture was allowed to warm to 23 °C. After stirring for 18 h, the excess reagent was quenched by the addition of sat. aq. sodium thiosulfate

solution (30 mL). The layers were separated and the aq. layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and the organic solvent was removed by distillation (35 °C, ≥600 mbar, Vigreux column). The precipitate was filtered off and the filtrate was purified by flash chromatography (pure pentane). The fractions containing the product were concentrated by distillation to afford **199** (4.22 g, 28.7 mmol, 97%) as a colorless liquid. The obtained NMR spectra were in full agreement with those reported in the literature.[167]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79–5.74 (m, 2H), 4.60 (tt, *J* = 6.7, 3.1 Hz, 1H), 3.03–2.94 (m, 2H), 2.86–2.77 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 128.8, 48.7, 44.9.

(2*R*,3*R*)-1-(Cyclopent-3-en-1-yl)-3-methylocta-4,6-diyn-2-ol (201).

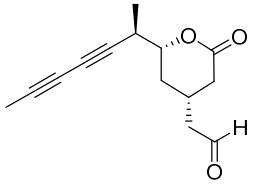
A catalytic amount of 1,2-dibromoethane (20 µL) was added to a suspension of flame dried magnesium (145 mg, 5.96 mmol, 4.00 equiv) in anh. diethyl ether (3 mL). The mixture was briefly heated using a heat gun until the formation of gas was observed. Compound **199** (438 mg, 2.98 mmol, 2.00 equiv) was added dropwise to the suspension. After stirring for 2 h, the solution of the Grignard reagent was cannulated carefully into a −40 °C cold suspension of copper(I) iodide (56.8 mg, 0.30 mmol, 20 mol%) in anh. diethyl ether (1 mL). Stirring was continued for 30 min −40 °C, before epoxide **206** (200 mg, 1.49 mmol, 1 equiv) in anh. diethyl ether (0.5 mL) was added dropwise. After stirring for 4 h at −40 °C, the excess reagent was quenched by the addition of sat. aq. ammonium chloride solution (10 mL) and the layers were separated. The aq. layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 6:1) to afford title compound (260 mg, 1.29 mmol, 86%).



$[\alpha]_D^{20}$ = +9.20 (c = 0.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.73–5.63 (m, 2H), 3.59 (dd, *J* = 9.0, 4.5 Hz, 1H), 2.64 (ddt, *J* = 6.7, 5.6, 1.4 Hz, 1H), 2.58–2.43 (m, 3H), 2.01 (tddd, *J* = 16.8, 8.3, 3.9, 2.4 Hz, 2H), 1.92 (d, *J* = 1.1 Hz, 3H), 1.66–1.62 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 130.2, 129.7, 78.0, 74.5, 73.4, 67.6, 64.3, 40.4, 39.6, 38.5, 34.3, 34.0, 15.8, 4.3; **IR** (film): ν = 3393, 2931, 2842, 1451, 1070, 1038, 971 cm^{-1}; **MS:** *m*/*z* calcd for $C_{14}H_{18}ONa$ [*M*+Na^+]: 225.1248, found 225.1250.

2-((2*R*,4*S*)-2-((*R*)-Hepta-3,5-diyn-2-yl)-6-oxotetrahydro-2*H*-pyran-4-yl)acetaldehyde (165)

Ozone was bubbled through a solution of cyclopentene **201** (150 mg, 0.742 mmol, 1 equiv) in anh. dichloromethane (10 mL) at −78 °C until a pale blue color persisted. The solution was flushed with argon, before triphenylphosphine (389 mg, 1.48 mmol, 2.00 equiv) was added. After stirring for 1 h at −78 °C, the mixture was allowed to warm to 23 °C and was concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1 grading to 1:1) to give dialdehyde **207** (153 mg, 0.653 mmol, 88%).



