Ringschluss-Alkin-Metathese von 1,3-Diinen:

Totalsynthese von Ivorenolide A und B

&

Studien zur Totalsynthese von Rhizoxin D

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

(Dr. rer. nat.)

des Fachbereichs Chemie der Technischen Universität Dortmund

vorgelegt von

Felix Ungeheuer

geboren am 25.10.1986

in Frankfurt am Main

Mülheim an der Ruhr, 2016

Die vorliegende Arbeit entstand unter Anleitung von Herrn Prof. Dr. Alois Fürstner in der Zeit von Januar 2013 bis Juni 2016 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bisher in folgenden Beiträgen veröffentlicht:

- Concise Total Synthesis of Ivorenolide B.
  F. Ungeheuer, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 11387 – 11392

- A Two-Component Alkyne Metathesis Catalyst System with an Improved Substrate Scope and Functional Group Tolerance: Development and Applications to Natural Product Synthesis.
  S. Schaubach, K. Gebauer, F. Ungeheuer, L. Hoffmeister, M. K. Ilg, C. Wirtz, A. Fürstner, *Chem. Eur. J.* **2016**, *22*, 8494 – 8507

Die praktischen Arbeiten des Rhizoxin Projektes entstanden teilweise in Zusammenarbeit mit Herrn Christian Wille.

Danksagung

Mein Dank geht an Herrn Prof. Dr. Alois Fürstner für die Aufnahme in seinen Arbeitskreis, die spannende und herausfordernde Themenstellung, das entgegengebrachte Vertrauen sowie für die mir gewährte wissenschaftliche Freiheit bei der Durchführung dieser Doktorarbeit.

Für die Übernahme des Zweitgutachtens danke ich Herrn Prof. Dr. Norbert Krause von der Technischen Universität Dortmund.

Für die gute Zusammenarbeit und den Zusammenhalt in Box 3 möchte ich mich bei Saskia Schulthoff, Johannes Preindl, Stephan Rummelt, sowie Dr. Yonghoon Kwon und Dr. Marc-André Müller bedanken.

Desweiteren möchte ich mich bei Dr. Michael Fuchs, Dr. Alicia Casitas Montero und Dr. Aaron Lackner für die hilfreichen Diskussionen während der Durchführung der Doktorabeit sowie bei Christian Wille für die Hilfe bei dem Rhizoxin Projekt bedanken.

Ferner möchte ich mich bei den technischen Mitarbeitern der Abteilung Fürstner, namentlich Helga Krause, Karin Radkowski, Jennifer Lenartowicz, Sebastian Auris und Roswitha Leichtweiß, für das große Engagement in allen Belangen des Laboralltages bedanken. Den Mitarbeitern der analytischen Abteilungen danke ich für die gewissenhafte und zügige Messung und Auswertung zahlreicher Proben.

Frau Monika Lickfeld danke ich für die große Hilfe in allen organisatorischen Angelegenheiten.
Ein weiterer Dank gilt Dr. Yonghoon Kwon, Dr. Christophe Werlé, Stephan Rummelt, Saskia Schulthoff und Marc Heinrich für das schnelle und gründliche Korrekturlesen dieser Arbeit.

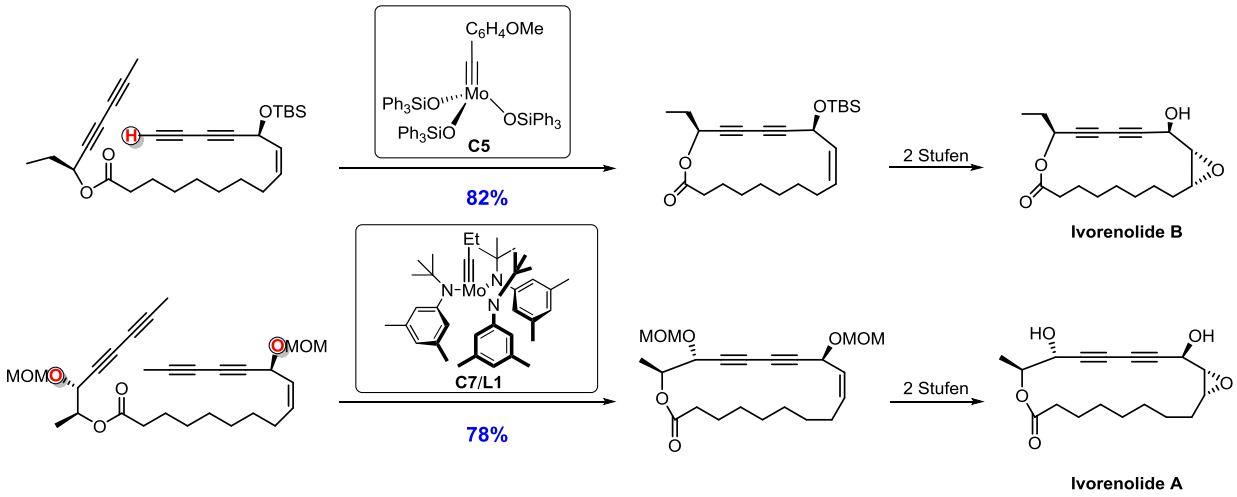
Meinen lieben ehemaligen und gegenwärtigen Kollegen aus der Arbeitsgruppe Fürstner sowie Prof. Dr. Manuel Alcarazo und seinen Mitarbeitern möchte ich für die gute Zusammenarbeit und die zahlreichen inspirierenden Diskussionen danken.
Den größten Dank verdient meine Familie, die mich immerzu unterstützt hat und mir stets liebevoll zur Seite stand. Ihnen sei diese Arbeit gewidmet.

Danke

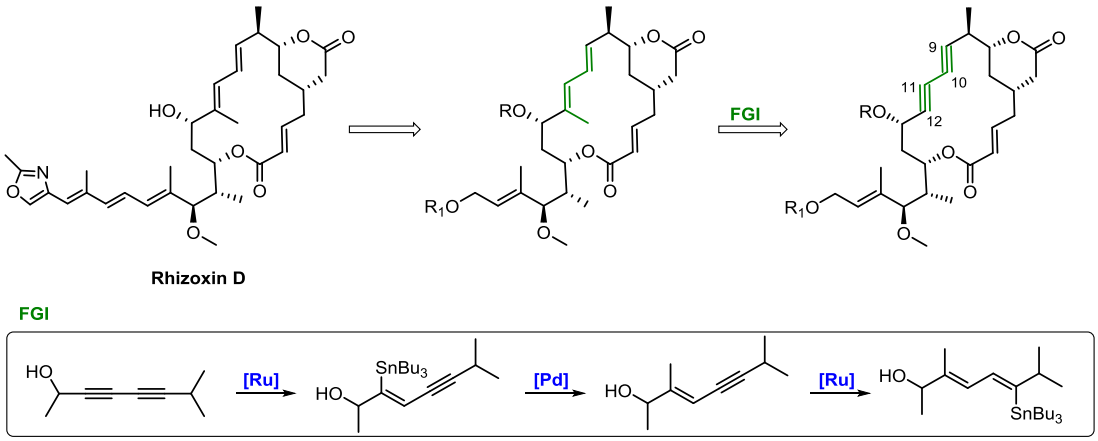
Zusammenfassung

Ivorenolide A und B sind Vertreter einer neuartigen Klasse von polyacetylenischen Naturstoffen, welche ein in ein makrozyklisches Gerüst eingebettetes 1,3-Diin-Motiv aufweisen. Biologische Studien ergaben, dass beide Naturstoffe vielversprechende immunosuppressive Aktivität aufweisen und somit als mögliche Leitstrukturen für die Entwicklung neuartiger Medikamente in Frage kommen.

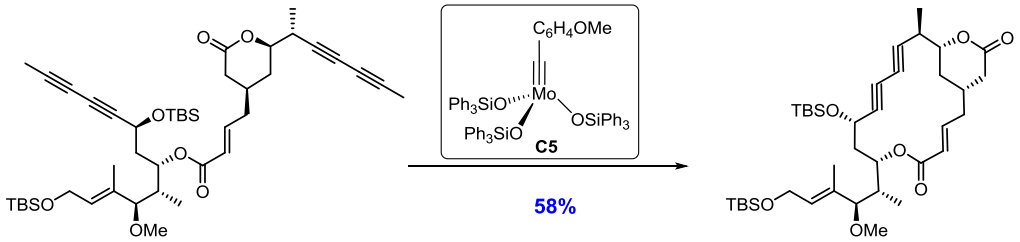
Die Anwendung der kürzlich publizierten Ringschluss-Alkin-Metathese von 1,3-Diinen (RCDM) erlaubte die Zyklisierung einer Vielzahl von verschienden acyclischen Substraten. Die Verwendung dieser Methode ermöglichte die Totalsynthese von Ivorenolide A und B, wobei die Synthese von Ivorenolide B die erste unsymmetrische RCDM zwischen einem terminalen und einem methyl-verkappten 1,3-Diin darstellte. Die Totalsynthese von Ivorenolide A ist das erste Beispiel einer Zyklisierung eines bis-propargylischen 1,3-Diines.



Rhizoxin D und verwandte Verbindungen gehören zu einer Klasse von polyketidischen Makroliden, welche ein breites Spektrum an biologischen Eigenschaften aufweisen. Eine neue Strategie, welche den Zugang zu dieser Klasse von Verbindungen ermöglicht, wurde erarbeitet. Diese Route basiert auf der RCDM als Schlüsselschritt und einer eigens entwickelten Synthese von (*E*,*E*)-1,3-Dienen durch eine hydroxy-dirigierende *trans*-Hydrostannierung von 1,3-Diin-Verbindungen.



Das hoch funktionalisierte makrozyklische Gerüst von Rhizoxin D weist eine Vielzahl von Sauerstoff-funktionalitäten sowie mehrere ungesättigte Positionen auf und besitzt durch das annulierte δ-Lakton sowie durch die (*E*)-konfiguerierte Doppelbindung eine signifikante Ringspannung. Die Zyklisierung eines solchen Substrates stellte somit eine große Herausforderung für die neue Methodik dar.

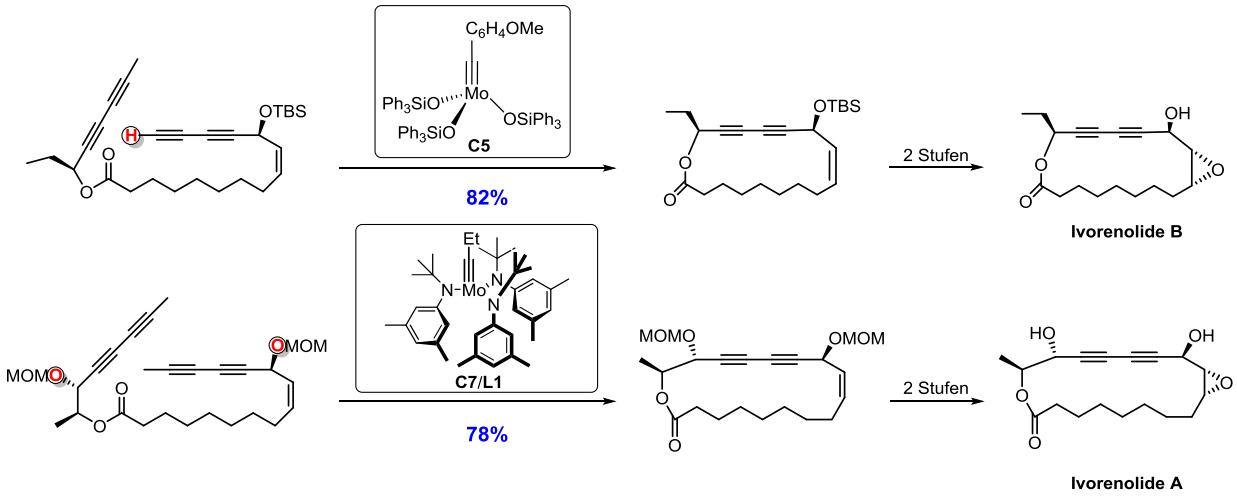


Nach den Synthesen beider Fragmente, sowie deren erfolgreicher Verknüpfung, erlaubte die Verwendung des Molybdänalkylidin-Komplexes **C5** die problemlose Zyklisierung des Substrates. Dieses Beispiel verdeutlicht die Vielseitigkeit dieser Methodik und stellt somit eine wertvolle Ergänzung zu etablierten Methoden wie der Olefin-Metathese dar.

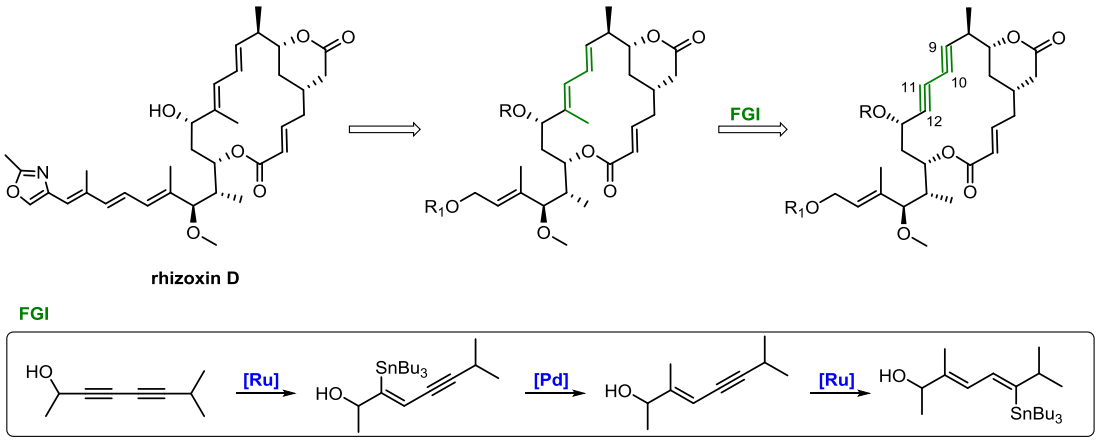
Abstract

Ivorenolide A and B are representatives of a novel class of polyacetylenic natural products featuring a 1,3-diyne motif embedded in a macrocyclic core. Biological surveys revealed their promising immunosuppressive activity. Both compounds might serve as possible lead structures in the evolutionary process of developing novel highly active drugs.

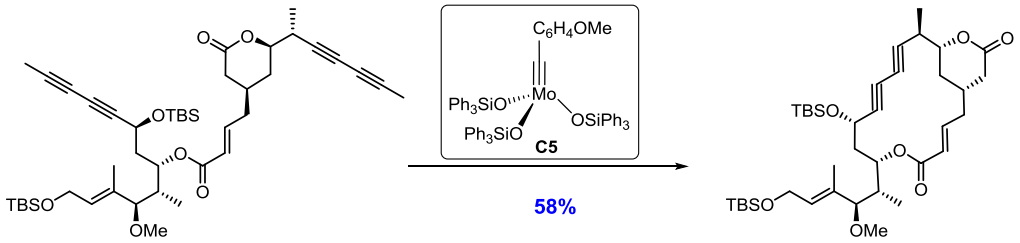
The application of the recently reported ring-closing alkyne metathesis of 1,3-diynes (RCDM) allowed the cyclization of a broad variety of acyclic 1,3-diynes. Application of this methodology culminated in the total syntheses of ivorenolide A and B. The total synthesis of ivorenolide B represented the first unsymmetrical RCDM between a terminal and a methyl capped 1,3-diyne and the total synthesis of ivorenolide A was the first cyclization of a bis-propargylic 1,3-diyne.



Rhizoxin D and related family members are a class of polyketide macrolides which exhibit a wide array of interesting biological properties. A novel strategy for the total synthesis of this class of antitumor macrolides was established. The strategy relied on RCDM as the key transformation followed by a specifically developed selective conversion of the resulting 1,3-diyne to the corresponding (*E*,*E*)-1,3-diene via hydroxyl group directed *trans*-hydrostannation.



The highly decorated macrocyclic core of rhizoxin D represented a remarkably challenging substrate for RCDM as it exhibits a multitude of oxygen functionalities as well as several sites of unsaturation and significant ring strain due to the annulated δ-lactone as well as to the (*E*) configured olefin.



After the syntheses of both fragments and their successful assembly, the utilization of molybdenum alkylidyne complex **C5** allowed the RCDM to proceed smoothly to give the cyclized 1,3-diyne. This example highlights the versatility of this transformation, rendering it a valuable alternative to established methods such as olefin metathesis.

Eidesstattliche Versicherung (Affidavit)

Felix Ungeheuer
Name, Vorname
(Surname, first name)

165218
Matrikel-Nr.
(Enrolment number)

Belehrung:

Wer vorsätzlich gegen eine die Täuschung über Prüfungsleistungen betreffende Regelung einer Hochschulprüfungsordnung verstößt, handelt ordnungswidrig. Die Ordnungswidrigkeit kann mit einer Geldbuße von bis zu 50.000,00 € geahndet werden. Zuständige Verwaltungsbehörde für die Verfolgung und Ahndung von Ordnungswidrigkeiten ist der Kanzler/die Kanzlerin der Technischen Universität Dortmund. Im Falle eines mehrfachen oder sonstigen schwerwiegenden Täuschungsversuches kann der Prüfling zudem exmatrikuliert werden, § 63 Abs. 5 Hochschulgesetz NRW.

Die Abgabe einer falschen Versicherung an Eides statt ist strafbar.

Wer vorsätzlich eine falsche Versicherung an Eides statt abgibt, kann mit einer Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft werden, § 156 StGB. Die fahrlässige Abgabe einer falschen Versicherung an Eides statt kann mit einer Freiheitsstrafe bis zu einem Jahr oder Geldstrafe bestraft werden, § 161 StGB.

Die oben stehende Belehrung habe ich zur Kenntnis genommen:

Official notification:

Any person who intentionally breaches any regulation of university examination regulations relating to deception in examination performance is acting improperly. This offence can be punished with a fine of up to EUR 50,000.00. The competent administrative authority for the pursuit and prosecution of offences of this type is the chancellor of the TU Dortmund University. In the case of multiple or other serious attempts at deception, the candidate can also be unenrolled, Section 63, paragraph 5 of the Universities Act of North Rhine-Westphalia.

The submission of a false affidavit is punishable.

Any person who intentionally submits a false affidavit can be punished with a prison sentence of up to three years or a fine, Section 156 of the Criminal Code. The negligent submission of a false affidavit can be punished with a prison sentence of up to one year or a fine, Section 161 of the Criminal Code.

I have taken note of the above official notification.

Mülheim/Ruhr 08.08.2016
Ort, Datum
(Place, date)

Unterschrift
(Signature)

Titel der Dissertation:
(Title of the thesis):

Ringschluss-Alkin-Metathese von 1,3-Diinen:
Totalsynthese von Ivorenolide A und B &
Studien zur Totalsynthese von Rhizoxin D

Ich versichere hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel selbstständig und ohne unzulässige fremde Hilfe angefertigt habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie wörtliche und sinngemäße Zitate kenntlich gemacht.
Die Arbeit hat in gegenwärtiger oder in einer anderen Fassung weder der TU Dortmund noch einer anderen Hochschule im Zusammenhang mit einer staatlichen oder akademischen Prüfung vorgelegen.

I hereby swear that I have completed the present dissertation independently and without inadmissible external support. I have not used any sources or tools other than those indicated and have identified literal and analogous quotations.

The thesis in its current version or another version has not been presented to the TU Dortmund University or another university in connection with a state or academic examination.*

*Please be aware that solely the German version of the affidavit ("Eidesstattliche Versicherung") for the PhD thesis is the official and legally binding version.

Mülheim/Ruhr 08.08.2016
Ort, Datum
(Place, date)

Unterschrift
(Signature)

technische universität
dortmund

Ring-Closing Alkyne Metathesis of 1,3-Diynes:

Total Syntheses of Ivorenolide A and B

&

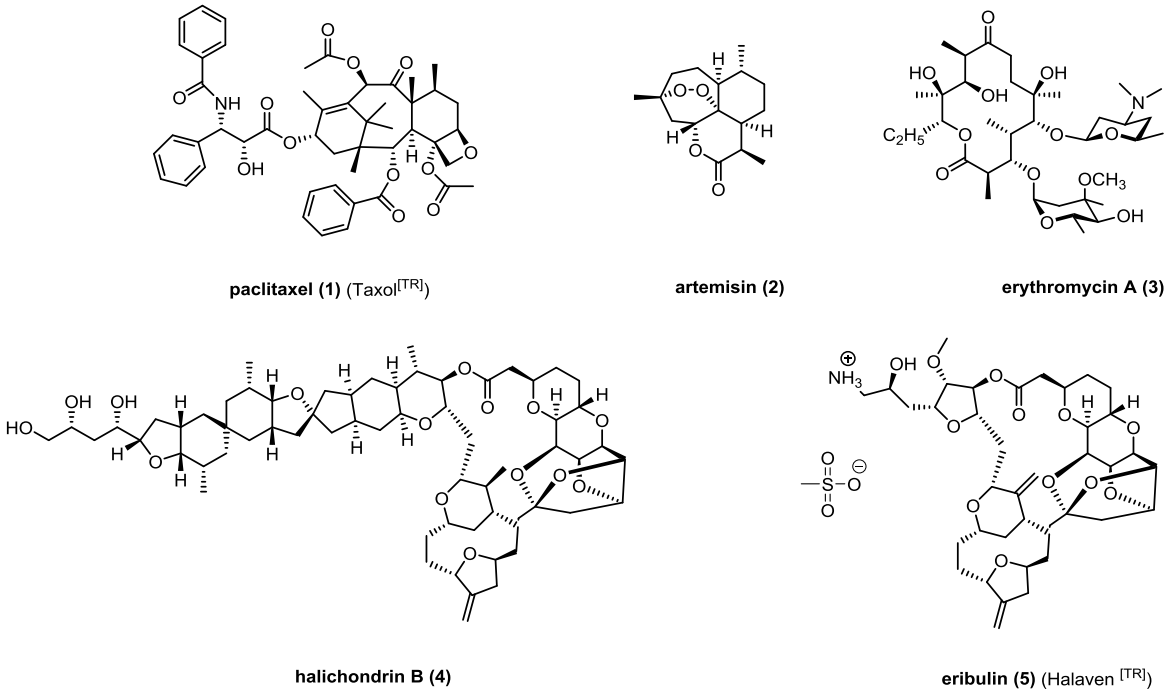
Studies towards the Total Synthesis of Rhizoxin D

Content

1. Introduction

1.1 Natural product synthesis

The necessity for the development of new and more efficient drugs in a rapidly changing and aging society provides a major challenge for life sciences. Substances isolated from natural sources play a significant role in this process, either as drugs or as possible lead structures in the evolutionary process of finding new highly biologically active compounds.[1] Natural products (NP) are often secondary metabolites isolated from a great variety of sources including plants,[2] microbes,[3] fungi[4] and marine sponges.[5] They undergo specific interactions with target enzymes or receptors and exhibit a wide variety of potentially interesting biological properties. Their often remarkable activity makes them interesting objects for interdisciplinary research. In addition natural products often exhibit structural features which are not regularly found in synthesis-based screening libraries. The span of their biological activity ranges from drugs for the treatment of different sorts of cancer, HIV, malaria and flu to compounds which are used for the treatment of mental disorders like Alzheimer or schizophrenia.[6] Their importance as potential drug candidates is demonstrated by the fact that in the time frame from January 2008 until December 2013 a total of 25 NP and NP-derived drugs have been approved for marketing.[1a] Prominent representatives of natural products or compounds based on natural products used as drugs include paclitaxel (**1**) (Taxol[TR], drug for the treatment of different sorts of cancers),[7] artemisin (**2**) (malaria treatment),[8] or erythromycin (**3**) (antibiotic).[9]

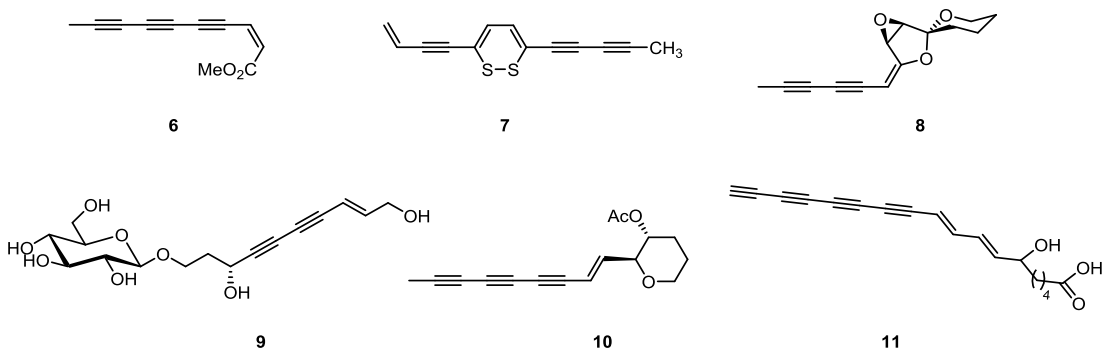


Scheme 1: Selected examples of natural products or natural product-derived drugs.

Despite the steady improvements of methods for the isolation and purification of compounds deriving from natural sources, total or semisynthesis often remains the method of choice for efficient and reliable material supply. This is owed to the fact that natural sources might be rare, hardly accessible or under environmental protection. The isolation often only yields trace amounts of substances, which make the structure determination particularly challenging and can lead to mistakes. Although analytical methods have rapidly developed and became more sophisticated in the last decades, wrong assignments of structurally demanding molecular frameworks are not uncommon and can result in severe consequences.[10] Since its early achievements, starting with the synthesis of urea by Friedrich Wöhler in 1828,[11] the field of total synthesis of natural products has rapidly grown and had an enormous impact on chemistry and on the human society. Milestones like the synthesis of vitamin B12 by Woodward and Eschenmoser[12] or the first synthesis of taxol by K. C. Nicolaou in 1994[13] have not only led to important developments in the field of organic chemistry, they also produced a plethora of synthetic methods for the assembly of molecular frameworks. In a reverse manner the total synthesis of complex targets represents a "challenging environment" for newly developed synthetic methods. A prominent example for such synergistic effects is the total synthesis of the complex polyether macrolide halichondrin B (**4**) by Kishi *et al*. in 1992.[14] It showed the utility of Nozaki-Hyama-Kishi coupling (NHK-coupling) and eventually led to the development of the structurally simplified halichondrin B derivative eribulin (**5**), a highly potent drug for the treatment of breast cancer.[15]

1.2 Naturally occuring polyacetylenes

The class of polyacetylenic natural products has recently attracted much attention not only because of their wide spectrum of structural diversity but also due to their promising biological properties.[16] According to F. Bohlmann, the first isolated polyacetylenic natural product was dehydromatricaria ester **6**, which was isolated but not fully characterized in 1826 from an *Artemisia* species.[16-17] In the following nearly two centuries over 1000 naturally occurring polyacetylenes have been isolated and characterized from a wide array of sources including bacteria, insects, higher fungi, plants, moss and lichens, marine sponges and corals.[16] These often unstable compounds tend to decompose by oxidative, photolytic or pH-dependent pathways, which make their isolation and characterization challenging. Polyacetylenic natural products have been used in traditional medicine for the treatment of a variety of diseases.[16, 18]

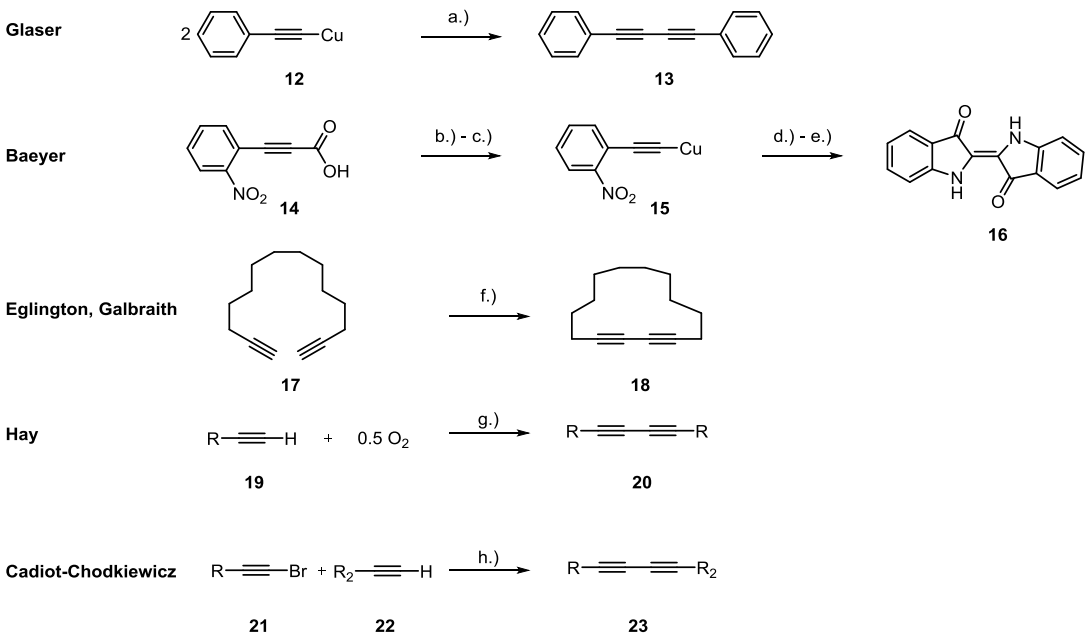


Scheme 2: Representative examples for polyacetylenic natural products.

The structural diversity includes 1,3-diynes like thiarubrine B (**7**), a natural occurring pigment which has been isolated from the giant ragweed *Ambrosia trifida* in 1964/1965.[19] It contains a rather unstable 1,2-dithiin motif and can be found in several plants which are used to treat skin infections and intestinal parasites.[20] Diacetylenic spiroacetals like Al-2 (**8**) have been isolated from plants of the *Asteracae* family (*Artemisia lactiflora*) and exhibit promising antitumor activity.[21] Among the isolated polyacetylenic natural products are also several glucosides, such as bidensyneoside C (**9**), isolated from species of the genus *B. parviflora*. Biological studies revealed their ability to inhibit histamine release and nitric oxide production.[22] In addition to naturally occurring 1,3-diynes, several triynes and tetraynes have been identified. (-)-Ichthyothereol (**10**) has been isolated in 1965 from *Dahlia coccinea* and has been used as a fish poison by the natives of the Lower Amazon Basin.[23] The terminal tetrayne caryoynencin (**11**) was isolated from the plant pathogen *Pseudomonas caryophylli*. Biological tests of the unstable compound demonstrated antimicrobial activity against Gram-positive and Gram-negative bacteria.[24]

1.3 Synthetic methods for the preparation of 1,3-diynes

The construction of bis-acetylenic motifs found in naturally occurring polyynes relies nearly exclusive on the transition metal assisted or catalyzed coupling of two alkyne fragments. The first coupling of two identical alkyne fragments, for the construction of a 1,3-diyne, was demonstrated by Glaser *et al*. in 1869.[25] He observed that copper(I)phenylacetylide (**12**) underwent dimerization under oxidative conditions to the corresponding diphenylbuta-1,3-diyne (**13**). Thirteen years later Baeyer *et al.* utilized Glaser´s observations for the synthesis of indigo (**16**), a naturally occurring blue dye.[26] Important contributions from Eglington, Galbraith (**17** → **18**)[27] and Hay (**19** → **20**)[28] further improved the synthetic utility of this transformation, making it the method of choice for the dimerization of acetylenic fragments (scheme 3).[29]

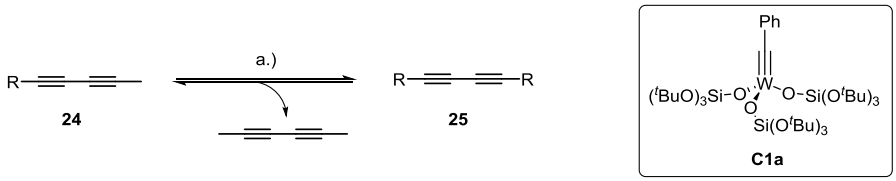


Scheme 3: Selected examples for the preparation of symmetrical and unsymmetrical 1,3-diynes: a.) O_2, NH_4OH, EtOH; b.) H_2O, Δ; c.) EtOH, CuCl, NH_4OH; d.) $K_3[Fe(CN)_6]$, H_2O; e.) H_2SO_4, $(NH_4)_2S$; f.) $Cu(OAc)_2$, pyridine, MeOH (high dilution), 20 – 40%; g.) CuCl·TMEDA; h.) CuCl, $NH_2OH{\cdot}HCl$, MeOH, $EtNH_2$, N_2.[29]

The coupling of two different alkyne fragments was reported in the 1950´s by Cadiot and Chodkiewicz and relies on the condensation of a 1-haloalkyne **21** and a terminal alkyne **22** in presence of a suitable Cu(I) salt and an amine base (scheme 3).[30] Since these early findings, modifications have been developed in terms of employed solvents, temperature, bases and acetylenes. Although other procedures for the construction of 1,3-diynes have been reported, the methods above mentioned and their modifications were the methods most utilized in present literature.[29]

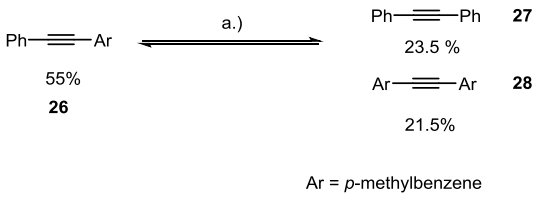
1.4 Alkyne metathesis

In 2012 Tamm and co-workers published a novel approach for the preparation of symmetrical and unsymmetrical 1,3-diynes based on alkyne metathesis. The reaction of a 1,3-diyne **24** in presence of catalytic amounts of tungsten benzylidyne complex **C1a** resulted in the formation of product **25** (scheme 4).[31] In 2014 the unsymmetrical version of this transformation was reported by the same group.[32]



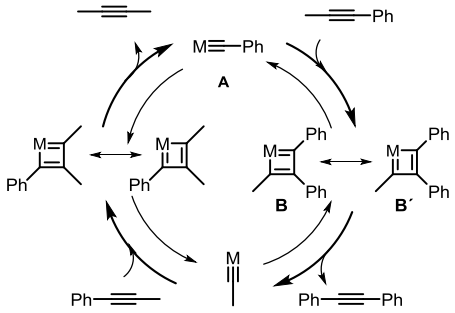
Scheme 4: Construction of symmetrical 1,3-diynes via tungsten-catalyzed alkyne metathesis: a.) **C1a** (cat.), toluene, 5 Å MS.

This contribution further expanded the already remarkable scope of alkyne metathesis and granted access to a new class of substrates. Alkyne metathesis was first reported in the late 1960´s by Penella *et al*.[33] In their contribution they observed scrambling of 2-pentyne with a heterogenous catalyst, namely WO_3 immobilised on SiO_2. The rather harsh reaction conditions (240 °C – 450 °C) and competing polymerization reactions prevented the method from being broadly applied. Mortreux and Blanchard reported in 1974 the first use of a homogenous catalytic system, consisting of $[Mo(CO_6)]$ and resorcinol, for the dimerization of bis-arylacetylene **26** (scheme 5).[34]



Scheme 5: First demonstration of a homogenously catalyzed alkyne metathesis reaction: a.) $[Mo(CO)_6]$ (cat), resorcinol, decalin, 3 h, 160 °C.

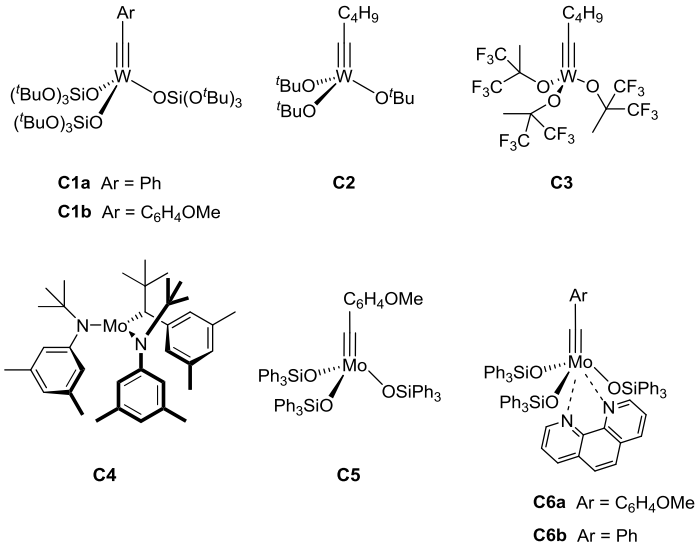
The mechanism was first proposed by Katz and McGinnis in the following year and is closely related to the Chauvin cycle for olefin metathesis.[35] The reactive metal alkylidyne **A** undergoes a formal [2+2] cycloaddition with the alkyne substrate forming a metallacyclobutadiene which can be best described by the two resonance structures **B** and **B´**. Cyclorevision releases the product and regenerates the active metal alkylidyne species, which undergoes the same elementary steps again (scheme 6).[36]



Scheme 6: Proposed and commonly accepted mechanism for the alkyne metathesis. Ancillary ligands are omitted for clarity.

Since these early discoveries plenty of effort was invested in the development of more efficient and functional group tolerant catalysts. In a series of important contributions the group of Schrock reported the preparation and use of molybdenum and tungsten alkylydine complexes such as **C2** and **C3** as active alkyne metathesis catalysts (scheme 7).[37] The molybdenum complex **C4** originally developed for the activation of N_2[38] proved to be a highly active alkyne metathesis catalyst after activation with CH_2Cl_2.[39] Fürstner and co-workers introduced the latest generation of remarkably active molybdenum complexes such as **C5** possessing a high functional group tolerance.[40] The complex **C5** could be made bench-stable by forming the adduct with an appropriate nitrogen donor

ligand such as 1,10-phenantroline. The resulting adducts **C6a/b** are highly crystalline and can be activated by stirring with a mild Lewis acid such as $MnCl_2$ or $ZnCl_2$ to release the active species.[40] All well-defined catalysts up to now are high valent tungsten(VI) and molybdenum(VI) Schrock alkylidyne complexes (scheme 7).

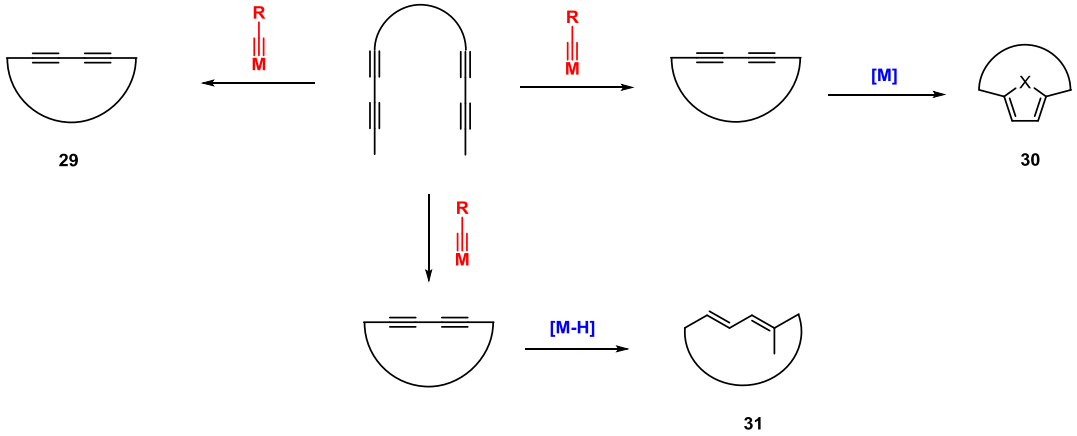


Scheme 7: Alkyne metathesis catalysts.

The rise of alkyne metathesis started with the application to forge medium and large-size cyclic systems via ring-closing alkyne metathesis (RCAM) representing a new and valuable alternative to established methods such as macrolactonization or ring closing olefin metathesis (RCM).[41] In particular the selective transformation of the resulting alkyne to either the *E* or *Z* alkene, a common motif in natural occurring macrolides, made this method particularly attractive.[42] In addition several other post-metathetic transformations were developed and successfully applied, which increased the product portfolio and provided access to new structural motifs.[43] The multitude of post-metathetic transformations combined with the excellent functional group tolerance, high reactivity and the convenient handling of the latest generation of catalysts rapidly led to many applications culminating in several total syntheses of complex biologically active molecules and applications in material science.[41a, 43-44]

The mechanism of alkyne metathesis for 1,3-diynes, as proposed by Tamm and co-workers in their first report, is in accordance with the established mechanism for regular alkyne metathesis.[31] Although initial studies already revealed the potential of ring-closing alkyne metathesis of 1,3-diynes (RCDM) for the preparation of cyclic 1,3-diynes, no detailed investigation of this transformation has been reported.

The objective of this thesis was to identify the scope and limitations of RCDM and to find possible applications. In the following chapter of this work the systematical investigation of the RCDM will be presented.



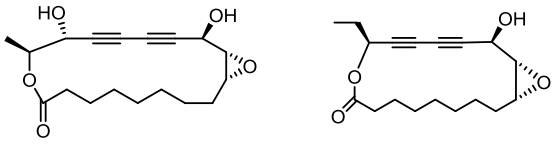
Scheme 8: Schematical description of transformations discussed in this work.

Initial studies for the cyclization of a model compound led to the identification of suitable catalysts and conditions for the desired transformation. Differently substituted precursors were prepared and cyclized. Application of these conditions to structurally demanding substrates culminated in the total syntheses of ivorenolide A and B (**29**). In addition, employment of transition metal catalyzed post-metathetic transformations of cyclic 1,3-diynes provided access to the synthesis of cyclophanes (**30**). Furthermore a novel strategy, based on RCDM, allowed the synthesis of the highly decorated macrocyclic core of rhizoxin D (**31**) and will be outlined in the second half of this work.

2. The ivorenolide family

2.1 Isolation, structure elucidation and biological properties

In 2012 the group of Ying Li and Jian-Min Yue reported the isolation and structure elucidation of ivorenolide A, a new type of macrocyclic lactone which features a structurally novel bis-acetylenic unit within a macrocyclic core.[45] Ivorenolide A (**32**) and ivorenolide B (**33**), which was reported two years later, were isolated from the well-known African mahagony tree *khaya Ivorenesis* A. chev. (Meliacae).[46] The isolation group obtained 8 mg of crystalline ivorenolide A and 15 mg of ivorenolide B out of 4.8 kg of air-dried plant material.



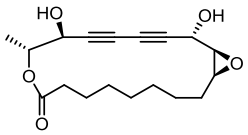
ivorenolide A 32 **ivorenolide B 33**

Scheme 9: Ivorenolide A and B.

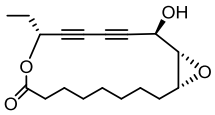
The crude extracts of the stem bark have been used in traditional medicine for the treatment of malaria and other tropical diseases. Biological surveys revealed the anti-plasmodial and anti-inflammatory activity of these extracts.[47] Furthermore, the most recent biological studies by the isolation group demonstrated significant immunosuppressive activity and remarkably high inhibition of concavalin A-induced T-cell proliferation. Immunosuppressive therapy is commonly applied in modern medicine for lowering the immune response during organ transplantations to avoid the rejection of the newly transplanted organ. Additionally immunosuppressive agents are used for the treatment of severe autoimmune diseases including psoriasis and multiple sclerosis.[48] The isolation group showed that ivorenolide A possesses selectivity comparable to the standard reference cyclosporin A (table 1).[45] All major immunosuppressive drugs currently used in medicine are either natural product derived or natural products themselves (present state).[49]

Table 1: Immunosuppressive effects of ivorenolide A and B (analogues included) on murine lymphocyte proliferation induced by ConA (5 μg/mL) or LPS (10 μg/mL).[a]

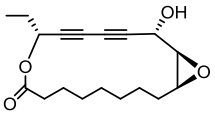
		ConA-induced T-cell proliferation		LPS-induced B-cell proliferation	
Cmpd	**CC_{50} (μM)**	**IC_{50}(μM)**	**SI**	**IC_{50}(μM)**	**SI**
32	>100	4.80	>20.83	8.12	>12.32
32b	>100	2.86	>34.97	4.55	>21.98
33	20.7	>10	-	7.2	2.9
33b	N	N	-	N	-
33c	N	N	-	N	-
33d	N	N	-	N	-
CsA	**4.79**	**0.11**	**44.80**	**0.33**	**14.50**
PSA	**18.85**	**0.68**	**27.72**	**2.17**	**8.69**



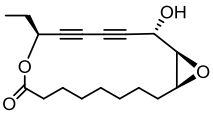
32b



33b



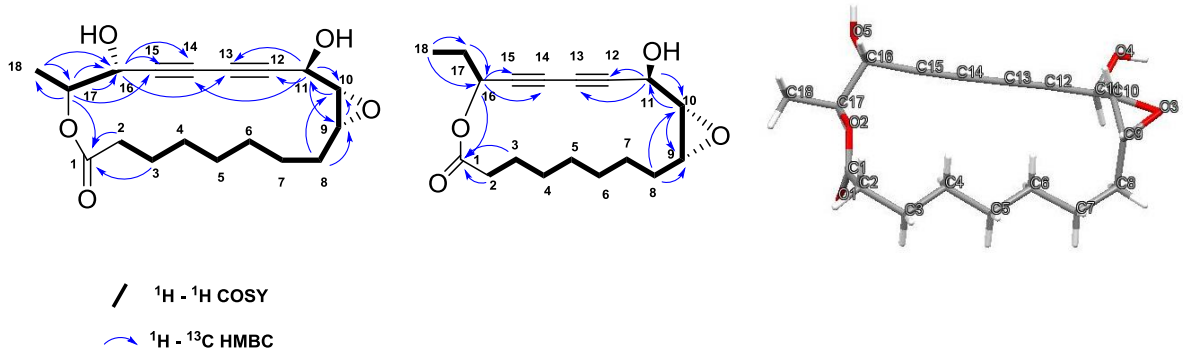
33c



33d

[a] CsA = cyclosporin A, PSA = periplocoside A, N = inactive (defined as inhibition rates lower than 30% at 10 μM). The selectivity index (SI) is defined as the ratio of the concentration of the compound that reduced cell viability to 50% (CC_{50}) to the concentration of the compound needed to inhibit the proliferation by 50% to the control value (IC_{50}).

The structure of ivorenolide A was elucidated using 2D-NMR-techniques (scheme 10), high-resolution positive-ion-mode electrospray ionization mass spectrometry [HR-ESI(+)-MS] and circular dichroism (CD-Spectroscopy). The relative stereochemistry was assigned via single-crystal-X-ray diffraction, but due to lack of absolute structure parameters the absolute configuration could not be assigned. Ivorenolide A features a 18-membered macrocyclic lactone exhibiting five stereogenic centers and a bis-acetylenic motif. The crystal structure revealed that the molecule is nearly planar and that two or three molecules are regularly overlapped in the unit cell. Intramolecular hydrogen bonds are formed between, the C16 hydroxy group and the ester moiety and between the C11 hydroxy group and the epoxide motif.