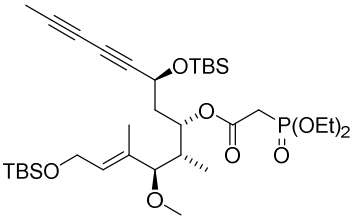
Ytterbium(III) trifluoromethanesulfonate hydrate (40.5 mg, 65.0 µmol, 10 mol%) was added at 0 °C to a solution of dialdehyde **207** (153 mg, 0.653 mmol, 1 equiv), 2,2,6,6-tetramethyl-1-piperidinyloxy (20.4 mg, 0.131 mmol, 20 mol%) and (diacetoxyiodo)benzene (442 mg, 1.37 mmol, 2.10 equiv) in anh. dichloromethane (6 mL). After stirring for 1 h at 23 °C, the mixture was diluted with dichloromethane (10 mL) and sat. aq. sodium thiosulfate solution (10 mL). The layers were separated and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography to give the title compound (139 mg, 0.598 mmol, 92%).

$[\alpha]_D^{20}$ = −18.6 (c = 0.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 4.16 (ddd, *J* = 11.5, 6.9, 3.3 Hz, 1H), 2.85–2.75 (m, 2H), 2.60–2.53 (m, 3H), 2.26 (dtd, *J* = 13.7, 3.1, 1.7 Hz, 1H), 2.14 (dd, *J* = 17.5, 10.5 Hz, 1H), 1.92 (d, *J* = 1.1 Hz, 3H), 1.39 (dt, *J* = 13.7, 11.5 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 199.5, 169.7, 81.9, 75.2, 75.2, 68.6, 64.1, 49.8, 35.9, 32.9, 32.0, 25.8, 17.0, 4.3; **IR** (film): ν = 2918, 1724, 1385, 1235, 1082 cm^{-1}; **MS:** *m*/*z* calcd. for $C_{14}H_{16}O_3Na$ [*M*+Na^+]: 255.0990 found 255.0992.

6.3.3. Combination of Fragments

(5*S*,7*S*,8*S*,9*R*,*E*)-9-Methoxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-yl 2-(diethoxyphosphoryl)acetate (194)

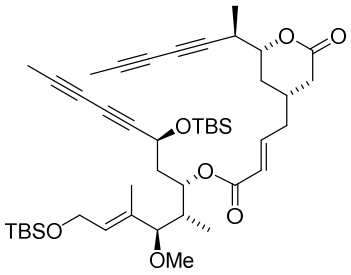
Molecular sieves (3Å, 15 pellets) and EDC (224 mg, 1.17 mmol, 1.80 equiv) were added at 0 °C to a solution of diethylphosphonoacetic acid (313 µL, 1.95 mmol, 3.00 equiv) in anh. dichloromethane (16 mL). After stirring for 15 min, a solution of alcohol **219** (330 mg, 0.649 mmol, 1 equiv) in anh. dichloromethane (12 mL) and 4-dimethylaminopyridine (23.8 mg, 0.195 mmol, 30 mol%) were successively added. The mixture was allowed to warm to 23 °C and stirring was continued for 2 h, before the mixture was filtered through a pad of cotton which was carefully rinsed with dichloromethane (50 mL). The filtrate was diluted with sat. aq. sodium chloride solution (50 mL) and extracted with dichloromethane (3 × 60 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 3:1 grading to 2:1) to afford **194** (400 mg, 0.649 mmol, 90%) as a pale yellow oil.



$[\alpha]_D^{20}$ = −10.0 (c = 0.20, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.53–5.48 (m, 1H), 4.98–4.89 (m, 1H), 4.42–4.35 (m, 1H), 4.31 (dd, *J* = 13.2, 7.1 Hz, 1H), 4.22–4.09 (m, 5H), 3.19 (d, *J* = 7.0 Hz, 1H), 3.17 (s, 3H), 2.93 (dq, *J* = 21.8, 14.3 Hz, 2H), 2.10–2.01 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.89 (td, *J* = 9.2, 8.3, 3.3 Hz, 2H), 1.61–1.58 (m, 3H), 1.34 (t, *J* = 7.1 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.9, 133.2, 129.3, 87.5, 76.5, 73.3, 63.8, 62.8, 62.6, 59.9, 59.9, 56.5, 38.5, 38.3, 35.3, 34.0, 26.1 (3C), 25.9 (3C), 18.5, 18.3, 16.4, 16.3, 16.3, 11.9, 9.8, 4.5, −4.5, −5.1 (2C), −5.2; **IR** (film): ν = 2955, 2929, 2856, 1735, 1471, 1463, 1255, 1090, 1048, 1024, 834, 777 cm^{-1}; **MS:** *m*/*z* calcd for $C_{34}H_{63}O_8PSi_2Na$ [*M*+Na^+]: 709.3689, found 709.3691.

(5*S*,7*S*,8*S*,9*R*,*E*)-9-Methoxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-yl (*E*)-4-((2*R*,4*R*)-2-((*R*)-hepta-3,5-diyn-2-yl)-6-oxotetrahydro-2*H*-pyran-4-yl)but-2-enoate (193)

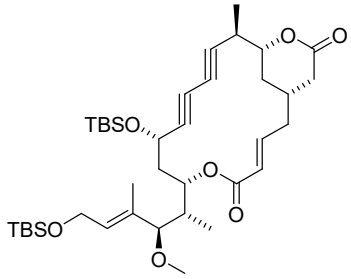
Phosphonate **194** (161 mg, 0.235 mmol, 1 equiv) was added to a suspension of anh. lithium chloride (24.9 mg, 0.588 mmol, 2.50 equiv) in anh. acetonitrile (6 mL). After stirring for 20 min, 1,8-diazabicyclo[5.4.0]undec-7-ene (38.8 µL, 0.259 mmol, 1.10 equiv) was added and the mixture was stirred for 30 min at 23 °C, before it was cooled to 0 °C. A solution of the aldehyde **165** (109 mg, 0.470 mmol, 2.00 equiv) in anh. acetonitrile (3 mL) was slowly added. After stirring 12 h at 23 °C, aq. phosphate buffer solution (pH 7, 10 mL) was added and the aq. layer was extracted with methyl *tert*-butyl ether (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 1:1) to afford **193** (138 mg, 0.180 mmol, 77%) and recovered starting material **194** (26 mg, 38.0 µmol, 16%).



$[\alpha]_D^{20}$ = −10.0 (c = 0.20, $CHCl_3$).;**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.83 (dt, *J* = 15.4, 7.3 Hz, 1H), 5.87 (dt, *J* = 15.5, 1.5 Hz, 1H), 5.51 (ddd, *J* = 8.2, 5.0, 1.4 Hz, 1H), 4.91 (ddd, *J* = 10.7, 4.3, 2.4 Hz, 1H), 4.39–4.28 (m, 2H), 4.17 (ddd, *J* = 13.2, 4.7, 1.2 Hz, 1H), 4.10 (ddd, *J* = 11.7, 7.0, 3.0 Hz, 1H), 3.16 (s, 3H), 3.14–3.18 (m, 1H), 2.81 (ddt, *J* = 8.0, 6.9, 1.1 Hz, 1H), 2.68 (td, *J* = 11.0, 10.4, 1.9 Hz, 1H), 2.28–2.18 (m, 3H), 2.16–2.08 (m, 3H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.94–1.80 (m, 2H), 1.64–1.61 (s, 3H), 1.41–1.31 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 6H), 0.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.9, 165.3, 144.4, 133.3, 129.7, 124.4, 88.1, 81.8, 76.9, 76.7, 75.2, 75.2, 71.8, 69.5, 68. 6.64.1, 63.9, 59.9, 59.7, 56.4, 38.7, 38.3, 37.9, 36.0, 32.9, 32.0, 30.8, 26.1 (3C), 25.8 (3C), 18.5, 18.1, 17.0, 11.6, 10.1, 4.5, 4.3, −4.5, −5.0(2C), −5.2; **IR** (film): ν = 2929, 2856, 1718, 1250, 1089, 1048, 835, 778 cm^{-1}; **MS:** *m*/*z* calcd for $C_{44}H_{68}O_7Si_2Na$ [*M*+Na^+]: 787.4396, found 787.4396.