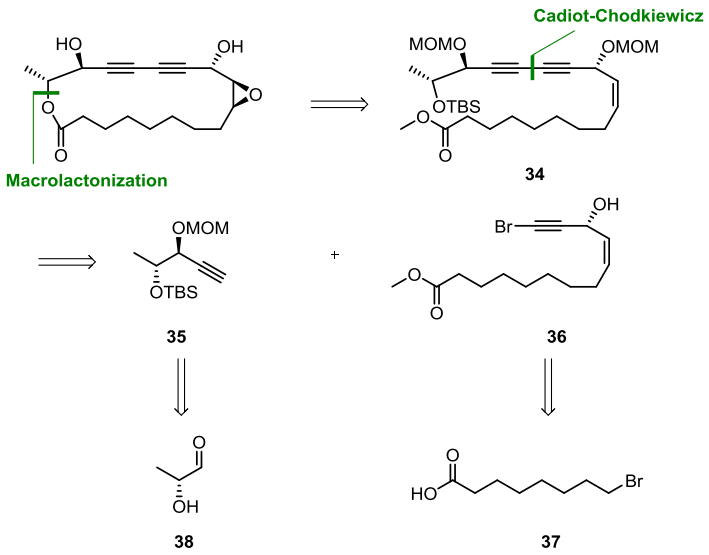
Scheme 10: Selected ^{1}H – ^{1}H COSY and ^{1}H – ^{13}C HMBC correlations for the structure determination of ivorenolide A and B. Single crystal X-Ray structure of ivorenolide A.

The same methods were employed for the structure determination of ivorenolide B (scheme 10), although the gum-like consistency of the compound prevented the use of single-crystal-X-ray diffraction. Ivorenolide B possesses four stereogenic centers and the same bis-acetylenic moiety within the 17-membered macrocyclic core. The structural features and the promising biological properties made both compounds interesting targets for the synthetic community.

2.2 Previous syntheses

2.2.1 Synthesis of *ent*-ivorenolide A by Li and Yue

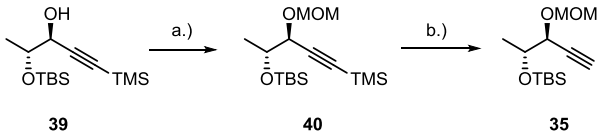
The single crystal did not refract well enough to unambigously determine the absolute configuration of ivorenolde A. For this reason the isolation group carried out a total synthesis to establish the absolute configuration.



Scheme 11: Retrosynthetic analysis of putative ivorenolide A.[45]

The disconnections were based on the macrolactonization of acyclic precursor **34** followed by deprotection and late-stage epoxidation. The acyclic precursor was planned to be assembled via Cadiot-Chodkiewicz coupling of terminal alkyne **35** with bromo alkyne **36**. Bromo alkyne **36** should be prepared from commercially available 8-bromooctanoic acid (**37**), and propargyl alcohol via a sequence of standard transformations. Terminal alkyne **35** should be accessible by an alkynylation reaction of aldehyde **38** derived from methyl-D-lactate (scheme 11).

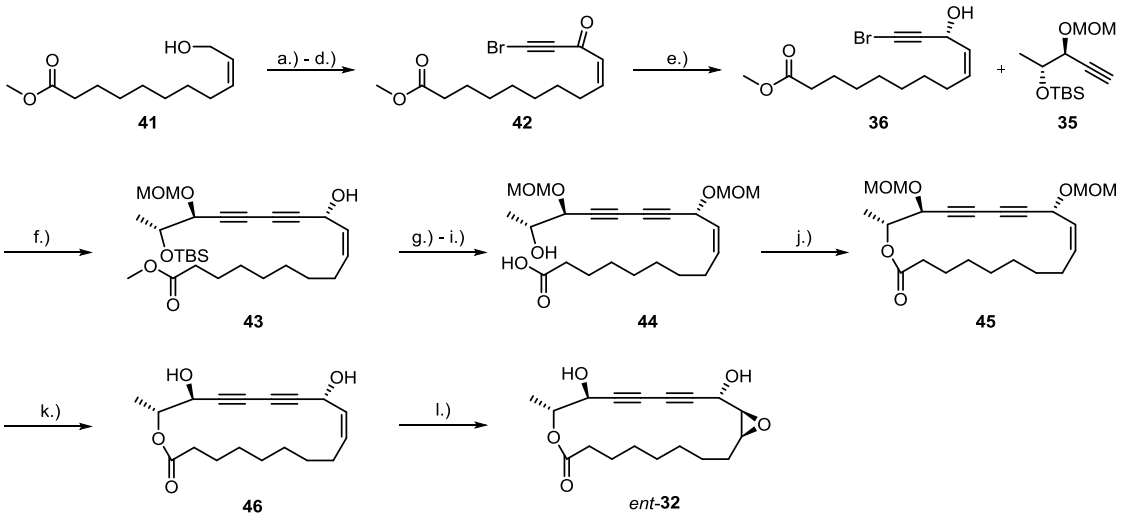
The forward synthesis commenced with the protection of literature known propargylic alcohol **39**, which was prepared in four steps from methyl-D-lactate.[50] The propargylic hydroxy group was protected as the corresponding MOM-ether **40** followed by subsequent removal of the alkyne protecting group with the aid of K_2CO_3/MeOH to yield the desired terminal alkyne **35**.



39 40 35

Scheme 12: Preparation of terminal the alkyne fragment (**35**): a.) MOMCl, *i*-Pr_2Net, CH_2Cl_2, 12 h 98%; b.) K_2CO_3, MeOH, 2 h, 93%.[45]

Coupling of 8-bromooctanoic acid (**37**) with propargyl alcohol, followed by methyl ester formation and hydrogenation of the alkyne under Lindlar conditions[51] yielded *cis*-allylic alcohol **41**. Through a four step sequence consisting of IBX-oxidation, TMS-acetylene addition, Dess-Martin oxidation (DMP-oxidation) and bromination of the alkyne, alcohol **41** was converted to ketone **42**. The stereoselective CBS-reduction of **42** yielded fragment **36** in good yield and with excellent selectivity (scheme 13).

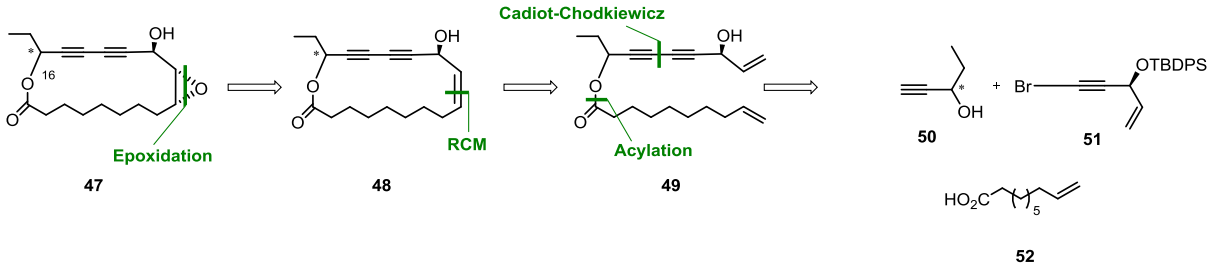


Scheme 13: Total synthesis of *ent*-ivorenolide A: a.) IBX, DMSO, CH_2Cl_2, 0 °C, 24 h 92; b.) TMS-acetylene, *n*-BuLi, THF, -78 °C, 3 h, 95%; c.) DMP, CH_2CL_2, 14 h, 95%; d.) NBS, $AgNO_3$, acetone, 3 h, 96%; e) CBS, BH_3·SMe, THF, -40 °C, 40 min, 89%, *ee* >99%; f.) CuCl, $BuNH_2$, H_2O, NH_2OH·HCl, CH_2Cl_2, 30 min, 70%; g.) MOMCl, *i*-Pr_2Net, CH_2Cl_2, 12 h, 99%; h.) TBAF, THF, 0 °C, 18 h, 97%; i.) aq. LiOH (2.0 M), *t*-BuOH, 12 h, 98%; j.) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C, then toluene DMAP, 75 °C, 90%; k.) aq. HCl (3.0 M), EtOH, 80 °C, 2 h, 67%; l.) *m*-CPBA, CH_2Cl_2, 12 h 84%.[45]

The Cu-catalyzed coupling of bromo alkyne **36** with terminal alkyne **35** afforded the required 1,3-diyne **43**. Standard transformations including MOM-protection of the free hydroxy group followed by removal of the TBS protecting group and hydrolysis of the methyl ester led to the acyclic seco-acid **44**. The cyclization was accomplished under conditions developed by Yamaguchi[52] providing the cyclic 1,3-diyne **45**. Simultaneous deprotection of the bis-MOM-ether with HCl at elevated temperature followed by epoxidation with *m*-CPBA completed the synthesis, which needed fifteen steps as the longest linear sequence and produced sufficient amounts of material for the determination of the absolute configuration of all five stereogenic centers. Comparison of the NMR data of synthetic *ent*-**32** matched those of the isolated compound but comparison of the CD-spectra and optical rotation revealed that the synthesized product was the enantiomer of ivorenolide A.

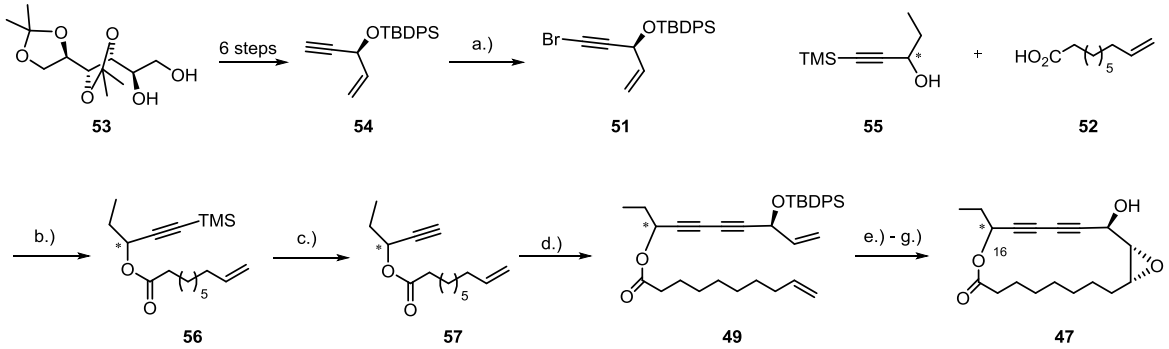
2.2.2 Synthesis of ivorenolide B by Li and Yue

The first synthesis of ivorenolide B **33** was reported, together with the isolation protocol, in 2014 by Ying Li and Jian-Min Yue.[46] The complete determination of the stereochemistry required the preparation of the four most likely stereoisomers **33**, **33b**, **33c**, **33d** which were synthesized and the recorded spectroscopic data were compared with the data of the isolated product.



Scheme 14: Retrosynthetic analysis of ivorenolide B.[46]

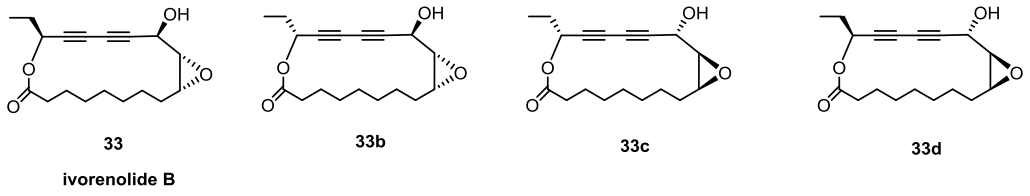
The main features of the utilized strategy were similar to those reported by the authors for the synthesis of *ent*-ivorenolide A (*ent*-**23**), except that the macrocycle **48** was prepared via RCM of diene **49**. The metathesis precursor was planned to be assembled via Cadiot-Chodkiewicz coupling of terminal alkyne **50** with bromo alkyne **51**. The requisite alkyl fragment should be obtained via acylation of **50** with 9-decenoic acid (**52**) (scheme 14).



Scheme 15: Total synthesis of ivorenolide B: a.) NBS, $AgNO_3$, 97%; b.) DCC, DMAP, CH_2Cl_2, Δ, (*S,R*)-98%; c.) TBAF, THF, (*S*)-97%, (*R*)-95%; d.) CuCl, $BuNH_2$, H_2O, $NH_2OH{\cdot}HCl$, 0 °C, (*S*)-90%, (*R*)-86%; e.) Grubbst 1$^{st.}$ gen, CH_2Cl_2, (16*S*)-93% (*Z* : *E* = 1.0 : 1.5), (16*R*)-90% (*Z* : *E* = 1.0 : 1.5); f.) *m*-CPBA, CH_2Cl_2, (16*S*)-92%, (16*R*)-91% g.) TBAF, THF, (16*S*)-90%, (16*R*)-88%.[46]

The synthesis started with the preparation of bromo alkyne **51**. D-Mannitol was converted to the suitable protected intermediate **53**[53], which was then transformed in six steps to alkyne **54**.[54] Subsequent bromination with NBS yielded the desired bromo alkyne **51**. In an analogous way, *ent*-**51**, was prepared from L-mannitol. Both enantiomers of literature-known alcohol **55**[55] were treated with 9-decenoic acid (**52**) under Steglich conditions[56] to obtain acylation product **56**. Deprotection of the alkyne with TBAF and subsequent coupling with **51** (*ent*-**51**) yielded 1,3-diyne **49**. With respect to the RCM elevated temperatures and high dilution were required to obtain the macrocyclic product in good yield as a mixture of stereoisomers (*Z : E* = 1.0 : 1.5), favoring the undesired *E*-isomer.

Epoxidation with *m*-CPBA followed by deprotection with TBAF gave the desired compounds. The recorded spectroscopic data were compared to the data obtained from the isolated compound (scheme 15, 16).

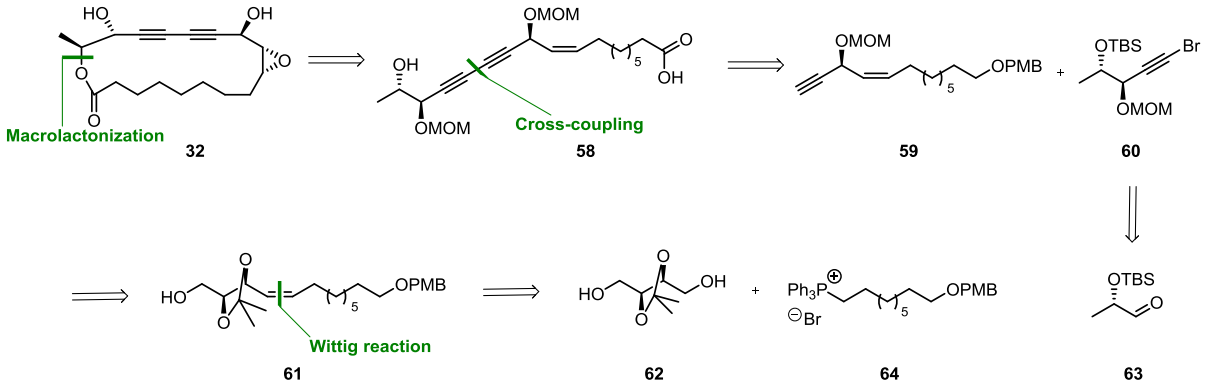


Scheme 16: Putative structures of ivorenolide B.

In this way the configuration at C16 was unambiguously determined and the structure of ivorenolide B was assigned as shown in scheme 16.

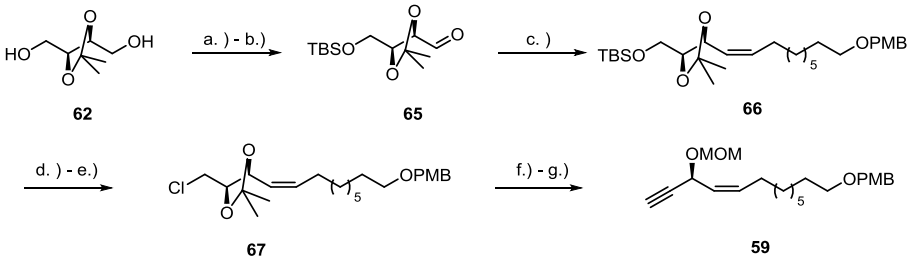
2.2.3 Synthesis of ivorenolide A by Yadav

In 2015 Yadav and co-workers reported the first total synthesis of ivorenolide A, employing a strategy similar to the previous synthesis of *ent*-ivorenolide A (*ent*-**32**).[57] Retrosynthetic analysis envisaged that the macrocycle is forged by macrolactonization applying conditions developed by Shiina,[58] followed by deprotection and epoxidation to yield ivorenolide A (**32**). The acyclic precursor **58** containing the bis-acetylenic motif should be prepared via palladium-catalyzed coupling of alkyne **59** with bromo alkyne **60**. The bromo alkyne should derive from aldehyde **63**. Terminal alkyne **59** should be accessible from (+)-2,3-*O*-isopropylidene-L-threitol **62** and nonyl phosphorane **64** (scheme 17).



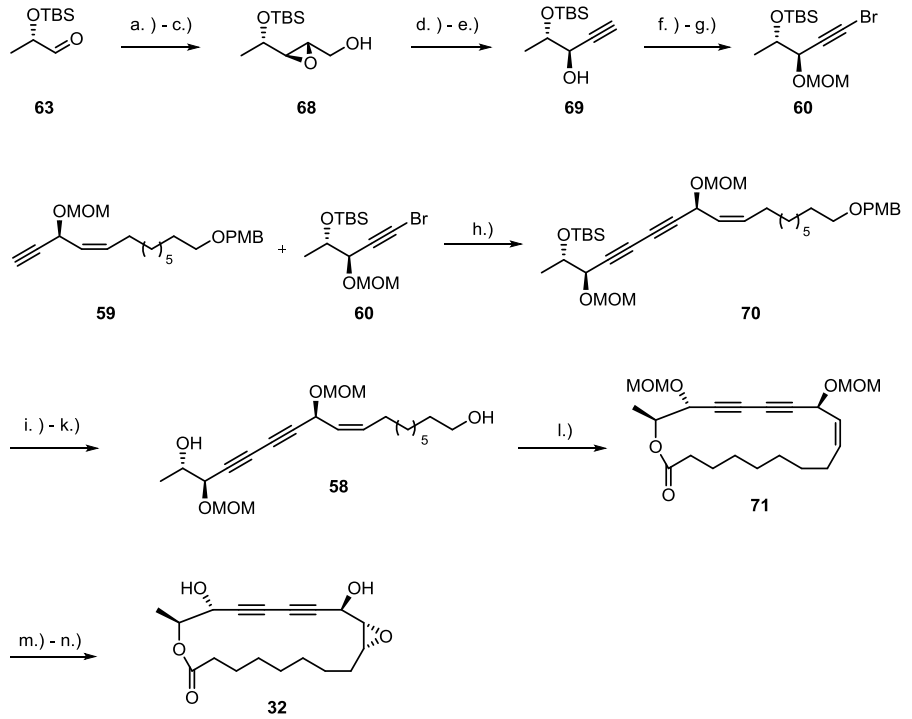
Scheme 17: Retrosynthesis of ivorenolide A by Yadav *et al*.[57]

The synthesis started with the preparation of terminal alkyne **59** from (+)-2,3-O-isopropylidene-L-threitol. Selective protection of one of the hydroxy groups, followed by Dess-Martin oxidation of the free alcohol yielded aldehyde **65**, which underwent Wittig olefination with the PMB-protected nonyl phosphorane **64** to furnish olefin **66**. Removal of the primary TBS group with TBAF and chlorination under Appel conditions afforded chloro-compound **67**. Conversion of **67** to alkyne fragment **59** was accomplished via the Fritsch-Buttenberg-Wiechell rearrangement followed by protection of the resulting propargylic hydroxy group as the corresponding MOM-ether (scheme 18).



Scheme 18: Yadav´s synthesis of the terminal alkyne fragment (**59**): a.) TBS-Cl, NaH, THF, 45 min, 0 °C, 98%; b.) DMP, CH_2Cl_2, 0 °C; c.) **64**, LiHMDS, HMPA, -78 °C, 78%; d.) TBAF, THF, 0 °C, 97%; e.) CCl_4, PPh_3, 5 h, 91%; f.) *n*-BuLi, THF, -78 °C, 87%; g.) MOMCl, *i*-Pr_2NEt, DMAP (cat), CH_2Cl_2, 95%.[57]

The preparation of bromo alkyne **60** started from methyl-L-lactate (scheme 19). Protection of the hydroxy group with TBS-Cl followed by reduction of the ester with DIBAL-H afforded aldehyde **63**. Two carbon homologation using a Horner-Wadsworth-Emmons olefination (HWE olefination) followed by DIBAL-H reduction of the α,β-unsaturated ester and Sharpless epoxidation led to allylic epoxide **68**. Compound **69** was obtained by using the above described sequence: chlorination followed by base-induced elimination and Fritsch-Buttenberg-Wiechell rearrangement. Protection of **69** as the corresponding MOM-ether followed by bromination under standard conditions gave bromo alkyne **60**. The assembly of both fragments was accomplished through a Pd-catalyzed Sonogashira coupling furnishing the desired 1,3-diyne **70**.



Scheme 19: Total synthesis of ivorenolide A by Yadav *et al.*: a.) $Ph_3P{=}CHCO_2Et$, toluene, 60 °C, 2 h 93%; b.) DIBAL-H, CH_2Cl_2, -78 °C, 1 h; c.) (+)-DIPT, Ti(*i*-PrO)$_4$, TBHP, CH_2Cl_2, -20 °C, 84% (over two steps); d.) CCl_4, TPP, 5 h; e.) *n*-BuLi, THF, -78 °C (82% over two steps); f.) MOMCl, $^{i}Pr_2Net$, DMAP (cat), CH_2Cl_2 0 °C, 95%; g.) NBS, $AgNO_3$, acetone, 1 h, 97%; h.) $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2Net, THF 1 h, 74%; i.) TBAF, THF, 0 °C, 1 h 97%; j.) DDQ, pH~7 buffer, CH_2Cl_2, 0 °C, 2 h, 92%; k.) PIDA, TEMPO, CH_2Cl_2, 0 °C, $NaClO_2/NaH_2PO_4$ 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C, 1 h, 91%; l.) MNBA, DMAP, toluene, 12 h, 84%; m.) aq. HCl, EtOH, 70 °C, 4 h, 74%; n.) *m*-CPBA, CH_2Cl_2, 12 h 84%.[57]

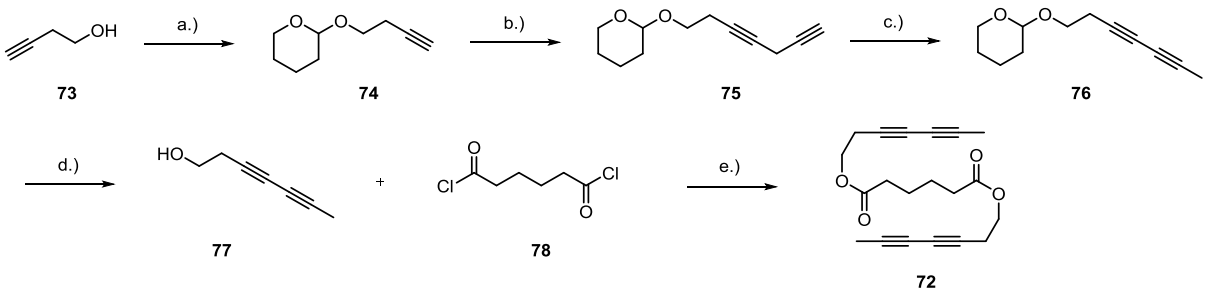
The seco-acid **58** was obtained by removal of the silyl protecting group followed by deprotection of the primary alcohol using DDQ in a buffered CH_2Cl_2 solution. Selective oxidation of the primary alcohol with PIDA in presence of TEMPO, followed by Pinnick oxidation[59] of the resulting aldehyde furnished the carboxylic acid. The cyclization was carried out under modified Shiina conditions yielding the 18-memberd lactone **71**.[60] The final transformations consisted of simultaneous deprotection of the MOM-ethers followed by epoxidation as previously described (scheme 19). A sixteen step longest linear sequence was necessary to yield ivorenolide A. The spectroscopic data of the obtained product were in agreement with those reported in the isolation paper.

2.3 Motivation

The aim of the project was to evaluate the recently reported ring-closing alkyne metathesis of 1,3-diynes (RCDM) in terms of substrates, reaction conditions and catalysts. The latest generation of molybdenum complexes developed in the Fürstner group should be applied and the scope and limitations of this transformation were first studied on a simplified model substrate. Ivorenolide A and B were chosen as suitable targets to demonstrate the utility of this method, culminating in concise total syntheses of both natural products with the RCDM as the key transformation. The versatility of the obtained cyclic 1,3-diynes was further proven by application of different types of post-metathetic transformations.

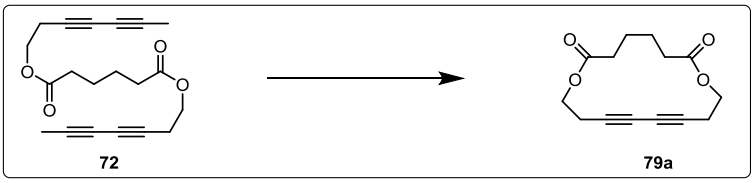
2.4 Model studies

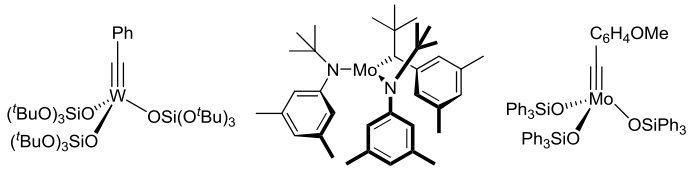
Di(hepta-3,5-diyn-1-yl) adipate (**72**), was chosen as a model compound for the examination of the RCDM. The preparation of **72** was accomplished utilizing the route described by Tamm and co-workers (scheme 20).[31] But-3-yn-1-ol (**73**) was converted to the corresponding THP-ether **74,** which was coupled with propargyl bromide to obtain the skipped diyne **75**. Base catalyzed rearrangement to the 1,3-diyne **76** followed by acid mediated THP deprotection yielded the desired hepta-3,5-diyn-1-ol (**77**). The reaction of this alcohol with adipoyl dichloride **78** in presence of pyridine afforded the desired model compound **72** (scheme 20).



Scheme 20: Synthesis of model substrate **72** for the investigation of the RCDM: a.) *p*-TSA, DHP, CH_2Cl_2, 0 °C, 1.5 h, 97%; b.) EtMgBr, CuBr, propargyl bromide, THF, 50 °C to 65 °C, 3 h, 60%; c.) *t*-BuOK, THF, -40 °C, 2 h, 93%; d.) *p*-TSA, MeOH, 2 h, 89%; e.) Pyridine, CH_2Cl_2, 20 h, 89%.

The RCDM survey started with the evaluation of **C5**, which has been the state-of-the-art catalyst in terms of RCAM applications. The catalyst converted **72** to the cyclic 1,3-diyne **79a** in 84% yield at a loading of 10 mol%. The reaction could be conducted at ambient temperature as well as at slightly elevated temperature with the same result. During the course of the reaction no dimerization of the starting material was observed. The molybdenum complex **C4** was next investigated. The catalytically active species was obtained by treatment of **C4** with stoichiometric amounts of CH_2Cl_2, which then yielded the desired product in 59% yield. To reach full conversion a catalyst loading of 20 mol% and slightly elevated temperatures were required.





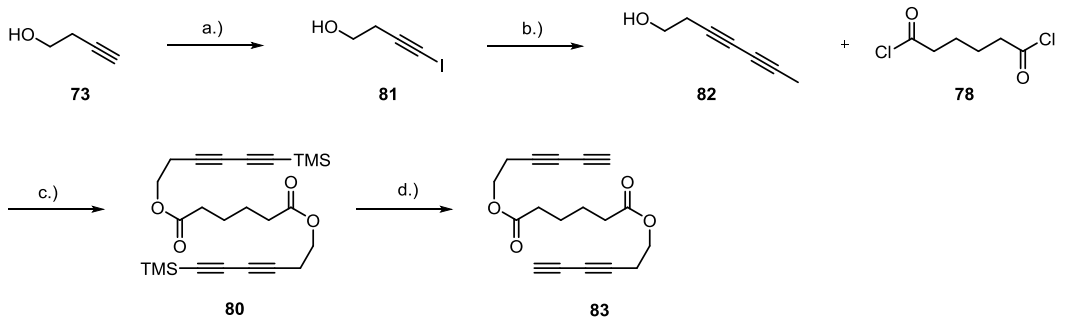
C1a C4 C5

Table 2: Screening of the influence of different catalysts on the outcome of the model reaction.[a]

Entry	Catalyst	Conditions	Yield [%]
1	**C1a** (4 mol%,)[31]	rt, 16 h	90
2	**C5** (10mol%)[b]	rt, 16 h	84
3	**C5** (10mol%)[b]	60 °C, 3 h	84
4	**C4** (20 mol%)	70 °C, 10 h	59

[a] All reactions were carried out in toluene [10 mM] in presence of 5 Å molecular sieves. [b] The catalyst loading was not optimized.

The next step was the variation of termini in the substrate. The methyl capped 1,3-diyne was replaced by the corresponding TMS-protected 1,3-diyne, which represents a more challenging substrate for the catalyst in terms of steric repulsion. The streamlined synthesis of the TMS-capped model substrate **80** commenced with the copper-catalyzed coupling of 4-iodobut-3-yn-1-ol (**81**) with TMS-acetylene.[61] The obtained hexa-3,5-diyn-1-ol **82** was again treated with adipoyl dichloride **78** and pyridine to give the desired cyclization precursor **80**. The TMS group was cleaved under mild conditions resulting in the formation of the bis-terminal 1,3-diyne cyclization precursor **83**, which proved to be highly unstable (scheme 21).



Scheme 21: Preparation of RCDM precursors (**80**, **83**): a.) KI, TBHP, MeOH, 6 h, 95%; b.) TMS-acetylene, CuI, piperidine 0 °C, 1 h, 80%; c.) Pyridine, CH_2Cl_2, 0 °C to rt, 16 h, 91%; d.) TBAF, THF, 0 °C, 61%.

Both substrates were subjected to standard conditions for the RCDM involving the use of **C5**, toluene as the solvent and 5 Å molecular sieves. The TMS-protected substrate **80** required rather harsh conditions and long reaction times to reach full conversion. The cyclized product **79a** was obtained together with an inseparable side product which was identified as the ring contracted product **79b**. The rather unstable terminal 1,3-diyne substrate **83** was converted to the cyclized 1,3-diyne under standard conditions in excellent yield (table 3).

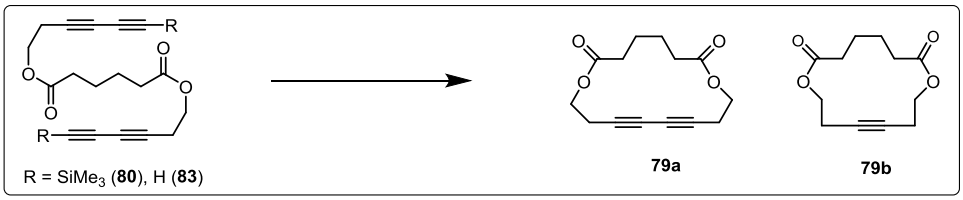


Table 3: Screening of the influence of different termini on the outcome of the model reaction.[a]

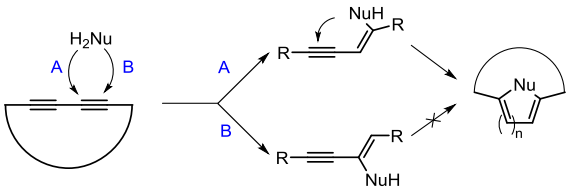
Entry	Substrate	Catalyst	Conditions	Yield [%]
1	**80**	**C5** (20mol%[c])	70 °C, 24 h	53[c]
2	**83**	**C5** (10mol%[c])	rt, 16 h	88

[a] All reactions were performed in toluene [10 mM] in presence of 4 Å and 5 Å MS. [b] The loading was not optimized. [c] **79a** : **79b** = 2.3 : 1

The obtained results marked the endpoint of the model studies for the RCDM. The use of **C5** allowed the preparation of cyclic 1,3-diyne **79a** from a variety of differently substituted acyclic precursors under relatively mild conditions with good yields.

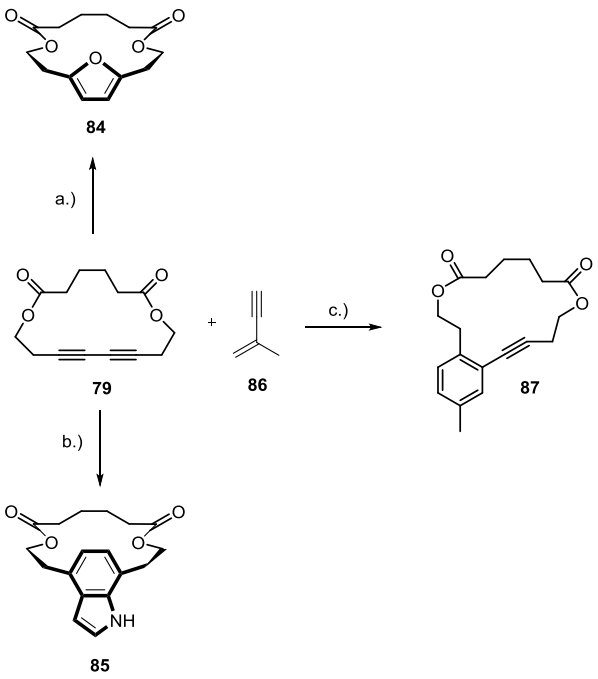
2.4.1 Post-metathetic transformations

1,3-Diynes are valuable substrates which had been recently employed in a multitude of different reactions such as Pauson-Khand,[62] hexadehydro-Diels-Alder[63] and reductive couplings.[64] The successful synthesis of the cyclic model 1,3-diyne **79a** allowed the investigation of possible post-metathetic transformations. The regioselective addition of nucleophiles to the activated 1,3-diyne enabled the preparation of heterocyclic cyclophane motifs (scheme 22).



Scheme 22: Proposed strategy for the activation mode of 1,3-diynes.[65]

First the gold-catalyzed hydration of cyclic 1,3-diyne **79a** was investigated. The desired transformation was accomplished with [(SPhos)AuNTf$_2$], which converted the 1,3-diyne to the corresponding *meta*-bridged furan derivative **84** in 61% yield.[65] By switching the nucleophile to pyrrole the structurally demanding *para*-indolophane **85** was obtained.[66] This compound proved to be prone to degradation, which made the isolation and characterization challenging. The removal of the pyrrole starting material, which needed to be used in excess to reach full conversion, required HPLC purification and resulted in a low yield of 21%. Reaction of cyclic 1,3-diyne **79a** with enyne **86** in presence of catalytic amounts of [Pd(PPh$_3$)$_4$] yielded the benzo-annulated product **87** in 85% yield.[67]

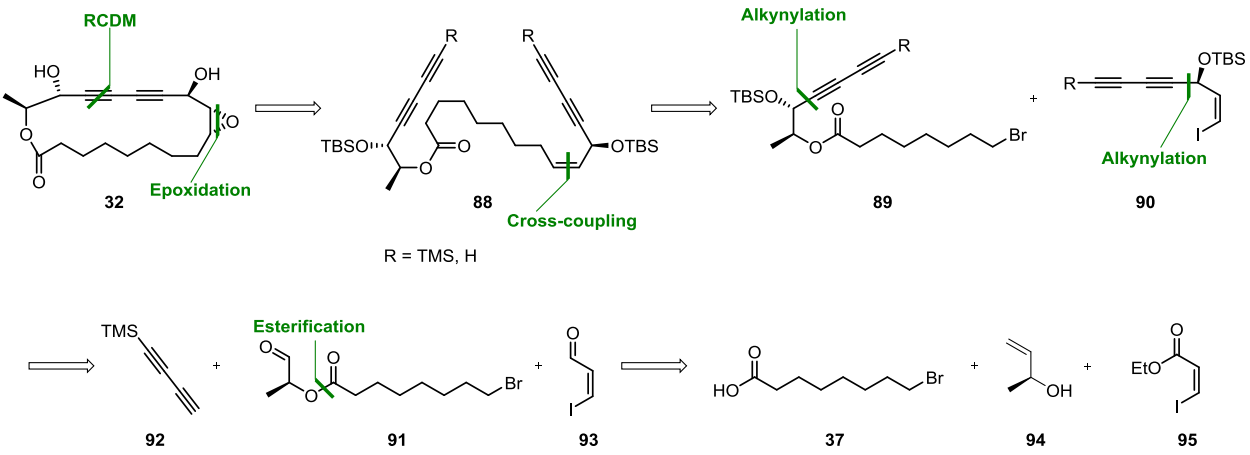


Scheme 23: Post-metathetic transformations of cyclic model 1,3-diyne **79a**: a.) [(SPhos)AuNTf$_2$] (cat), H$_2$O, THF, 60 °C, 16 h, 61%; b.) [(BrettPhos)Au(MeCN)]SbF$_6$ (cat), pyrrole, 1,2-DCE, 80 °C, 6 h, 21%; c.) [Pd(PPh$_3$)$_4$] (cat), THF, 65 °C, 85%.

These examples demonstrate the utility of cyclic 1,3-diynes as valuable building blocks for the synthesis of cyclophane derivatives and showcase the wide structural outreach of post-metathetic transformations.

2.5 RCDM: Synthesis of model compound (96) and initial attempt for the total synthesis of ivorenolide A

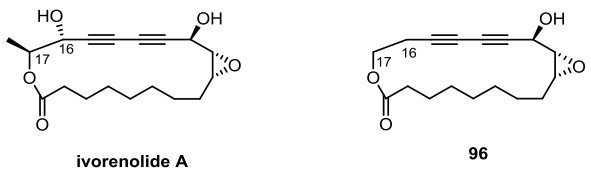
The project started with the retrosynthetic analysis of ivorenolide A (**32**). The strategy was based on the use of a RCDM reaction as the key transformation to forge the macrocyclic core. The obtained results for the cyclization of model compounds **80** and **83** suggested and allowed the use of TMS-capped 1,3-diynes, which could either serve as the RCDM precursor themselves or being conveniently converted to the terminal 1,3-diynes.



Scheme 24: Retrosynthetic analysis of ivorenolide A.

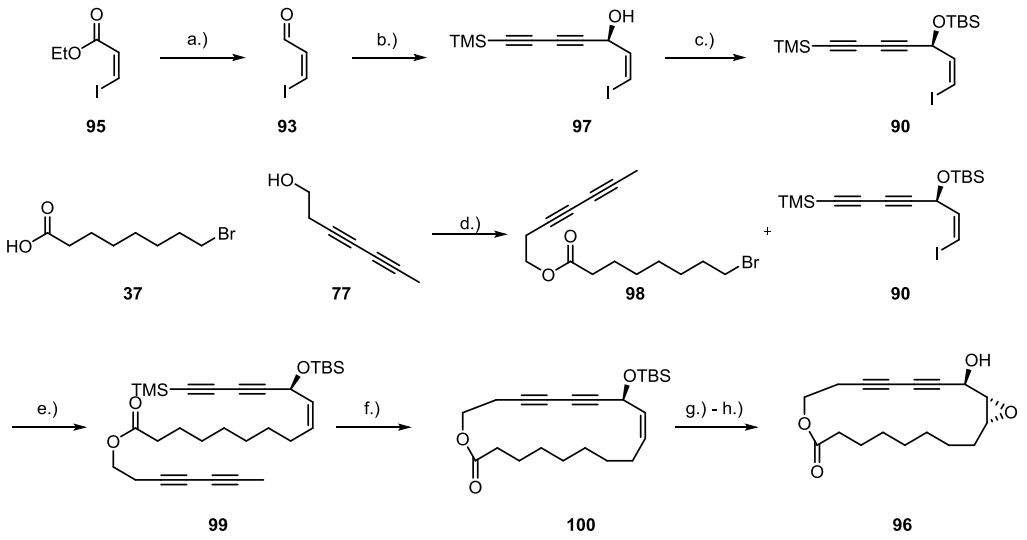
The required metathesis precursor **88** should be accessible by cross-coupling of alkyl bromide **89** with alkenyl iodide **90**. The alkyl bromide should be prepared by asymmetric alkynylation of aldehyde **91** with TMS-protected buta-1,3-diyne **92**. Aldehyde **91** should derive from esterification of commercially available 8-bromooctanoic acid (**37**) with allylic alcohol **94**. Reduction of commercially available ethyl (*Z*)-3-iodoacrylate (**95**) to the corresponding aldehyde **93** followed by asymmetric alkynylation with **92** should provide alkenyl iodide **90**.

In order to rule out possible interference of the catalytic system with propargylic oxygen functionalities, as present in ivorenolide A, the conditions previously employed for the cyclization of model compounds **72**, **80** and **83** (table 2 and 3) were first tested on a more elaborated substrate. Therefore compound **96** was prepared exhibiting already the same 18-membered macrocyclic core of ivorenolide A, but lacking the stereogenic centers at C16 and C17 (scheme 25).



Scheme 25: Ivorenolide A and model compound (**96**).

The preparation of model compound **96** started with the careful DIBAL-H reduction of ethyl (*Z*)-3-iodoacrylate at -80 °C yielding the unstable and volatile aldehyde **93**.[68] Due to the high instability, the crude aldehyde was not purified; rather it was dissolved in anhydrous toluene and kept under Ar atmosphere. The solution could be stored at -20 °C for at least 3 - 4 weeks without noticeable decomposition or isomerization of the double bond. With aldehyde **93** in hand, the focus was laid on the asymmetric alkynylation reaction. Preparation of the TMS-protected 1,3-diyne **92** was accomplished by treatment of bis-TMS-1,3-butadiyne with MeLi followed by careful protic work-up. The desired compound was obtained by destillation in 61% yield on several gram scale.[69] The asymmetric alkynylation was accomplished with $ZnMe_2$ and (*R*,*R*)-ProPhenol following a procedure described by Trost and co-workers.[70] Subsequent protection of the hydroxy group as the TBS-ether yielded alkenyl iodide **90** (scheme 26). The requisite coupling partner **98** was prepared by treatment of hepta-3,5-diyn-1-ol **77** with 8-bromooctanoic acid **37** under standard Steglich conditions.[56]

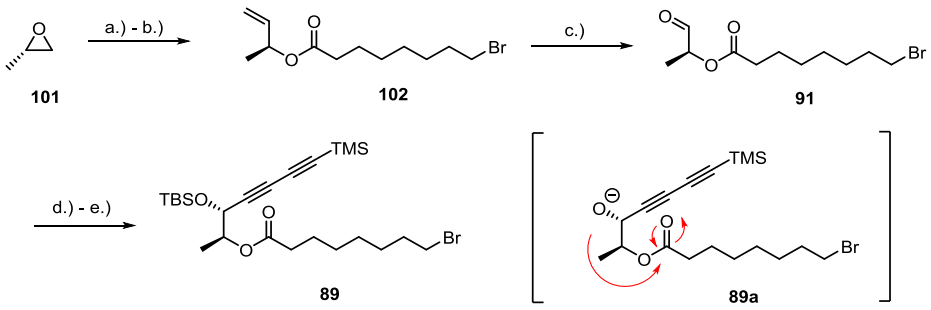


Scheme 26: Synthesis of model compound (**96**). a.) DIBAL-H, CH_2Cl_2, -80 °C, 30 min, 85%; b.) **74**, $ZnMe_2$, Ph_3P=O, (*R*,*R*)-ProPhenol, toluene, 0 °C, 4 h 86% 89% *ee* c.) TBS-Cl, 1-methylimidazole, I_2, CH_2Cl_2, 3 h, 98%; d.) DCC, DMAP, CH_2Cl_2, 16 h , 86%; e.) Zn, I_2, DMF, 75 °C, 4 h; (ii) **71**, $PdCl_2$, P(*o*-tol)$_3$, THF, 4 h, 36%; f.) **C5**, 4 Å MS/ 5 Å MS, toluene, 16 h, 82%; g.) *m*-CPBA, CH_2Cl_2, 16 h, 74%; h.) TBAF, THF, 0 °C, 10 min, 83%.

The assembly of both fragments was accomplished via Negishi cross-coupling of alkenyl iodide **90** with the organozinc species derived from alkylbromide **98**. Zinc was activated with iodine and treated with the alkyl bromide at 75 °C in DMF.[71] Subsequent coupling using $PdCl_2$ and P(*o*-tolyl)$_3$ gave the desired compound **99** in poor yield.[72] It was reasoned that the rather low outcome of the reaction is owed to the fact that the employed alkenyl iodide is prone to degradation and the 1,3-diyne motif of the organozinc compound is far from being innocent. Despite the disappointing yield of the cross-coupling reaction, sufficient quantities of material were carried forward to test the cyclization. The reaction was carried out under previously described conditions which converted metathesis precursor **99** to the desired cyclic 1,3-diyne **100** in good yield. Remarkably no dimerization was

detected during the course of the reaction, which was conducted at ambient temperature with a catalyst loading of 10 mol%. The subsequent treatment of cyclic 1,3-diyne **100** with *m*-CPBA followed by reaction with TBAF yielded model compound **96** (scheme 26).

The successful synthesis of the model compound comprised already the requisite alkenyl iodide **90**, which could be used for the total synthesis of ivorenolide A as well. The preparation of alkyl bromide **89** commenced with the one-carbon homologation of (*S*)-2-methyloxirane **101** using trimethylsulfonium iodide and *n*-BuLi.[73] The obtained allylic alcohol **94** proved to be highly volatile which made the isolation process difficult; purification was always accompanied by loss of significant amounts of material. As a consequence a one-pot procedure was developed which avoided the isolation of the alcohol. The crude solution was directly treated with 8-bromooctanoic acid **37** in presence of DCC and DMAP, which furnished the desired ester **102** in 66% yield over two steps. Subsequent ozonolysis of the olefin gave the desired aldehyde **91**, which was then subjected to different asymmetric alkynylation conditions. Initial attempts were based on a methodology reported by Carreira *et al*. in their total syntheses of strongyldiol A and B.[74] They described the asymmetric addition of 1,3-diynes to aldehydes with the use of $Zn(OTf)_2$ and (±)-*N*-methyl ephedrine. The advantage of this methodology was the use of only one equivalent 1,3-diyne compared to other methodologies which require excess of the 1,3-diyne. Unfortunately the reaction gave no desired product and only led to recovery of starting aldehyde **91**. The alkynylation was then carried out under Trost conditions[70] and the product was obtained as an inseparable mixture together with the 1,2-acyl migration (**89a**) compound. Alkyl bromide **89** was obtained in pure form by conversion of the hydroxy group to the corresponding TBS-ether which could then be separated from the byproduct (scheme 27).