Macrocyle 223

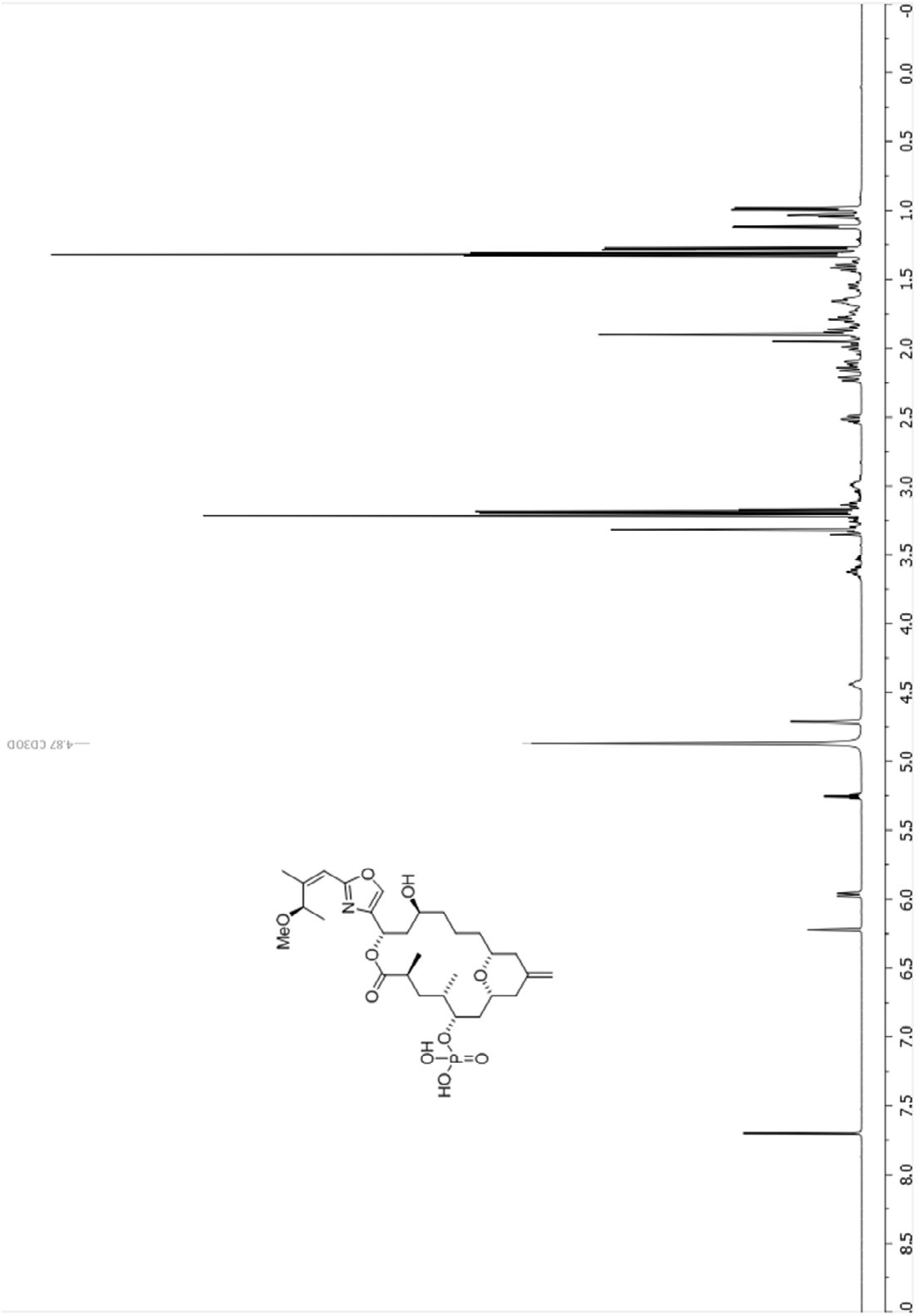
Molecular sieves (4 Å, 100 mg and 5 Å, 200 mg) were added to a solution of **193** (15.4 mg, 20.1 µmol, 1 equiv) in anh. toluene (20 mL). After stirring for 1 h, a solution of alkyne metathesis catalyst **8** (4.19 mg, 4.02 mmol, 20 mol%)[31] in anh. toluene (1 mL) was added. The suspension was stirred for 45 min at 23 °C, before a second batch of the catalyst **8** (4.19 mg, 4.02 mmol, 20 mol%) in anh. toluene (1 mL) was added. After stirring for additional 1 h, the mixture was filtered through a plug of silica which was rinsed with methyl *tert*-butyl ether (30 mL). The filtrate was concentrated and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1 grading to 1:1) to afford title compound (7.3 mg, 11.0 µmol, 53%).