Scheme 27: Synthesis of alkyl bromide **85**: a.) Me_3SI, *n*-BuLi, THF, -10 °C 3 h; b.) 8-bromoctanoic acid, DCC, DMAP, THF 16 h 66% over two steps; c.) O_3, CH_2Cl_2, - 78 °C, then DMS; 16 h, 81%; d) **74**, $ZnMe_2$, $Ph_3P{=}O$, (*R*,*R*)-ProPhenol, toluene 0 °C 16 h; e.) TBS-Cl, 1-methylimidazole, I_2, CH_2Cl_2, 49% (over two steps).

Negishi cross-coupling of **89** with alkenyl iodide **90** afforded fragment **103**. The activation of zinc with TMS-Cl and 1,2-dibromethane in the presence of LiCl as reported by Knochel *et al.*[75] did not yield the desired organozinc species, which was instead obtained by treatment of alkyl bromide **89** with zinc, activated with iodine. The zinc-insertion occurred only sluggishly and examination of a hydrolysed

sample indicated the formation of several byproducts during the insertion reaction.The use of different palladium-based catalytic systems gave only low yields of the desired product (table 4).[72]

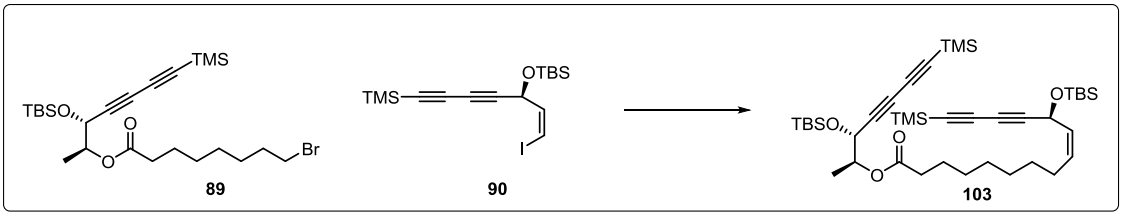
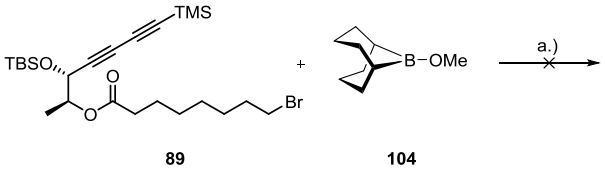


Table 4: Screening of the Negishi cross-coupling reaction.[a]

Entry	Conditions	Yield [%]
1	Zn, LiCl, THF, 50 °C[75]	-
2	$PdCl_2$, P(*o*-tolyl)$_3$, THF, rt.	15[a]
3	$Pd(PPh_3)Cl_2$, TMEDA, THF, rt.	17[a]
4	$Pd(PPh_3)Cl_2$, THF, rt.	5<[a]

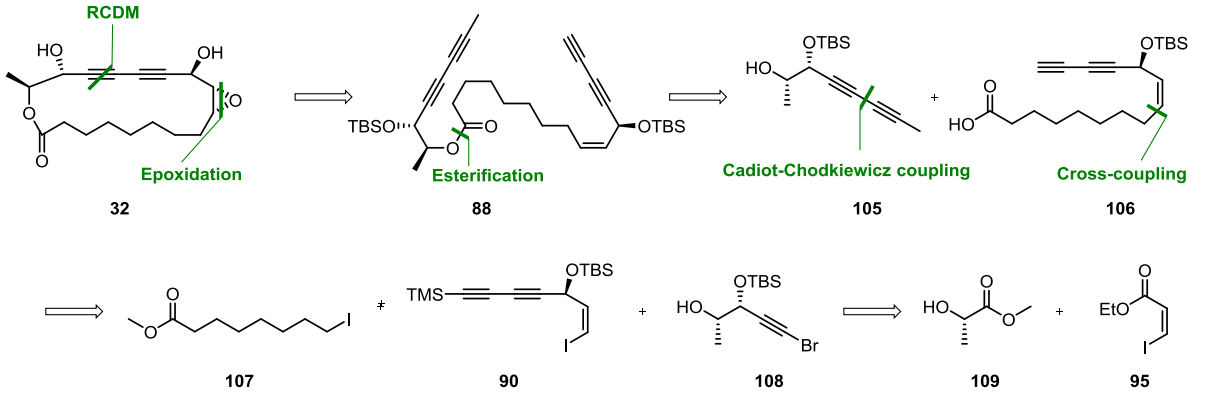
[a] The insertion was done with Zn dust (activated with 5 mol% I_2) in DMF [0. 5 M] at 80 °C for 4 h.

Therefore the Suzuki-Miyaura sp^3-sp^2 cross-coupling reaction was tested as an alternative to the Negishi coupling. The alkyl bromide **89** was subjected to Li/Br exchange conditions in presence of 9-(MeO)-9-BBN (**104**), but no formation of the desired borate was observed according to ^{11}B-NMR.[76] Deprotonation of the ester might occur faster than the lithium/bromide exchange and result in decomposition of the compound.



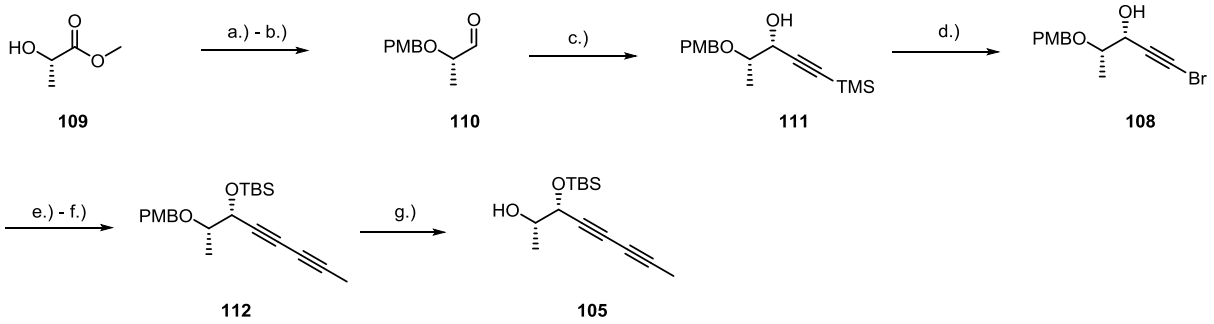
Scheme 28: Attempted preparation of the borate complex: a.) *t*-BuLi, Et_2O/pentane, -78 °C.

The obtained results led to a revision of the retrosynthetic strategy as shown in scheme 29. The assembly of RCDM precursor **88** should be accomplished by esterification of alcohol **105** and carboxylic acid **106**. The acid should be accessible from methyl ester **107** via alkyl cross-coupling reaction with alkenyl iodide **90**. The alcohol **105** should derive from a Cadiot-Chodkiewicz coupling of bromo alkyne **108** with propyne (scheme 29).



Scheme 29: Retrosynthetic revision of ivorenolide A.

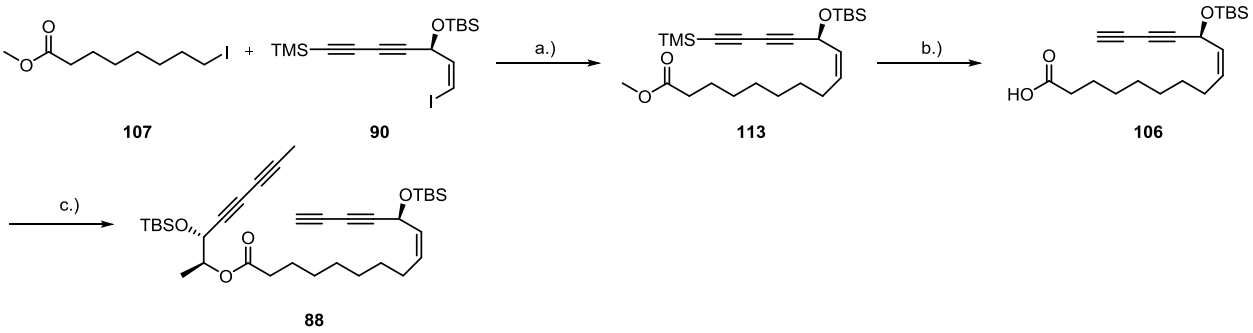
Methyl-L-lactate **109** was protected as the corresponding benzyl ether and treated with DIBAL-H to afford aldehyde **110**. Diastereoselective addition of TMS-acetylene yielded the propargylic alcohol **111** in good yield and with good selectivity (9:1, d.r.). The propargylic alcohol underwent bromination using NBS in presence of catalytic amounts of $AgNO_3$, and the unstable bromo alkyne **108** was subjected to Cadiot-Chodkiewicz conditions in order to obtain the 1,3-diyne. Initial attempts for the coupling of **108** with propyne relied on the employment of piperidine as the solvent and proved unsuccessful. Changing the solvent to aq. $BuNH_2$ (30% in water) and raising the temperature to 0 °C yielded the desired 1,3-diyne. Protection of the free hydroxy group as the TBS-ether **112**, followed by removal of the PMB-group using DDQ in a buffered solution of CH_2Cl_2 gave the desired alcohol **105**. It proved crucial for the success of the reaction that the temperature was kept at 0 °C and that prolonged stirring was avoided (scheme 30).



Scheme 30: Preparation of alcohol fragment **105**: a.) PMB-trichloroacetimidate, TfOH, Et_2O, -78 °C to rt, 16 h, 88%; b.) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, 89%; c.) TMS-acetylene, Et_2Zn, Ti(*i*-PrO)$_4$, (*R*)-BINOL, Et_2O, 16 h , 71%, 9:1 d.r.; d) NBS, $AgNO_3$, acetone, 16 h, 76%; e.) propyne, CuCl, aq. $BuNH_2$ (30% in water), 0 °C, 1 h, 67%; f.) TBS-Cl, 1-methylimidazole, I_2, CH_2Cl_2, 2 h, 84%; g.) DDQ, CH_2Cl_2/aq. buffer (pH~7), 0 °C, 2 h, 64%.

The synthesis of acid fragment **106** started with the preparation of literature-known alkyl iodide **107** from 8-bromooctanoic acid.[77] Recently reported examples revealed that coupling between mixed halogen species sometimes results in diminished yields of the coupling product.[72] For this reason the alkyl iodide **107** was used as the coupling partner of alkenyl iodide **90**.[72] Insertion of zinc into the C-I bond proved to be more successful without the 1,3-diyne motif and coupling with alkenyl iodide **90**

was successfully achieved using $Pd(PPh_3)Cl_2$ in presence of TMEDA (scheme 31). It proved essential for the reproducibility and success of the reaction that the employed TMEDA was rigorously dried before use. The coupling product **113** was then subjected to basic hydrolysis conditions to liberate the carboxylic acid **106**. During the course of the reaction the TMS-group was cleaved and partial loss of the TBS-group was observed. The acid fragment bearing the terminal 1,3-diyne proved prone to degradation. The assembly of alcohol fragment **87** and acid fragment **106** was accomplished via esterification using modified Steglich conditions (scheme 31).[78]



Scheme 31: Synthesis of metathesis precursor (**88**): a.) Zn, I_2, DMF, 75 °C, 4 h, (ii) **90**, $Pd(PPh_3)Cl_2$, TMEDA, THF, 68%; b.) LiOH THF/H_2O, 6.5 h, 78%; c.) **105**, EDC·HCl, DMAP, CH_2Cl_2 16 h, 58%.

The metathesis precursor **88** was then subjected to RCDM. The use of molybdenum catalysts **C4** and **C5** only gave recovered starting material. Even at high temperatures no cyclized product was observed. The use of 2,4-hexadiyne as an initiator for the cyclization failed. Switching from molybdenum catalysts **C4** and **C5** to tungsten alkylydine **C1b** did not change the outcome either (table 5). Simultaneous removal of both propargylic TBS-ethers was attempted with the aid of TBAF at low temperature but only led to decomposition of the starting material.

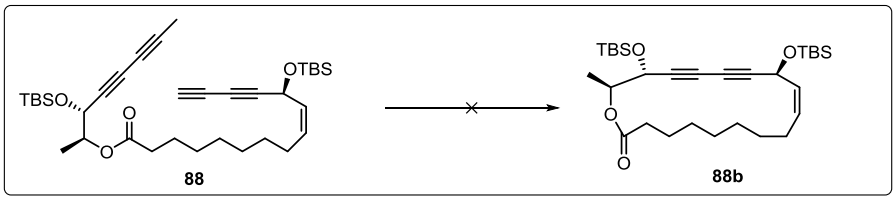


Table 5 : Screening of conditions and catalysts for the RCDM.[a]

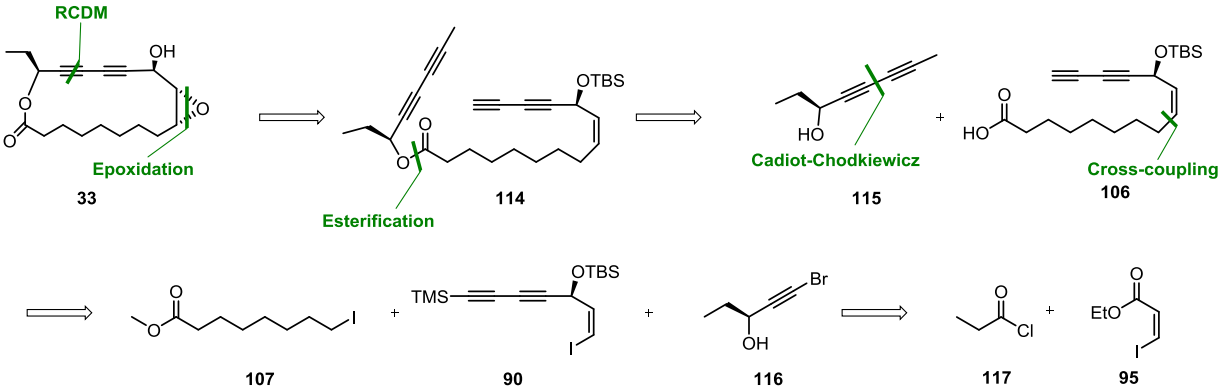
Entry	Catalyst	Temp.[°C]	Additive	Yield [%]
1	**C4**	70	-	sm
2	**C4**	110	-	**-**
3	**C5**	rt	-	sm
4	**C5**	70	-	sm
5	**C5**	110	-	**-**
6	**C5**	60	2,4-Hexadiyne	sm
7	**C5**	110	2,4-Hexadiyne	**-**
8	**C1b**	70	-	sm

[a] All reactions were performed with a catalyst loading of 20 mol% in toluene [10 mM] in presence of 4 and 5 Å MS. sm = recovered starting material; **-** = decomposition of starting material.

Despite the positive results obtained with all the previously employed cyclization precursors (**72**, **80**, **83**, **100**), substrate **88** failed to cyclize. One reason for these unsuccessful attempts might be the additional propargylic oxygen functionality at C16, which not only provides another possible coordination site for the catalyst, also the steric bulk derived from the second protecting group could prohibit the required arrangement of the catalyst and the substrate. Therefore the focus shifted towards ivorenolide B, which lacks the second propargylic oxygen functionality. If this hypothesis proved to be correct and the cyclization of ivorenolide B would be possible, a second attempt for the synthesis of ivorenolide A was planned utilizing a different strategy.

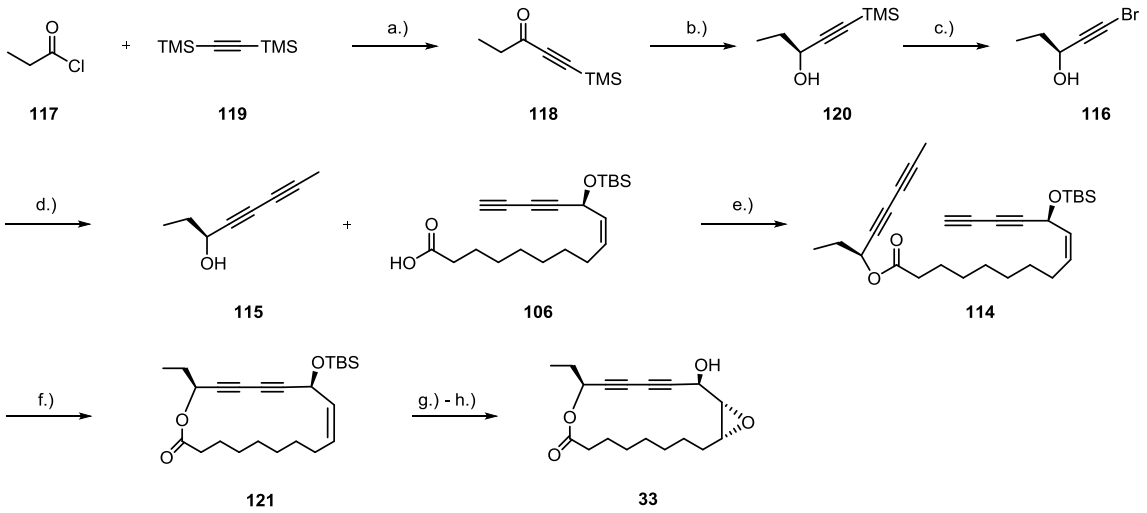
2.6 Total synthesis of ivorenolide B

The project started with the idea in mind to utilize the same carboxylic acid fragment **106** as previously used for the attempted synthesis of ivorenolide A. The fragments should be assembled by an esterification reaction between carboxylic acid **106** and alcohol **115** to obtain the requisite metathesis precursor **114**. Alcohol **115** should be accessible from propionyl chloride (**117**) via a Friedels-Crafts type reaction followed by enantioselective reduction (scheme 32).



Scheme 32: Retrosynthetic analysis of ivorenolide B.

The synthesis of alcohol **115** commenced with the preparation of literature known alkynone **118** from propionyl chloride (**117**) and bis-TMS-acetylene **119** by an $AlCl_3$-mediated Friedel-Crafts type reaction. The subsequent reduction of the ketone using Noyori transfer hydrogenation conditions yielded the desired alcohol **120** in good yield and with excellent enantioselectivity.[55b] The 1,3-diyne **115** was obtained by bromination of the TMS-alkyne with NBS in the presence of catalytic amounts of $AgNO_3$, followed by copper-catalyzed Cadiot-Chodkiewizc coupling with propyne. The alcohol and the acid fragment were connected by esterification to yield metathesis precursor **114**. Gratifyingly, the metathesis proceeded smoothly to the cyclic 1,3-diyne **121** with the use of standard catalyst **C5** at ambient temperature. The product was obtained in good yield and no dimerization was observed, although fairly high catalysts loading were required to drive the reaction to full conversion. The example represents the first unsymmetrical RCDM between a terminal 1,3-diyne and a methyl capped 1,3-diyne (scheme 33).

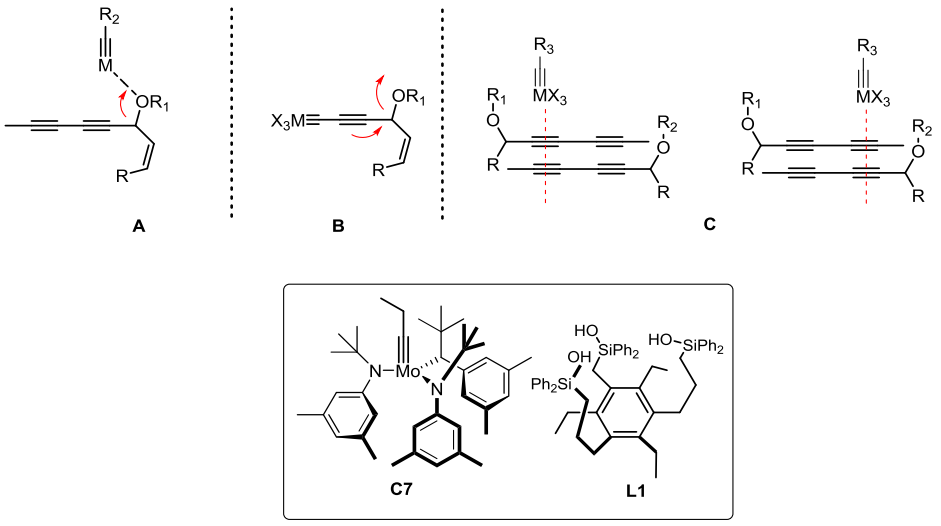


Scheme 33: Total synthesis of ivorenolide B: a.) $AlCl_3$, CH_2Cl_2, 0 °C, 2 h, 97%; b.) [(*p*-cymene)$RuCl_2$]$_2$, (*S,S*)-Ts-DPEN, KOH, CH_2Cl_2; ii) **118**, *i*PrOH, 89% (97% *ee*); c.) NBS, $AgNO_3$, acetone, 2 h, 88%; d.) propyne, CuCl, aq. $BuNH_2$ (30% in water), $NH_2OH{\cdot}HCl$, -5 °C to rt. 1 h, 62%; e.) EDC·HCl, DMAP, CH_2Cl_2, 16 h, 62%; f.) **C5**, 4 Å MS/ 5 Å MS, toluene, 16 h, 82%; g.) *m*-CPBA, CH_2Cl_2, 8 h, 80%; h.) TBAF, THF, 0 °C, 74%.

The cyclic 1,3-diyne **121** was epoxidized with *m*-CPBA and the resulting epoxide was treated with TBAF at low temperature to remove the TBS protecting group yielding ivorenolide B (**33**) as a colorless viscous oil (scheme 32). Comparison of the obtained spectroscopic data with those reported in the literature confirmed the correct structure (table 9a). In conclusion, ivorenolide B was synthesized in ten steps in the longest linear sequence by applying the RCDM of a terminal 1,3-diyne with a methyl capped 1,3-diyne as the key step.[79]

2.7 Total synthesis of ivorenolide A

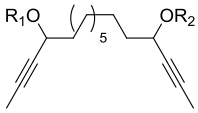
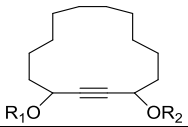
The use of substrates bearing bis-propargylic oxygen functionalities have been a long standing issue for RCAM.[41a, 80] Until recently such compounds have never been cyclized. Most notably only substrates bearing one propargylic oxygen functionality and one "regular alkyne" have been successfully used in RCAM. The challenge for a catalytic system to construct a macrocycle bearing a propargylic alcohol motif arises from several possible decomposition pathways Alkyne metathesis catalysts are Schrock alkylidynes, which possess a high Lewis acidity; if not properly adjusted by an ancillary ligand. The high Lewis acidity could lead to decomposition via pathways **A** and **B** at any activated position. Another challenge arises from the steric bulk of protected propargylic alcohol functionalities (scheme 33).



Scheme 34: Challenges for the cyclization of 1,3-diynes bearing propargylic functionalities.

The recently developed catalytic system consisting of molybdenum complex **C7** and the multivalent ancillary ligand **L1** allowed for the first time to react substrates bearing two propargylic hydroxy groups (scheme 34, table 6).[80] It was assumed that a chelating cross linking ligand such as **L1** provides a higher resistance towards protic functionalities and a higher thermal stability, which is advantageous since high temperatures are often required for the metathesis of bis-propargylic substrates.

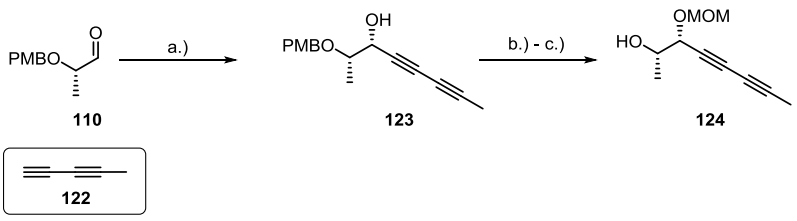
Table 6: Performance of the novel catalytic system **C7/L1** compared to standard catalyst **C5**.[80][a]

Entry	Substrate	Product		Yield [%]	
				C5	C7/L1
1			R_1 = MOM, R_2 = OH	0	67
2			R_1 = R_2 = TES	0	71
3			R_1 = TES, R_2 = OH	0	64
4			R_1 = R_2 = OH	0	58
5			R_1 = R_2 = Ac	0	0

[a] All reactions were performed with a catalyst loading of 20 mol% in refluxing toluene [1mM].

The promising results obtained using the new catalytic system for RCAM moved the attention back to ivorenolide A. It was rationalized that a change in the protecting group strategy might facilitate the cyclization. Therefore the bulky TBS-groups on both sides of the metathesis precursor were replaced by sterically less demanding MOM-groups. Additionally, the termini of the metathesis precursor were adjusted. Although the successful conversion of substrate **114** proved that the cyclization of an unsymmetrically substituted 1,3-diyne proceeds well (scheme 33), the termini of the acyclic metathesis precursor in the second attempt were changed to the methyl-capped ones. It was considered that this change should facilitate the synthesis of the metathesis precursor in terms that building block **122** could be employed for the elaboration of both fragments (scheme 35).

The second approach towards ivorenolide A started with the preparation of 1,3-pentadiyne **122** for the asymmetric alkynylation reaction. Despite the fact that this compound has never been used for such a transformation, its use would be beneficial in terms of step economy compared to the previous applied strategy consisting of TMS-acetylene addition, bromination and Cadiot-Chodkiewicz coupling with propyne. The difficult preparation protocol of 1,3-pentadiyne and the high volatility and instability of the compound made the preparation of sufficient quantities of **122** challenging.[81] Asymmetric alkynylation of aldehyde **110**, derived from methyl-L-lactate, afforded the desired product **123** in 61% yield. Subsequent protection of the free hydroxy group as the MOM-ether and removal of the PMB-group under oxidative conditions furnished the free alcohol fragment **124** for the planned esterification (scheme 35).



Scheme 35: Preparation of alcohol (**124**): a.) **122**, Me_2Zn, (*R*,*R*)-ProPhenol, Ph_3P=O, toluene, 0 °C, 61% (2.5: 1 d.r.); b.) MOMCl, *i*-Pr_2Net, CH_2Cl_2, 85%; c.) DDQ, CH_2Cl_2/ aq. Buffer (pH~7), 0 °C, 72%.

The asymmetric alkynylation of (*Z*)-3-iodoacrylaldehyde **93** was carried out under the same conditions as described for the alkynylation with TMS-buta-1,3-diyne **92**. The product was obtained in good yield but only with moderate enantiomeric excess (table 7).

It was assumed that the rather poor selectivity is owed to the fact that 1,3-pentadiyne **122** lacks any steric bias which proved essential to obtain good enantiodiscrimination.[62b, 70]

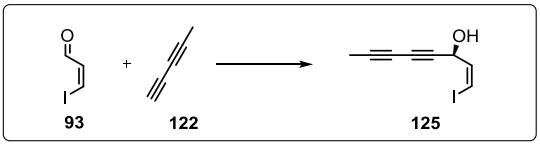
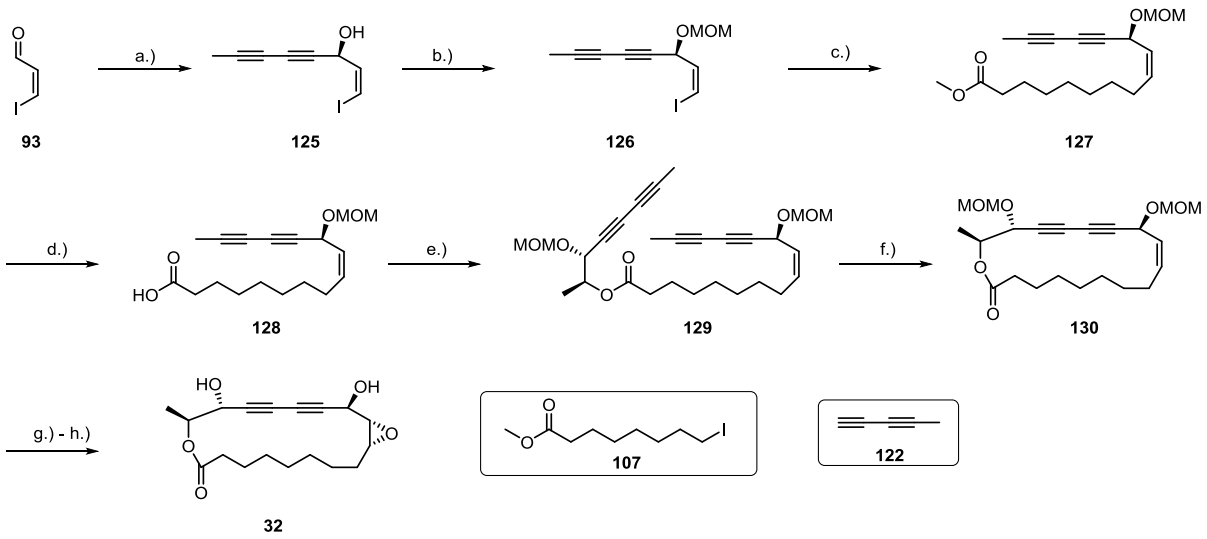


Table 7 : Screening of conditions for asymmetric alkynylation of (*Z*)-3-iodoacrylaldehyde.

Entry	Conditions	Yield [%]
1[70]	$ZnMe_2$, $Ph_3P{=}O$, (*R*,*R*)-ProPhenol, toluene, 0 °C	86 (70% *ee*)
2[62b]	$ZnEt_2$, Ti(*i*-PrO)$_4$, (*R*)-BINOL, Cy_2NH, Et_2O	90 (63% *ee*)
3[74]	$Zn(OTf)_2$, (-)-*N*-methylephedrin, Et_3N, toluene	-

The free hydroxy group was protected as the corresponding MOM-ether **126** using standard conditions. Subsequent coupling with the organozinc species derived from alkyl iodide **107** yielded alkene **127**. The necessary organozinc species was prepared using the protocol reported by Knochel and co-workers[75] and the coupling to the desired product proceeded without any noticeable isomerization of the double bond. Hydrolysis of the methyl ester under basic conditions produced the carboxylic acid **128** in nearly quantitative yield. Gratifyingly, no loss of the MOM-group was observed under the applied conditions. The assembly of both fragments via Yamaguchi esterification gave the desired tetrayne **129** in 79% yield.



Scheme 36: Total synthesis of ivorenolide A: a.) **122**, Me_2Zn, (*R*,*R*)-ProPhenol, $Ph_3P{=}O$, toluene, 0 °C, 86% (70% *ee*); b.) MOMCl, *i*-Pr_2Net, CH_2Cl_2, 86%; c.) **107**, Zn, LiCl, THF, 40 °C, 5 h (ii) $Pd(PPh_3)_2Cl_2$, TMEDA, THF, 50 °C, 45 min, 75%; d.) LiOH, THF/MeOH (2:1), 95%; e.) 2,4,6-trichlorbenzoic acid chloride, Et_3N, then **124**, DMAP, toluene 0 °C to rt, 79%; f.) **C7**/**L1**, toluene, 5 Å MS, 60 °C, 78%; g.) aq. HCl, EtOH, 70 °C, 64%; h.) *m*-CPBA, CH_2Cl_2, 85%.

The metathesis precursor **129** was subjected to RCDM conditions using **C5** at elevated temperatures but the desired cyclic 1,3-diyne **130** was observed only in poor yields. Fairly high catalyst loadings and long reaction times were required to reach full conversion. Upon switching to the novel catalytic system **C7/L1**, the reaction proceeded cleanly to give the desired product in 78% yield; no dimeric species was observed. The reaction was done in less than 1 h and the catalyst loading could be decreased to 20 mol% (table 8).

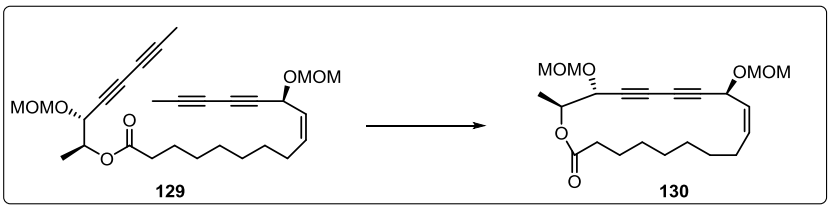


Table 8: Screening of the influence of different catalysts for the cyclization.[a]

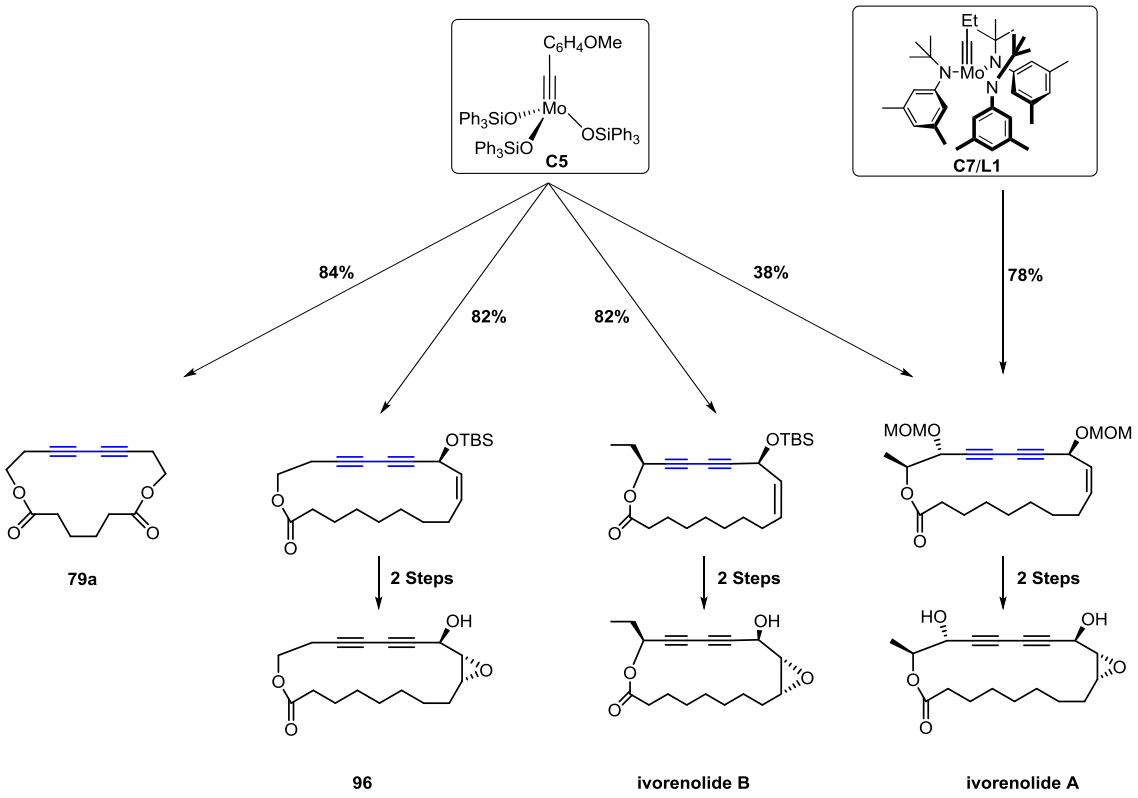
Entry	Catalyst	Conditions	Yield [%]
1	**C5** (35 mol%)	60 °C, 4 h	38%
2	**C5** (35 mol%)	110 °C, 4 h	33%
3	**C7/L1** (20 mol%)	60 °C 1 h	78%
4	**C7/L1** (20 mol%)	110 °C 1 h<	75%

[a] All reactions were performed in toluene [8 mM] in presence of 5 Å molecular sieves.

Ivorenolide A (**32**) was obtained via a two step sequence from the cyclic 1,3-diyne **130** consisting of simultaneous removal of both MOM protecting groups with aq. HCl at elevated temperature followed by subsequent epoxidation employing *m*-CPBA (scheme 36). Comparison of the obtained analytical data was in excellent agreement with those reported in the literature (table 9b).

2.8 Summary

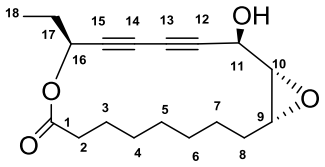
This study represents the first systematical investigation of RCDM. Model studies revealed that the use of molybdenum alkylydine complex **C5** allowed the efficient cyclization of differently substituted acyclic precursors (**72**, **80**, **83**, **100**) to cyclic 1,3-diynes **79a** and **96** (scheme 37). Application of the conditions obtained during the model studies provided access to the naturally occurring cyclic 1,3-diynes ivorenolide A and B.



Scheme 37: Compounds prepared by RCDM.

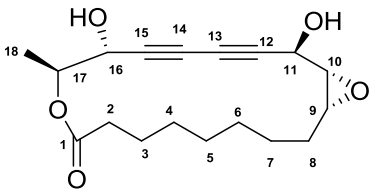
Concise total syntheses of ivorenolide A and B were accomplished, each in a ten step longest linear sequence from commercially available starting material.[79-80] Both syntheses represent the shortest access to these structurally unique natural products known to date. Moreover the total synthesis of ivorenolide B represents the first unsymmetrical RCDM between a terminal 1,3-diyne and a methyl capped 1,3-diyne (scheme 33). The total synthesis of ivorenolide A illustrates the utility of the novel catalytic system **C7**/**L1** for the cyclization of bis-propargylic substrates. Although the cyclization of acyclic precursor **129** to the corresponding cyclic 1,3-diyne **130** was possible, the use of **C7**/**L1** improved the yield from 38% to 78% (scheme 36, table 7). The conducted surveys proved that RCDM is a valuable tool for the construction of macrocyclic compounds, offering a promising alternative to classical methodologies for the total synthesis of cyclic natural products.

Table 9a: Comparison of synthetic and natural ivorenolide B.



	Isolated ^{13}C	Isolated ^{1}H	Synthetic ^{13}C	Synthetic ^{1}H
1	173,2	Carbonyl	173,2	
2	34,8	2,43(m, 2H)	34,8	2,43 (m, 2H)
3a	27,0	1,68 (m)	27,0	1,68 (m)
3b		1,64 (m)		1,64 (m)
4a	28,7	1,47 (m)	28,6	1,47 (m)
4b		1,36 (m)		1,36(m)
5	30,8	1,23 (m, 2H)	30,7	1,23(m)
6a	30,5	1,32 (m)	30,5	1,32(m)
6b		1,22 (m)		1,22(m)
7a	26,4	1,56 (m)	26,3	1,53(m)
7b		1,30 (m)		1,30(m)
8a	29,6	1,98 (m)	29,6	1,98 (m)
8b		1,38 (m)		1,36(m)
9	56,8	3,11 (ddd)	56,8	3,11 (ddd,)
10	62,0	3,60 (dd)	62,0	3,60 (dd)
11	62,8	4,87 (d)	62,8	4,87 (d)
12	80,5		80,5	
13	70,0		70,0	
14	70,0		69,9	
15	79,0		79,0	
16	65,7	5,49 (t)	65,7	5,49 (t)
17	27,6	1,79 (dq, 2H)	27,6	1,79 (dq, 2H)
18	9,8	0,94 (t, 3H)	9,8	0,94 (t, 3H)
-OH		8,48		8,48

Table 9b: Comparison of synthetic and natural ivorenolide A.

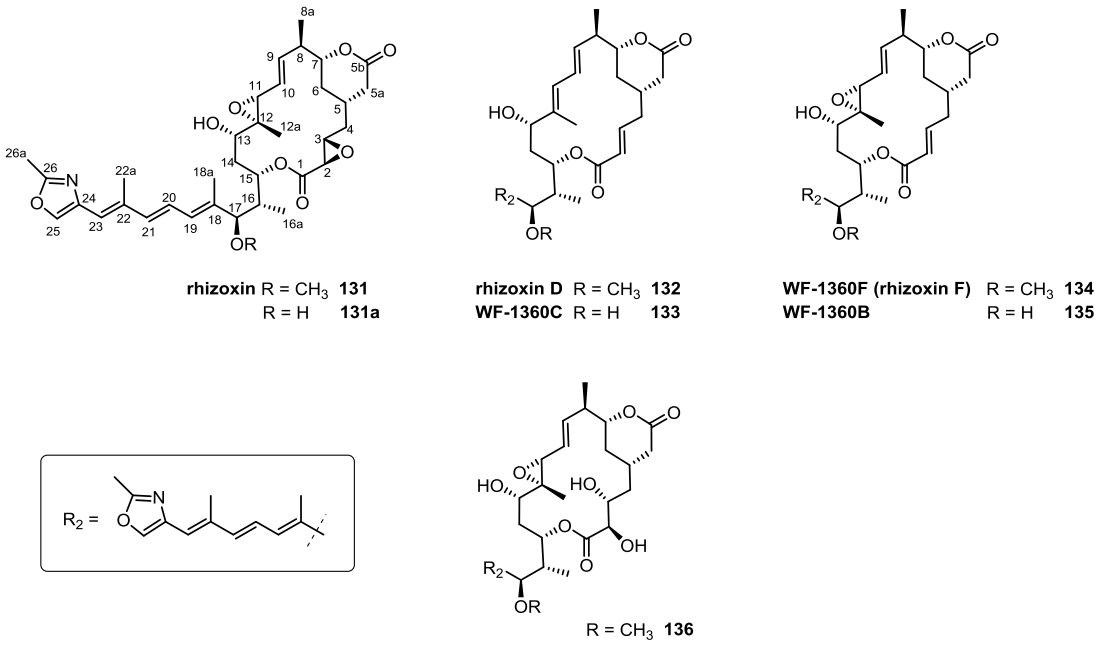


	Isolated ^{13}C	Isolated ^{1}H	Synthetic ^{13}C	Synthetic ^{1}H
1	172.9	Carbonyl	172.9	
2	34.9	2.43 (2H, m)	35.0	2.47 – 2.37 (2H, m)
3a	25.6	1.81 (m)	25.6	1.81 (m)
3b		1.55 (m)		1.54 (m)
4a	29.0	1.42 (2H, m)	29.1	1.43 (2H, ddd, 11.6, 9.3, 6.2)
4b				
5	30.0	1.23 (2H, m)	30.0	1.25 (2H, m)
6a	29.8	1.29 (m)	29.8	1.29 (m)
6b		1.23 (m)		1.23 (m)
7a	26.1	1.47 (m)	26.2	1.45 (m)
7b		1.36 (m)		1.34 (m)
8a	28.5	1.99 (m)	28.6	1.99 (m)
8b		1.32 (m)		1.33 (m)
9	57.0	3.10 (m)	57.0	3.09(ddd, 10.1, 4.3, 3.0)
10	61.0	3.53 (dd, 8.1, 4.2)	61.1	3.51 (dd, 8.1, 4.2)
11	62.0	4.77 (d, 8.1)	62.2	4.79 – 4.67 (m, 2H)
12	78.5		78.5	
13	68.7		68.7	
14	70.3		70.3	
15	81.3		81.3	
16	65.4	4.74 (d, 8.3)	65.5	4.79 – 4.67 (2H, m)
17	72.7	5.45 (dq, 8.3, 6.2)	72.8	5.44(dq, 8.2, 6.2)
18	17.6	1.50 (3H, d, 6.2)	17.7	1.48 (3H, d, 6.2)
-OH		8.44		8.27(2H, s)
		8.37		

3 The rhizoxin family

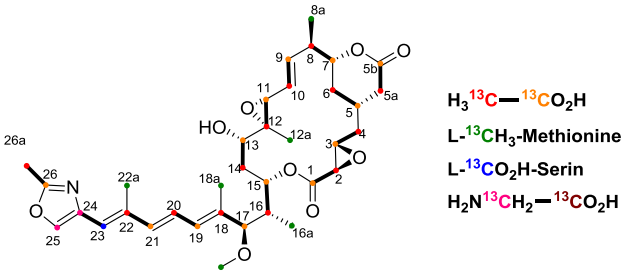
3.1 Isolation and structure elucidation

The polyketide macrolide rhizoxin (**131**) was isolated three decades ago from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and co-workers in a case study aimed at revealing the origin of the economically costly rice seedling blight disease.[82] Congeners of rhizoxin like the didesepoxy compound rhizoxin D (**132**), which is the putative biosynthetic precursor of the parent compound rhizoxin, were isolated from the same fungus shortly after the original report.[83] Tremendous efforts were devoted to elucidate the structure of this complex class of macrolides. These efforts included NMR-studies, X-ray crystallography, mass spectroscopy, IR-spectroscopy and degradation methods. The unprecedented structure of rhizoxin exhibits eleven stereogenic centers, a δ-lactone annulated in a 16-membered macrocyclic lactone, two epoxides and a triene side chain which is terminated with a methyl substituted oxazole heterocycle.[82b, 84]



Scheme 38: Antitumor macrolides from *Rhizopus chinensis*.

Initial biosynthetic studies by the isolation group revealed the origin of all carbon atoms via incorporation of ^{13}C enriched biosynthetic precursors. The enriched building blocks were fed to *Rhizopus chinensis* grown on a nutrition medium.[82b] NMR studies showed that O-acetyl-L-serine acts as the starter unit for the synthesis of the polyketide chain C1 to C22 and that all methyl groups as well as the methylated hydroxy group at C17 originated from 6 eq. of methionine.[85] The exception is the C26a methyl group which is derived from an acetate unit, which is also the supposed origin of the annulated δ lactone. [85]



Scheme 39: Initial biosynthetic studies towards the origin of all carbon atoms in rhizoxin.

In 2005 Hertweck and co-workers revealed that rhizoxin is not produced by the fungus itself but is instead synthesized by a bacteria that lives symbiotically inside the fungus.[86] The bacteria from the genus *Burkholderia* lives in a remarkably complex relationship to the host fungus. Early isotope labelling studies uncovered the involvement of a polyketide synthase (PKS) for the biosynthesis of rhizoxin.[85] Hertweck *et al*. were unable to detect any fungal PKS genes in the genome of the rhizoxin producing fungus via polymerase chain reaction (PCR).[87] Instead they were able to amplify bacterial 16S rDNA via PCR from the fungal genome. A database search showed that these amplified genes are most likely belonging to a type of polyketide synthase ("*trans*-AT" PKS) which is exclusively known from bacteria.[88] The use of the antibiotic ciprofloxacin allowed them to cultivate the *Rhizopus* fungus with complete suppression of rhizoxin production. Isolation of the bacteria and re-introduction into the symbiont-free culture led to a stable rhizoxin production, which ultimately proved their fungus symbiont hypothesis.[86, 89]

3.2 Biological properties

Early biological studies already demonstrated the great potential of this class of polyketide macrolides as antimitotic agents. Iwasaki and co-workers showed the antimitotic activity of rhizoxin by assaying the mycelium growth inhibition activity against a variety of phytopathogenic fungi.[82b] The mode of action is believed to occur via binding to the structural protein β-tubulin which interferes with the cell cycle and blocks cell division leading to the death of the plant. These results prompted researchers to explore the ability of rhizoxin and related compounds as potential chemotherapeutic agents. Inhibition of the mitosis of the tumor cells follows a similar pathway as known for the Vinca alkaloids such as vincristine, which is used as a chemotherapeutic agent.[90] Rhizoxin has been found to be less toxic and more potent than vincristine against L1210 and P388 leukemia cells.[91]

Table 9: Cytotoxicity of rhizoxin and vincristine in mouse and human tumor cell lines sensitive and resistant to vincristine and adriamycin.[91]

	IC_{50} (nm)				
Compound	**P388**	**P388/VCR**	**P388/ADM**	**K562**	**K562/VCR**
Rhizoxin	0.91 ± 0.01[a]	3.84 ± 0.39(4.2)[b]	4.13 ± 0.49(4.5)	0.51 ± 0.04	1.28 ± 0.05 (2.5)
Vincristine	2.10 ± 0.10	32.4 ± 2.3(15.4)	54.0 ± 2.3(25.7)	2.68 ± 0.25	56.3 ± 1.3 (21.0)

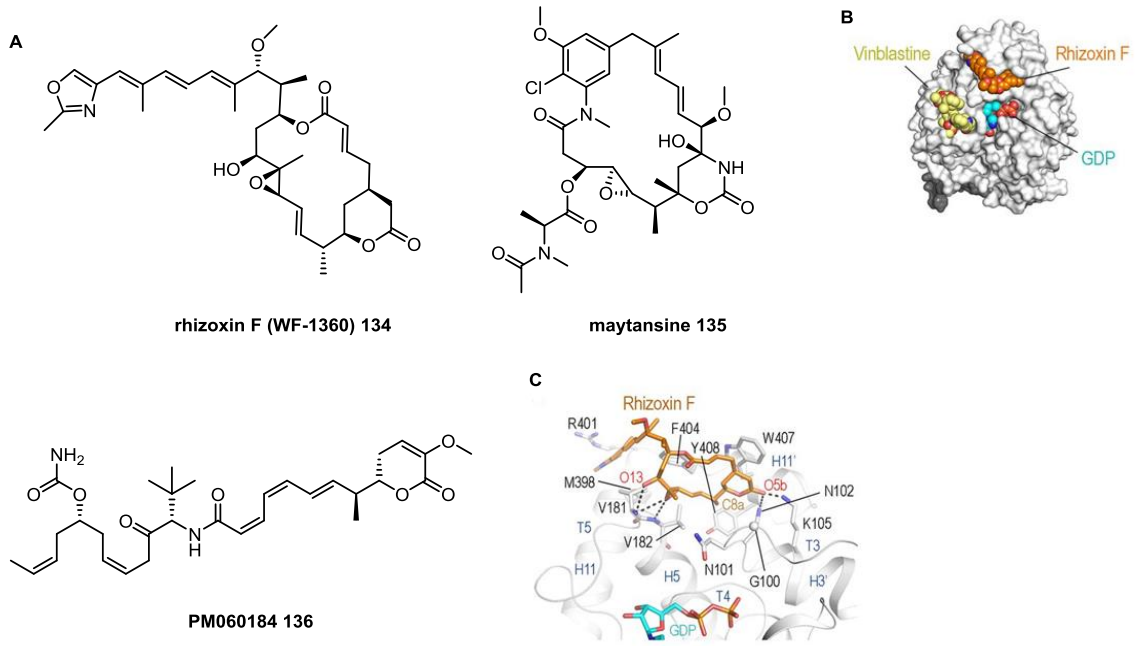
[a] Mean ± SD of three determinations [b] Numbers in parentheses, degree (x-fold) of resistance as compared to parent cells. VCR = vincristine, ADM = Adriamycin, P388/VCR = leukemia resistant to VCR, P388/ADM = leukemia resistant to ADM, K562 = human myleogenous leukemia, K562/VCR = human myleogenous leukemia resistant to VCR.

Most notably, rhizoxin has significant efficacy against vincristine and adriamycin resistant human tumor cells in-vitro and in-vivo. Further studies were conducted and pre-clinical evaluation demonstrated moderate to good in-vivo activity against murine tumors such as B-16 melanoma, M5076 sarcoma and human xenografts LOX melanoma, MX1 breast cancer and A549 non-small lung cancer.[91-92] The absence of cross-reactivity with other chemotherapeutic agents was confirmed by the in-vivo activity against small cell lung cancers such as LXFS 605 and LXFS 650, which were vincristine sensitive and –resistant, respectively. [92b] The promising properties and the observed activities of rhizoxin initiated Phase I and II clinical trials, in the US by the NCI, in Japan by Fujisawa and in Europe by the EORTC, but no therapeutic advantages compared to other chemotherapeutics were observed and surveys were shut down.[93]

Rhizoxin acts by binding to β-tubulin thus causing the inhibition of tubulin polymerization. The inhibition prevents the formation of microtubule, the key components of the cytoskeleton, leading to the death of the cell. Binding studies revealed that the rhizoxin binding site is identical with that of ansamitocin p-3, a maytansine derivative, but differs significantly from those of colchicin.[94] The binding is reversible and it is believed that interaction mainly occurs via the macrocyclic structure which is also present in ansamitocin p-3.[91, 94b, 95] The recent success of antibody drug conjugates (ADC´s) led to a revived interest in microtubule destabilizing compounds like rhizoxin. Altmann and co-workers examined the binding modalities of rhizoxin, maytansine and PM060184, a phase I drug. Maytansine, which exhibits only poor efficacy in in-vivo experiments, is now part of an ADC recently approved by the FDA for the treatment of breast cancer.[96] In their survey they were able to obtain ligand-tubulin complexes which were suitable for X-ray crystallography and proved that maytansin, rhizoxin and PM060184 bind to the same site of β-tubulin and that this binding site differs from the Vinca alkaloids site (scheme 39).[97]

Altmann *et al.* proposed a more specified mode of action for the microtubule destabilizing effect of rhizoxin and related compounds (maytansine, PM060184).[97] The steric clash of a ligand bound to the maytansine site (rhizoxin site) of β-tubulin stabilizes the curved tubulin oligomers. As a consequence of this stabilization the curved oligomers prevent the formation of longitudinal tubulin-

tubulin interactions, which are necessary for the formation of straight tubulin structures found in the microtubule.[97]



Scheme 40: Microtubule destabilizing agents (**A**). Overall (**B**) and close-up (**C**) view of the tubulin–rhizoxin F interactions (**B** and **C** adapted from Altmann *et al.*[97]).

SAR studies revealed that the epoxides at C2 – C3 and C11 – C12 can be replaced by double bonds as in rhizoxin D, without any loss of activity. The side chain is required for hydrophobic interactions between rhizoxin and adjacent hydrophobic pockets formed by helices and loops of β-tubulin. Implementation of polar substituents like hydroxy or carbonyl groups led to loss of activity. The oxygen functionalities at C5b, C7 and C1 are required for hydrogen bonding between the active site of β-tubulin and rhizoxin. The hydroxy group at C13 is also essential for hydrogen bonding and the methyl group C8a is required for hydrophobic interactions. The C17 methoxy group is not essential and could be replaced by a hydroxy group, without loss of activity.[90, 92a, 97-98]

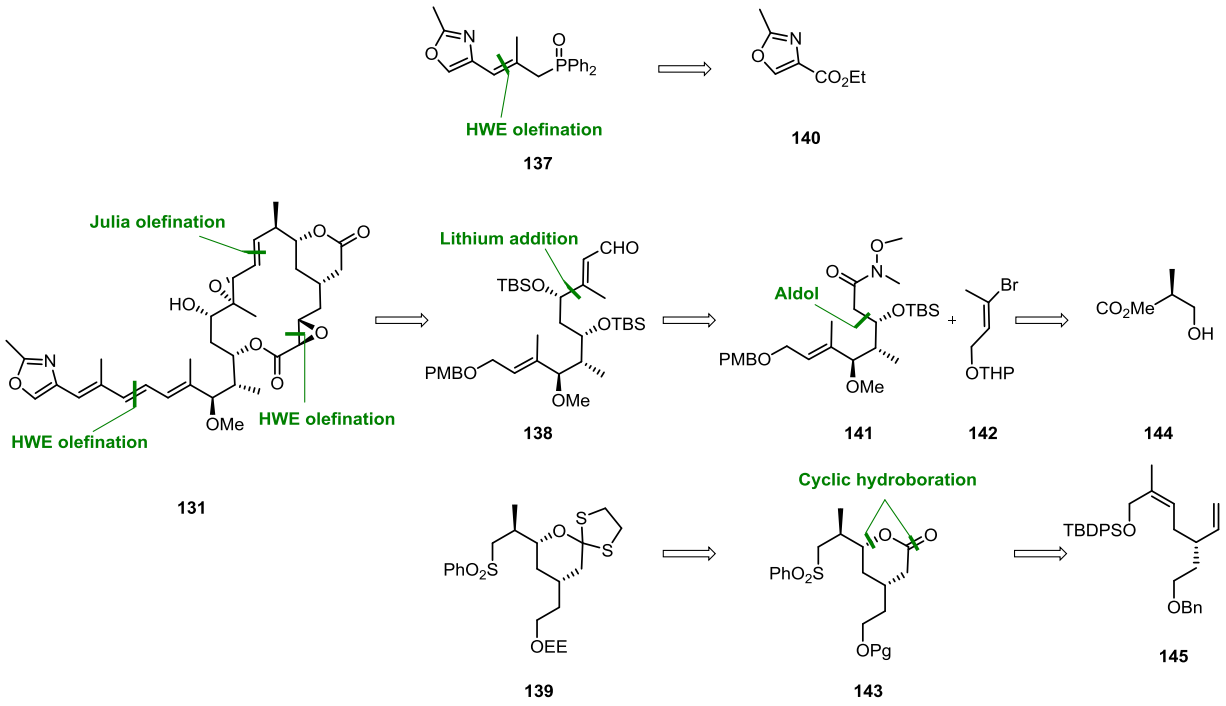
3.3 Previous syntheses

The structural complexity of this polyketide and its interesting biological properties attracted much attention from the synthetic community. This attention culminated in one total synthesis of rhizoxin (**131**) by Ohno *et al.*[99] nine total syntheses of rhizoxin D (**132**)[100] and one total synthesis of rhizoxin F (WF-1360F, **134**).[42d] The total synthesis of rhizoxin by Ohno and co-workers is outlined in detail in the following chapter.[99a] The most recent synthesis of rhizoxin F by the Altmann group is based on a RCAM approach and will be discussed in-depth in the following chapter as well.[42d] The synthesis of Ohno and co-workers serves as a guideline for the brief discussion of the other accomplished

syntheses of rhizoxin D, since these syntheses exhibit significant similarities. The key features will be discussed, similarities and differences will be emphasized in the next chapters.

3.3.1 The synthesis of rhizoxin by Ohno and co-workers

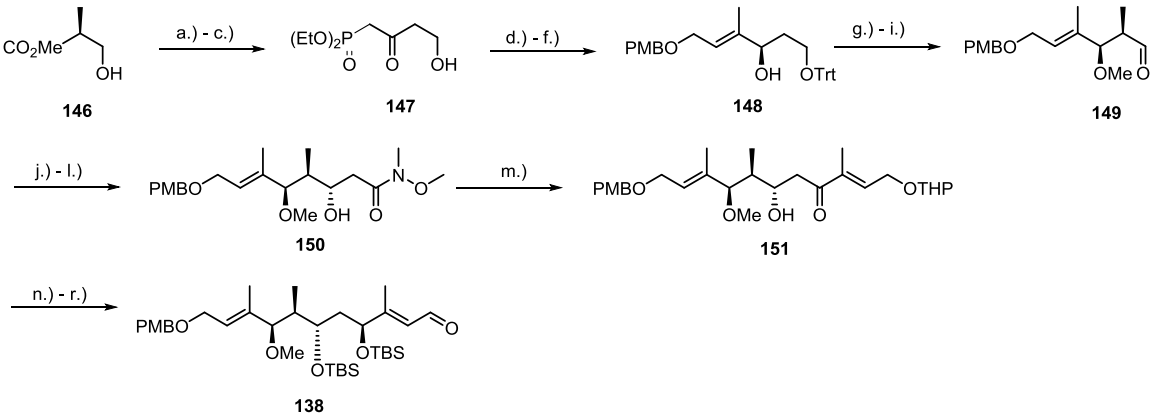
The first and so far only total synthesis of rhizoxin was reported by Ohno and co-workers in 1993.[99] Retrosynthetic analysis divided the molecule in three parts **137**, **138** and **139**, which were assembled via Julia or HWE olefination. The main fragment **138** was further disconnected in two subunits consisting of Weinreb amide **141** and alkenyl compound **142**. Fragment **139** could be accessed by double hydroboration of the diene **145**. The literature known chromophore side chain was prepared via a sequence of standard transformations starting from the commercially available oxazole building block **140**.



Scheme 41: Retrosynthetic analysis of rhizoxin by Ohno and co-workers.[99a]

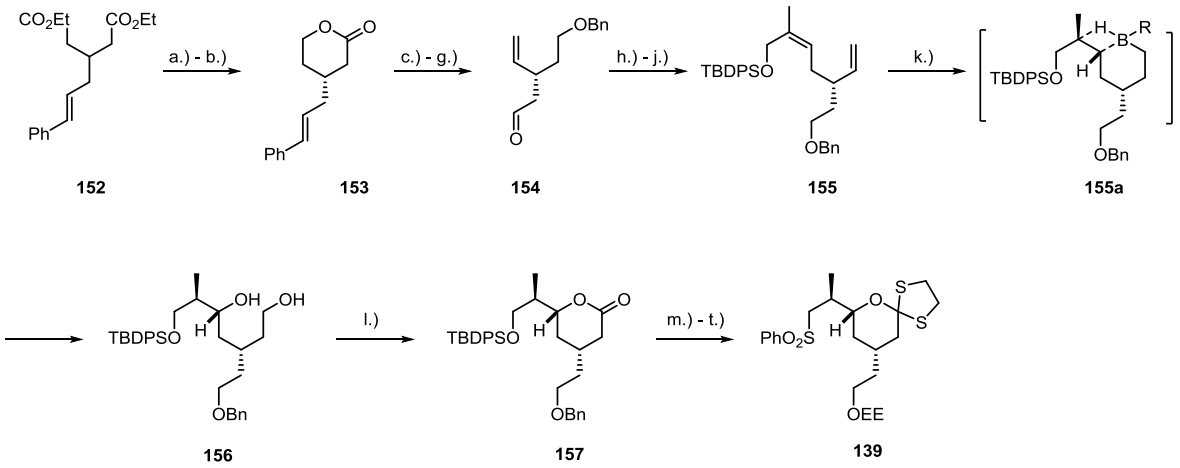
The synthesis commenced with the preparation of fragment **138** from commercially available (*S*)-Roche ester **146**. Benzyl protection of the free alcohol, followed by Claisen-type reaction with diethyl-ethyl phosphonate and deprotection of the primary alcohol gave the phosphonate **147.** Subsequent HWE olefination yielded the trisubstituted olefin which was then converted to the diol by $Zn(BH_4)_2$ reduction followed by selective protection of the primary alcohol as the corresponding trityl-ether **148**. The secondary alcohol was methylated using CH_3I and NaH and subsequent cleavage of the trityl group followed by Swern oxidation afforded chiral aldehyde **149**. The aldehyde was transformed to the Weinreb amide **150** in three steps and the second trisubstituted olefin was introduced by lithiation of alkenyl bromide **142** and addition to the Weinreb amide. The resulting

ketone **151** was then reduced using Evans-Saksena conditions to obtain the 1,3-*anti*-diol, which was converted to the corresponding TBS-ether. Removal of the THP protecting group furnished the allylic alcohol which was converted to the desired fragment **138** via MnO_2 oxidation.



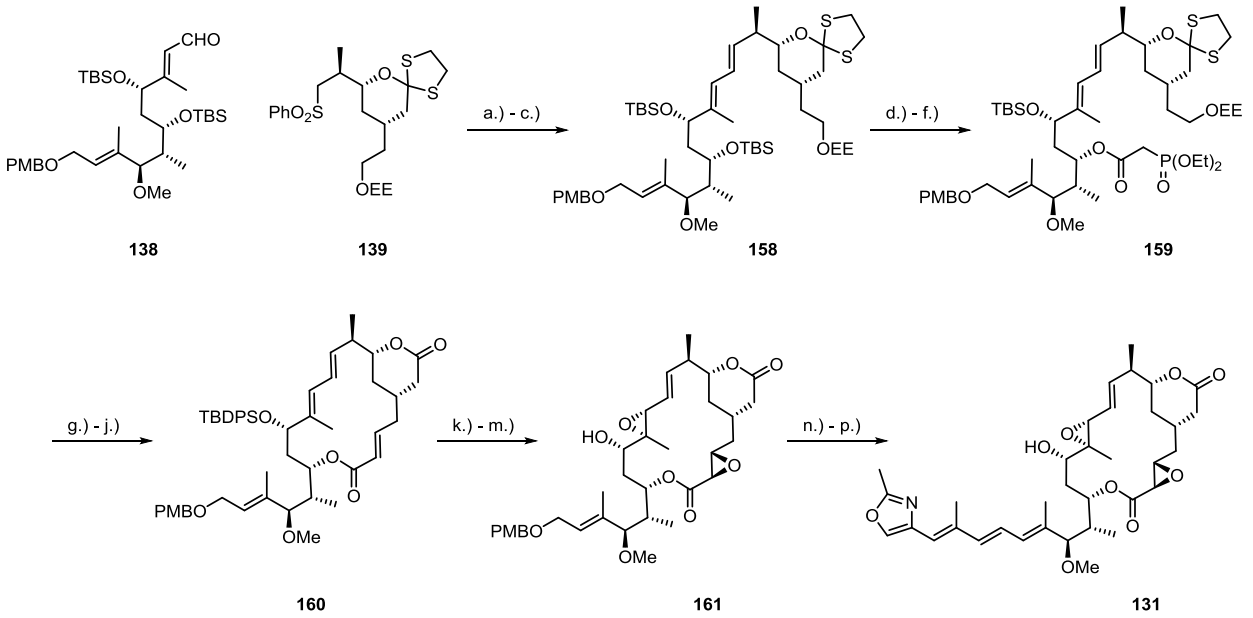
Scheme 42: Ohno´s synthesis of aldehyde **138**: a.) $PhCH_2OCH_2Cl$, *i*Pr_2Net, 0 °C to rt, 12 h, 100%; b.) $(EtO)_2P(O)CH_2CH_3$, *n*-BuLi, THF, -78 °C, 10 min, 86%; c.) H_2/Pd, EtOH, 12 h, 100%; d.)$MPMOCH_2CHO$, LiCl, *i*Pr_2Net, CH_3CN, 24 h, 72%; e.) $Zn(BH_4)_2$, Et_2O, 0 °C, 30 min, 94%; f.) TrBr, pyridine, CH_2Cl_2, 12 h, 97%; g.) MeI, NaH, THF, 12 h, 100%; h.) CSA, MeOH, CH_2Cl_2, 12 h, 97%; i.) $(COCl)_2$, DMSO, *i*Pr_2Net, CH_2Cl_2, -60 °C, 98%; j.) $CH_3CONCH_2(OCH_3)$, LDA, THF, -78 °C, 20 min, 92%; k.) $(COCl)_2$ DMSO, *i*Pr_2Net, CH_2Cl_2, -60 °C, 88%; l.) L-Selectride, THF, -78 °C, 30 min, 91%, m.) *E*-$CH_3CHBrCHCH_2OTHP$ (**142**), *t*-BuLi, Et_2O/THF, -100 °C to -78 °C, 20 min, 75%; n.) $CH_3NBH(OAc)_3$, CH_3CN, AcOH, -20 °C, 24 h, (ii) PPTS, MeOH, 12 h, 78%; o.) $(CH_3)_3CCOCl$, pyridine, CH_2Cl_2 12 h, 90%; p.) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 81%; q.) $LiAlH_4$, Et_2O, 0 °C, 30 min, 99%; r.) MnO_2, CH_2Cl_2, 30 min, 97%.[99]

The construction of the second fragment started with the desymmetrization of *meso*-diester **152** with the aid of pig liver esterase. Reduction with $LiBH_4$ and dehydration with Ac_2O gave the δ-lactone **153**, which was converted to aldehyde **154** via a sequence of five steps involving basic hydrolysis of the lactone followed by esterification of the resulting carboxylic acid. The methyl ester was reduced to the alcohol and converted to the corresponding selenide which yielded, after Grieco elimination and ozonolysis, the desired aldehyde **154**. Reaction of aldehyde under Still-Gennari conditions afforded the α,β-unsaturated ester, which was treated with DIBAL-H followed by subsequent TBDPS protection of the resulting alcohol. Hydroboration of the diene followed by oxidation yielded the diol **156**. A bicyclic transition state **155a** for the hydroboration was proposed to explain the obtained selectivity. Fétizon oxidation of the diol **156** afforded lactone **157**, which was converted to the requisite fragment **139** in nine additional steps.



Scheme 43: Ohno´s synthesis of the eastern fragment **139**: a.) Pig liver esterase, 0.1 mol/l KPB, (pH~8), 10% acetone, quant. (>91% *ee*); b.) $LiBH_4$, MeOH, DME, 1 h, (ii) Ac_2O, pyridine, CH_2Cl_2, 81%; c.) KOH, MeOH, 0 °C, 1 h, (ii) CH_2N_2, MsCl, Et_3N, 0 °C, 88%; d.) $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C to reflux, 1 h, 85%; e.) $LiAlH_4$, Et_2O, 0 °C, 30 min, 95%; f.) BnBr, NaH, THF, DMF, 12 h, 91%; g.) O_3, CH_2Cl_2 -78 °C, 45 min, (ii) DMS, Et_3N, CH_2Cl_2, reflux, 1 h, 50%; h.) $(CF_3CH_2O)_2POCH(CH_3)CHCO_2Et$, KHMDS, 18-crown-6, THF, -78 °C, 30 min, 95%; i.) DIBAL-H, CH_2Cl_2, -78 °C, 20 min, 98%; j.) TBDPS-Cl, imidazole, 0 °C to rt, 2 h, 98%; k.) thexylboran, THF, -78 °C to 0 °C, 12 h, then NaOH, H_2O_2, 0 °C, 30 min, 70% (7:1); l.) Ag_2CO_3/Celite, C_6H_6, reflux, 12 h, 88%; m.) TBAF, AcOH, 12 h, 96%; n.) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 98%; o.) $PhSO_2Na$, DMF, 100 °C, 12 h, 86%; p.) H_2/$Pd(OH)_2$, 12 h, 100%; q.) TBDPS-Cl, imidazole, 0 °C to rt, 6 h, 99%; r.) Me_3Al, $(CH_2SH)_2$, 12 h, (ii) PPTS, CH_2Cl_2 3 h, 98%; s.) TBAF, THF, 3 h, 98%; t.) $C_2H_2OCHCH_2$, PPTS, CH_2Cl_2, 12 h, 100%.[99]

The end game started with the assembly of both fragments through Julia olefination, which furnished the (*E*,*E*)-diene **158**. Both silyl protecting groups were removed with the aid of TBAF followed by selective protection of the allylic alcohol. The remaining hydroxy group was then treated with diethylphosphonoacetic acid to afford the corresponding phosphonate **159**. Removal of the 1,3-dithiolane, followed by deprotection of the ethoxyethyl acetal and Swern oxidation yielded the desired aldehyde. Macrocyclization was achieved via intramolecular HWE reaction to give the α,β-unsaturated lactone **160** in 73% yield. The final transformations started with the stereoselective and regioselective epoxidation of the α,β-unsaturated lactone motif. Ohno and co-workers rationalized that during the biosynthesis the epoxidation occured after formation of the macrocyclic ring; therefore a selective epoxidation should be possible. The use of the lithium salt derived from TBHP and a quaternary ammonium salt gave the desired epoxide. The TBDPS protecting group was removed with the aid of HF·Pyr to liberate the hydroxy group which was required for the directed vanadium-catalyzed second epoxidation to yield **161**. Deprotection of the PMB group followed by oxidation of the allylic alcohol to the aldehyde set the stage for the attachment of the side chain.



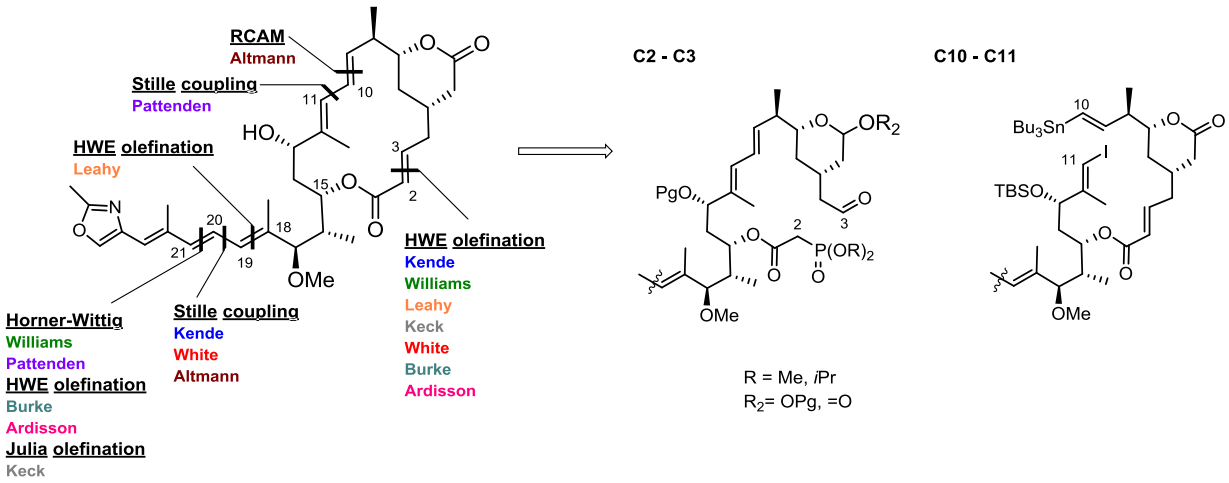
Scheme 44: Completion of Ohno´s synthesis of rhizoxin: a.) **139** *n*-BuLi, -78 °C to 0 °C, 30 min, then **138**, -78 °C to 0 °C 2 h; b.) Ac_2O, pyridine, DMAP, CH_2Cl_2, 12 h; c.) 5% Na-Hg, Na_2HPO_4, MeOH, -20 °C, 1 h, 56% (over three steps); d.) TBAF, THF, 12 h, 86%; e.) TBDPS-Cl, imidazole, 0 °C to rt, 12 h, 81%; f.) $(EtO)_2P(O)CH_2CO_2H$, EDC·HCl, DMAP, 0 °C to rt, 12 h, 97%; g.) PPTS, EtOH, 12 h, 97%; h.) $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, 1 h, 88%; i.) $(COCl)_2$, DMSO, *i*-Pr_2Net, -60 °C, 75%; j.) K_2CO_3, 18-crown-6, toluene, reflux, 24 h, 73%; k.) *t*-BuOOLi, Me_4NClO_4, THF, 4 days; l.) HF·Pyr, pyridine, 40 °C, 12 h, 49% (over two steps); m.) *t*-BuOOH, $VO(acac)_2$, 0 °C to rt, 10 min, 86%; n.) DDQ, CH_2Cl_2, H_2O, 1 h, 82%; o.) MnO_2, CH_2Cl_2, 30 min, 76%; p.) **137** KHMDS, THF, -78 °C to 0 °C 30 min, 80%.[99]

The necessary phosphine oxide **137** was prepared from oxazole carboxylate **140** in a seven step sequence and assembled with the macrocyclic core through a HWE olefination. Rhizoxin (**131**) was obtained via a longest linear sequence consisting of thirty-nine steps.

3.3.2 Total syntheses of rhizoxin D

3.3.2.1 Late stage transformations

The first asymmetric synthesis of naturally occurring didesepoxyrhizoxin (rhizoxin D, **132**) was accomplished in 1995 by Kende *et al.*[100a] Two years later Williams and co-workers reported their successful approach towards this 16-membered macrolide. [100b] In the following years Leahy,[101] Keck,[100d] Pattenden,[100d] White,[100f] Burke,[100g] Ardisson[100h] and most recently Altmann and co-workers[42d] reported the total synthesis of didesepoxyrhizoxin. The disconnections for the construction of the macrocyclic lactone as well as for the attachment of the chromophoric side chain are outlined in scheme 43**.**



Scheme 45: Retrosynthetic analysis of rhizoxin D: Disconnection of the macrocyclic core structure and the chromophore side chain.

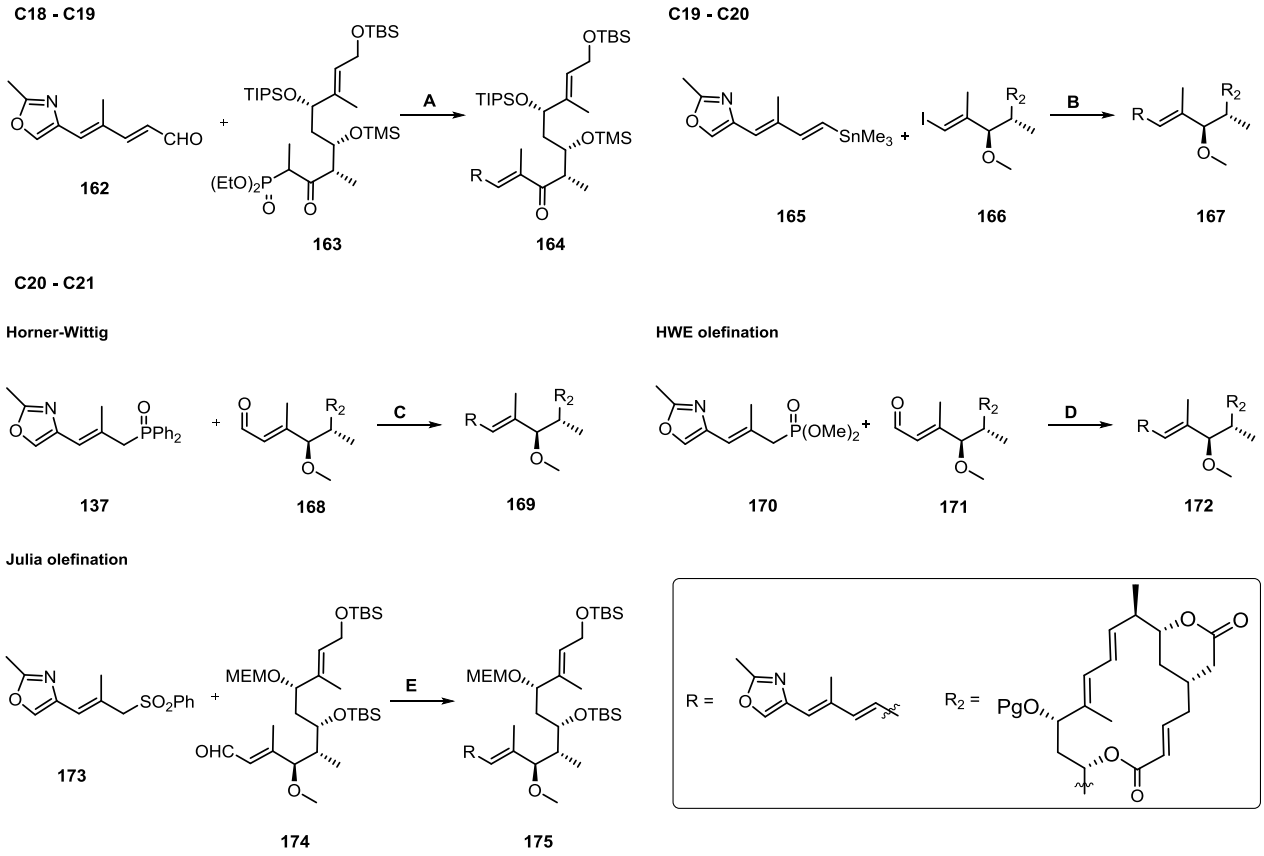
Comparison of the reported strategies shows that seven out of nine approaches were based on a disconnection between the C2 - C3 olefin to forge the macrocyclic lactone. The method of choice was the HWE olefination reaction of the C2 phosphonate with the C3 aldehyde (scheme 45). In all cases the phosphonate was prepared by esterification of the C15 hydroxy group with the corresponding phosphonoacetic acid in yields between 49% and 84% (table 11). In contrast to the HWE approach Pattenden and co-workers used a Stille coupling between C10 alkenyl stannane and C11 alkenyl iodide for the macrocyclic closure which provided only moderate yield of the desired (*E*,*E*)-diene (table 11).

Table 11: Comparison of conditions for the macrocyclic closure.

Entry	Conditions	Yield [%]
Kende	LiCl, *i*-Pr_2Net, MeCN	55
Williams	LiCl, DBU, MeCN	84
Leahy	$Ba(OH)_2$, THF, H_2O	49
Keck	LiCl, *i*-Pr_2Net, MeCN	87
Pattenden	Pd_2dba_3, $AsPh_3$, DMF, 70 °C	48
White	LiCl, *i*-Pr_2Net, MeCN	57
Burke	LiCl, DBU, MeCN	80
Ardisson	LiCl, DBU, MeCN	50
Altmann	**C6a**, 5 Å MS, toluene, 125 °C	69

The construction of the triene side chain relied on three different disconnections. Leahy *et al*. used the disconnection between C18 - C19, whereas Kende, White and Altmann used a C19 - C20 Stille coupling. A C20 - C21 disconnection was utilized by Williams, Pattenden, Burke, Ardisson and Keck. Leahy and co-workers used a HWE olefination between oxazole aldehyde **162** and the phosphonate **163** to construct (*E*)-olefin **164**. In contrast to the other approaches, Leahy and Keck introduced the side chain prior to formation of the macrocycle in an early stage of the synthesis.

The C19 – C20 bond connection was established between oxazole-dienylstannane **165** and alkenyl iodide **166** via Pd-catalyzed Stille coupling.



Scheme 46: Attachment of the side chain to the core structure.[99]

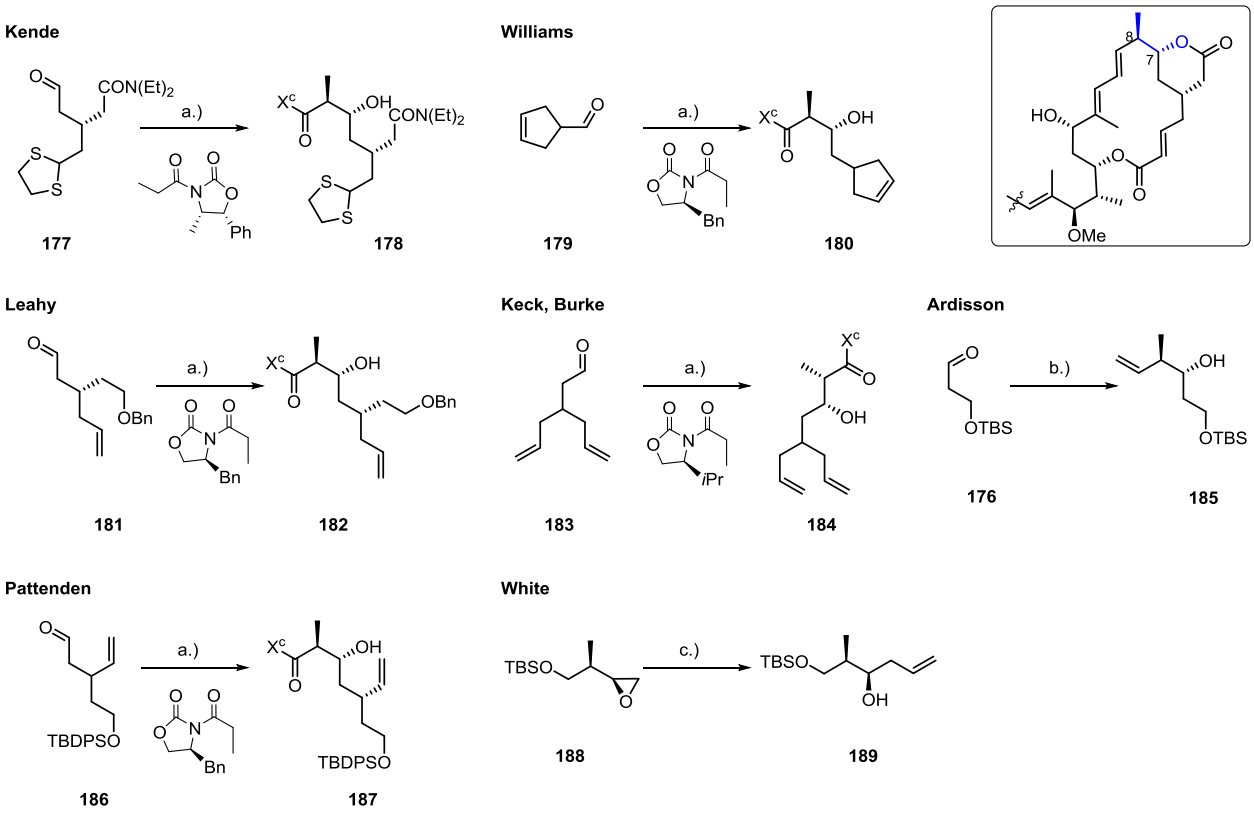
The C20 – C21 disconnection was accomplished by three different olefinations. Williams and Pattenden used a Wittig-Horner reaction between the oxazole containing phosphine oxide **137** and aldehyde **168**. The strategies of Burke and Ardisson were based on the HWE olefination (**170** + **171**) whereas Keck used a Julia olefination (**173** + **174**) to construct the olefinic C20 – C21 double bond (scheme 46). The conditions and yields are summarized in table 12.

Table 12: Comparison of conditions for side chain attachment.

Entry		Conditions	Yield [%]
Kende	**B**	$[Pd(MeCN)_2]Cl_2$, DMF	95
Williams	**C**	KHMDS, THF	44
Leahy	**A**	$Ba(OH)_2 \cdot 8H_2O$, THF	85
Keck	**E**	LiHMDS, THF, (ii) Ac_2O, DMAP, (iii) DBU, THF (iiii) SmI_2, DMPU, MeOH/THF	73
Pattenden	**C**	KHMDS, THF	38
White	**B**	$[Pd(MeCN)_2]Cl_2$, DMF	84
Burke	**D**	*t*-BuOK, DME	39
Ardisson	**D**	*t*-BuOK, DME	30
Altmann	**B**	$[Pd(MeCN)_2]Cl_2$, DMF	68

3.3.2.2 Fragment synthesis

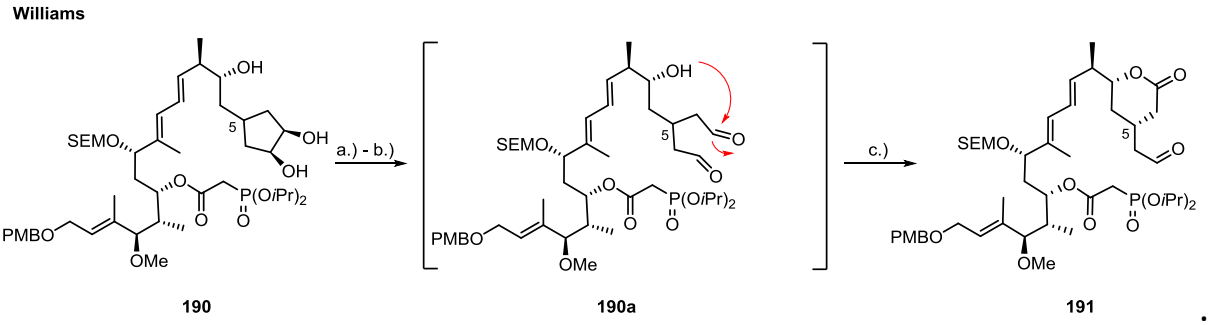
Many of the published syntheses pursued a similar strategy for the fragment preparation. For this reason the elaboration of the stereogenic centers at C7 and C8 were chosen as representative examples for the extensive use of Evans aldol chemistry. Six out of nine reported syntheses relied on the use of this method, demonstrating their importance and reliability (scheme 47). The exceptions were Ardisson, who applied an allylation reaction, and White who used copper-catalyzed regioselective epoxide opening to construct the desired structural motif. Ardisson used the Brown allylation of aldehyde **176**, which provided the desired product in good yield and excellent selectivity.[102] After initially using the Keck allylation, White and co-workers switched to the regioselective opening of epoxide **188**, which avoided tedious chromatographic separation.



Scheme 47: Construction of the C7, C8 structural element via Evans aldol reaction, Brown allylation and epoxide opening: a.) *n*-Bu_2BOTf, Et_3N (Leahy,Kende = *i*-Pr_2NEt), CH_2Cl_2, -78 °C; Kende 92%; Williams 95%; Leahy 80%; Keck 86%; Pattenden 79%; Burke 88%; b.) *t*-BuOK, *n*-BuLi, (*Z*)-2-butene, (-)-IPc_2BOMe, $BF_3{\cdot}OEt_2$, THF, -78 °C, 4 h, 82%; c.) CH_2=CHMgBr, CuI (cat), Et_2O/THF, -78 °C to -20 °C, 90%.[42d, 99]

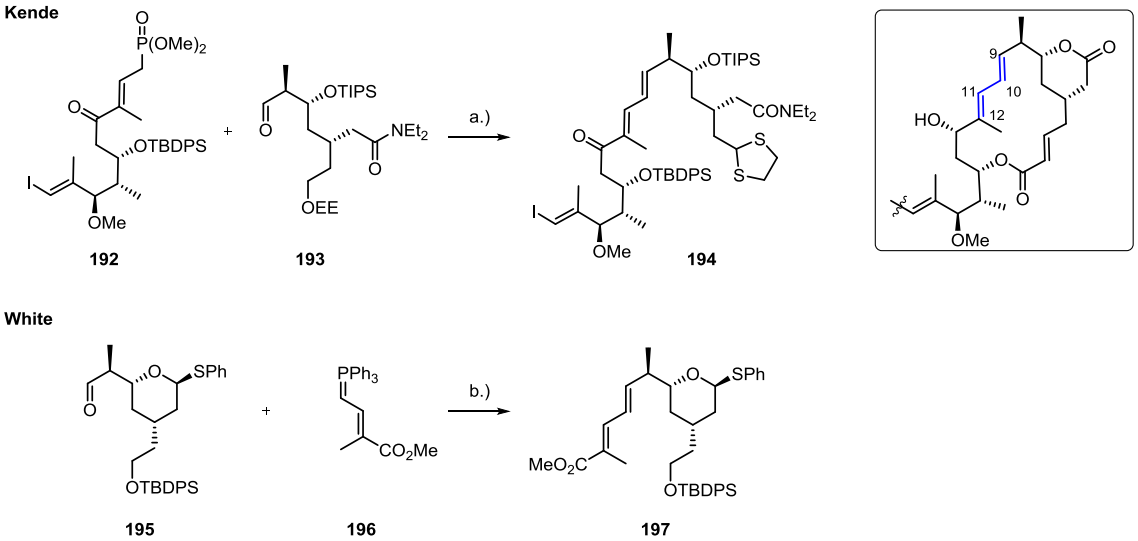
Williams *et al*. introduced a novel strategy for the construction of the C5 δ-lactone stereogenic center. An elegant sequence consisting of the oxidative cleavage of diol **190**, derived from OsO_4-catalyzed dihydroxylation of an early intermediate, led to the formation of an anomeric mixture of δ-lactols. This mixture could be conveniently converted to the desired lactone **191** through Fétizon[103] or Ley-Griffith oxidation.[104] This strategy relied upon the thermodynamic differentiation of the diastereotopic aldehydes resulting from the diol cleavage (scheme 48). It was assumed that a chair

like transition state is applicable to explain the observed selectivity. In this case the diequatorial deployment of the side chains is favored over the axial alignment, leading to the desired isomer. This strategy was subsequently employed by Keck and Burke.[100d, 100g]



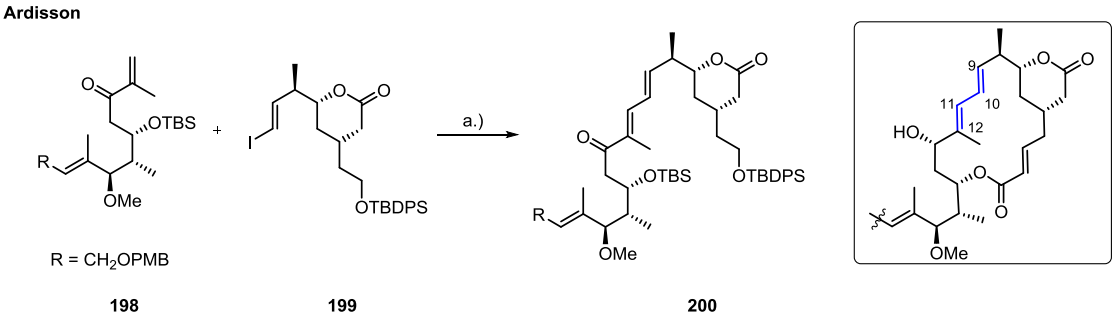
Scheme 48: Synthesis of the δ-lactone **191** by Williams and co-workers: a.) $NaIO_4$, THF/H_2O; b.) TPAP, NMO, 4 Å MS, CH_2Cl_2, 67% (over two steps).[100b]

The construction of the (*E*,*E*)-diene was accomplished with the aid of three different types of transformations. Kende and White used Wittig or Wittig-type transformations to prepare the (*E*,*E*)-diene. Ardisson and Pattenden employed palladium-catalyzed reactions, whereas the method of choice for Williams, Leahy, Keck and Burke was a Julia type reaction. Kende *et al.* used the HWE olefination between phosphonate **192** and aldehyde **193** to afford diene **194** in 56% yield (scheme 49). The Wittig-olefination of aldehyde **195** with the stabilized phosphorane **196** was utilized by White and co-workers (scheme 49).