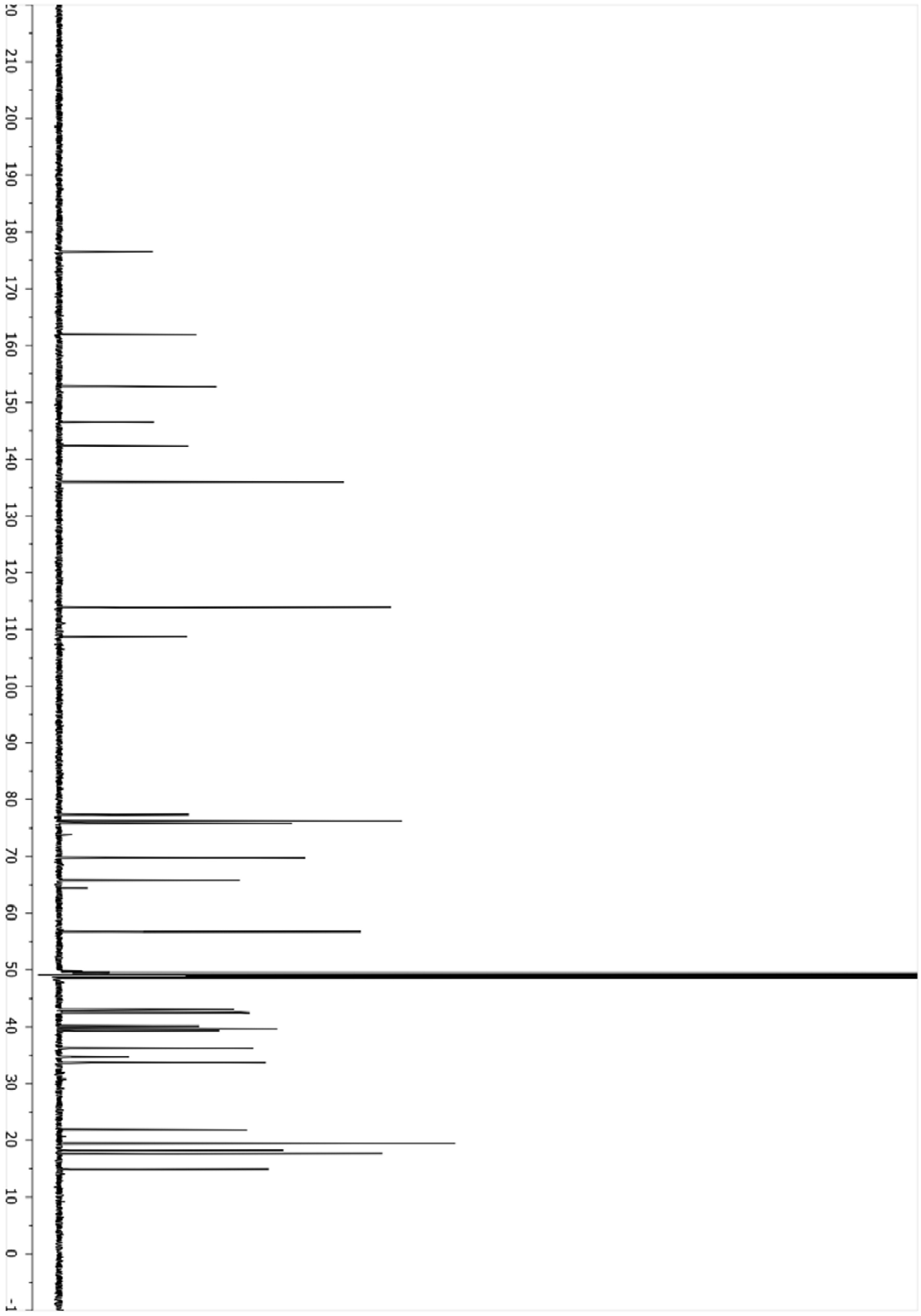


$[\alpha]_D^{20}$ = +4.00 (c = 0.10, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.84 (ddd, *J* = 15.7, 10.0, 5.7 Hz, 1H), 5.92 (d, *J* = 15.8 Hz, 1H), 5.45 (t, *J* = 5.4 Hz, 1H), 4.74 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.35–4.28 (m, 2H), 4.20 (dd, *J* = 13.3, 4.4 Hz, 1H), 4.02 (ddd, *J* = 11.2, 7.4, 4.0 Hz, 1H), 3.17 (s, 3H), 3.16–3.14 (m, 1H), 2.79–2.67 (m, 2H), 2.53–2.39 (m, 2H), 2.24 (dd, *J* = 17.3, 10.8 Hz, 1H), 2.16–2.01 (m, 3H), 2.00–1.89 (m, 1H), 1.82 (dd, *J* = 14.2, 4.0 Hz, 1H), 1.66 (s, 3H), 1.38–1.28 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.3, 165.6, 144.4, 134.6, 129.8, 126.3, 88.7, 82.4, 80.6, 78.8, 72.6, 69.6, 68.8, 63.2, 59.9, 56.4, 39.3, 38.0, 37.6, 36.4, 34.1, 30.7, 29.7, 26.1 (3C), 25.9 (3C), 18.5, 18.2, 16.6, 11.4, 10.0, −4.3, −4.8, −4.99, −5.01; **IR** (film): ν = 2927, 2855, 1718, 1463, 1258, 1083, 837, 779 cm^{-1}; **HRMS** (ESI): *m*/*z*: calcd. for $C_{38}H_{62}O_7Si_2Na$ [*M*+Na^+]: 709.3926, found: 709.3924.