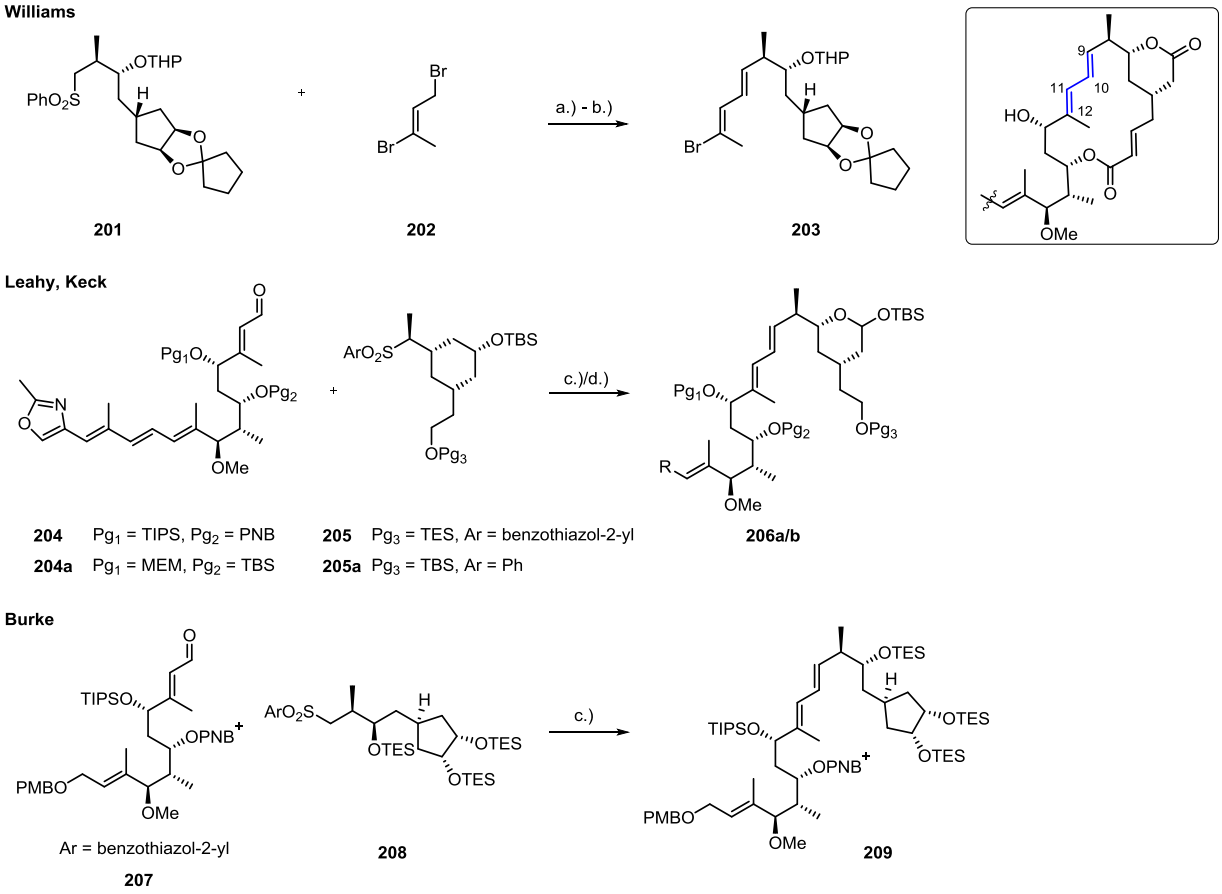
Scheme 49: Synthesis of the (*E*,*E*)-diene by Kende and White: a.) LiHMDS, 0 °C to rt, 56%; b.) THF, Δ, 77%.[100a, 100f]

Ardisson utilized Jeffrey-Heck conditions for the Pd-catalyzed coupling of the *exo*-olefin **198** with the requisite alkenyl iodide **199** yielding the desired product **200** in 55% yield (scheme 50).[105] The 1,3-diene in Williams´s synthesis was prepared via the alkylation of α-sulfone **201** with allyl bromide **202** followed by subsequent base induced elimination (scheme 51).



Scheme 50: Synthesis of the (*E*,*E*)-diene by Ardisson: a.) $Pd(OAc)_2$, PPh_3, K_2CO_3, *n*-Bu_4NCl, DMF/H_2O (10:1), 40 °C, 12 h, 55%.[99h]

Leahy and co-workers initially attempted to prepare the macrocyclic core of rhizoxin D via Julia olefination. This approach failed and they moved to the strategy shown in scheme 45. Prior to the cyclization they prepared the 1,3-diene via Julia-Kociensky reaction (scheme 51). This strategy was adapted by Burke and co-workers employing the same conditions. A slight variation of this transformation was utilized by Keck *et al*. who applied Julia-Lythgoe conditions with SmI_2 as the reducing agent (scheme 51).

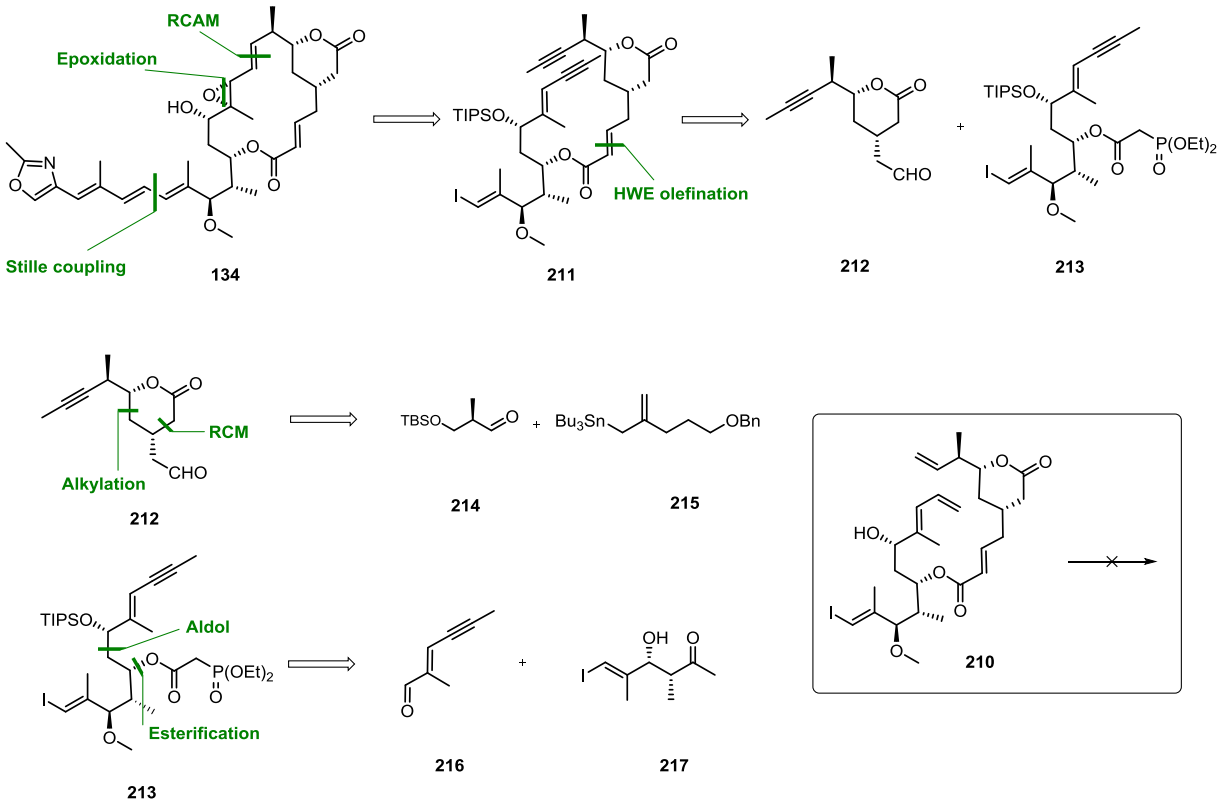


Scheme 51: Synthesis of the (*E*,*E*)-diene by Williams, Leahy, Keck and Burke: a.) LDA, HMPA, THF, -78 °C, 88%; b.) DBU, toluene, 105 °C, 70%. c.) LiHMDS, Leahy 79%, Burke 80%; d.) *n*-BuLi, THF, -78 °C, ii.) Ac_2O, DMAP, pyridine, iii.) DBU, THF, iiii.) SmI_2, DMPU, MeOH, THF, 84% (over four steps).[99b-d,99g]

In summary the presented strategies demonstrate the pertinence of this class of polyketides natural products. Although isolated nearly three decades ago, rhizoxin and its congeners still remain challenging targets for synthetic chemists to evaluate novel methodologies and eventually get deeper insights into the structure-activity relationship of this class of compounds.

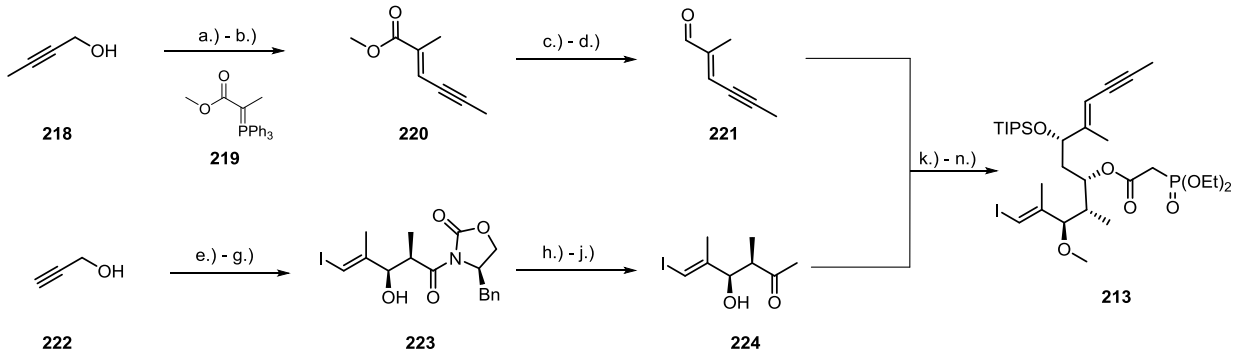
3.3.3 The synthesis of rhizoxin F by Altmann

The most recent synthetic approach towards members of the rhizoxin family was reported in 2013 by the Altmann group and demonstrated the significance of this target.[42d] Their initial attempt relied on the closure of the macrocycle by RCM (**210)**, which proved to be unsuccessful. Therefore their focus was shifted towards a strategy based on RCAM of metathesis precursor **211**, which should be accessable via HWE olefination of aldehyde **212** with phosphonate **213.** Further disconnections of both fragments led to advanced intermediates **214**, **215**, **216** and **217**, the preparations of which are described in this chapter (scheme 52).



Scheme 52: Retrosynthetic analysis by Altmann and co-workers and unsuccessful attempt to forge the macrocyclic lactone via RCM.[42d]

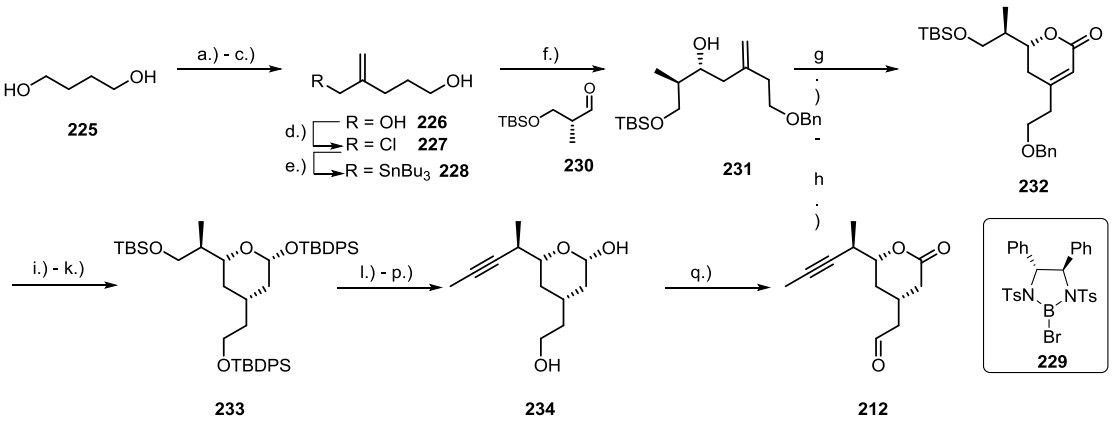
The synthesis started with the preparation of phosphonate **213** from 2-butynol **218**. Oxidation with MnO_2 followed by Wittig olefination gave the α,β-unsaturated ester **220**. Subsequent reduction afforded the allylic alcohol which underwent upon treatment with MnO_2 oxidation to the aldehyde **221**. The preparation of the requisite coupling partner started from 2-propynol which was transformed in a six step sequence to the methyl ketone **224**. The ketone was treated with (+)-DIP-Cl to furnish the chiral boron enolate and the subsequent Paterson aldol reaction yielded the desired product in 70% yield. Evans-Saksena reduction of the β-hydroxy ketone afforded the 1,3-*anti*-diol, in which the allylic position was selectively protected as the corresponding TIPS-ether. Subsequent treatment with diethylphosphonoacetic acid resulted in the formation of desired phosphonate **213** in a longest linear sequence of ten steps (scheme 53).



Scheme 53: Altmann´s synthesis of the phosphonate fragment (**213**): a.) MnO_2, CH_2Cl_2; b.) **219**, CH_2Cl_2, reflux 45% (based on **219**); c.) $LiAlH_4$, Et_2O, 0 °C; d.) MnO_2, CH_2Cl_2, 82% (over two steps); e.) Cp_2ZrCl_2, Me_3Al, then I_2, Et_2O, -30 °C, 60%; f.) MnO_2, Et_2O, 0 °C, 89%; g.) (*R*)-4-benzylpropionyloxazolidin-2-one, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C 77%; h.) MeNH(OMe)·HCl, Me_3Al, CH_2Cl_2, 0 °C, 85%; i.) NaH, MeI, THF/DMF 3:1, 0 °C, 99%; j.) MeMgCl, THF, -20 °C to 0 °C, 93%; k.) (+)-DIP-Cl, Et_3N, CH_2Cl_2, -78 °C to -25°C; l.) $Me_4NBH(OAc)_3$, AcOH, MeCN, -40 °C to -20 °C, 66% (over two steps); m.) TIPSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 97%; n.) CME-carbodiimide-TsO, DMAP, $(EtO)_2P(O)CH_2COOH$, CH_2COOH, CH_2Cl_2, 0 °C to rt, 82%.[42d]

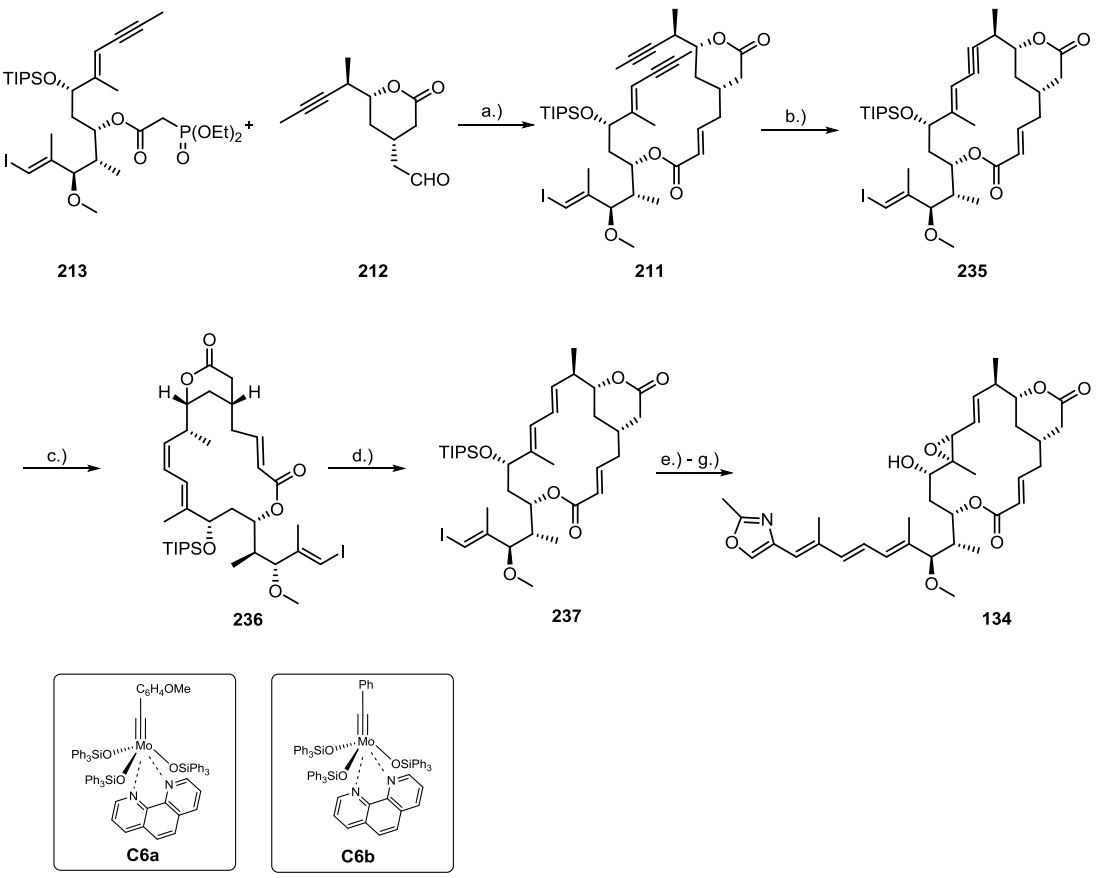
The synthesis of the δ-lactone fragment commenced with benzyl protection of butane-1,4-diol (**225**), followed by subsequent Swern oxidation and *in situ* α-methylenation by a procedure originally reported by Ogasawara.[106] The resulting aldehyde was then reduced to the allylic alcohol **226** and subsequent treatment with CCl_4 gave allylic chloride **227**. The allylic chloride was converted to the corresponding Grignard reagent which was treated with Bu_3SnCl to furnish stannane **228**. Transmetalation with Corey´s bromoborane complex **229**,[107] followed by treatment with chiral aldehyde **230**[108] at low temperature afforded the allylic alcohol **231** with good diastereoselectivity (d.r. 10 : 1). The allylic alcohol was treated with acryloyl chloride and the corresponding acryl ester underwent RCM with the aid of 2nd generation Hoveyda-Grubbs catalyst.[109] The obtained dihydropyrone **232** was hydrogenated with Pearlman´s catalyst[110] to the lactone. After reduction with DIBAL-H the resulting hemiacetal was protected with TBDPS chloride. Removal of the primary TBS protecting group followed by oxidation and Corey-Fuchs homologation gave the acetylide which was trapped with MeI to furnish the methyl capped alkyne. The silyl protecting groups were removed

by treatment with TBAF and the lactol **234** was oxidized with PIDA/TEMPO to the desired aldehyde **212** (scheme 54). The δ-lactone fragment was synthesized in a seventeen steps longest linear sequence.



Scheme 54: Altmann´s synthesis of the δ-lactone fragment (**212**): a.) BnBr, NaH, THF, 0 °C, 95%[111]; b.) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C, then $CH_2N(CH_3)_2Cl$, DBU, 86%; c.) $LiAlH_4$, THF, 0 °C, 96%; d.) CCl_4, PPh_3, MeCN, 95%; e.) Mg, Bu_3SnCl, THF, ultrasound, 0 °C to rt, quant. (80% purity); f.) **229**, CH_2Cl_2 18 h, then **230**, -78 °C, 74% (over two steps, d.r. 10 : 1); g.) acryloyl chloride, *i*-Pr_2Net, CH_2Cl_2, -40 °C, 85%; h.) Hoveyda-Grubss 2nd gen. DCE, reflux, 89%, i.) H_2 (9 bar), $Pd(OH)_2/C$, EtOAc, 98%; j.) DIBAL-H, CH_2Cl_2, -78 °C; k.) TBDPS-Cl, imidazole, CH_2Cl_2 90% (over two steps); l.) $NaIO_4$, THF/H_2O (4:1), 87%; m.) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 96%; n.) CBr_4, PPh_3, CH_2Cl_2, -78 °C, 99%; o.) *n*-BuLi, MeI, THF, -78 °C to rt, 94%; p.) TBAF, AcOH, THF, 0 °C to rt, quant. q.) TEMPO, PIDA, $Yb(OTf)_3$ (cat), CH_2Cl_2, 0 °C to rt, 62%.[42d]

The endgame started with the assembly of both fragments via HWE olefination, affording the requisite metathesis precursor **211.** The cyclization was carried out with Fürstner´s catalyst **C6a/b,** which yielded, after activation with $MnCl_2$, the corresponding macrocyclic lactone **235** in good yield. The reduction of the triple bond failed and no transition-metal catalyzed procedure achieved the desired transformation. Altmann and co-workers ultimately needed to prepare the acetylenehexacarbonyl dicobalt complex which gave, after reductive cleavage, the undesired (*Z*)-olefin **236**. Three reaction cycles were necessary to achieve full conversion. The isomerization of the (*Z*)-olefin to the desired configuration was finally accomplished with AIBN/PhSH to yield the (*E*,*E*)-diene **237**. Deprotection of the TIPS group with HF·Pyr followed by Stille coupling to attach the side chain yielded rhizoxin D which was then converted to rhizoxin F (**134**) via hydroxy directed epoxidation using $VO(acac)_2$ and TBHP (scheme 55).



Scheme 55: Completion of the rhizoxin F synthesis by Altmann and co-workers: a.) LiCl, DBU, THF/MeCN, 3:1, 0 °C to rt, 81% (88% brsm); b.) **C6a** or **C6b**, $MnCl_2$, toluene, 5 Å MS, 125 °C, **C6a** : 69%, **C6b** = 63% (67% brsm); c.) $[Co_2(CO)_8]$, CH_2Cl_2, (ii) 1-ethylpiperidine hypophosphite, C_6H_6, reflux, 74% over 3 cycles, (*Z*)-alkene only; d.) AIBN, PhSH, C_6H_6, reflux, 88% (*E*/*Z* = 20:1) e.) $[PdCl_2(MeCN)_2]$, DMF, 68%; f.) HF·Pyr, pyridine, THF, 0 °C to rt, 54%; g.) *t*-BuOOH, $[VO(acac)_2]$, C_6H_6, 0 °C to rt, 65%, 29% after prep. RP-HPLC.

In summary Altmann and co-workers accomplished the total synthesis of rhizoxin F by the use of RCAM as the key transformation. The natural product was obtained through a longest linear sequence of twenty-four steps.[42d] The strategy allowed the preparation of several derivatives, which were used for biological tests. This approach demonstrated the utility of the latest generation of alkyne metathesis catalysts developed in the Fürstner group.

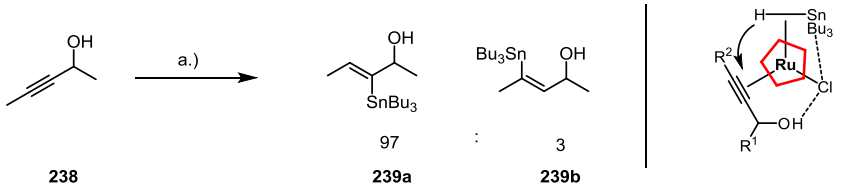
3.4 Objective

Rhizoxin D was chosen as a potential target for the application of the RCDM due to its structural complexity and its interesting biological properties, particularly because of the revived interest in microtubule destabilizing compounds. The structurally challenging polyketide would provide the ultimate testing ground for the utility of RCDM. Notably the problems with the conversion of enyne **235** to the corresponding (*E*,*E*)-diene **237** in Altmann´s synthesis of rhizoxin F (scheme 55) encouraged us to develop a novel strategy for the conversion of 1,3-diynes to differently substituted 1,3-(*E*,*E*)-dienes. The chosen strategy should further be concise, enable access to several members of the family and should allow the preparation of analogues for biological evaluation. In view of the

requirements the planned route should be reliable, scalable and rely on catalytic and stereoselective transformations to establish an efficient pathway to the required scaffold.

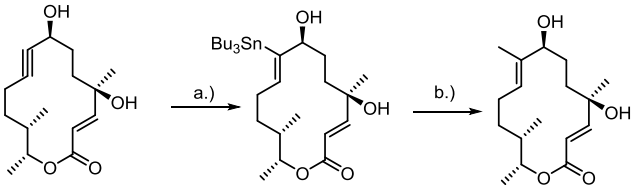
3.4.1 Preliminary studies

Recently the Fürstner group reported a series of ruthenium-catalyzed *trans*-hydrometalation reactions of alkynes[112] which culminated in total syntheses of brefeldin A and 5,6-dihydrocineromycin B.[113] The selective conversion of an alkyne to the corresponding alkenyl stannane proved to be the most robust and successful transformation in terms of functional group tolerance and practicability. The use of unsymmetrically substituted alkynes in hydrometalation reactions usually leads to a mixture of regioisomers. In order to obtain good selectivity for one regioisomer, a protic directing group, for instance a hydroxy group, was found to be crucial. These findings allowed the preparation of alkenyl stannanes with good proximal to distal selectivity (**293a** : **293b**, scheme 56). The selectivity is achieved through the interaction of the propargylic hydroxy group and the [Ru-Cl] unit of the catalyst (scheme 53). Spectroscopic data suggest that the chloride forms a hydrogen bond which aligns and blocks the orientation of the alkyne. At the same time the incoming stannane is predispositionally orientated by an additional interaction with the [Ru]-catalyst to ensure the selective *trans*-addition to the alkyne.[112c, 112d, 113b]



Scheme 56: *Trans*-hydrostannation reaction and possible explanation for the observed regioselectivity: a.) $[Cp^*RuCl_2]_n$, Bu_3SnH, CH_2Cl_2, 88% (*Z* : *E* 99:1, proximal : distal 97:3).[112d]

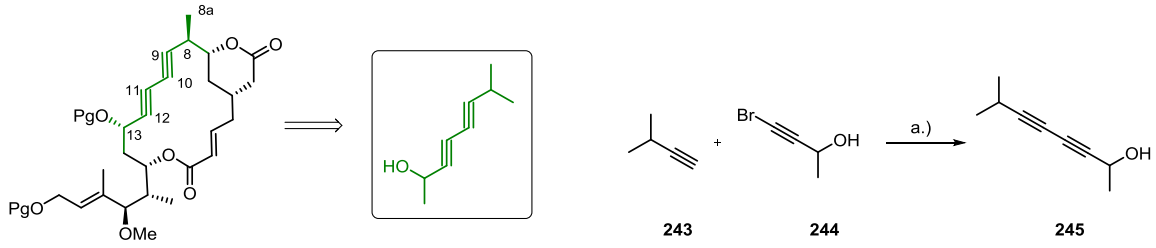
The methodology was successfully applied as the key step in the recently reported synthesis of 5,6-dihydrocineromycin B. The regioselective *trans*-hydrostannation of alkyne **239**, followed by subsequent Pd-catalyzed Stille coupling with MeI, yielded the desired trisubstituted alkene **241**, a structural element present in several natural products.



Scheme 57: Keystep in Fürstner´s total synthesis of 5,6-dihydrocineromycin B: a.) $[Cp^*RuCl_2]_n$, Bu_3SnH, CH_2Cl_2, 83%; b.) $[Pd(PPh_3)_4]$, $[Ph_2PO_2][NBu_4]$, CuTc, MeI, DMF, 92%.[113b]

The extension of this methodology to 1,3-diynes should allow the differentiation between the two triple bonds. The conversion of the triple bond adjacent to the directing protic group into the trisubstituted alkene, followed by a second *trans*-hydrometalation reaction would give access to (*E*,*E*)-dienes such as present in members of the rhizoxin familiy.

For the evaluation of this hypothesis a structurally simple acyclic model substrate was prepared, which mimicked the C8 – C13 subunit of the proposed cyclic 1,3-diyne **242** (scheme 58).



Scheme 58: Preparation of the acyclic model compound (**245**): a.) CuCl, $NH_2OH{\cdot}HCl$, aq. $BuNH_2$ (30% in water), 81%.

Test substrate **245** was prepared via copper-catalyzed coupling of literature known bromo alkyne **244**[114] with 3-methylbut-1-yne (scheme 58). With the model substrate in hand the attention was laid on the regioselective hydrostannation reaction. The tetrameric complex $[Cp^*RuCl_4]$ (**C8a**) and the polymeric complex $[Cp^*RuCl_2]_n$ (**C8b**) were chosen as catalysts, which provided the best results in previous studies.[112c, 112d, 113b] After optimization of several reaction parameters such as addition time and amount of Bu_3SnH, the desired product **246** was obtained in 74% yield along with 20% of the bis-stannane **247** (table 13). It was found that slow addition was necessary to reach full conversion of the starting material. Unfortunately the formation of the bis-stannylated side product **247** could not be suppressed by variation of the reaction parameters. NMR studies revealed that the *trans*-addition products were obtained exclusively. The most indicative parameter for this assignment was the observed $^1H - ^{119}Sn$ coupling constant. The $^3J_{Sn,H}$ coupling constant is about twice as large if tin and hydrogen are in a *trans* arrangement than if they are *cis* to each other.[115] The observed values were in accordance with previous studies[112d, 113b] and can be found in the experimental part (chapter 4.6).

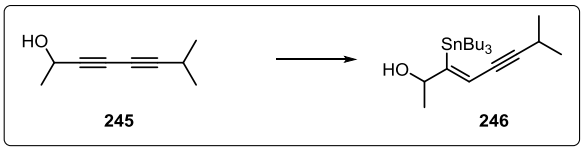
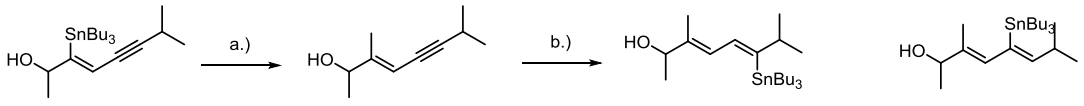


Table 13: Screening of the influence of different conditions for the *trans*-hydrostannation.[a]

Entry	Catalyst	Bu_3SnH	Addition time	Yield [%]
1	**C8a**	1.15 eq.	10 min.	(**245**) <5; (**246**) 69; (**247**) 26
2	**C8b**	1.25 eq.	10 min.	**246** : **247** 3 : 1.2[c]
3	**C8b**	1.15 eq.	60 min.[b]	(**246**) 74; (**247**) 20

[a] All reaction were carried out in CH_2Cl_2 at ambient temperature. [b] Addition via syringe pump. [c] Determined by crude NMR.

The subsequent palladium-catalyzed methyl-Stille reaction afforded the desired trisubstituted alkene **248** in 84% yield. The stoichiometry as well as the order of addition is important to ensure full conversion of the starting material and avoid competing proto-destannation. Application of the described stannylation conditions (table 13) to enyne **248** provided the desired stannane **249** as a 10:1 mixture of regioisomers. NMR studies confirmed that again exclusively the *trans*-addition product was obtained.

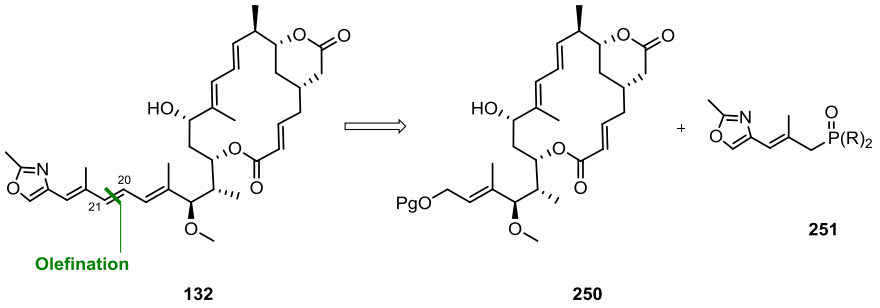


Scheme 59: Preparation of alkenyl stannane **249**: a.) $[Pd(PPh_3)_4]$, $[Ph_2PO_2][NBu_4]$, CuTc, MeI, DMF, 92%; b.) **C8b**, Bu_3SnH, CH_2Cl_2, 83%.

In view of these positive preliminary results a novel retrosynthetic strategy for the total synthesis of rhizoxin D was developed.

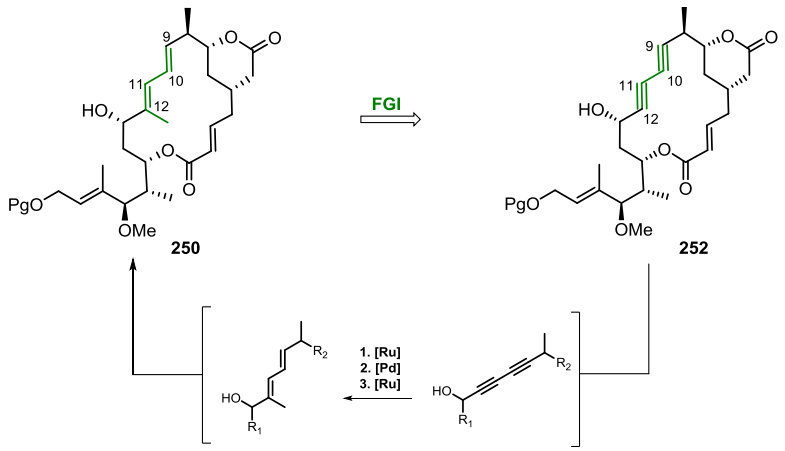
3.4.2 Retrosynthetic analysis of rhizoxin D

The retrosynthetic analysis of rhizoxin D was designed in a way that several members of the family should be accessible. The key step of the outlined strategy should be the application of the RCDM to construct the 16-membered macrocyclic lactone. The retrosynthetic analysis started with the disconnection of the chromophoric side chain **251** which should be attached via olefination (Wittig-Horner or HWE) at C20 – C21 (scheme 60).



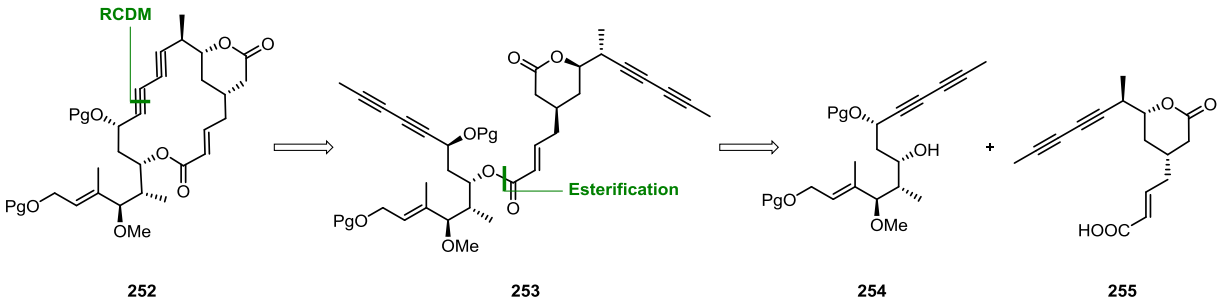
Scheme 60: Retrosynthetic analysis for the endgame part I.

Construction of the (*E*,*E*)-diene (C9 - C12) should rely on the successful preliminary results described in the previous chapter. The C13 hydroxy group should function as a directing group for the ruthenium-catalyzed *trans*-hydrostannation of the proximal alkyne followed by a palladium-catalyzed methyl-Stille coupling with MeI. The second ruthenium-catalyzed *trans*-hydrometalation reaction of the distal alkyne followed by proto-demetalation should provide access to the desired (*E*,*E*)-diene structural motif (scheme 61). Furthermore this strategy could enable the preparation of a wide array of substitution patterns.



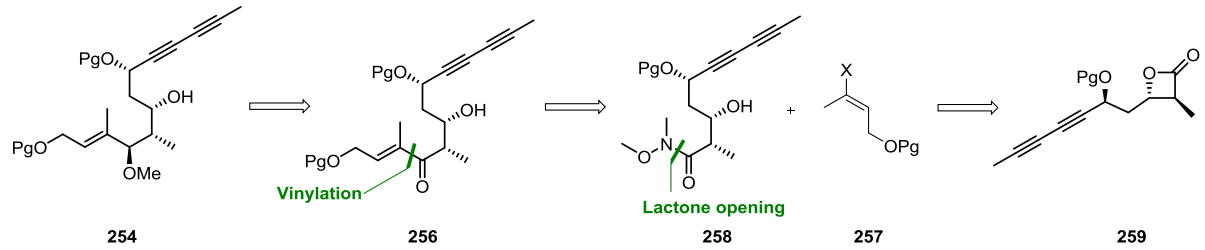
Scheme 61: Retrosynthetic analysis for the endgame part II.

The 16-membered macrocycle **252** should be obtained via RCDM of tetrayne **253**, by application of the previously elaborated conditions (chapter 2).[79-80] The metathesis precursor should be assembled by esterification of the western fragment **254** with the δ-lactone containing eastern part **255.**



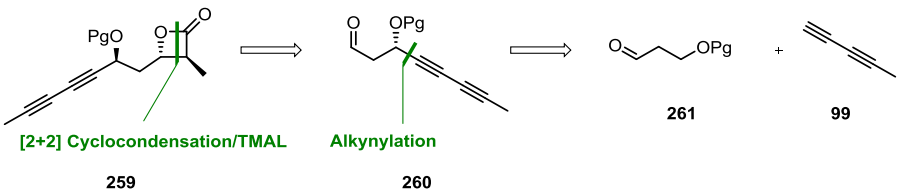
Scheme 62: Retrosynthetic disconnection for the macrocyclic core of rhizoxin D**.**

The retrosynthetic analysis of the western fragment (**254**) envisages the *trans*-selective 1,3-reduction of β-hydroxy ketone **256**, derived from addition of alkenyl halogenide **257** to Weinreb amide **258**. The Weinreb amide should be prepared by selective cleavage of the acyl-oxygen bond of the corresponding β-propiolactone **259**.



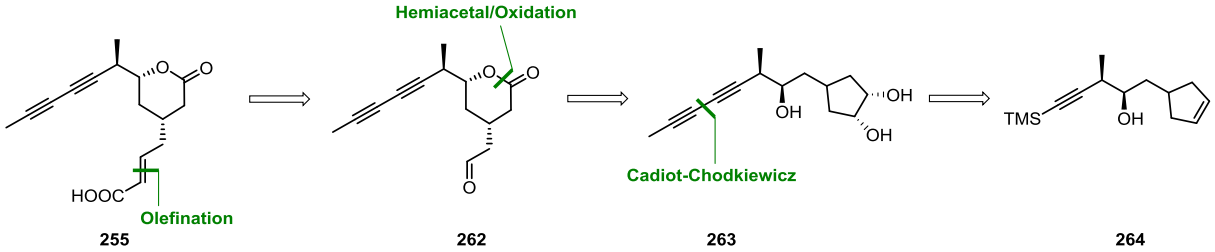
Scheme 63: Retrosynthetic analysis of the western fragment **254** part I.

The β-propiolactone bearing already three of the four required stereogenic centers should be obtained via *trans*-selective asymmetric [2+2] cyclocondensation of aldehyde **260** with propionyl bromide.[116] The preparation of aldehyde **260** should be accomplished by a sequence of standard transformations including oxidation, asymmetric alkynylation and a second oxidation reaction. The suitable protected aldehyde **261** and 1,3-pentadiyne **99** were chosen as a starting point for the preparation of the western fragment.



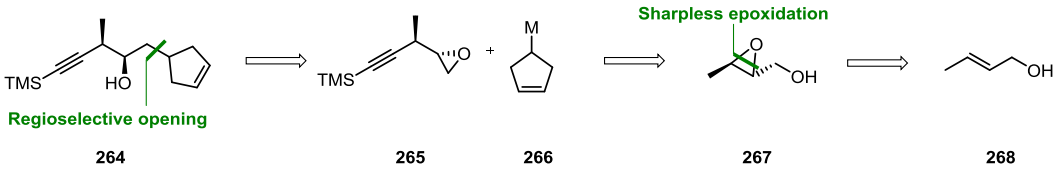
Scheme 64: Retrosynthetic analysis of the western fragment **254** part II.

The eastern fragment (**255**) should be obtained via olefination of aldehyde **262** accessible by oxidative cleavage and subsequent oxidation of diol **263**. The diol should be installed via OsO_4-catalyzed dihydroxylation of the cyclopentene derivative **264**.



Scheme 65: Retrosynthetic analysis of the eastern fragment **255** part I.

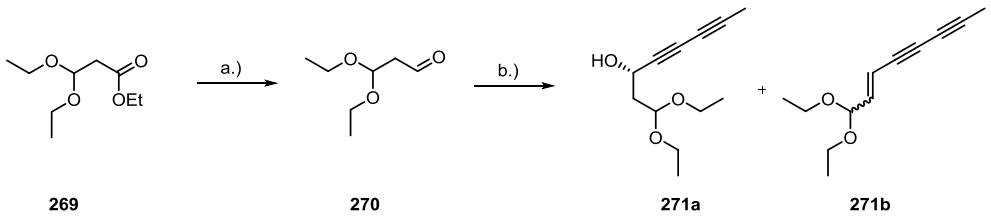
The cyclopentene motif should arise from regioselective opening of epoxide **265** with the metalated cyclopentene donor **266.** Epoxide **265** could be synthesized from commercially available *trans*-crotyl alcohol by a sequence of standard transformations including Sharpless epoxidation, regioselective epoxide opening followed by mono-tosylation and treatment with base (scheme 66).[117]



Scheme 66: Retrosynthetic analysis of the eastern fragment part II.

3.4.3 Synthesis of the western fragment

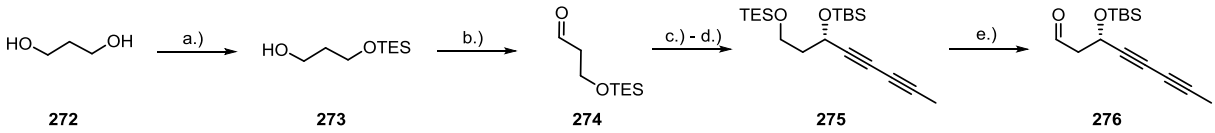
The forward synthesis commenced with the preparation of aldehyde **260**, which was the first key intermediate in the outlined strategy. Initial attempts were based on the use of commercially available acetal protected ethyl ester **269**. The ester was carefully reduced with DIBAL-H to the corresponding aldehyde **270**, which was then subjected to standard conditions for the asymmetric 1,3-diyne addition[70] producing an inseparable 1 : 1 mixture of desired product **271a** together with olefin **271b** (scheme 67).



Scheme 67: Initial attempts for the synthesis of aldehyde **260**: a.) DIBAL-H, CH_2Cl_2, -78 °C, 75%; b.) **99**, Me_2Zn, (*R,R*)-ProPhenol, $Ph_3P{=}O$, toluene, 0 °C, 54% (**271a** 26% , **271b** 28%, calculated by NMR).

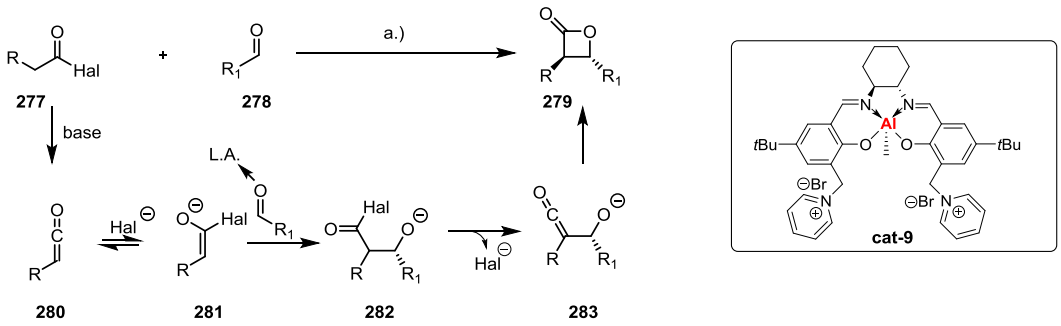
Further exploration of this route proved to be unsuccessful since the stability of the acetal protecting group was insufficient for the planned transformations. Therefore ethyl ester **269** was discarded as starting material. A second attempt for the preparation of aldehyde **276** started from propane-1,3-diol. Selective protection as the corresponding TES-ether **273**, followed by Parikh-Doering oxidation provided aldehyde **274** which was subjected to asymmetric alkynylation utilizing the conditions

described in the total synthesis of ivorenolide A (scheme 36). The desired 1,3-diyne was obtained in good yield and the hydroxy group was protected as the corresponding TBS-ether **275**.



Scheme 68: Synthesis of aldehyde **276**: a.) TESCl, Et_3N, DMAP (cat), CH_2Cl_2, 87%; b.) SO_3·Py, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C to rt, 16 h, 85%; c.) **122**, Me_2Zn, (*R,R*)-ProPhenol, Ph_3P=O, toluene, 0 °C, 84%; d.) TBS-Cl, imidazole, CH_2Cl_2, 87%; e.) $(ClCO)_2$, DMSO, -78 °C to -30 °C, 1 h then -78 °C, Et_3N, 76%.

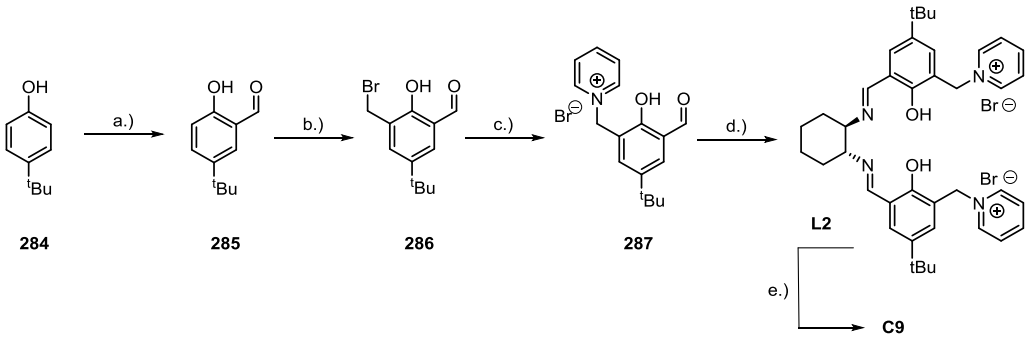
The primary TES-ether **273** was cleaved under modified Swern conditions while the resulting alcohol was oxidized to aldehyde **276**.[118] With aldehyde **276** in hand, preparation of the *trans*-configured β-propiolactone was investigated. In 2008 Peters and co-workers reported the first *trans*-selective catalytic asymmetric [2+2] cyclocondensation reaction between aliphatic aldehydes **278** and acyl halides **277** furnishing 3,4-disubstituted *trans*-configured β-lactones (**279**) (scheme 69). This transformation represents a surrogate for the catalytic enantioselective *anti*-aldol reaction and was accomplished using chiral Lewis acid **C9**.[116a]



Scheme 69: Working hypothesis for the formation of *trans*-configured β-lactones (left), chiral Lewis acid catalyst **C9** (right): a.) **C9** (cat), *i*-Pr_2Net, CH_2Cl_2, -70 °C. [116]

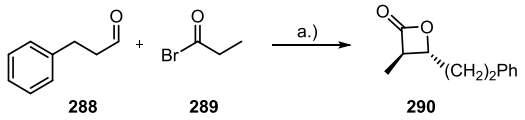
The proposed mechanism relies on the assumption that enolate **281** represents the reactive intermediate, which undergoes an enantioselective aldol reaction with the aldehyde activated through interactions with the chiral Lewis acid. The resulting acyl halide alcoholate **282** would decompose to the ketene intermediate **283** which, upon cyclization, forms the thermodynamically more stable *trans*-configured product **279** (scheme 69).[116]

The streamlined preparation of the chiral Lewis acid **C9** is shown in scheme 70. The sequence started with *ortho*-formylation of phenol **284**,[119] followed by bromomethylation of salicylaldehyde **285**[120] and reaction with pyridine to give pyridinium bromide **287**. Condensation of (*R,R*)-diaminocyclohexane with two eq. of **287** in presence of 4 Å MS afforded chiral compound **L2** as deep orange crystals. Reaction of **L2** with $AlMe_3$ formed **C9** via release of two eq. of methane.[116, 121]



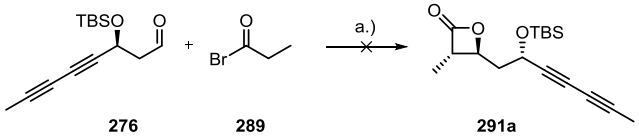
Scheme 70: Preparation of Lewis acid catalyst **C9**: a.) $MgCl_2$, $(CH_2O)_n$, Et_3N, THF, 70 °C, 95%; b.) HBr, $(CH_2O)_n$, H_2SO_4 (cat), 70 °C, 87%; c.) Pyridine, CH_3CN, quant. d.) (*R*,*R*)-diaminocyclohexane, 4 Å MS, EtOH, quant. e.) $AlMe_3$, CH_2Cl_2 quant.

Two protocols were described for the [2+2] cyclocondensation reaction; one relies on the isolation of the active aluminum-complex formed from **L2** and $AlMe_3$ by precipitation with pentane. The second procedure relies on the *in situ* formation of the active species. Generation of active complex **C9** was confirmed by reproduction of cyclocondensation of aldehyde **288** and propionylbromide (**289**).[116a]



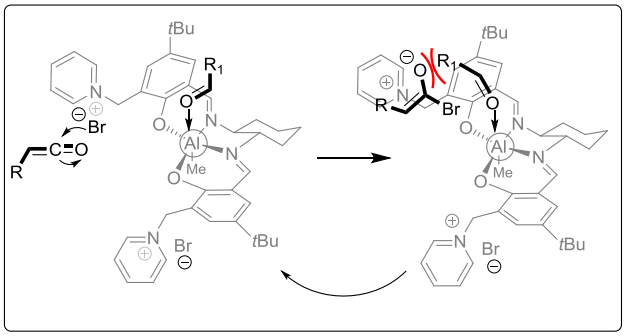
Scheme 71: Model reaction for the catalyst validation: a.) **L2,** $AlMe_3$, CH_2Cl_2 3 h, then propionyl bromide, *i*-Pr_2Net, CH_2Cl_2, -70 °C (90% conversion after 3 h, calculated by GC/MS).

Applying these reaction conditions to the cyclocondensation of aldehyde **276** and propionyl bromide (**289**) did not afford the desired product. Neither the use of the isolated nor the *in situ* formed catalyst resulted in the formation of the desired β-lactone. Increasing the temperature had no positive effect on the reaction.



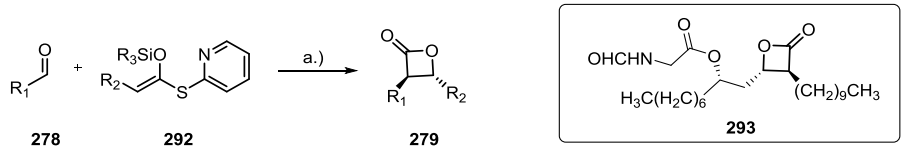
Scheme 72: Attempted preparation of the *trans*-configured β-lactone (**291a**): a.) **L2,** $AlMe_3$, CH_2Cl_2 3 h, then propionyl bromide, *i*-Pr_2Net, CH_2Cl_2, -70 °C.

One possible explanation for the failure is that the bulky TBS protecting group interferes with the sterically demanding Lewis acid and prohibits the alignment of the aldehyde, necessary for the [2+2] cyclocondensation. Another conceivable explanation is that the additional oxygen functionality present in the aldehyde interacts with the oxophilic aluminum-center preventing the desired transformation.



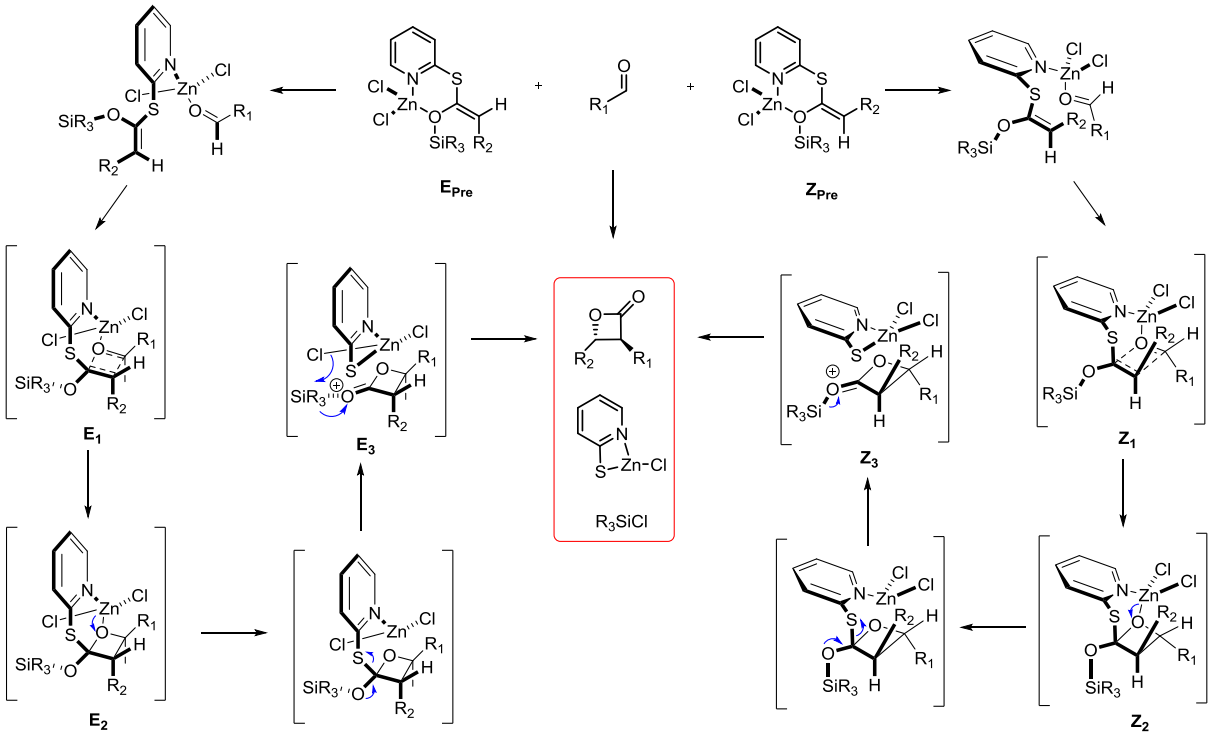
Scheme 73: Mode of action of Lewis acid catalyst and conceivable explanation for the failure of the [2+2] cyclocondensation.[116b]

In order to stick to the selected strategy an alternative method for the preparation of the *trans*-configured β-lactone **291a** was tested. In 1997 Romo and co-workers reported the use of a tandem Mukayama aldol-lactonization (TMAL) for the total synthesis of the lipase inhibitor (-)-panclicin D (**293**).[122] The $ZnCl_2$ mediated reaction between thiopyridine ketene acetal **292** and aldehyde **278** led to the formation of *trans*-configured β-lactone **279**. This methodology was built on early observations by Hirai and co-workers[123] and allowed the convenient preparation of 3,4-disubstituted-β-lactones with high diastereoselectivity.[122, 124]



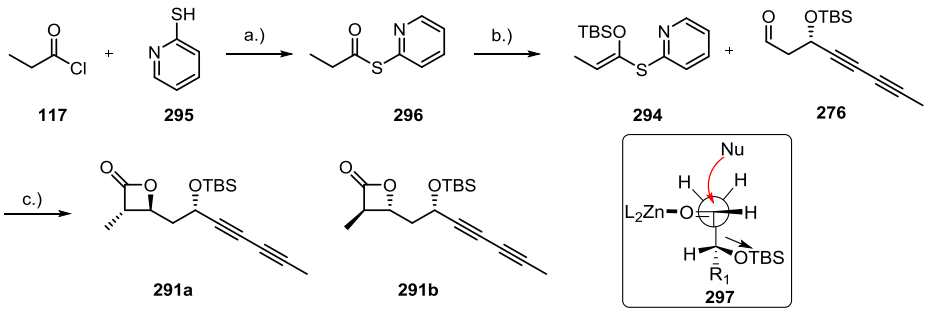
Scheme 74: Tandem Mukayama aldol-lactonization (left) and (-)-panclicin D (right): a.) $ZnCl_2$, CH_2Cl_2.

This method has been extensively employed by the group of Romo and these efforts culminated in several total syntheses[125] and in a detailed description of the mechanism based on computational and experimental findings.[126] The TMAL reaction is a stereoconvergent process in terms of the ketene acetal geometry. The proposed mechanism is based on theoretical and experimental results and is in good accordance with the observed stereoselectivity (scheme 75). Coordination of $ZnCl_2$ to either the (*Z*) or the (*E*)-configured acetal afforded adducts $\mathbf{Z_{Pre}}$ and $\mathbf{E_{Pre}}$ which upon addition of the aldehyde result in transition states $\mathbf{E_1}$ and $\mathbf{Z_1}$. The C - O bond as well as the C - C bond formation occurs concertedly but asynchronously, resulting in the formation of the oxetanes $\mathbf{E_2}$ and $\mathbf{Z_2}$. This process was found to be slightly endothermic. Subsequent cleavage of the Zn - O bond, followed by cleavage of the S - C bond and loss of the silyl group in the silylated intermediates $\mathbf{E_3}$ and $\mathbf{Z_3}$ give the *trans*-configured β-lactone (scheme 75).[126]



Scheme 75: Overall mechanistic proposal and explanation for the observed diastereoselectivity for the $ZnCl_2$-mediated TMAL reaction of non chiral aliphatic aldehydes.[126]

The (*E*)-thiopyridyl ketene acetal **294** was prepared by treatment of propionyl chloride (**117**) with 2-mercaptopyridine in presence of Et_3N. In a second step, the resulting 2-propionylthiopyridine (**296**) was deprotonated with LiHMDS and the enolate was trapped with TBS-Cl to afford the desired acetal **294**.[127] The acetal was treated with chiral aldehyde **276** in presence of stoichiometric amounts of freshly dried $ZnCl_2$ to yield the desired β-lactone **291a** in 62% yield as a 5:1 mixture of inseparable *trans*-diastereoisomers (scheme 76).

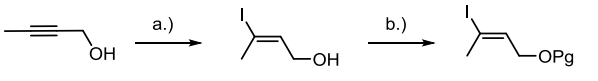


Scheme 76: Preparation of β-lactones **291a/b** via TMAL reaction (left). Possible explanation of the observed selectivity based on the model of 1,3-asymmetric induction (**297**)[128]: a.) Et_3N, CH_2Cl_2, 30 min, 89%; b.) LiHMDS, DMF, TBS-Cl, -78 °C, THF, 91%; c.) $ZnCl_2$, CH_2Cl_2, 3 h, 62% (5:1 d.r.).

The relative configuration was confirmed by NOE experiments and the coupling constants ($J_{Ha,Hb}$ ~ 4.0 Hz). The obtained outcome of the reaction is in accordance with the model originally proposed by Evans for the 1,3-asymmetric induction of β-silyl oxy aldehydes.[128] The model includes both steric and electrostatic interactions and relied on experimental and computational data. The proposed

transition state is based on the fact that steric interactions are minimized if the aldehyde adopts the staggered conformation **297**. This also favours electrostatic interactions between the polarized carbonyl carbon and the β-heteroatom substituent (scheme 76).[128]

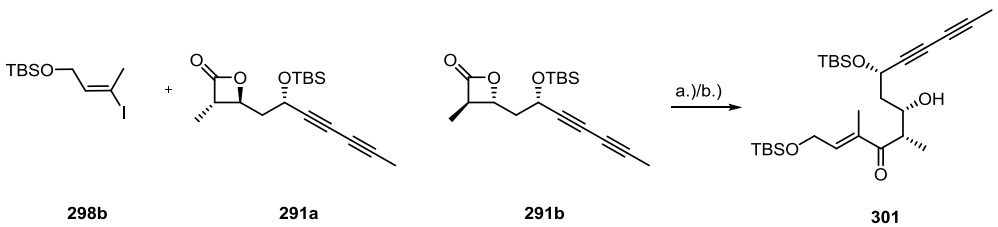
After successful preparation of the key intermediate **291a**, the alkenyl motif should be introduced. This transformation proved to be more challenging than expected. Initial approaches were based on the direct cleavage of the acyl-oxygen bond via mono-addition of the metalated species derived from Li/I exchange of alkenyl iodide **298a**/**b**. The alkenyl iodides were prepared in two steps from commercially available but-2-yn-1-ol (**299**). Ti-catalyzed hydromagnesation of butynol, followed by iodine quench, afforded (*E*)-alkenyl iodide **300.** This could be protected as the corresponding MOM-ether **298a** and TBS-ether **298b** under standard conditions (scheme 77).[129]



299 **300** **298a** Pg = MOM
298b Pg = TBS

Scheme 77: Preparation of alkenyl iodide **298a**/**b**: a.) Cp_2TiCl_2, *i*-BuMgCl, I_2, Et_2O, -78 °C to 0 °C, 5 h, 45%; b.) (**a**) MOM-Cl, *i*-Pr_2Net, CH_2Cl_2, 16 h, 64%; (**b**) TBS-Cl, imidazole, THF, 0 °C, 1 h, 68%.

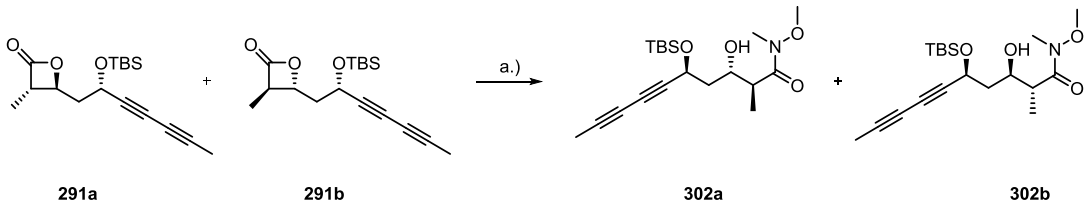
First attempts started with the Li/I exchange followed by subsequent addition to the β-lactone. The MOM-ether **298a** proved to be unstable under the reaction conditions; therefore TBS-ether **298b** was utilized in all later attempts. The exchange reaction was conducted at low temperature, followed by slow addition of the lithium reagent to the lactone. The reaction afforded the desired product only in low yields and the transformation lacked reproducibility. Additionally significant erosion of the optical purity of resulting ketone **301** was observed, which was in accordance with previous reports for the direct addition of alkenyllithium reagents to lactones bearing a α-stereogenic center.[130] Lowering the temperature from -78 °C to -90 °C as well as decreasing the addition rate had no beneficial effect on the outcome. Treatment of the alkenyllithium compound with anhydrous $CeCl_3$ yielded a deep orange solution of an organocerium reagent, which proved to be fairly temperature sensitive. Addition of the organocerium compound to the β-lactone gave the desired product along with recovered starting material and the bis-addition product (scheme 78).



298b **291a** **291b** **301**

Scheme 78: Initial attempts for the preparation of the α,β-unsaturated ketone **301**: a.) **298b**, *t*-BuLi, Et_2O/pentane, -90 °C, then **291a**/**b**, -78 °C, 20 min, 24%, b.) **298b**, *t*-BuLi, Et_2O/pentane, -78 °C, then $CeCl_3$, 1 h, then **259a**/**b**, -78 , 1 h, 20%.

Due to these unsuccessful attempts the β-lactone **291a** was converted to Weinreb amide **302a** by reaction with the aluminum-reagent prepared *in situ* from $CH_3NH(OCH_3)$ and $AlMe_3$ (scheme 79). At this stage the separation of the diastereoisomers was accomplished.



Scheme 79: Preparation of the Weinreb amide (**302a**): a.) $CH_3NH(OCH_3)$, $AlMe_3$, CH_2Cl_2, 0 °C, 3 h , 78% (**302b**, 11%).

Again, addition of the alkenyllithium reagent to the Weinreb amide (**302a**) proved to be problematic. Deprotonation of the hydroxy group with *n*-BuLi prior to the addition of the alkenyllithium reagent had no positive effect on the yield of the reaction. Transmetalation of the lithium species with $MgBr_2 \cdot (OEt)_2$ afforded the corresponding Grignard reagent, which also furnished only trace amounts of product. Since the direct formation of the corresponding Grignard reagent via Mg/I exchange led to isomeration of the olefin, the method of Oshima for the preparation of stereodefined Grignard reagents was tested.[131] In their report they used trialkylmagnesates for the halogen-magnesium exchange. The magnesium reagent prepared by this protocol afforded, upon addition to the Weinreb amide, again only trace amounts of the product.

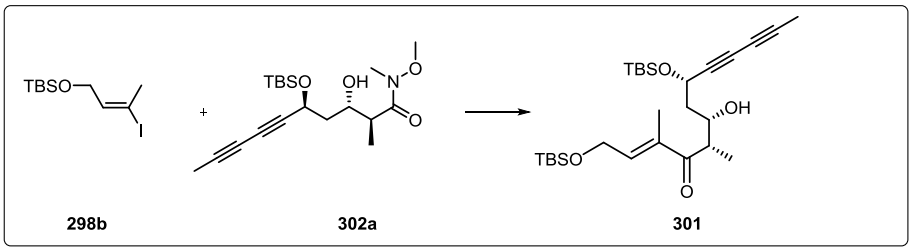


Table 14: Conditions for the addition of alkenyl iodide to the Weinreb amide.[a]

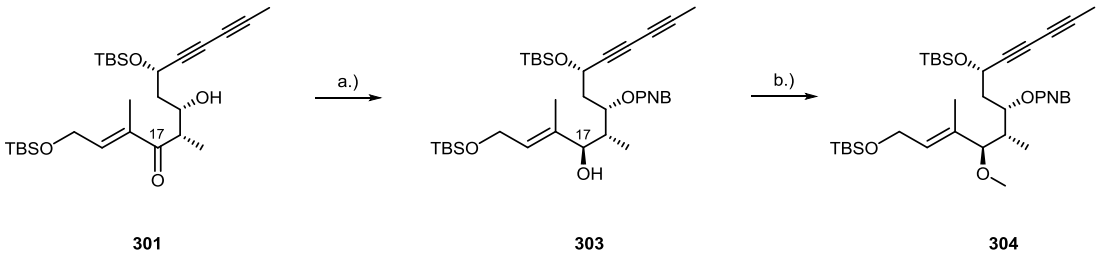
Entry	Conditions	Yield [%]
1	**298b**, *t*-BuLi, -78 °C then **302a**, -78 °C	24
2	**298b**, *t*-BuLi, -78 °C then **302a**[b], -78 °C	16
3	**298b**, *t*-BuLi, -78 °C then $MgBr_2 \cdot (OEt)_2$, then **302a**, - 78 °C to 0 °C	trace
4	**298b**, *t*-BuLi, -78 °C then $CeCl_3 \cdot 2LiCl$, then **302a**, -78 °C	38 (96, bsrm)

[a] Li/I exchange was conducted in Et_2O for 20 min at -78 °C, Weinreb amide was added as a solution in THF to the alkenyl reagent dropwise. [b]Prior treated with 0.6 eq. of *n*-BuLi at -78 °C and stirred for 15 min.

The best results for the preparation of ketone **301** were ultimately achieved by treatment of the alkenyllithium reagent with $CeCl_3 \cdot 2LiCl$[132] to afford the organocerium compound, followed by subsequent addition of the Weinreb amide (**302a**). This procedure yielded the desired compound in 38% yield together with 58% of recovered starting material (table 14). Although 5 eq. of the alkenylcerium reagent were employed, the reaction never reached full conversion. Increasing the

amount of the cerium reagent did not enhance the conversion but led to formation of side products. Performing the reaction at higher temperature did only result in decomposition of the organocerium reagent which was not stable above -60 °C. Despite the moderate yield, the good reproducibility and convenient recovery of starting material allowed sufficient amounts of the desired ketone **301** to be produced.

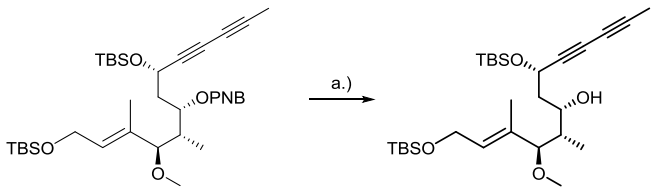
The construction of the stereogenic center C17 was accomplished by Evans-Tishenko reaction utilizing a freshly prepared solution of SmI_2 and *p*-nitrobenzaldehyde, which yielded the desired 1,3-*anti*-diol mono-ester **303** as the only detectable isomer.[133] The advantage of this procedure compared to similar transformations was the concurrent protection of the C15 hydroxy group as the corresponding benzoate, which allowed the subsequent methylation of the C17 hydroxy group in the next step to be performed (scheme 80). The methylation proved more challenging than originally envisaged in that most of the standard conditions afforded only recovered starting material or led to decomposition of the substrate. In fact the use of MeI or MeOTf in presence of amine bases like *i*-Pr_2Net, 2,6-di-*tert*-butyl-4-methylpyridine or 2,6-di-*tert*-butylpyridine induced no conversion, whereas the use of *t*-BuOK or LiHMDS led to degradation of alcohol **303**. Other methods such as $(CH_3)_3SiCHN_2$ or Ag_2O/MeI also failed to yield the desired product. Methylation was finally accomplished via treatment of alcohol **303** with 1,8-bis-(dimethylamino)naphthalin (Proton Sponge[TR]) and $(CH_3)_3OBF_4$, which provided the desired product **304** in good yield (scheme 80).



301 **303** **304**

Scheme 80: Preparation of methyl-ether **305**: a.) SmI_2, *p*-nitrobenzaldehyde, THF, -10 °C, 2 h, 70%; b.) $(CH_3)_3OBF_4$, 1,8-bis-(dimethylamino)naphthalin, CH_2Cl_2, 4 h, 69% (77% bsrm.)

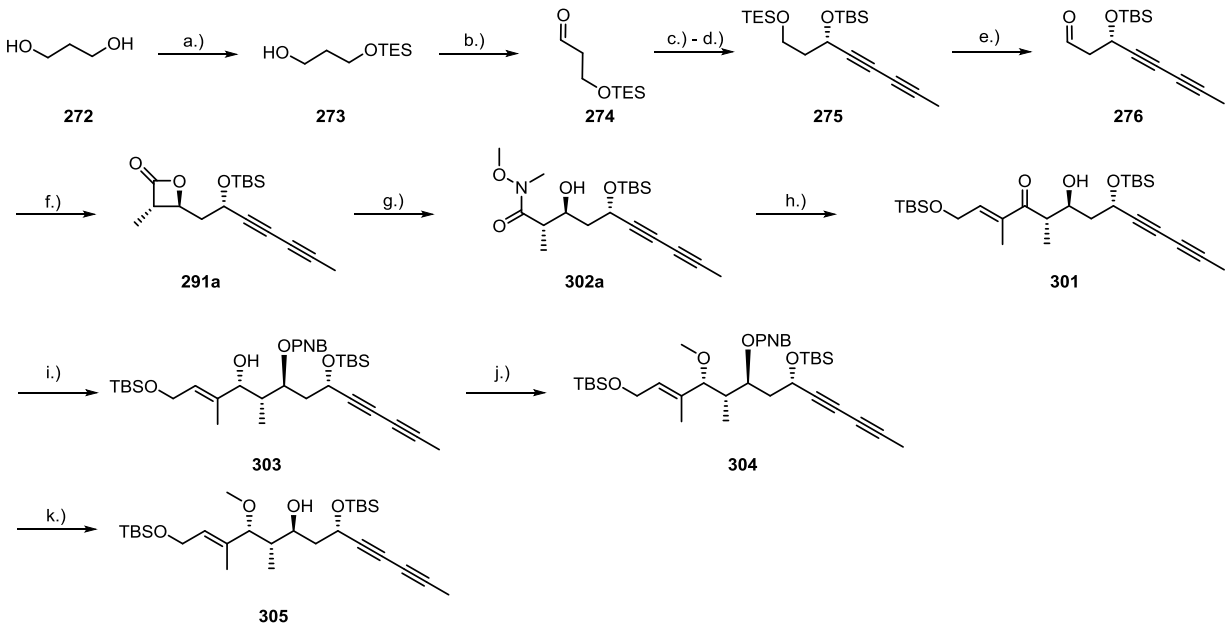
The final step was the removal of the benzoate protecting group, which was achieved with the aid of K_2CO_3 to yield the desired fragment **305** in 71% yield (scheme 81).



304 **305**

Scheme 81: Preparation of the western fragment (**305**): a.) K_2CO_3, MeOH/THF 1:1, 6 h, 71%.

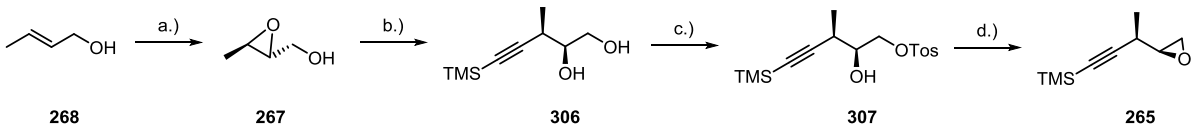
This transformation marked the endpoint of the western fragment synthesis, which was achieved in a longest linear sequence of eleven steps, starting from commercially available propane-1,3-diol. The TMAL reaction for the preparation of the chiral β-lactone **291a** was the key step in this sequence which allowed any auxiliary based transformations to be avoided. The complete route for the synthesis of the western fragment is shown in scheme 82.



Scheme 82: Overview of the western fragment synthesis: a.) TESCl, Et_3N, DMAP (cat), CH_2Cl_2, 87%; b.) SO_3·Py, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C to rt, 16 h, 85%; c.) **122**, Me_2Zn, (*R,R*)-ProPhenol, Ph_3P=O, toluene, 0 °C, 84%; d.) TBS-Cl, imidazole, CH_2Cl_2, 87%; e.) $(ClCO)_2$, DMSO, , -78 °C to -30 °C, 1 h then -78 °C, Et_3N, 76%; f.) **294**, $ZnCl_2$, CH_2Cl_2, 3 h, 62% (5:1 d.r.); g.) MeNH(OMe), $AlMe_3$, CH_2Cl_2, 0 °C, 3 h , 78%; h.) **298b**, *t*-BuLi, Et_2O/pentane, -78 °C, 15 min, then $CeCl_3$·2LiCl, 30 min, then **302a**, -78 °C, THF, 45 min, 38% (96% bsrm); i.) SmI_2, *p*-nitrobenzaldehyde, THF, -10 °C, 2 h, 70%; j.) $(CH_3)_3OBF_4$, 1,8-bis-(dimethylamino)naphthalin, CH_2Cl_2, 4 h, 69% (77% bsrm.); k.) K_2CO_3, MeOH/THF 1:1, 6 h, 71%.

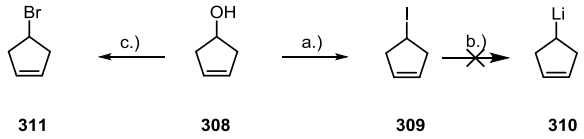
3.4.4 Synthesis of the eastern fragment

The preparation of the eastern fragment commenced with literature known Sharpless epoxidation of *trans*-crotyl alcohol (**268**),[134] followed by regioselective addition of the aluminum-reagent derived from TMS-acetylene.[135] The resulting diol **306** was selectively mono-tosylated with the aid of Bu_2SnO and the resulting tosylate **307** was treated with DBU to yield the desired epoxide **265** (scheme 83).[117]



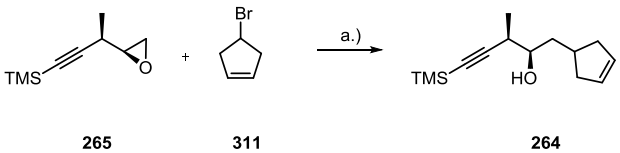
Scheme 83: Preparation of epoxide **265**: a.) (-)-DIPD, Ti(*i*-PrO)$_4$, TBHP, 3 Å MS, CH_2Cl_2, -20 °C to rt, 16 h, 78%; b.) TMS-acetylene, *n*-BuLi, toluene, -78 °C then Et_2AlCl, 0 °C then **307**, 16 h, 95%; c.) Tos-Cl, Bu_2SnO, Et_3N, CH_2Cl_2, 6 h, 75%; d.) DBU, CH_2Cl_2, 3 h, 85%.

With the epoxide in hand, the regioselective addition of the cyclopentene moiety was investigated. Therefore commercially available cyclopent-3-en-1-ol (**308**) was transformed to the corresponding iodide **309**. The conversion of the iodide to the alkyllithium reagent **310** was attempted with *t*-BuLi at low temperature, which only led to decomposition of the substrate (scheme 84).



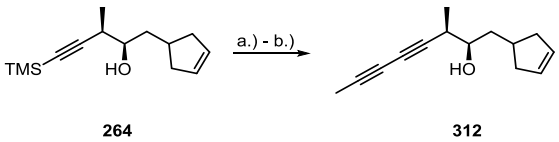
Scheme 84: Preparation of cyclopenten iodide **309** and bromide **311**: a.) PPh_3, imidazole, I_2, CH_2Cl_2, 16 h, 81%; b.) *t*-BuLi, Et_2O/pentane, -78 °C; c.) PPh_3, imidazole, Br_2, CH_2Cl_2, 16 h, 54%;

As an alternative, the alcohol was converted to the literature known bromide **311** followed by treatment with freshly activated Mg to obtain the Grignard reagent.[136] The regioselective addition was then accomplished by reaction of the Grignard reagent with epoxide **265** in presence of a stoichiometric amount of CuI, which gave the desired product in good yield (scheme 85).



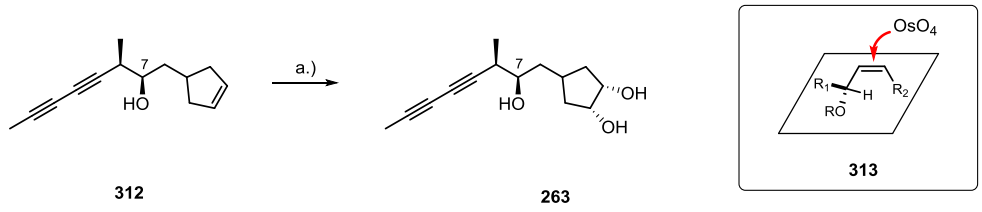
Scheme 85: Preparation of cyclopentene derivative **264**: a.) **312**, Mg, Et_2O, 2 h, then **265**, CuI, THF, -40 °C, 40 min, 87%.

To install the requisite 1,3-diyne, the TMS-alkyne was converted to the corresponding bromide followed by a copper-catalyzed coupling with propyne. Product **312** was obtained in 60% yield over two steps (scheme 86).



Scheme 86: Installation of the 1,3-diyne via Cadiot-Chodkiewicz coupling: a.) NBS, $AgNO_3$ (cat), acetone, 2 h; b.) propyne, CuCl, $NH_2OH{\cdot}HCl$, aq. $BuNH_2$ (30% in water), 30 min, 60% (over two steps).

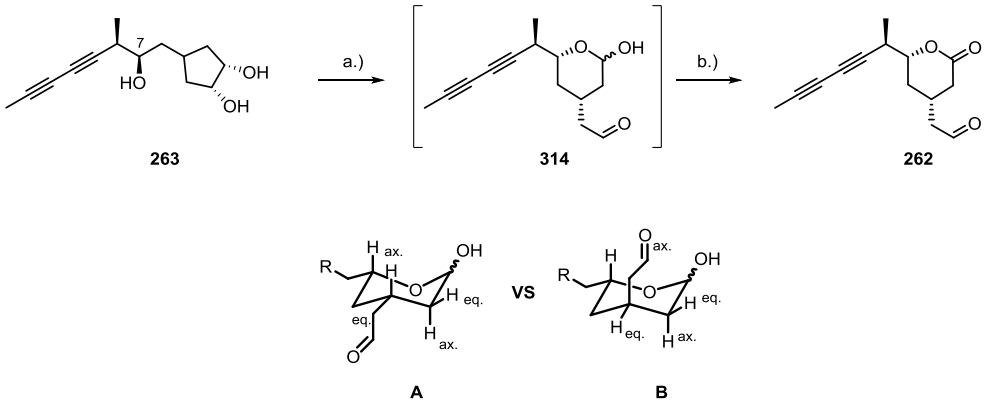
Cyclopentene **312** was subjected to OsO_4-catalyzed dihydroxylation conditions[137] to yield the desired *cis*-diol **263** as a 7.1 : 1 mixture of diastereoisomers. During the course of the reaction no interaction of the OsO_4 with the 1,3-diyne motif was observed. The stereochemical outcome of the reaction was in accordance with Kishi´s empirical rule for OsO_4-catalyzed dihydroxylations.[138] The newly formed diol lies in an *anti*-relationship to the directing hydroxy group at C7, which is in line with Kishi´s observation that osmium tetroxide approaches preferentially from the face of the double bond opposite to the pre-existing hydroxy group (scheme 87).[138-139]



.

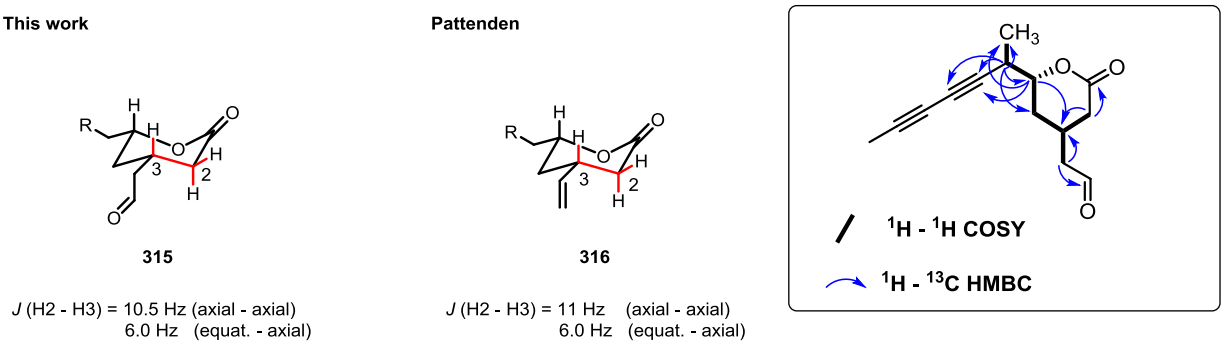
Scheme 87: Diyhdroxylation using Upjohn conditions: a.) OsO_4 (cat), NMO, acetone/H_2O (2:1), 6 h, 70% (7.7 : 1 d.r.).

The δ-lactone was prepared by a sequence related to the one originally described by Williams and co-workers.[100b] The diol was treated with $NaIO_4$ immobilized on SiO_2, which produced the expected mixture of anomeric lactols (**314**). As previously described (chapter 3.3.2), in a chair like conformation the diequatorial alignment (**A**) of the side chains is sterically favored over the axial-equatorial disposition (**B**). Additionally the diequatorial conformation (**A**) might be favored due to the electrostatic repulsion between the aldehyde group and the hydroxy group of the resulting lactol (scheme 88). The anomeric mixture was first subjected to Dess-Martin oxidation which produced the desired aldehyde only in trace amounts. The utilization of $Yb(OTf)_3$-catalyzed PIDA oxidation[140] finally gave the desired lactone aldehyde **262** in remarkable 76% yield over two steps from diol **263** (scheme 88).



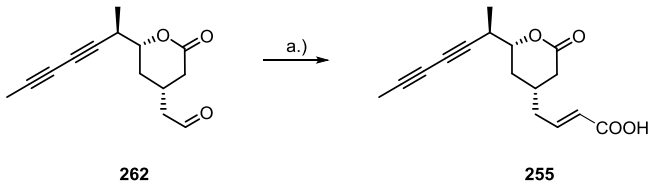
Scheme 88: $NaIO_4$ mediated diol cleavage and subsequent PIDA oxidation: a.) $NaIO_4$ (10% on SiO_2), CH_2Cl_2, 20 min; b.) PIDA, TEMPO (cat), $Yb(OTf)_3$ (cat), CH_2Cl_2, 1 h, 76% (over two steps).

The conformation of the lactone was unambiguously assigned via coupling constants and 2D-NMR-spectroscopy. Careful comparison of the H2 - H3 coupling constants of the obtained lactone with the data reported by Pattenden and co-workers confirmed the diequatorial arrangement of the side chains (scheme 89).[100e]



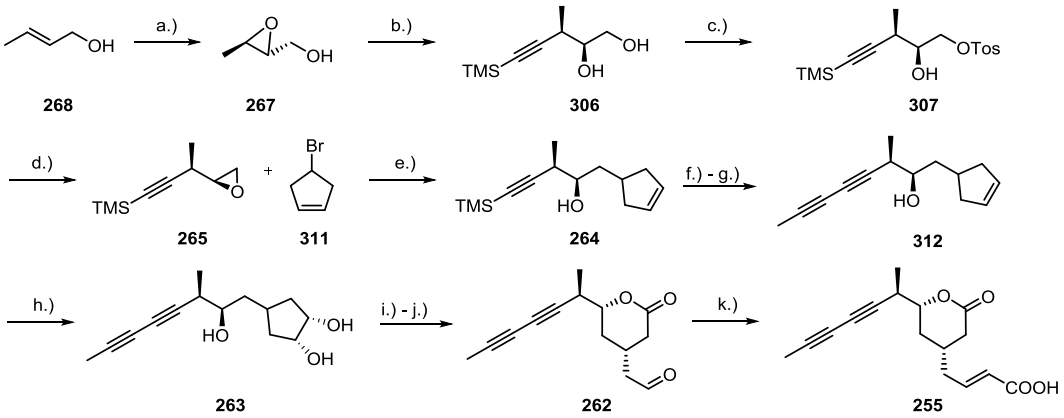
Scheme 89: NMR investigation of δ-lactone **262** and comparison with literature known compound **316**.[100e]

The final step of the fragment synthesis was the olefination of aldehyde **262** to install the α,β-unsaturated carboxylic acid. The transformation was realized by the method reported by Helquist and co-workers in 2006, who described the Zn promoted HWE olefination of diprotic phosphonate reagents.[141] The reaction proceeded smoothly to the desired unsaturated carboxylic acid **255**, with a *E* : *Z* ratio of 10 : 1.



Scheme 90: Preparation of α,β-unsaturated carboxylic acid **255**: a.) $Zn(OTf)_2$, DBU, TMEDA, diethylphosphonoacetic acid, THF, 16 h, 73% (10: 1, *E* : *Z*).

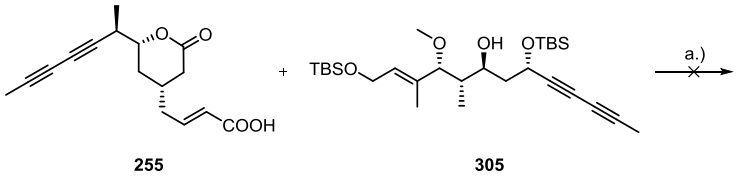
In total this fragment was synthesized in a longest linear sequence of eleven steps from commercially available *trans*-crotyl alcohol. The key steps were the regioselective addition of cyclopentenyl bromide **311** to epoxide **265**, followed by the dihydroxylation/oxidation sequence for the construction of the δ-lactone. The complete route for the synthesis of the eastern fragment is shown in scheme 91.



Scheme 91: Overview of the eastern fragment synthesis: a.) (-)-DIPD, $Ti(i\text{-}PrO)_4$, TBHP, 3 Å MS, CH_2Cl_2, -20 °C to rt, 16 h, 78%; b.) TMS-acetylene, *n*-BuLi, toluene, -78 °C then Et_2AlCl, 0 °C then **267**, 16 h, 95%; c.) Tos-Cl, Bu_2SnO, Et_3N, CH_2Cl_2, 6 h, 75%; d.) DBU, CH_2Cl_2, 3 h, 85%; e.) **311**, Mg, Et_2O, 1 h, then CuI, THF, -40 °C, 1 h, 87%; f.) NBS, $AgNO_3$ (cat), acetone, 2 h; g.) propyne, CuCl, $NH_2OH{\cdot}HCl$, aq. $BuNH_2$ (30% in water), 30 min, 60% (over two steps); h.) OsO_4 (cat), NMO, acetone/H_2O (2:1), 6 h, 70% (7.7 : 1 d.r.); h.) $NaIO_4$ (10% on SiO_2), CH_2Cl_2, 20 min; i.) PIDA, TEMPO (cat), $Yb(OTf)_3$ (cat), CH_2Cl_2, 1 h, 76% (over two steps); j.) $Zn(OTf)_2$, DBU, TMEDA, diethylphosphonoacetic acid, THF, 16 h, 73% (10: 1, *E* : *Z*).

3.4.5 Fragment assembly and RCDM

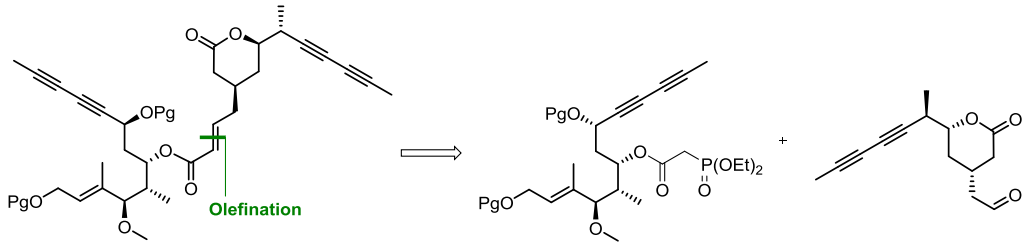
After the successful preparation of both fragments, their assembly was investigated next. The first attempt for the desired esterification of α,β-unsaturated carboxylic acid **255** with alcohol fragment **305** was conducted under Yamaguchi conditions. The approach proved to be problematic since the carboxylic acid was insoluble in the solvents commonly employed for this transformation. The use of toluene and CH_2Cl_2 only resulted in recovery of the alcohol fragment and decomposition of the acid.



255 **305**

Scheme 92: Attempted assembly of both fragments via Yamaguchi esterification: a.) 2,4,6-trichlorbenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C, then **305**, DMAP, toluene, 4 h.

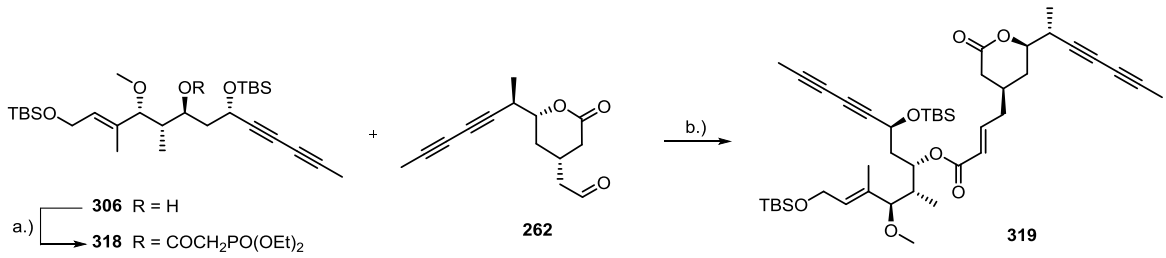
Due to this unsuccessful approach an alternative strategy for the fragment assembly was envisaged. The metathesis precursor should be obtained via olefination of aldehyde **262** with phosphonate **317** (scheme 93).



253 **317** **262**

Scheme 93: Revised retrosynthetic analysis of tetrayne **253**.

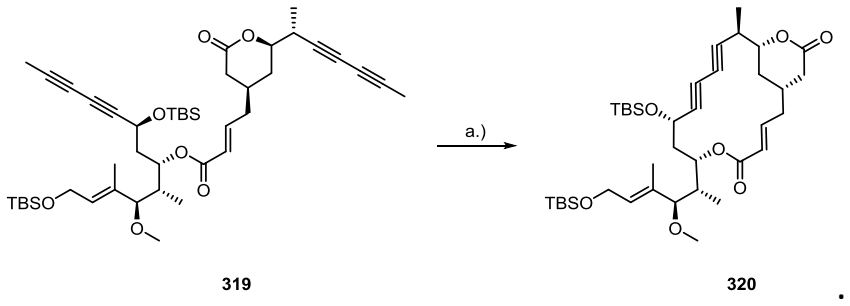
Therefore alcohol **305** was first converted to the corresponding phosphonate **318** by reaction with diethylphosphonoacetic acid in presence of EDC·HCl and DMAP. Product **318** was obtained in 94% yield. Phosphonate **318** was then treated with LiCl and DBU followed by addition of aldehyde **262**, which afforded the desired metathesis precursor **319** (scheme 94).



262 **319**

Scheme 94: Preparation of metathesis precursor **319**: a.) EDC·HCl, diethylphosphonoacetic acid, 3 Å MS, DMAP, CH_2Cl_2, 8 h, 94% b.) LiCl, DBU, MeCN/THF, 5 h, 50%.

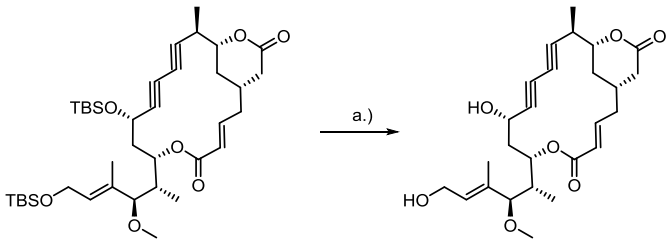
With the metathesis precursor in hand, the RCDM key transformation was examined. The reaction was carried out under conditions previously used for the cyclization of precursor **129** in the total synthesis of ivorenolide A (chapter 2.7, scheme 36). In presence of 30 mol% of **C7**/**L1** the reaction proceeded smoothly at 65 °C in 1.5 h to the desired cyclic 1,3-diyne **320**. The product was obtained together with an impurity derived from the silanol ligand **L1**, which could not be removed at this stage. As an alternative the cyclization was performed using complex **C5**. In presence of 30 mol% of **C5**, the cyclic 1,3-diyne was obtained in 58% yield, without notable amounts of impurities derived from the employed catalyst (scheme 95).



319 **320**

Scheme 95: Preparation of cyclic 1,3-diyne **320**: a.) **C5**, 5 Å MS, toluene, 65 °C, 1.5 h, 58%.

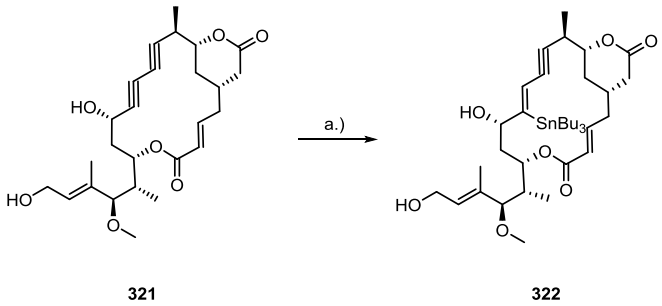
The conversion of metathesis precursor **319** to the highly decorated cyclic product **320** proves the robustness and reliability of this transformation. The next step was the simultaneous removal of both silyl protecting groups. This transformation was accomplished with the aid of TBAF at low temperature (scheme 96).