7. Appendix

7.1. Spectra

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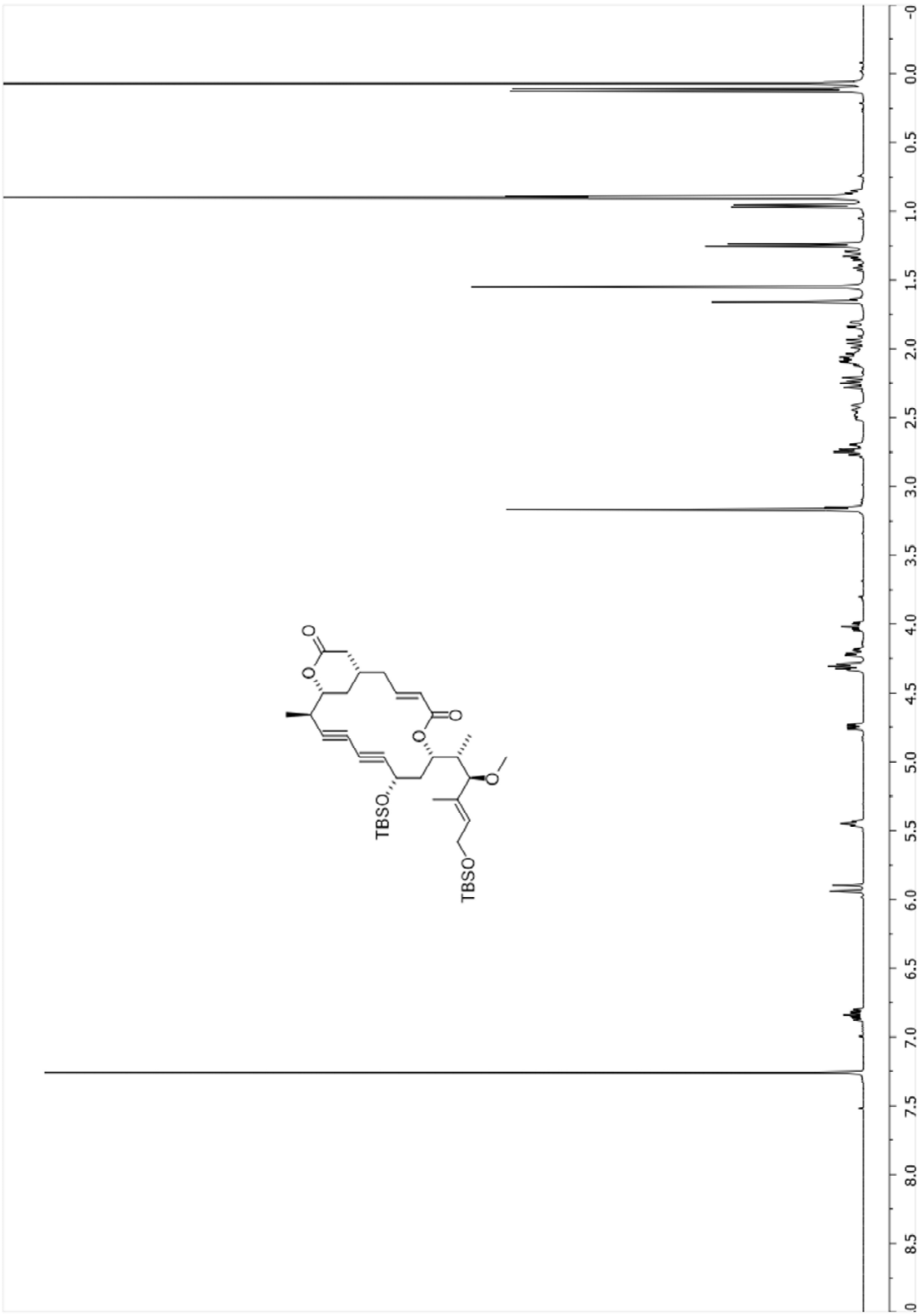
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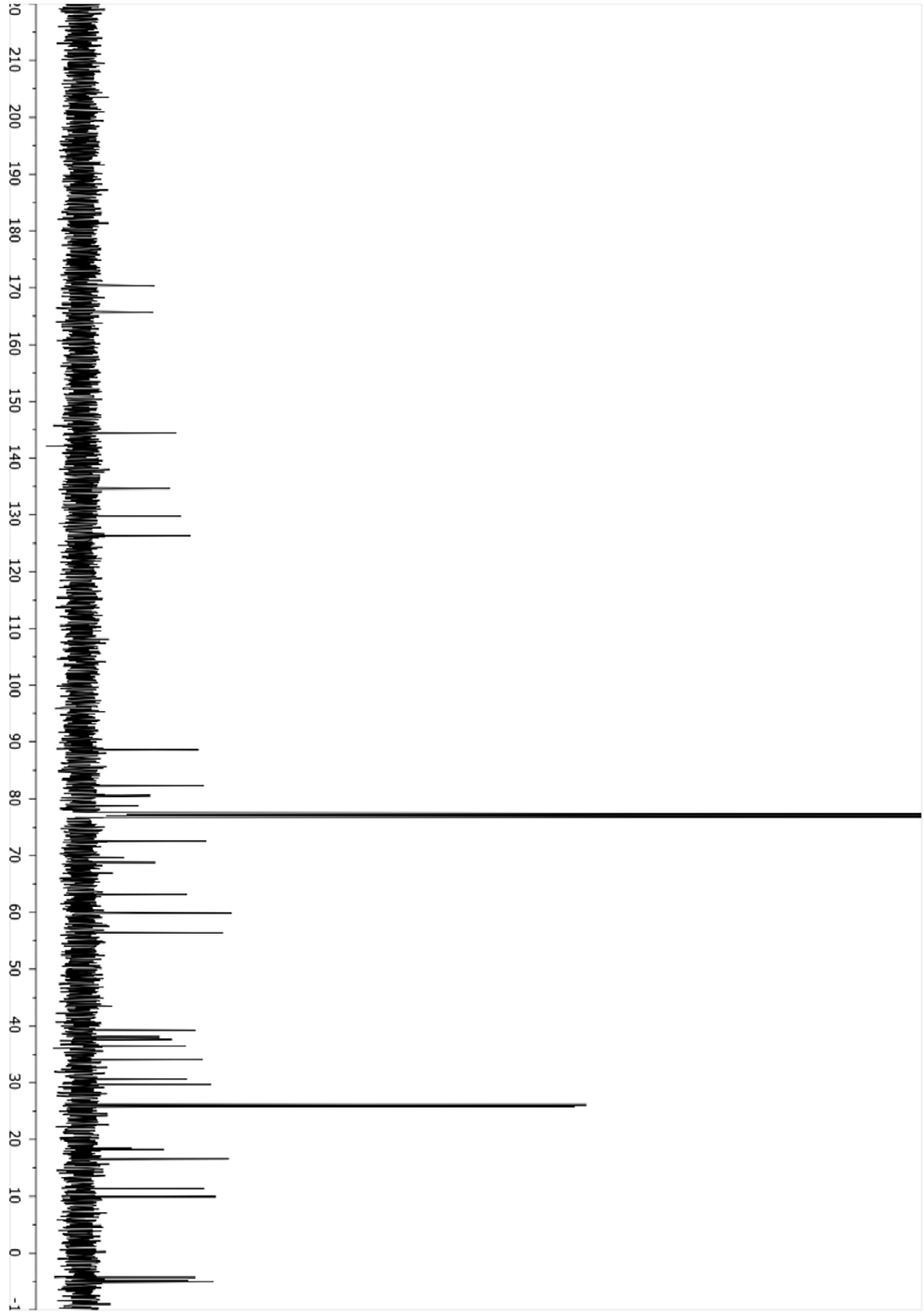
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7.2. List of Abbreviations