320 **321**

Scheme 96: Preparation of diol **321**: a.) TBAF, THF, -50 °C to -10 °C, 71%

The diol in hand, the second keystep, the hydroxy directed *trans*-hydrostannation reaction was examined. The use of 15 mol% of tetrameric complex **C8a** allowed the smooth conversion of **321** to the desired alkenyl stannane **322** (scheme 97). NMR-investigations confirmed the desired regioselectivity as well as the correct configuration of the resulting double bond. The observed $^{1}H - {}^{119}Sn$ coupling constant was in accordance with the values obtained during the model studies (chapter 3.4.1).



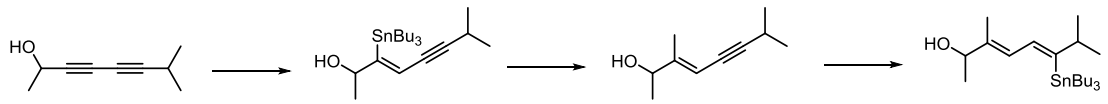
321 322

Scheme 97: Preparation of stannane **322**: a.) Bu_3SnH, **C8a** (cat), CH_2Cl_2 45 min,

This step marks the endpoint of this work. Both keysteps were successfully applied and studies to finalize the total synthesis of rhizoxin D are currently ongoing in the Fürstner group.

3.5 Summary

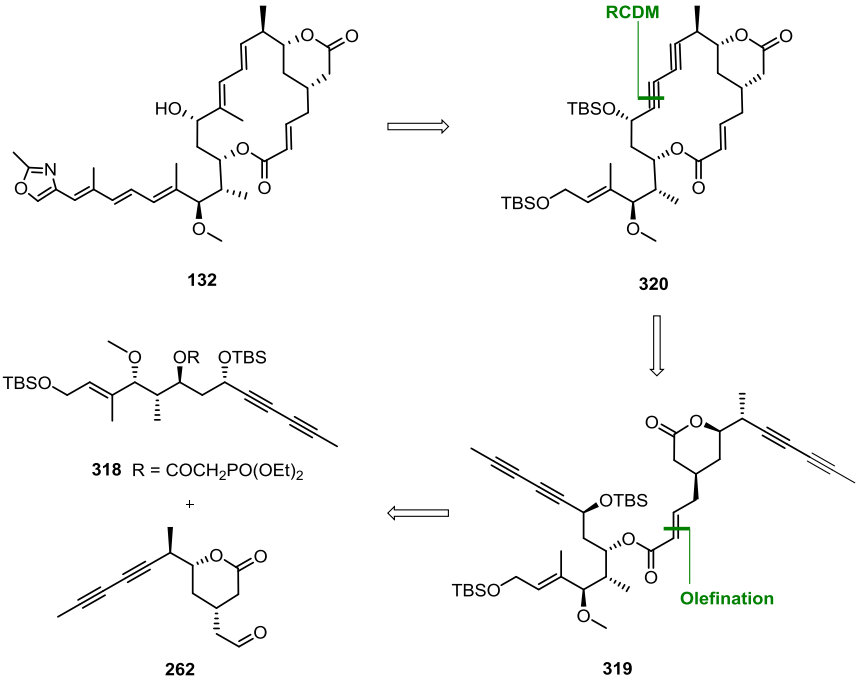
In summary, a novel strategy for the total synthesis of rhizoxin D, based on RCDM, was developed. Preliminary studies showed that the hydroxy group directed regioselective *trans*-hydrostannation reaction of **245** allowed the preparation of alkenyl stannane **246**. The subsequent palladium-catalyzed methyl-Stille coupling followed by a second *trans*-hydrostannation reaction of the distal alkyne furnished alkenyl stannane **249** which, upon proto-destannation, would yield the (*E*,*E*)-1,3-diene, a common motif in natural products.



245 246 248 249

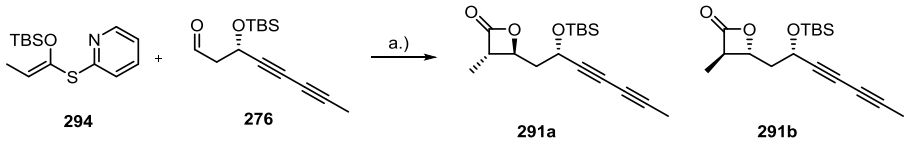
Scheme 98: Preparation of (*E*,*E*)-1,3-dienes via *trans*-selective hydrostannation.

After the successful application of this reaction sequence on a simplified model compound a novel retrosynthetic strategy for the total synthesis of the antitumor polyketide rhizoxin D was developed. The key transformation of this strategy was the RCDM of the acyclic tetrayne **319** to afford cyclic 1,3-diyne **320**. Further disconnection of the metathesis precursor led to two different fragments (**318** and **262**) exhibiting similar complexity (scheme 99).



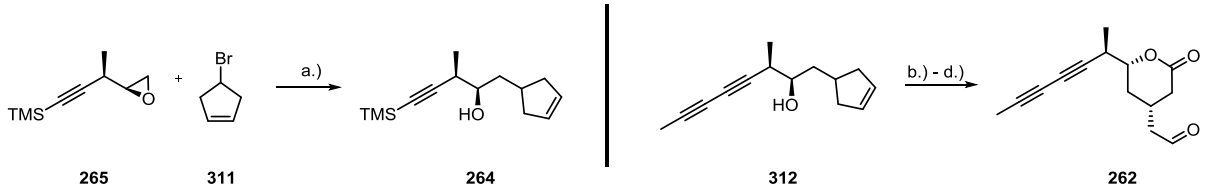
Scheme 99: Revised retrosynthetic analysis of rhizoxin D.

Fragment **318** was prepared in twelve steps from commercially available 1,3-propane diol. The TMAL reaction between ketene acetal **294** and chiral aldehyde **276** to afford the *trans*-configured β-propiolactone **291a** was the key transformation of this route (scheme 100).



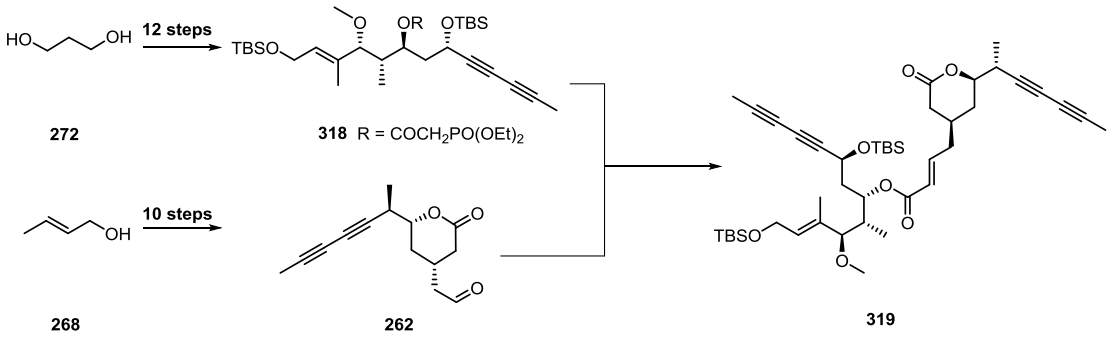
Scheme 100: Keystep of the western fragment synthesis a.) $ZnCl_2$, CH_2Cl_2, 3 h, 62% (5:1 d.r.)

Fragment **262** was obtained in ten steps from commercially available *trans*-crotyl alcohol. The utilized strategy relied on a regioselective epoxide opening, followed by a dihydroxylation/oxidation sequence (scheme 101).



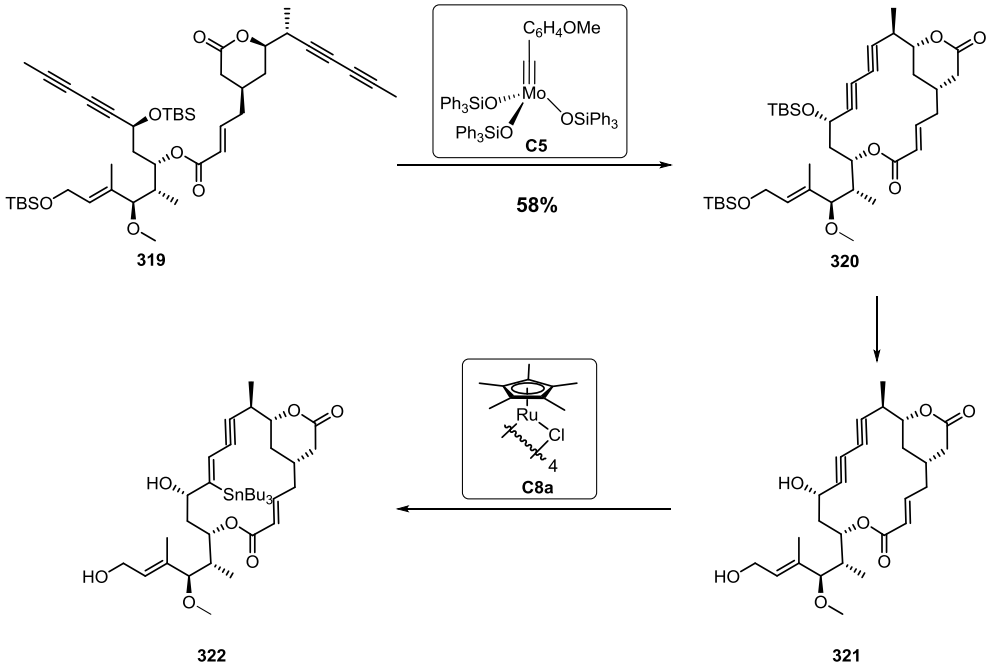
Scheme 101: Keysteps in the eastern fragment synthesis: a.) **311**, Mg, Et_2O, 1 h, then CuI, THF, -40 °C, 1 h, 87%; b.) OsO_4 (cat), NMO, acetone/H_2O (2:1), 6 h, 70% (7.7 : 1 d.r.); h.) $NaIO_4$ (10% on SiO_2), CH_2Cl_2, 20 min; i.) PIDA, TEMPO (cat), $Yb(OTf)_3$ (cat), CH_2Cl_2, 1 h, 76% (over two steps)

The synthesis of both fragments was exclusively based on stereoselective transformations, the minimum use of protecting groups, as well as the complete avoidance of any auxiliary-based transformations. The assembly of both fragments was accomplished through a HWE olefination (scheme 102).



Scheme 102: Synthesis of the macrocyclic core of rhizoxin D via RCDM.

The use of molybdenum alkylydine complex **C5** allowed the conversion of tetrayne **319** to the highly decorated cyclic product **320**. Treatment of diol **321** with Bu_3SnH in the presence of **C8a** enabled the preparation of alkenyl stannane **322**.

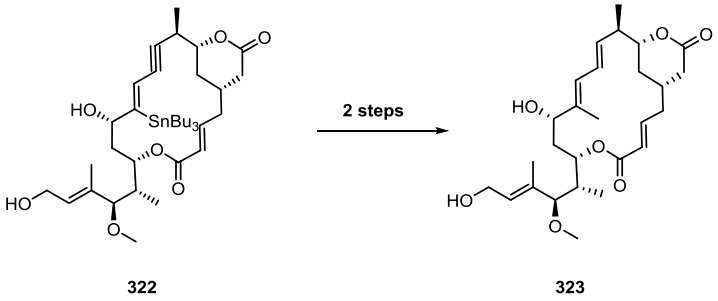


Scheme 103: Cyclization of tetrayne **319** and subsequent *trans*-hydrostannation of diol **321**.

Studies to convert **322** to the desired natural product are currently ongoing in the Fürstner group.

3.6 Outlook

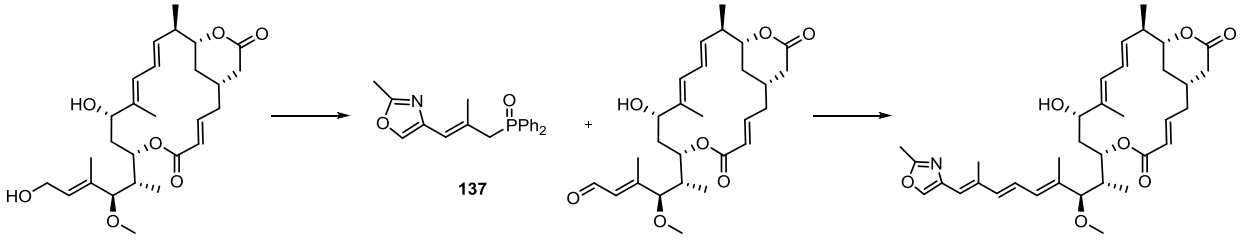
Previous results from the Fürstner group suggest that the catalysts used for the planned *trans*-hydrostannation interferes with aromatic moieties present in the substrate. Therefore, the heterocycle containing polyene side chain should be attached as the last step. After the successful first *trans*-hydrostannation reaction described in chapter 3.4.5, the subsequent methyl-Stille reaction followed by a second *trans*-hydrometalation reaction should afford, after proto-destannation, the desired 1,3-diene. The proto-destannation could either be achieved via CuTC or by simple stirring of the substrate in presence of SiO_2 as observed in preliminary studies (scheme 104).



322 323

Scheme 104: Proposed sequence for the preperation of cyclic 1,3-diene **323**.

Oxidation of the primary allylic hydroxy group in presence of a secondary alcohol has been reported in the total synthesis of rhizoxin by Ohno in which the application of MnO_2 afforded the desired product.[99a] The preparation of the polyene side chain is known in the literature starting from commercially available 2-methyloxazole-4-carboxylate.[92a] The attachment of the chromophoric side chain to the macrocyclic scaffold should be accomplished via an olefination reaction to complete the total synthesis of rhizoxin D (scheme 105).[92a]



323 137 324 132

Scheme 105: Proposed finalization of the total synthesis of rhizoxin D.

Further modification of this strategy would allow the preparation of different members of the rhizoxin family which could be utilized for biological tests. Moreover the utilization of the previously described *trans*-hydrostannation methodology (chapter 3.4.1) should allow the synthesis of differently substituted derivatives.

4. Experimental

4.1 General

All reactions were carried out under argon in flame-dried glassware unless H_2O was used as solvent. The following solvents and organic bases were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, DMSO (CaH_2), pentane, hexane, toluene (Na/K), MeOH (Mg, stored over 3 Å MS), DMF (4 Å MS), DMSO (distilled over CaH_2, stored over 4 Å MS). DMF, MeCN, Et_3N and pyridine were dried by an adsorption solvent purification system based on molecular sieves. DBU, Cy_2NH, *i*-Pr_2NEt (CaH_2) were distilled under Ar prior to use. NBS was freshly recrystallized from EtOH/H_2O and *p*-nitrobenzaldehyde was freshly recrystallized from EtOH prior to use. SmI_2 (0.1 M in THF) was freshly prepared prior to use according to the cited protocol.[100c] All other commercially available compounds (Acros, Aldrich, Alfa Aesar, Fluka, Fluorochem, TCI, Lancaster, Matrix Scientific,) were used as received.

The following compounds were prepared within the department of Prof. Fürstner: **C1b** (Dr. A. Lackner), **C4**, **C5**, **C7**, **L1**, **C8a**, **C8b**, **104**, Dess–Martin periodinane (DMP), [$Pd(PPh_3)_4$], $Pd(PPh_3)_2Cl_2$.

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

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

NMR spectra were recorded on Bruker DPX 300, AMX 300, AV 400, AV 500 or AVIII 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.13 ppm; pyridine-d5: δ_H = 8.74 ppm; δ_C = 150.35 ppm; CD_3OD δ_H = 3.31 ppm, δ_C = 49.00). Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet; hept: heptet, m: multiplet. The abbreviation "br" indicates a broad signal. ^{13}C NMR spectra were recorded [1H]-decoupled and the values of chemical shifts are rounded to one position after the decimal point. All spectra from the 500 MHz and 600 MHz spectrometers were acquired by co-workers of the NMR department under guidance of Dr. Christophe Farès at the Max-Planck-Institut für Kohlenforschung.

IR spectra were recorded on a Spectrum One (Perkin-Elmer) spectrometer or Alpha Platinum ATR (Bruker) at room temperature; wavenumbers are given in cm^{-1}.

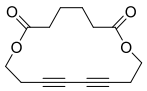
Mass spectrometric samples were measured by the department for mass spectrometry at the Max-Planck-Institut für Kohlenforschung. The following equipment was used: MS (EI): Finnigan MAT 8200

(70 eV), ESI-MS: Bruker ESQ3000, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan).

Optical rotations were measured with a Perkin-Elmer Model 343 polarimeter at a wavelength of 589 nm at 20 °C with a concentration (*c* = 1.0 = 10 mg/mL) in the indicated solvent.

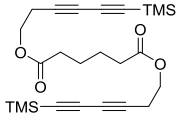
The following compounds were prepared according to the cited literature and the obtained spectroscopic data were in good agreement with those reported: **72**, **74**, **75**, **76**, **77**;[31] **81**, **82**;[61] **107**;[77] **122**;[81] **244**;[114] **270;**[142] **284**;[119] **285**;[120] **286**, **L2**, **C9**;[116b] **306**, **307**, **265**;[117] **311**.[136]

4.2 RCDM model studies



Representative procedure for Ring-Closing Alkyne Metathesis of 1,3-diynes (RCDM) using C5 (GP-1): 1,8-dioxacyclohexadeca-11,13-diyne-2,7-dione (79a). A flame dried Schlenk flask was charged under Ar with activated 5 Å molecular sieves (2 mg/µmol, 300mg) or a mixture of 4 Å/5 Å molecular sieves (2 mg/µmol of each pore size for terminal alkynes). The flask was then evacuated (0.01 mbar) and the molecular sieves were dried by heating with a heat gun (400 °C, 5 min). This procedure was repeated and after cooling to ambient temperature the flask was backfilled with Ar. Substrate **72** (50 mg, 0.15 mmol, 1.0 eq.) was dissolved in toluene (15 mL) and the solution was transferred via syringe to the flask containing the molecular sieves. The suspension was stirred for 1 h, before **C5** (16.1 mg, 0.0015 mmol, 10 mol%) was added. The mixture was stirred at ambient temperature until complete conversion of starting material as indicated by TLC. The mixture was filtered through a short pad of SiO_2, which was then rinsed with EtOAc (30 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO_2, 10% →15% EtOAc in Hexane) to afford 31.3 mg (84%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (t, *J* = 5.7 Hz, 4H), 2.58 (t, *J* = 5.7 Hz, 4H), 2.31- 2.43 (m, 4H), 1.67 – 1.79 (m, 4H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.2, 74.4, 67.6, 60.7, 35.0, 25.7, 20.3. **IR** (film, cm^{-1}): 2960, 1728, 1282, 1230, 1171, 1128, 1011 **MS:** *m/z* calcd for $C_{14}H_{16}O_4Na$ 271.09405, found 271.09408.

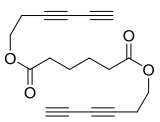


Bis-(6-(trimethylsilyl)hexa-3,5-diyn-1-yl) adipate (80). Adipoyl dichloride (0.22 mL, 1.5 mmol, 1.0 eq.) was added dropwise at 0 °C to a solution of 6-(Trimethylsilyl)hexa-3,5-diyn-1-ol **82** (500 mg, 3.0 mmol, 2.0 eq.) in CH_2Cl_2 (33 mL) and pyridine (1.6 mL). The mixture was stirred at ambient temperature for 16 h. Excess base was neutralized by addition of aq. HCl (0.1 N, 10 mL) and diluted with H_2O (10 mL). The organic layer was separated and the

aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure yielding 605 mg (91%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (t, *J* = 6.7 Hz, 4H), 2.62 (t, *J* = 6.7 Hz, 4H), 2.41 – 2.28 (m, 4H), 1.74 – 1.54 (m, 4H), 0.18 (s, 18H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.1, 88.0, 84.3, 75.3, 66.9, 61.6, 33.8, 24.3, 19.9, -0.3(3C). **IR** (film, cm^{-1}): 1738, 1251, 1181, 845 **MS:** *m*/*z* calcd for $C_{24}H_{34}O_4Si_2Na$ 465.18870, found 465.18879.

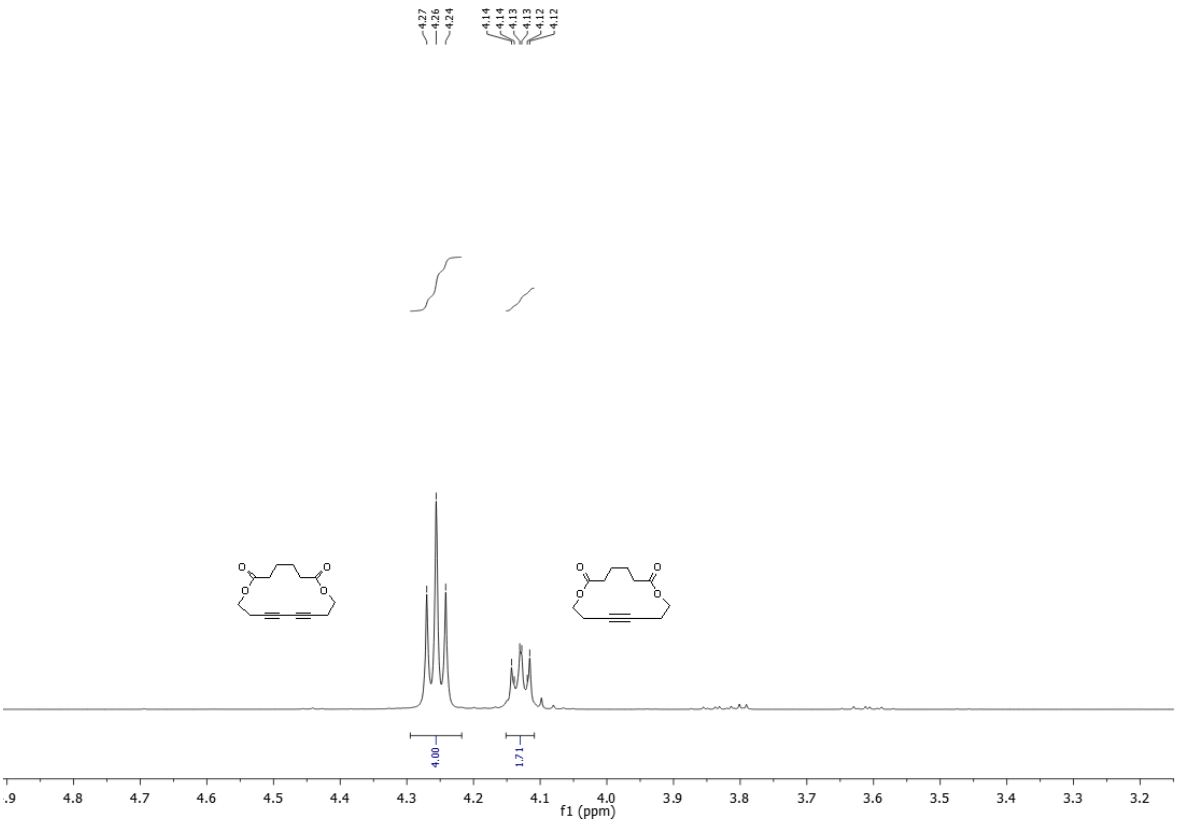
Di-(hexa-3,5-diyn-1-yl)-adipate (83). TBAF (1.0 M in THF, 0.42 mL, 0.42 mmol, 2.0 eq.) was added at 0 °C dropwise to a solution of **80** (92.1 mg, 0.208 mmol, 1.0 eq.) in THF (6 mL) causing an immediate color change from yellow to dark red. Stirring was continued for 20 min at 0 °C before the reaction was quenched with H_2O (5 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) yielding 39 mg (62%) of the title compound as an orange solid which rapidly decomposes on standing.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (t, *J* = 6.6 Hz, 4H), 2.61 (td, *J* = 6.7, 1.2 Hz, 4H), 2.41 – 2.33 (m, 4H), 2.00 (t, *J* = 1.2 Hz, 2H), 1.77 – 1.63 (m, 4H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.1, 73.9, 68.1, 66.2, 65.5, 61.5, 33.8, 24.4, 19.8. **IR** (film, cm^{-1}): 3263, 1731, 1370, 1259, 1177, 1146, 979 **MS:** *m*/*z* calcd for $C_{18}H_{18}O_4Na$ 321.10947, found 321.10973

Cyclization: Substrate **83** (30.0 mg, 0.1 mmol, 1.0 eq.), catalyst **C5** (10.1 mg, 0.01 mmol, 10 mol%), toluene (10 mL) according to **GP-1** yielded 22.3 mg (88%) of the desired product.

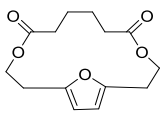
Cyclization: Substrate **80** (66.1 mg, 0.15 mmol, 1.0 eq.), catalyst **C5** (16.1 mg, 0.015 mmol, 10 mol% + another 10 mol% after 12 h), toluene (15 mL), 24 h 60 °C according to **GP-1**. In this case the product was an inseparable mixture of desired and the ring contracted macrocycle[a] (**79a** : **79b**, 2.3 : 1, 32.1 mg, 53% calculated by NMR purity).



[a] Identified by comparison with an authentic sample, cf: J. Heppekause, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2012,** 132, 11045 - 11057

4.2.1 Post-metathetic transformations

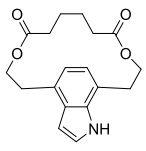
4,11-Dioxa-1(2,5)-furanacyclotridecaphane-5,10-dione (84). H_2O (72.0 mg, 4 mmol, 10.0 eq.) and



$SPhosAuNTf_2$ (15.8 mg, 0,018 mmol, 5 mol%) were added to a solution of cyclic 1,3-diyne **79a** (90 mg, 0,362 mmol, 1.0 eq.) in THF (4 mL). The solution was heated to 60 °C and maintained at this temperature for 16 h. The mixture was filtered through a short pad of SiO_2 and the obtained crude material was purified by flash chromatography (SiO_2, 15% → 20% EtOAc in hexane) to yield 59 mg (61%) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (s, 2H), 4.34 – 4.30 (m, 4H), 2.96 – 2.92 (m, 4H), 2.30 – 2.24 (m, 4H), 1.55 – 1.49 (m, 4H) **^{13}C NMR** (101 MHz, $CDCl_3$):173.5, 151.6, 107.4, 63.2, 34.9, 27.8, 25.1 **IR** (cm^{-1}): 1731, 1279, 1170, 1141 **MS:** *m*/*z* calcd for $C_{14}H_{18}O_5Na$ 298.10454, found 289.10404

11H-4,11-Dioxa-1(4,7)-indolacyclotridecaphane-5,10-dione (85). Pyrrole (13.0 mg, 0.2 mmol, 10.0

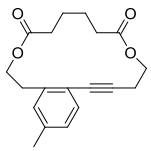


eq.) and [BrettPhosAu(MeCN)SbF_6] (2.1 mg, 0,002 mmol, 10 mol%) were added to a solution of cyclic 1,3-diyne **79a** (5 mg, 0,02 mmol, 1.0 eq.) in 1,2-dichloroethane (0.2 mL). The solution was heated to 80 °C for 6 h. The mixture was filtered through a short

pad of SiO_2, which was rinsed with EtOAc (15 mL). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 15% EtOAc in hexane). The product was further purified by HPLC (Kromasil, C18, 5µm, 150*21.4 mm, MeOH/H_2O 80/20) yielding 1.2 mg (21%) of the title compound as a dark green solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.93 (s, br N-H), 6.84 (td, *J* = 2.7, 1.5 Hz, 1H), 6.35 – 6.20 (m, 2H), 5.80 (t, *J* = 7.2 Hz, 1H), 4.37 (t, *J* = 5.6 Hz, 2H), 4.31 (t, *J* = 5.4 Hz, 2H), 2.78 (q, *J* = 6.1 Hz, 2H), 2.68 (t, *J* = 5.7 Hz, 2H), 2.39 – 2.33 (m, 2H), 2.30 – 2.25 (m, 2H), 1.69 – 1.62 (m, 4H) **^{13}C NMR** (600 MHz, $CDCl_3$) δ = 174.1, 173.5, 131.6, 118.1, 109.6, 109.0, 62.7, 61.3, 35.2, 34.7, 32.1, 29.5, 25.6, 25.4, 22.9, 20.7, 14.3, 1.2 **IR** (cm^{-1}): 2925, 2854, 1730, 1460, 1283, 1243, 1175

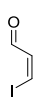
Compound 87: Cyclic 1,3-diyne **79a** (5.0 mg, 0.021 mmol, 1.0 eq.) and enyne **86** (2.71 mg, 0.042 mmol, 2.0 eq.) were added to a solution of [$Pd(PPh_3)_4$] (2.3 mg, 0.002 mmol, 10 mol%) in THF (0.3 mL) and the mixture was stirred at 65 °C until TLC analysis showed complete consumption of **79a**. The mixture was filtered through a short pad of SiO_2, which was rinsed with EtOAc (15 mL). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 10% EtOAc in hexane) to yield 5.6 mg (85%) of the desired compound as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 7.8 Hz, 1H), 7.02 – 6.97 (m, 2H), 4.34 – 4.24 (m, 4H), 3.12 (t, *J* = 7.6 Hz, 2H), 2.79 (dd, *J* = 5.9, 4.9 Hz, 2H), 2.42 – 2.38 (m, 2H), 2.33 (m, 5H), 1.79 – 1.72 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.6, 173.4, 132.2, 139.4, 138.4, 129.5, 127.5, 120.8, 89.6, 80.1, 64.8, 62.8, 34.1, 33.7, 33.4, 24.4, 24.1, 21.6, 20.4 **IR** (cm^{-1}): 2924, 1732, 1458, 1340, 1238, 1144, 1066, 1030, 1005 **MS:** *m*/*z* calcd for $C_{19}H_{22}O_4Na$ 337.14083, found 337.14103

4.3 RCDM: Synthesis of model compound (96) and initial attempt for the total synthesis of ivorenolide A

(*Z*)-3-Iodoacrylaldehyde (93). A 50 mL three-neck flask equipped with a thermometer, a gas inlet and a rubber septum was charged with ethyl-(*Z*)-iodoacrylate (0.64 mL, 5.0 mmol, 1.0 eq.) and CH_2Cl_2 (10 mL). The solution was cooled to -80 °C before DIBAL-H (1.0 M in CH_2Cl_2, 5.1 mL, 5.1 mmol, 1.02 eq.) was added very carefully at such a rate to keep the internal temperature between -75 °C and -80 °C. After complete addition the mixture was stirred at -78 °C until GC/MS indicated complete consumption of starting ester. The reaction was cooled to -82 °C and cold MeOH (2.5 mL) was carefully added, followed by addition of sat. aq. Na/K-tatrate (12.5 mL). The mixture was allowed to warm to ambient temperature and further stirred for 30 min at this temperature. The mixture was filtered through a short pad of Celite®. CH_2Cl_2 was carefully removed under reduced pressure keeping

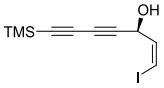


the temperature of the water bath at 0 °C. The crude aldehyde (810 mg, 86%) was not purified due to the high instability. Rather it was dissolved in anhydrous toluene (8.1 mL) and transferred to a Schlenk flask. The solution can be stored under argon in a -20 °C fridge for at least 3- 4 weeks, without noticeable decomposition or isomerization of the double bond.

Buta-1,3-diyn-1-yltrimethylsilane (74). Bis-TMS-Butadiyne (4.0 g, 20.0 mmol, 1.0 eq.) was dissolved in Et_2O (40 mL) and the solution was cooled to 0 °C, before MeLi (1.6 M in Et_2O, 20.6 mL, 24.0 mmol, 1.2 eq.) was added over a period of 20 min. After the addition was complete the solution was stirred at room temperature until GC/MS revealed complete mono-desilylation. The mixture was cooled to -78 °C and the reaction was quenched with sat. aq. NH_4Cl (20 mL). After warming up to room temperature, the layers were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was carefully evaporated. The crude material was purified by distillation (bp. 55 °C, 60 mbar) to yield 1.80 g (73%) of the title compound as a colorless solution which turns yellow upon standing.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 1H), 0.21 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 87.5, 84.9, 68.4, 66.8, -0.40(3C) **IR** (film, cm^{-1}): 2960, 1250, 840, 759 **MS:** *m/z* calcd for $C_7H_{10}Si$ 122.05506, found 122.05518.

(*S*,*Z*)-1-Iodo-7-(trimethylsilyl)hepta-1-en-4,6-diyn-3-ol (97). A Schlenk flask was charged with Ph_3P=O (122.2 mg, 0,44 mmol, 20 mol%), (*R*,*R*)-ProPhenol (140.0 mg, 0,22 mmol, 10 mol%), and toluene (9 mL). Diyne **74** (0.66 mL, 4.40 mmol, 2.0 eq.) was added via syringe, followed by dimethylzinc (1.2 M in toluene, 3.65 mL, 4.40 mmol, 2.0 eq.). The resulting alkynylzinc solution was stirred at room temperature for 30 min, before it was cooled to 0 °C. A cold (0 °C) solution of aldehyde **93** (4 mL of previously prepared solution, 400 mg, 2.2 mmol, 1.0 eq.) was added over the course of 1 h. The reaction was left to proceed at 0 °C for additional 3 h. The reaction was then quenched at -20 °C with sat. aq. NH_4Cl (10 mL) and stirred vigorously for 20 min. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 4% EtOAc in hexane) to yield 575 mg (86%, 89% *ee.*) of the title compound as a light yellow oil which darkens on standing.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.38 (t, *J* = 7.7 Hz, 1H), 5.18 (dd, *J* = 7.8, 4.2 Hz, 1H), 0.20 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.8, 89.1, 87.1, 85.3, 75.1, 71.0, 66.0, -0.4(3C) **IR** (film, cm^{-1}): 2960, 1683, 1611, 1251, 1130, **MS:** *m/z* calcd for $C_{10}H_{13}IOSi$ 303.97812, found 303.97804 $[\alpha]_{20}$ = +340.1 (c = 1.0, $CHCl_3$).

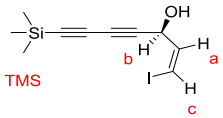
The absolute configuration was determined as (*S*) by the advanced Mosher Ester method.[143] The *ee* of **97** was determined by integration of H_a in the spectra of the derived (*S*)-MTPA ester.

(*R*)-MTPA-Ester: (*S*)-*α*-Methoxy-*α*-trifluoromethyl phenylacetic acid chloride (10.0 mg, 0.064 mmol, 2.0 eq.) was added to a solution of alcohol (10.0 mg, 0.032 mmol, 1.0 eq.), pyridine (0.008 mL, 0.1 mmol, 3.1 eq.) in CH_2Cl_2 (0.5 ml). The mixture was stirred for 16 h at room temperature and quenched with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL), the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was of sufficient purity for the determination of the absolute configuration.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.46 (t, *J* = 8.1 Hz, 1H), 6.24 (dd, *J* = 8.2, 0.9 Hz, 1H), 0.21 (s, 9H).

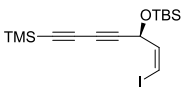
(*S*)-MTPA-Ester. Prepared analogously, using (*R*)-*α*-methoxy-*α*-trifluoromethyl phenylacetic acid chloride as the reagent. Reaction was conducted on the same scale as described above.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.41 – 6.35 (m, 1H), 6.28 (dd, *J* = 8.1, 0.9 Hz, 1H), 0.21 (s, 9H).



Proton	(*R*)-MTPA	(*S*)-MTPA
a	6.44 – 6.48	6.36 – 6.40
b	6.22 – 6.25	6.27 – 6.29
c	6.77 – 6.80	6.73 – 6.75
TMS	0.205	0.209

(*S*,*Z*)-*tert*-Butyl((1-iodo-7-(trimethylsilyl)hepta-1-en-4,6-diyn-3yl)oxy)dimethylsilane (90).

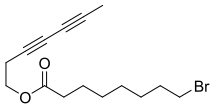


TBS-Cl (313.0 mg, 2.1 mmol, 1.1 eq.), 1-methylimidazol (0.45 mL, 5.7 mmol, 3.0 eq.) and I_2 (960.2 mg, 3.8 mmol, 2.0 eq.) were successively added at 0 °C to a solution of alcohol **97** (575.0 mg, 1.9 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL). The mixture was stirred at room temperature until TLC indicated complete consumption of starting material. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and stirred until disappearance of orange color (30 min). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with 10 mL sat aq. NaCl, dired over $MgSO_4$ and the solvent

was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 1% EtOAc in hexane) to afford 785 mg (98%) of the title compound as a yellow oil.

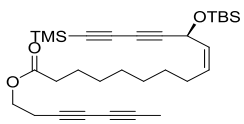
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.31 (t, *J* = 7.6 Hz, 1H), 5.14 (dd, *J* = 7.6, 0.9 Hz, 1H), 0.90 (s, 9H), 0.19 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.0, 88.1, 87.4, 83.0, 76.0, 69.8, 67.1, 25.8(3C), 18.3, -0.3(3C), -4.4, -4.6. **IR** (film, cm^{-1}): 2957, 2929, 2857, 2108, 1253, 1076, 1005, **MS:** *m/z* calcd for $C_{16}H_{27}OISi_2Na$: 441.05379, found 441.05374 $[\alpha]_{20}$ = + 221.3 (c = 1.0, $CHCl_3$).

Hepta-3,5-diyn-1-yl 8-bromooctanoate (98). DMAP (149.1 mg, 1.11 mmol, 0.3 eq.) and DCC (1.53 g, 7.2 mmol, 2.0 eq.) were successively added at 0 °C to a solution of **77** (400 mg, 3.7 mmol, 1.0 eq.) and 8-bromoctanoic acid (946 mg, 4.25 mmol, 1.15 eq) dissolved in CH_2Cl_2 (20 mL). The mixture was stirred overnight at room temperature before the reaction was quenched with sat. aq. NaCl (20 mL) and the organic layer was separated. The aqueous phase was extracted with EtOAc (4 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 5% EtOAc in hexane) yielding 994 mg (86%) of the title compound as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (t, *J* = 6.7 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.90 (t, *J* = 1.2 Hz, 3H), 1.88 – 1.79 (m, 2H), 1.65 – 1.59 (m, 2H), 1.45 – 1.39 (m, 2H), 1.35 – 1.29 (m, 4H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.6, 74.0, 72.2, 66.9, 64.3, 61.8, 34.2, 34.1, 32.8, 29.0, 28.5, 28.1, 24.9, 19.8, 4.3 **IR** (film, cm^{-1}): 2932, 2856, 1734, 1234, 1164, 1121, **MS** *m/z* calcd for $C_{15}H_{21}BrO_3Na$ 335.06168, found 335.06172.

6-(Trimethylsilyl)-hexa-3,5-diyn-1-yl(*S*,*Z*)-11-((tert-butyldimethylsilyl)oxy)hexadeca-9-en-12,14-diynoate (**99**)**.** A Schlenk flask was charged with Zn dust (32.6 mg, 0.5 mmol, 2.0 eq.) and I_2 (3.5 mg, 0.012 mmol, 5 mol%). The flask was evacuated for ca. 30 seconds and backfilled with Ar before DMF (0.5 mL) was added. The resulting slurry was vigorously stirred until disappearance of the orange color (2-4 min). At this point alkylbromide **98** (78.3 mg, 0.25 mmol, 1.0 eq.) was added and the solution was heated to 75 °C for 4 h. After reaching ambient temperature the remaining zinc dust was allowed to settle (20 min) yielding a 0.5 M solution of organozinc compound.

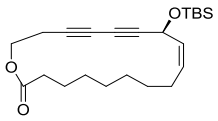


A second Schlenk flask was charged with alkenyl iodide **90** (41.1mg, 0.1 mmol), $PdCl_2$ (0.8 mg, 0.005 mmol, 2 mol%), tri-*o*-tolylphosphine (4.6 mg, 0.015 mmol, 6 mol%) and THF (0.5 mL). The mixture

was stirred for 5 min, before an aliquot of the freshly prepared solution of organozinc compound (0.5 M in DMF, 0.28 mL, 0.14 mmol, 1.4 eq.) was added dropwise. The mixture was stirred for 4 h at ambient temperature. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 0.5% EtOAc in hexane) to yield 18.5 mg (36%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 – 5.40 (m, 2H), 5.18 – 5.13 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 2.58 (td, *J* = 6.7, 1.2 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.10 – 2.01 (m, 2H), 1.90 (d, *J* = 1.2 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.41 – 1.22 (m, 8H), 0.88 (s, 9H), 0.18 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.7, 132.0, 129.3, 87.7, 87.4, 78.3, 74.0, 72.2, 69.0, 66.9, 64.3, 61.8, 59.5, 34.3, 29.4, 29.3, 29.2, 29.2, 27.8, 25.9(3C), 25.0, 19.9, 18.3, 4.4, -0.3(3C), -4.4, -4.6. **IR** (film, cm^{-1}): 2928, 2856, 2105, 1738, 1251, 1165, 1072, 839 **MS** *m/z* calcd. for $C_{31}H_{48}O_3Si_2Na$ 547.30372, found 547.30342 **$[\alpha]_{20}$** =+ 93.7 (c = 1.0, $CHCl_3$).

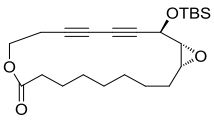
(*S*,*Z*)-12-((*tert*-Butyldimethylsilyl)oxy)oxacyclooctadeca-10-en-13,15-diyn-2-one (100). Cyclization



was done according to **GP-1**: Substrate **99** (4.1 mg, 0.0076 mmol, 1.0 eq.), 4 Å/5 Å MS (16 mg, each), **C5** (0.7 mg, 0,0008 mmol, 10 mol%), toluene (0.76 mL), 16 h, rt, yielded 2.5 mg (82%) of the title compound

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 – 5.35 (m, 2H), 5.22 – 5.18 (m, 1H), 4.24 – 4.11 (m, 2H), 2.64 (ddt, *J* = 8.1, 4.8, 1.1 Hz, 2H), 2.38 – 2.28 (m, 2H), 2.15 – 2.03 (m, 2H), 1.70 – 1.58 (m, 2H), 1.40 – 1.29 (m, 6H), 1.24 – 1.18 (m, 2H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.0, 131.4, 130.8, 77.3, 76.7, 69.1, 66.4, 61.6, 59.8, 35.3, 30.1, 29.7, 29.3, 29.0, 28.3, 26.1, 25.9(3C), 20.1, 1.2, -4.5, -4.6. **IR** (film, cm^{-1}): 2957, 2928, 2856, 1731, 1274, 1075 **MS** *m/z* calcd for $C_{23}H_{36}O_3SiNa$ 411.23228, found 411.23259 **$[\alpha]_{20}$** = + 39.6 (c = 1.0, $CHCl_3$).

(1*R*,2*R*,18*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-9,19-dioxabicyclo[16.1.0]nonadeca-3,5-diyn-10-one

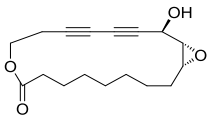


(100b). *m*-CPBA (10.8 mg, 0.063 mmol, 3.5 eq.) was added at 0 °C to a solution of alkene **100** (7.0 mg, 0,018 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL). The cooling bath was removed and the solution was stirred at room temperature for 16 h until TLC showed complete conversion of starting material. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced

pressure and the resulting crude material was purified by flash chromatography (SiO_2, 3% → 5% EtOAc in hexane) yielding 5.3 mg (74%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 – 4.13 (m, 3H), 3.14 (dd, *J* = 7.7, 4.2 Hz, 1H), 2.96 (ddd, *J* = 10.6, 4.3, 2.8 Hz, 1H), 2.70 – 2.64 (m, 2H), 2.39 – 2.34 (m, 2H), 2.09 – 1.97 (m, 2H), 1.71 – 1.57 (m, 2H), 1.53 – 1.36 (m, 6H), 1.18 – 1.09 (m, 2H), 0.91 (s, 9H), 0.14 (d, *J* = 2.4 Hz, 6H) **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 174.0, 78.0, 73.4, 70.9, 65.7, 63.7, 61.6, 61.0, 57.0, 34.6, 30.2, 30.2, 28.9, 28.6, 27.1, 26.1, 25.9, 25.9(3C), 20.1, -4.6, -4.7 **IR** (film, cm^{-1}): 2927, 2856, 1738, 1253, 1076, 1005, **MS** *m/z* calcd for $C_{23}H_{36}O_4SiNa$ 427.22797, found 427.22751 $[\alpha]_{20}$ = +5.7 (c = 1.0, $CHCl_3$).

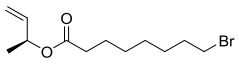
(1*S*,2*R*,18*R*)-2-Hydroxy-9,19-dioxabicyclo[16.1.0]nonadeca-3,5-diyn-10-one (96). TBAF (1.0 M in



THF, 0.043 mL, 0.043 mmol, 1.5 eq.) was added dropwise at 0 °C to a solution of TBS-ether **100b** (5.3 mg, 0.012 mmol, 1.0 eq.) in THF (0.85 mL). After stirring for 10 min, the solution was quenched with sat. aq. NH_4Cl (2 mL). The organic layer was separated and the aqueous phase was extracted with MTBE (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude material was purified by flash chromatography (SiO_2, 15% → 20% EtOAc in hexane) yielding 3.0 mg (83%) of the title compound as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.28 – 4.23 (m, 2H), 4.16 (ddd, *J* = 10.7, 6.3, 4.3 Hz, 1H), 3.39 – 3.34 (m, 1H, OH), 3.17 (dd, *J* = 8.2, 4.2, Hz, 1H), 3.03 (ddd, *J* = 10.7, 4.2, 2.9 Hz, 1H), 2.70 – 2.66 (m, 2H), 2.40 – 2.33 (m, 2H), 2.15 – 2.06 (m, 1H), 1.69 – 1.62 (m, 2H), 1.51 – 1.45 (m, 2H), 1.43 – 1.32 (m, 5H), 1.20 – 1.13 (m, 2H) **^{13}C NMR** (600 MHz, $CDCl_3$): δ = 173.7, 78.5, 72.0, 71.9, 65.4, 62.5, 61.3, 60.3, 57.5, 34.6, 30.2, 30.0, 28.9, 28.2, 25.9, 25.8, 20.0. **IR** (film, cm^{-1}): 2923, 2853, 1735, 1462, 1261, 1038, **MS** *m/z* calcd for $C_{17}H_{22}O_4Na$ 313.14065, found 313.14103 $[\alpha]_{20}$ = +17.5 (c = 0.5, $CHCl_3$).

(*S*)-But-3-en-2-yl 8-bromooctanoate (102). Trimethylsulfoniumiodide (8.57 g, 42.0 mmol 3.0 eq.)