Å	Ångström, 1 Å = 10^{-10} m
Ac	Acetyl
Acac	Acetylacetonate
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
approx	approximately
Ar	Aromatic group
ARC	Anion Relay Chemistry
aq.	Aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2- Naphthol
Bn	Benzyl
Biphep	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl
br	Broad
brsm	Based on recovered starting material
Bu	Butyl
calcd.	Calculated
cat.	Catalytic
CBS	Corey-Bakshi-Shibata
CI	Chemical ionization
conc.	Concentrated
conv.	Conversion
cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
δ	Chemical shift
d	Day
d	Doublet
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N*,*N*´-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane

DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinon
decomp.	Decomposition
deg.	Degassed (freeze-pump-thaw method)
Dibal-H	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)-pyridine
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
DTB	Di-*tert*-butyl
DTBM	Di-*tert*-butyl methoxy
e.e.	Enantiomeric excess
EI	Electron ionization
epi	Epimer
ESI	Electronspray ionization
Et	Ethyl
equiv	Equivalents
eV	Electronvolt
Fm	Fluorenylmethyloxycarbonyl
GC	Gas chromatography
h	Hour
HMDS	Bis(trimethylsilyl)amine
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
HSAB	Hard and soft acids and bases
HWE	Horner–Wadsworth–Emmons
Hz	Hertz, 1 Hz = 1 s^{-1}
i	iso
IC_{50}	Half maximal inhibitory concentration
IG_{50}	Half inhibition of growth
Ipc	Diisopinocampheyl
IPr	1,3-Bis(2,6-diisopropylphenyl)-imidazolium

IR	Infrared spectroscopy
J	Coupling constant
LA	Lewis acid
LB	Lewis base
LC	Liquid chromatography
LDA	Lithiumdiisopropylamid
Lit.	Literature
LLS	Longest linear sequence
m	Meta
m	Multiplet
M	Molar: $mol \cdot l^{-1}$
m/z	Mass per charge
Me	Methyl
min	Minute
Ms	Methanesulfonyl
MS	Mass spectrometry
MS	Molecular sieves
MW	Microwave
n	Normal
n.d.	Not determined
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-Butyllithium
NCI	National Cancer Institute
NHC	N-heterocyclic carbene
NIS	N-Iodosuccinimide
NMI	1-Methylimidazole
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
p	Para
p-Ts	*p*-Toluenesulfonic
pd	Product

PG	Protecting group
Ph	Phenyl
phen	1,10-Phenanthroline
PIDA	Diacetoxyiodo)benzene
PMB	*p*-Methoxybenzyl
ppm	Parts per million
PPT	Palmitoyl-protein thioesterase
PPTS	Pyridinium *p*-toluenesulfonate
py	Pyridine
quart	Quartet
quant.	Quantitative
R	Organic substituent
RCAM	Ring closing alkyne metathesis
RCDM	Ring closing diyne metathesis
RCM	Ring closing olefin metathesis
rec.	Recovered
rt	Ambient temperature
s	Singlet
SAR	Structure-activity relationship
sat.	Saturated
sm	Starting material
sp	Side product
sp.	Species
t	Tertiary
t	Triplet
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBA	Tetrabutylammonium
TBAF	Tetra-*n*-butylammoniumfluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
t-BuLi	*tert*-Butyllithium

TC	Thiophene-2-carboxylate
TEA	Triethanolamine/Triethylammonium
TEAA	Triethylammonium acetate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
tert	Tertiary
TES	Triethylsilyl
TfO	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tos	Tosyl
TPAP	Tetrapropylammonium perruthenate
Troc	2,2,2-Trichlorethoxycarbonyl
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

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