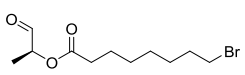


was placed in a 250 mL Schlenk flask and THF (55 mL) was introduced. The suspension was cooled to -78 °C and *n*-BuLi (1.6 M in hexane, 25.6 mL, 40.6 mmol, 2.9 eq.) was added. The mixture was stirred for 30 min, before (*S*)-2-methyloxirane **101** (0.98 mL, 14 mmol, 1.0 eq.) in THF (5 mL) was added carefully. The cooling bath was removed and the solution was allowed to warm to ambient temperature. The mixture was stirred for 1.5 h, before the reaction was quenched with sat. aq. NH_4Cl (30 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully reduced to 1/3 and the mixture was added to a stirred solution of 8-bromooactanoic acid (3.12 g, 14 mmol, 1.0 eq.), DCC (5.72 g, 28.0 mmol, 2.0 eq.), and DMAP (0.51 g,

4.2 mmol, 0.3 eq.) in THF (30 mL). The mixture was stirred at room temperature overnight before the reaction was quenched with aq. HCl (0.5 N, 30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 0.5% EtOAc in hexane) to yield 2.55 g (66% over two steps) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.24 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.13 (dt, *J* = 10.5, 1.3 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.63 (tt, *J* = 5.7, 2.6 Hz, 2H), 1.44 (t, *J* = 7.4 Hz, 2H), 1.36 – 1.32 (m, 4H) 1.31 (d, *J* = 6.5 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.1, 137.9, 115.8, 70.9, 34.6, 33.5, 30.4, 29.0, 28.3, 25.0, 20.1, 7.3 **IR** (film, cm^{-1}): 2931, 2856, 1733, 1453, 1372, 1237, 1179 **MS:** *m*/*z* calcd for $C_{12}H_{21}O_2BrNa$ 299.06185 found 299.06172 **$[\alpha]_{20}$** = -3.2 (c = 0.4, $CHCl_3$).

(*S*)-1-Oxopropan-2-yl 8-bromooctanoate (91). A 250 mL two neck flask was charged with olefin **102**



(1.5 g, 5.4 mmol, 1.0 eq.) and CH_2Cl_2 (50 mL) was added. The solution was cooled to -78 °C and O_3 was bubbled through the solution until a blue color persisted, then O_2 was bubbled through the solution until the blue color disappeared. Dimethylsulfid (3.9 mL, 54.0 mmol, 10.0 eq.) was added at -78 °C and the reaction was slowly warmed to ambient temperature over the course of 16 h. H_2O (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with sat. aq. NaCl (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 15% EtOAc in hexane) to yield 1.2 g (81%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 0.6 Hz, 1H), 5.08 (qd, *J* = 7.2, 0.6 Hz, 1H), 3.19 (t, *J* = 7.0 Hz, 2H), 2.42 (td, *J* = 7.4, 2.4 Hz, 2H), 1.88 – 1.77 (m, 2H), 1.67 (t, *J* = 7.3 Hz, 2H), 1.46 – 1.30 (m, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ =198.6, 173.2, 74.5, 34.0, 33.5, 30.4, 28.9, 28.3, 14.3, 7.3. **IR** (film, cm^{-1}): 2934, 2857, 1737, 1236, 1174, 1074 **MS:** *m*/*z* calcd for $C_{11}H_{20}O_3Br$ 279.05883 found 279.05905 **$[\alpha]_{20}$** = -13.7 (c = 1.0, $CHCl_3$).

(2*S*,3*R*)-3-Hydroxy-7-(trimethylsilyl)hepta-4,6-diyn-2-yl 8-bromooctanoate (89). A 25 mL Schlenk flask was charged with (*R*,*R*)-ProPhenol (27.4 mg, 0.04 mmol, 10 mol%), $Ph_3P{=}O$ (23.9 mg, 0.08 mmol, 20mol%), and toluene (2.6 mL). The solution was stirred for 10 min at room temperature, then $ZnMe_2$ (1.2 M in toluene, 1.0 mL, 1.29 mmol, 3.0 eq.) was added followed by dropwise addition of diyne **74** (0.21 mL, 1.29 mmol, 3.0 eq.). Stirring was continued for 45 min before the solution was cooled to 0 °C. Aldehyde **91** (120.1 mg, 0.43 mmol, 1.0 eq.) was introduced and the reaction was left to proceed at 0 °C for 16 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the obtained crude material was used directly for the next step.

TBS-Cl (56.2 mg, 0.43 mmol, 1.0 eq.), 1-methylimidazol (0.062 mL, 0.77 mmol, 1.8 eq.) and iodine (131.9 mg, 0.54 mmol, 1.2 eq.) were added successively to a solution of crude alcohol in CH_2Cl_2 (2.5 mL). The solution was stirred until complete conversion of starting material as indicated by TLC. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 1% EtOAc in hexane) to yield 108 mg (49% over two steps) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (qd, *J* = 6.4, 4.1 Hz, 1H), 4.47 (d, *J* = 4.1 Hz, 1H), 3.40 (t, *J* = 6.9 Hz, 2H) 2.29 (t, *J* = 7.5 Hz, 2H), 1.85 (p, *J* = 7.0 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.46 – 1.41 (m, 2H), 1.36 – 1.31 (m, 4H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.20 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.0, 87.4, 87.3, 76.0, 72.7, 70.4, 65.6, 34.5, 34.0, 32.8, 29.6, 28.5, 28.1, 25.7(3C), 24.9, 18.3, 14.9, -0.3(3C), -4.5, -5.1. **IR** (film, cm^{-1}): 2932, 2858, 1739, 1252, 842 **MS:** *m*/*z* calcd for $C_{24}H_{43}O_3Br_1Si_2Na$ 537.18335, found 537.18265 $[\alpha]_{20}$ = -17.4 (c = 0.5, $CHCl_3$).

Methyl (*S*)-2-((4-methoxybenzyl)oxy)propanoate (109b). Methyl-L-lactate **109** (1.04 g, 10 mmol, 1.0 eq.) and freshly prepared PMB-trichloracetimidat (2.96 g, 10.5 mmol, 1.05 eq.) were dissolved in Et_2O (50 mL) and the solution was cooled to -78 °C. Triflic acid (0.017 mL, 0.2 mmol, 2 mol%) was added dropwise and the mixture was stirred for 20 min at -78 °C. The cooling bath was removed and the solution was allowed to warm to ambient temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified

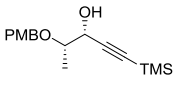
by flash chromatography (SiO_2, 10% Et_2O in pentane) to afford 2.01 g (88%) of title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.26 (m, 2 H), 6.90 – 6.85 (m, 2H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.05 (q, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.9, 159.5, 129.7(2C), 129.7, 113.9(2C), 73.7, 71.8, 55.4, 52.0, 18.8 **IR** (film, cm^{-1}): 1747, 1512, 1245, 1205, 1140, 1109, 1064, 1030, 819 **MS:** *m/z* calcd for $C_{12}H_{16}O_4Na$ 247.09432, found 247.09408 $[\alpha]_{20}$ = -85.1 (c = 1.0, $CHCl_3$).

(*S*)-2-((4-Methoxybenzyl)oxy)propanal (110). Methylester **109b** (1.15 g, 5.12 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (25 mL) and cooled to -78 °C. To this solution was added DIBAL-H (1.0 M in CH_2Cl_2, 5.64 mL, 5.64 mmol, 1.1 eq.) slowly over the course of 1 h and the reaction was left to proceed at -78 °C for 20 min. For work-up the reaction was quenched by slow addition of cold MeOH (3 mL), followed by addition of sat. aq. Na/K-tatrate (25 mL). The mixture was allowed to warm to room temperature and stirred for 1 h until clear phase separation was observed. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The crude material was purfied by flash chromatography (SiO_2, 15% Et_2O in pentane) to yield 0.88 g (89%) of the aldehyde as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.8 Hz, 1H), 7.30 – 7.27 (m, 2H), 6.91 – 6.87 (m, 2H), 4.56 (d, *J* = 3.7 Hz, 2H), 3.91 – 3.83 (m, 1H), 3.81 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 203.8, 159.6, 129.8(2C), 129.5, 114.1(2C), 79.3, 71.9, 55.4, 15.5 **IR** (film, cm^{-1}): 2837, 1732, 1612, 1513, 1302, 1246, 1174, 1090, 1032, 820 **MS:** *m/z* calcd for $C_{11}H_{14}O_3Na$ 217.08357, found 217.08351 $[\alpha]_{20}$ = -20.2 (c = 1.0, $CHCl_3$).

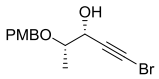
(3*R*,4*S*)-4-((4-Methoxybenzyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (111). TMS-acetylene (3.65 mL, 25.75 mmol, 4.0 eq.) was carefully added to a solution of Et_2Zn (15% in toluene, 23.2mL, 25.75 mmol, 4.0 eq.). A reflux condenser was placed on the flask and the solution was heated to reflux for 1 h, during this time a large amount of grey precipitate was formed. After 1 h the mixture was allowed to cool down to ambient temperature, before (*R*)-BINOL (0.73 g, 2.5 mmol, 40 mol%), Ti(*i*-PrO)$_4$ (1.9 mL, 6.4 mmol, 1.0 eq.) and Et_2O (40 mL) were successively added. The suspension was stirred for 1 h at ambient temperature, before aldehyde **110** (1.25 g, 6.4 mmol, 1.0 eq.) dissolved in Et_2O (10 mL) was introduced. The reaction was left to proceed overnight at room temperature before quenched with aq. Na/K-tatrate (40 mL). The mixture was stirred for 2 h until clear phase separation was observed. The aqueous phase was



extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with sat. aq. NaCl (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 15% Et_2O in pentane) to give 1.35 g (72%) of the title compound as a white solid.

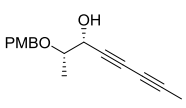
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.26 (m, 2H), 6.91 – 6.86 (m, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.48 – 4.43 (m, 1H), 3.81 (s, 3H), 3.65 (qd, *J* = 6.3, 3.7 Hz, 1H), 2.34 (d, *J* = 5.6 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.17 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.4, 130.3, 129.4(2C), 114.0(2C), 103.5, 91.1, 76.5, 70.8, 65.4, 55.4, 14.6, -0.0(3C). **IR** (film, cm^{-1}): 3349, 1511, 1248, 1077, 1024, 975, 837, 760, 655, **MS:** *m/z* calcd for $C_{16}H_{24}O_3SiNa$ 315.13879, found 315.13869 **$[\alpha]_{20}$** = +11.4 (c = 1.0, $CHCl_3$).

(3*R*,4*S*)-1-Bromo-4-((4-methoxybenzyl)oxy)pent-1-yn-3-ol (108). NBS (402.5 mg, 2.25 mmol, 1.5 eq.) and $AgNO_3$ (127.1 mg, 0.75 mmol, 0.5 eq.) were added to a solution of TMS-alkyne **111** (440 mg, 1.5 mmol, 1.0 eq.) in acetone (12 mL). The mixture was stirred in the dark for 16 h. For work-up the reaction was quenched with H_2O (10 mL) and diluted with Et_2O (15 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and purification of the crude material by flash chromatography (SiO_2, 15% Et_2O in pentane) yielded 342 mg (76%) of the title compound as a volatile liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.21 (m, 2H), 6.94 – 6.83 (m, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.42 (dd, *J* = 6.7, 3.6 Hz, 1H), 3.81 (s, 3H), 3.65 (qd, *J* = 6.3, 3.7 Hz, 1H), 2.46 (d, *J* = 6.7 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.5, 130.0, 129.6(2C), 114.0(2C), 78.2, 76.3, 70.9, 66.2, 55.4, 46.2, 14.9 . **IR** (film, cm^{-1}):1709, 1512, 1245, 1174, 1075, 1030, 821, 751, **MS:** *m/z* calcd for $C_{13}H_{15}BrO_3Na$ 321.00987, found 321.00969 **$[\alpha]_{20}$** = -1.5 (c = 0.5, $CHCl_3$).

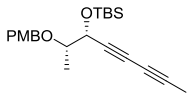
(2*S*,3*R*)-2-((4-Methoxybenzyl)oxy)octa-4,6-diyn-3-ol (123) GP-2. A 25 mL two-neck flask equipped with a pressure equalizer and a magnetic stir bar, was charged with aq. $BuNH_2$ (30% in water, 8 mL) and CuCl (14.9 mg, 0.15 mmol, 15 mol%). The solution was cooled to 0 °C before liquid propyne (0.1 mL), which had been condensed into a separate flask, was added via a pre-cooled syringe. A few crystals of $NH_2OH{\cdot}HCl$ were added until a yellow color persisted. The solution was allowed to warm to ambient temperature and bromo alkyne **108** (300.2 mg, 1.0 mmol, 1.0 eq.) was added dropwise over 5 min. During the course of the reaction several



portions of $NH_2OH{\cdot}HCl$ were added to maintain the yellow/golden color of the reaction mixture. The mixture was stirred for 30 min before being transferred into a separation funnel and extracted with of Et_2O (3 x 10 mL). The combined organic extracts were washed with sat. aq. $CuSO_4$ (10 mL) and sat. aq. NaCl (10 mL), before being dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 10% → 20% Et_2O in pentane) to yield 172 mg (67%) of the title compound as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 – 4.41 (m, 1H), 3.81 (s, 3H), 3.65 (qd, *J* = 6.4, 3.7 Hz, 1H), 2.41 (s, broad 1H, OH), 1.93 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), **^{13}C NMR** (101 MHz, $CDCl_3$): δ =130.1, 129.6(2C), 114.0(2C), 76.5, 72.9, 71.2, 63.9, 70.9, 65.8, 55.4, 15.0, 4.5, 1.2. (1C underneath $CDCl_3$ peak) **IR** (film, cm^{-1}): 2932, 1612, 1513, 1302, 1248, 1175, 1083, 822: **MS:** *m/z* calcd for $C_{16}H_{18}O_3Na$ 281.11486, found 281.11481 $[\alpha]_{20}$ = -11.2 (c = 1.0, $CHCl_3$).

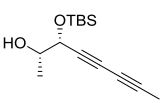
***tert*-Butyl(((2*S*,3*R*)-2-((4-methoxybenzyl)oxy)octa-4,6-diyn-3-yl)oxy)dimethylsilane (112).** TBS-Cl



(56.2 mg, 0.37 mmol, 1.23 eq.), 1-methylimidazol (72.5 mg, 0.87 mmol, 2.9 eq.) and iodine (132.4 mg, 0.52 mmol, 1.7 eq.) were added successively to a solution of alcohol **123** (80.3 mg, 0.3 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The mixture was stirred at ambient temperature until complete conversion of starting material as judged by TLC. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 5% Et_2O in pentane) to yield 96 mg (84%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.27 (m, 2H), 6.89 – 6.85 (m, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.33 (dq, *J* = 5.3, 1.0 Hz, 1H), 3.80 (s, 3H), 3.56 (qd, *J* = 6.2, 5.2 Hz, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.2, 130.8, 129.5(2C), 113.8(2C), 78.0, 76.5, 75.2, 71.6, 70.1, 66.9, 64.2, 55.4, 25.9(3C), 18.3, 16.4, 4.5, -4.5, -5.0. **IR** (film, cm^{-1}): 2955, 2931, 2857, 1514, 1249, 1095, 1036, 838, 779 **MS:** *m/z* calcd for $C_{22}H_{32}O_3Si_1Na_1$ 395.20112, found 395.20129 $[\alpha]_{20}$ = -12.7 (c = 0.4 , $CHCl_3$).

(2*S*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)octa-4,6-diyn-2-ol (105). DDQ (136 mg, 0.6 mmol, 1.5 eq.)



was added at 0 °C to a solution of PMB-ether **112** (150 mg, 0.4 mmol, 1.0 eq.) in CH_2Cl_2 (4.5 ml) and aq. pH~7 (0.5 mL) buffer. The solution was stirred at this temperature for 3 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the

organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the obtained crude material was purified by flash chromatography (SiO_2, 20% Et_2O in pentane) to affford 48 mg (72%) of the title compound as a yellow oil.

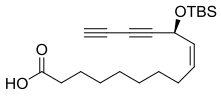
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (dq, *J* = 4.2, 1.0 Hz, 1H), 3.79 (qd, *J* = 6.3, 4.2 Hz, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 77.0, 73.4, 71.4, 70.9, 68.2, 63.9, 25.9(3C), 18.3, 17.7, 4.4, -4.4, -5.0 **IR** (film, cm^{-1}): 2930, 2857, 2258, 1472, 1361, 1318, 1252, 1067, 1024, 936, 913, 836, 777, 671 **MS:** *m*/*z* calcd for $C_{14}H_{24}O_2SiNa$ 275.14379, found 275.14378 $[\alpha]_{20}$ = -44.6 (c = 1.0, $CHCl_3$).

Methyl-(*S*,*Z*)-11-((*tert*-butyldimethylsilyl)oxy)-15-(trimethylsilyl)pentadeca-9-en-12,14 diynoate (113). A Schlenk flask was charged with Zn dust (65.4 mg, 1.0 mmol, 2.0 eq.) and iodine (12.3 mg, 0.05 mmol, 10 mol%). The flask was evacuated for ca. 30 seconds and backfilled with Ar before DMF (0.5 mL) was added. The resulting slurry was vigorously stirred until disappearance of the orange color (2-4 min). Methyl-8-iodooctanoate **107** (142.2 mg, 0.5 mmol, 1.0 eq.) was introduced via syringe and the solution was heated to 75 °C for 4 h. After reaching ambiente temperature the remaining zinc dust was allowed to settle (20 min) yielding a ca 1.0 M solution of organozinc compound.

A second Schlenk flask was charged with alkenyl iodide **90** (81.1 mg, 0.2 mmol, 0.4 eq.), $Pd(PPh_3)_2Cl_2$ (7.1 mg, 0.01 mmol, 5 mol%), anhydrous TMEDA (0,045 mL, 0.3 mmol, 1.1 eq.) and THF (0.5 mL). The mixture was stirred for 5 min before an aliquot of the freshly prepared organozinc solution (1.0 M in DMF, 0.28 mL, 0.28 mmol, 1.4 eq.) was added dropwise and the mixture was left to proceed at ambient temperature for 14 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and EtOAc (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 0.5% EtOAc in hexane) to yield 75.5 mg (68% yield based on NMR purity) of the title compound, together with a trace impurity which was best removed in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 – 5.41 (m, 2H), 5.17 – 5.14 (m, 1H), 3.66 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.10 – 2.00 (m, 2H), 1.67 – 1.57 (m, 2H), 1.41 – 1.33 (m, 2H), 1.34 – 1.24 (m, 6H), 0.89 (s, 9H), 0.18 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H) **^{13}C NMR** (400 MHz, $CDCl_3$): δ = 174.5, 132.0, 129.4, 87.7, 87.4, 78.3, 69.1, 59.5, 51.6, 34.3, 29.4, 29.3, 29.2, 29.1, 27.8, 25.9(3C), 25.1, 18.3, -0.3(3C), -4.4, -4.6 **IR** (film, cm^{-1}): 2952, 2930, 2857, 1742, 1252, 1075 **MS:** *m*/*z* calcd for $C_{25}H_{44}O_3Si_2Na$ 471.27210, found 471.27212 $[\alpha]_{20}$ = + 43.6 (c = 1.0, $CHCl_3$)

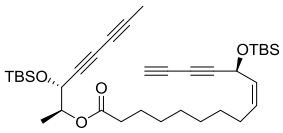
(*S*,*Z*)-11-((*tert*-Butyldimethylsilyl)oxy)pentadeca-9-en-12,14-diynoic acid (106). A flask open to air



was charged with methyl ester **113** (40.1 mg, 0.089 mmol, 1.0 eq.) and THF/H_2O (2:1, 1 mL). LiOH (6.5 mg, 0.271 mmol, 3.0 eq.) was added and the mixture was stirred at room temperature for 6.5 h until TLC indicated complete consumption of starting material. The pH was carefully adjusted to 3 – 4 by dropwise addition of aq. HCl (0.1 N). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 10% → 15% EtOAc in hexane) yielding 25.2 mg (78%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 – 5.43 (m, 2H), 5.17 – 5.14 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.18 (d, *J* = 1.0 Hz, 1H), 2.10 – 2.04 (m, 2H), 1.69 – 1.59 (m, 2H), 1.45 – 1.23 (m, 8H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 180.6, 132.3, 129.3, 77.0, 68.4, 67.9, 59.4, 33.9, 31.8, 29.3, 29.2, 29.2, 29.1, 27.9, 25.9(3C), 24.8, 18.4, -4.4, -4.6. **IR** (film, cm^{-1}): 2928, 2856, 1709, 1253, 1076, 838 **MS:** *m*/*z* calcd for $C_{21}H_{34}O_3SiNa$ 385.21693, found 385.21694 **$[\alpha]_{20}$** = + 62.1 (c = 1.0, $CHCl_3$).

Metathesis precursor (88). A Schlenk flask was charged with acid **106** (10.1 mg, 0.027 mmol, 1.0 eq.),



alcohol **105** (8.5 mg, 0.033 mmol, 1.25 eq.) and CH_2Cl_2 (1 mL). The resulting mixture was cooled to 0 °C, before EDC·HCl (16.1 mg, 0.08 mmol, 3.0 eq.) and DMAP (4.5 mg, 0.036 mmol, 1.3 eq.) were introduced. The mixture was stirred at ambient temperature for 16 h. The reaction was quenched with H_2O (5 mL) and excess base was neutralized with aq. HCl (0.5 N, 2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified via flash chromatography (SiO_2, 1% EtOAc in hexane) to yield 9.5 mg (58%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 – 5.40 (m, 2H), 5.19 – 5.12 (m, 1H), 4.93 (qd, *J* = 6.4, 4.2 Hz, 1H), 4.44 (dq, *J* = 4.3, 1.0 Hz, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.18 (d, *J* = 1.0 Hz, 1H), 2.10 – 2.02 (m, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.96 – 1.91 (m, 2H), 1.42 – 1.28 (m, 8H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 18H), 0.13 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.2, 132.5, 129.5, 77.0, 73.3, 72.8, 70.6, 68.4, 67.9, 65.6, 63.9, 59.4, 34.6, 29.3, 29.3, 29.2, 29.2, 27.9, 25.8(3C), 25.8(3C), 25.0, 18.3, 18.3, 14.9, 4.5, 1.1, -4.4, -4.5, -4.6, -5.1 (one carbon of diyne underneath $CDCl_3$) **IR** (film, cm^{-1}): 2856, 1737, 1258, 1072, 1033, 838, 780 **MS:** *m*/*z* calcd for $C_{35}H_{56}O_4Si_2Na$ 619.36095, found 619.36094 **$[\alpha]_{20}$** = + 21.2 (c = 0.3, $CHCl_3$).

4.4 Total synthesis of ivorenolide B

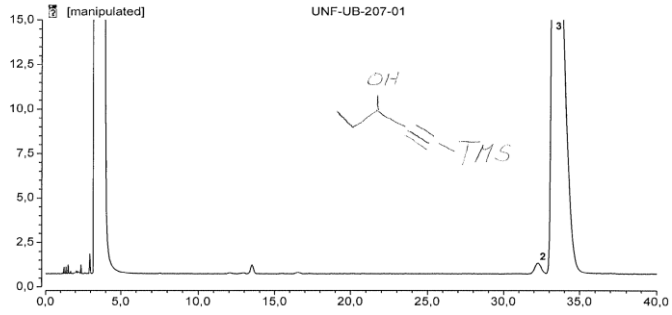
1-(Trimethylsilyl)pent-1-yn-3-one (118). A mixture of bis-trimethylsilylacetylene **119** (4.50 g, 26.5 mmol, 1.0 eq.) and propionyl chloride **117** (2.3 mL, 26.5 mmol, 1.0 eq.) were added dropwise at 0 °C to a suspension of $AlCl_3$ (3.53 g, 26.5 mmol, 1.0 eq.) in CH_2Cl_2 (80 ml). The mixture was stirred at 0 °C for 1 h, allowed to warm to ambient temperature and stirred for an additional hour. After cooling to -78 °C, aq. HCl (1.0 N, 20 mL) was added and the mixture was allowed to warm to ambient temperature. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield 4.01 g (97%) of the title compound as a light yellow liquid which was directly used for the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.58 (q, *J* = 7.4 Hz, 2H), 1.13 (t, *J* = 7.4 Hz, 3H), 0.24 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ= 188.6, 102.0, 97.8, 38.8, 8.1, -0.6(3C) **IR** (film, cm^{-1}): 1681, 1253, 1130, 846 **MS:** *m/z* calcd for $C_8H_{14}OSi$ 154.08125, found 154.08139.

(*S*)-1-(Trimethylsilyl)pent-1-yn-3-ol (120). Dichloro(*p*-cymene)ruthenium-(II)-dimer (25.1 mg, 0.041 mmol, 1.0 eq.), (*1S,2S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (30.0 mg, 0.082 mmol, 2.0 eq.), and KOH (32.5 mg, 0.579 mmol, 14.1 eq.) were added to a flask containing CH_2Cl_2 (1 mL). The orange mixture was stirred for 10 min, after which time a purple color appeared. H_2O (2 mL) and CH_2Cl_2 (2 mL) were added, the organic layer was separated and washed with H_2O (2 mL). The organic extracts were dried with CaH_2, filtered and the solvent was evaporated to afford the activated catalyst (50.3 mg) as a purple solid.

The catalyst was dissolved in *i*-PrOH (6 mL) and upon complete dissolution of the catalyst, the solution turned orange. Alkynone **118** (1.0 g, 6.5 mmol, 1.0 eq.) was added as solution in *i*-PrOH (3 mL) and the mixture was stirred at room temperature for 30 min. After complete consumption of starting material the solvent was carefully evaporated under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 3% Et_2O in pentane) to yield 902 mg (89%, 97% *ee*) of the title compound as a pale yellow liquid. The enantiomeric excess (*ee*) was measured by chiral GC/MS. See attachment below.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (t, *J* = 6.5 Hz, 1H), 1.80 – 1.63 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.17 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 106.7, 89.6, 64.3, 30.9, 9.6, 0.03(3C) **IR** (film, cm^{-1}): 2964, 1250, 1014, 967, 837 **MS:** *m/z* calcd for $C_8H_{16}OSiNa$ 179.08629, found 179.08626 $[\alpha]_{20}$ = -4.7 (c = 1.0, $CHCl_3$).



Sample: **UNF-UB-207-01**
Sequenz: **94408 UNF-UB Die_314**
Sequenz date: **19.01.15**
Instrument: **GC_412**
Measured: **19.01.15 10:48**
Processing M.: c17121 UNF-UB-207-01
Report-File: c17121 UNF-UB-207-01

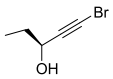
chirale Messung, ee-Verhältnis
Probe gelöst in 100µL Toluol dest.
Zuordnung siehe GC/MS c17121 UNF-UB-207-01;15/94408/K und Racematprobe UNF-UB-266-01;3 15/94409/K
GC-Analyse ELNA Nr. 314

No.	Ret.Time min	Rel.Area %	Peak Name
2	32,23	1,18	MG:156;1 c17121 =P3 UNF-UB-266-01
3	33,26	98,82	MG:156;2 c17121 = P4 UNF-UB-266-01

Instrument parameters:

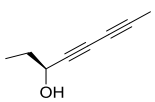
Column:	25,0 m	Hydrodex-ß-TBDAc-CD 0,25/ ?df G/625
Temperature:	220 / 65 iso / 350	
Gas:	0,50 bar	Hydrogen
Sample size:	0,2 µL	

(*S*)-1-Bromopent-1-yn-3-ol (116). NBS (710.0 mg, 3.98 mmol, 1.65 eq.) and $AgNO_3$ (89.0 mg, 0.52 mmol, 20 mol%) were added to a solution of pentynol **120** (376.1 mg, 2.41 mmol, 1.0 eq.) in acetone (6 mL). The resulting mixture was stirred at room temperature in the dark for 2 h. After cooling to 0 °C, the reaction was quenched with cold H_2O (10 mL) and diluted with Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$ and the solvent was carefully removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 4% → 5% Et_2O in pentane) to afford 345 mg (88%) of the title compound.



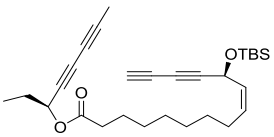
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (t, *J* = 6.4 Hz, 1H), 2.17 (s, 1H, OH) 1.77 – 1.69 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 81.1, 64.8, 45.2, 30.9, 9.5. **IR** (film, cm^{-1}): 3332, 2969, 2936, 2878, 2210, 1462, 1336, 1117, 1100, 1054 **MS:** *m/z* calcd for C_5H_7BrONa 184.95732, found 184.95732 $[\alpha]_{20}$ = -4.3 (c = 1.0, $CHCl_3$).

(*S*)-Octa-4,6-diyn-3-ol (115). Prepared according to **GP-2:** Bromo pentynol **116** (320.3 mg, 1.9 mmol, 1.0 eq.), aq. $BuNH_2$ (30% in water, 4 mL), CuCl (19.0 mg, 0.19 mmol, 10 mol%), liquid propyne (0.1 mL). The crude material was purified by flash chromatography (SiO_2, 10% → 15% Et_2O in pentane) to yield 144 mg (62%) of the title compound as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (t, *J* = 6.8 Hz, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.89 (s, 1H, OH) 1.78 – 1.67 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 75.8, 70.1, 66.0, 64.2, 63.8, 30.9, 9.5, 4.5. **IR** (film, cm^{-1}): 3362, 2970, 2936, 1460, 1333, 1379, 1335, 1280, 1238, 1097, 1047 **MS:** *m*/*z* calcd for $C_8H_{10}ONa$ 145.06245, found 145.06238 $[\alpha]_{20}$ = -5.5 (c = 1.0, $CHCl_3$).

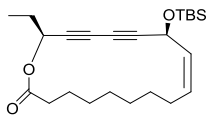
(*S*)-Octa-4,6-diyn-3-yl (*S*,*Z*)-11-((*tert*-butyldimethylsilyl)oxy)pentadeca-9-en-12,14-diynoate (114).



A 10 mL Schlenk flask was charged with acid **106** (17.0 mg, 0.046 mmol, 1.0 eq.), alcohol **115** (6.5 mg, 0.053 mmol, 1.15 eq.) and CH_2Cl_2 (1 mL). The mixture was cooled to 0 °C before EDC·HCl (22.1 mg, 0.115 mmol, 2.5 eq.) and DMAP (6.5 mg, 0.069 mmol, 1.5 eq.) were added and the mixture was stirred at ambient temperature for 16 h. The reaction was quenched with H_2O (2 mL) and excess base was neutralized with aq. HCl (0.5 N). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified via flash chromatography (SiO_2, 1% EtOAc in hexane) to yield 13.2 mg (62%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 – 5.43 (m, 2H), 5.34 (td, *J* = 6.4, 1.0 Hz, 1H), 5.17 – 5.14 (m, 1H), 2.35 – 2.29 (m, 2H), 2.18 (d, *J* = 1.0 Hz, 1H), 2.08 – 2.04 (m, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.78 (qd, *J* = 7.4, 6.4 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.41 – 1.35 (m, 2H), 1.30 – 1.24 (m, 6H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.8, 132.3, 129.3, 77.0, 72.4, 70.4, 68.4, 67.9, 65.2, 63.8, 59.4, 34.4, 29.9, 29.3, 29.2, 29.2, 29.1, 28.2, 27.9, 25.9(3C), 25.0, 18.4, 9.5, 4.4, 1.2, -4.4, -4.6 **IR** (film, cm^{-1}): 2929, 2856, 1739, 1252, 1073, 837, 805 **MS:** *m*/*z* calcd for $C_{29}H_{42}O_3SiNa$ 489.27961, found 489.27954 $[\alpha]_{20}$ = + 18.3 (c = 1.0, $CHCl_3$).

(12*S*,17*S*,*Z*)-12-((*tert*-Butyldimethylsilyl)oxy)-17-ethyloxacycloheptadeca-10-en-13,15-diyn-2-one

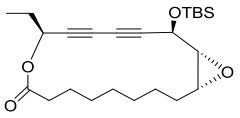


(121). Cyclization was done according to **GP-1:** Substrate **114** (20 mg, 0.042 mmol, 1.0 eq.), 4 Å /5 Å MS (100 mg , each), **C5** 2*(8.7 mg, 0,008 mmol, 20 mol%), toluene (4.4 mL), 22 h, rt. The crude material was purified by flash chromatography (SiO_2, 0.3% → 2% EtOAc in hexane). The title compound was obtained contaminated with traces of triphenylsilanol 17.8 mg (comprising 14.2 mg of product, 82% calculated by NMR) which were best removed after the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 – 5.42 (m, 2H), 5.28 (td, *J* = 6.7, 1.0 Hz, 1H), 5.21 (d, *J* = 4.7 Hz, 1H), 2.39 – 2.27 (m, 2H), 2.10 – 2.01 (m, 2H), 1.83 – 1.75 (p, 2H), 1.72 – 1.60 (m, 2H), 1.44 – 1.29 (m, 8H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ =

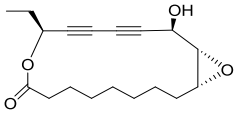
173.5, 132.1, 130.8, 80.9, 77.7, 69.8, 68.3, 65.3, 59.9, 34.6, 30.4, 29.7, 29.3, 28.7, 27.3, 26.5, 25.9(3C), 18.4, 9.6, 1.2, -4.5, -4.8 .**IR** (film, cm^{-1}): 2929, 2856, 1741, 1257, 1077, 909, 836 **MS:** *m*/*z* calcd for $C_{24}H_{38}O_3Si$ 402.25897, found 402.25902 $[\alpha]_{20}$ = - 21.4 (c = 1.0, $CHCl_3$).

(1*R*,2*R*,7*S*,17*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-7-ethyl-8,18-dioxabicyclo[15.1.0]octadeca-3,5-diyn-9-one (121b). Alkene **121** (15.1 mg, 0.04 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL), cooled to 0 °C and *m*-CPBA (26.0 mg, 0.12 mmol, 4.0 eq.) was added in one portion. The cooling bath was removed and the mixture was stirred at ambient temperature for 8 h. The reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 3% → 5% EtOAc in hexane) to afford 13.1 mg (80%) of the title compound as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.28 (td, *J* = 6.7, 0.9 Hz, 1H), 4.23 (dd, *J* = 7.2, 0.9 Hz, 1H), 3.15 (dd, *J* = 7.3, 4.3 Hz, 1H), 2.96 (ddd, *J* = 11.0, 4.3, 2.9 Hz, 1H), 2.47 – 2.43 (m, 1H), 2.41 – 2.37 (m, 1H), 2.04 – 1.96 (m, 2H), 1.82 (q, *J* = 7.3 Hz, 2H), 1.75 – 1.61 (m, 2H), 1.46 – 1.22 (m, 8H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 9H), 0.13 (d, *J* = 2.2 Hz, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.2, 77.9, 69.8, 69.1, 65.1, 63.9, 61.5, 56.5, 34.5, 30.3, 30.0, 29.1, 28.0, 27.2, 26.4, 25.9(3C), 25.8, 18.4, 9.6, 1.2, -4.7, -4.8 **IR** (film, cm^{-1}): 2932, 1731, 1279, 1170 **MS:** *m*/*z* calcd for $C_{24}H_{38}O_4SiNa$ 441.24348, found 441.24316 $[\alpha]_{20}$ = -14.3 (c = 1.0, $CHCl_3$).

Ivorenolide B (33). TBAF (1.0 M in THF, 0.043 mL, 0.043 mmol, 1.5 eq.) was added dropwise at 0 °C to a solution of TBS-ether **121b** (12.1 mg, 0.029 mmol, 1.0 eq.) in THF (1.0 mL). After stirring for 30 min, the yellow solution was quenched with sat. aq. NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 10% → 15% EtOAc in hexane) yielding 6.5 mg (74%) of the title compound as a colorless oil.

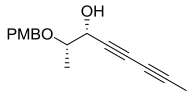


^{1}H NMR (600 MHz, C_5D_5N)**:** δ = 8.42 (s, 1H, OH) 5.49 (td, *J* = 6.7, 0.9 Hz, 1H), 4.86 (d, *J* = 7.6, Hz, 1H), 3.59 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.08 (ddd, *J* = 10.8, 4.3, 2.9 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.00 – 1.94 (m, 1H), 1.81 – 1.76 (m, 2H), 1.71 – 1.64 (m, 1H), 1.63 – 1.56 (m, 1H), 1.55 – 1.51 (m, 1H), 1.48 – 1.41 (m, 1H) 1.36 – 1.17 (m, 7H) 0.92 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (600 MHz, C_6D_5N): δ = 173.0, 80.4, 78.8, 69.8, 69.8, 65.6, 62.7, 61.9, 56.7, 34.7, 30.6, 30.4, 29.5, 28.5, 27.5, 26.8, 26.2, 9.7 **IR** (film, cm^{-1}): 2928, 2857, 1741, 1462, 1236, 1085, 1041, 981 **MS:** *m/z* calcd for $C_{18}H_{24}O_4Na$ 327.15688, found 327.15668 $[\alpha]_{20}$ = - 9.3 (c = 0.2, MeOH).

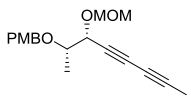
4.5 Total synthesis of ivorenolide A

(2S,3R)-2-((4-Methoxybenzyl)oxy)octa-4,6-diyn-3-ol (123). A 25 mL Schlenk flask was charged with (*R*,*R*)-ProPhenol (83.2 mg, 0.13 mmol, 10 mol%), Ph_3P=O (72.5 mg, 0.26 mmol, 20mol%) and toluene (5 mL). The solution was stirred for 10 min at room temperature, before $ZnMe_2$ (1.2 M in toluene, 3.2 mL, 3.86 mmol, 3.0 eq.) was introduced followed by dropwise addition of diyne **122** (0.25 g, 3.86 mmol, 3.0 eq.). Stirring was continued for 45 min at ambient temperature before the solution was cooled to 0 °C and aldehyde **110** (0.25 g, 1.28 mmol, 1.0 eq.) was added. The reaction was left to proceed for 16 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl (15 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the obtained crude material was purified by flash chromatography (SiO_2, 20% Et_2O in pentane) yielding 205 mg (61%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 – 4.41 (m, 1H), 3.81 (s, 3H), 3.65 (qd, *J* = 6.4, 3.7 Hz, 1H), 2.41 (s, broad 1H, OH), 1.93 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), **^{13}C NMR** (101 MHz, $CDCl_3$): δ =130.1, 129.6(2C), 114.0(2C), 76.5, 72.9, 71.2, 63.9, 70.9, 65.8, 55.4, 15.0, 4.5, 1.2 (1C underneath $CDCl_3$ peak) **IR** (film, cm^{-1}): 2932, 1612, 1513, 1302, 1248, 1175, 1083, 822: **MS:** *m/z* calcd for $C_{16}H_{18}O_3Na_1$ 281.114860 found 281.114814 $[\alpha]_{20}$ = -11.2 (*c* = 1.0, $CHCl_3$).

1-Methoxy-4-((((2*S*,3*R*)-3-(methoxymethoxy)octa-4,6-diyn-2-yl)oxy)methyl)benzene (123b).

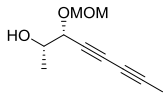


MOM-Cl (0.061 mL, 0.81 mmol, 1.76 eq.) and *i*-Pr_2NEt (0.174 mL, 1.0 mmol, 2.2 eq.) were added at 0 °C to a solution of alcohol **123** (120.0 mg, 0.46 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The cooling bath was removed and the mixture was stirred for 16 h at room temperature. The reaction was quenched with H_2O (10 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the obtained crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to afford 118 mg (85%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.30 – 7.26 (m, 2H), 6.89 – 6.85 (m, 2H), 4.91 (d, *J* = 6.7 Hz, 1H), 4.65 – 4.52 (m, 3H), 4.45 (dd, *J* = 4.2, 1.1 Hz, 1H), 3.80 (s, 3H), 3.67 (qd, *J* = 6.4, 4.2 Hz, 1H), 3.38 (s, 3H), 1.94

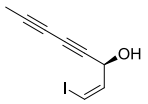
(d, *J* = 1.0 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.3, 130.5, 129.5(2C), 113.9(2C), 94.6, 76.0, 76.3, 72.0, 71.6, 71.3, 68.8, 64.0, 55.9, 55.4, 16.0, 4.5. **IR** (film, cm^{-1}): 2932, 1513, 1247, 1148, 1097, 1023, 808 **MS:** *m*/*z* calcd for $C_{18}H_{22}O_4Na$ 325.14096, found 325.14103 $[\alpha]_{20}$ = -43.0 (c = 0.5, $CHCl_3$).

(2*S*,3*R*)-3-(Methoxymethoxy)octa-4,6-diyn-2-ol (124). DDQ (163 mg, 0.72 mmol, 2.0 eq.) was added at 0 °C to a solution of alcohol **123b** (110 mg, 0.36 mmol, 1.0 eq.) dissolved in CH_2Cl_2 (4.5 ml) and aq. pH~7 buffer (0.5 mL). The solution was stirred at 0 °C for 3 h, before quenched with sat. aq. NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the obtained crude material was purified by flash chromatography (SiO_2, 20% Et_2O in pentane) to yield 48 mg (72%) of the title compound as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.92 (d, *J* = 6.8 Hz, 1H), 4.66 (dd, *J* = 6.8, 0.5 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.00 – 3.91 (m, 1H), 3.39 (s, 3H), 2.32 (d, *J* = 5.6 Hz, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 94.6, 77.2, 72.6, 71.5, 70.5, 69.5, 63.7, 56.0, 18.3, 4.4. **IR** (film, cm^{-1}): 3441, 2892, 2258, 1098, 1026 **MS:** *m*/*z* calcd for $C_{10}H_{14}O_3Na$ 205.08373, found 205.08351 $[\alpha]_{20}$ = -59.1 (c = 0.5, $CHCl_3$).

(*S*,*Z*)-1-Iodooct-1-en-4,6-diyn-3-ol (125). Procedure 1: A 25 mL Schlenk flask was charged with $Ph_3P{=}O$ (42.0 mg, 0.15 mmol, 20 mol%), (*R*,*R*)-ProPhenol (48.1 mg g, 0.076 mmol, 10 mol%) and toluene (3 mL). The solution was stirred for 5 min, before diyne **122** (0.16 g, 2.5 mmol, 3.3 eq.) and $ZnMe_2$ (1.2 M in toluene, 1.62 mL, 1.95 mmol, 2.5 eq.) were added The solution was stirred for 1 h at room temperature before it was cooled to 0 °C and aldehyde **93** (1.4 mL of previously prepared solution, 140 mg, 0.76 mmol, 1.0 eq.) was introduced. The mixture was stirred for 16 h at 0 °C before quenched with sat. aq. NH_4Cl (5 mL). The suspension was stirred for 1 h at ambient temperature until clear phase separation was observed. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 15% Et_2O in pentane) to give 0.18 g (86%, 70% *ee*) of the title compound.



Procedure2: A 25 mL Schlenk flask was charged with diyne **122** (0.166g, 2.6 mmol, 4.0 eq.) dissolved in Et_2O (6 mL). (*R*)-BINOL (0.074 g, 0.26 mmol, 40 mol%), Cy_2NH (0.006 mL, 0.0325 mmol, 5 mol%), and $ZnEt_2$ (15% in toluene, 1.76 mL, 1.95 mmol, 3.0 eq.) were successively added at ambient

temperature and the solution was stirred for 16 h at room temperature. Ti(*i*-PrO)$_4$ (1.9 mL, 0.65 mmol, 1.0 eq.) was added and stirring was continued for 30 min. Aldehyde **93** (1.2 mL of previously prepared solution, 120 mg, 0.65 mmol, 1.0 eq.) was added dropwise causing a immediate color change from yellow to dark red. The mixture was stirred for 3 h at room temperature, before quenched with sat. aq. NH_4Cl (5 mL). The slurry was stirred for 1 h at ambient temperature until clear phase separation was observed. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the crude matieral was purified by flash chromatography (SiO_2, 15% Et_2O in pentane) yielding 0.14 g (90%, 63% *ee*) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.53 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.38 (t, *J* = 7.7 Hz, 1H), 5.16 (ddt, *J* = 6.7, 4.0, 1.1 Hz, 1H), 2.11 (d, *J* = 5.0 Hz, 1H), 1.94 (d, *J* = 1.1 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.1, 84.9, 78.6, 72.4, 71.2, 65.9, 63.6, 4.5. **IR** (film, cm^{-1}): 3333, 2257, 1607, 1427, 1261, 1029, 1008, 933, 735, 594 **MS:** *m*/*z* calcd for C_8H_7IONa 268.94355, found 268.94338 **$[\alpha]_{20}$** = +275.9 (c = 1.0, $CHCl_3$).

The absolute configuration was determined as (*S*) by the advanced Mosher Ester method.[143] The *ee* of **125** was determined by integration of H_a in the spectra of the derived (*S*)-MTPA ester.

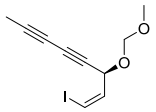
(*R*)-MTPA-Ester: (*S*)-*α*-Methoxy-*α*-trifluoromethyl phenylacetic acid chloride (10.0 mg, 0.064 mmol, 3.2 eq.) was added to a solution of alcohol (5.0 mg, 0.02 mmol, 1.0 eq.), and pyridine (0.063 mL, 0.08 mmol, 4.0 eq.) in CH_2Cl_2 (0.5 ml). The mixture was stirred for 16 h at room temperature and quenched with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL), the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was of sufficient purity for the determination of the absolute configuration.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.55 – 7.50 (m, 2H), 7.44 – 7.39 (m, 3H), 6.76 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.47 (t, *J* = 7.9 Hz, 1H), 6.22 (dt, *J* = 8.2, 1.0 Hz, 1H), 3.56 (d, *J* = 1.2 Hz, 3H), 1.96 (d, *J* = 1.2 Hz, 3H).

(*S*)-MTPA-Ester. Prepared analogously, using (*R*)-*α*-methoxy-*α*-trifluoromethyl phenylacetic acid chloride as the reagent. Reaction was conducted on the same scale as described above.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 – 7.47 (m, 2H), 7.40 (qd, *J* = 4.2, 1.9 Hz, 3H), 6.72 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.39 (t, *J* = 7.9 Hz, 1H), 6.26 (dt, *J* = 8.1, 1.0 Hz, 1H), 3.60 (d, *J* = 1.2 Hz, 3H), 1.96 (d, *J* = 1.1 Hz, 3H).

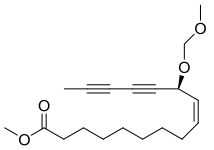
(*S*,*Z*)-1-Iodo-3-(methoxymethoxy)octa-1-en-4,6-diyne (126). *i*-Pr_2NEt (0.87 mL, 5.0 mmol, 6.8 eq.)



and MOM-Cl (0.26 mL, 3.5 mmol, 4.8 eq.) were added at 0 °C to a solution of alcohol **125** (180 mg, 0.73 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The cooling bath was removed and the mixture was stirred for 16 h at room temperature until complete consumption of starting material. The reaction was quenched with H_2O (5 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure. Purification of the crude material by flash chromatography (SiO_2, 5% Et_2O in pentane) yielded 181 mg (85%) of the title compound as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.53 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.38 (t, *J* = 7.7 Hz, 1H), 5.16 (ddt, *J* = 6.7, 4.0, 1.1 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 3.41 (s, 3H), 1.94 (d, *J* = 1.1 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.5, 93.9, 85.6, 78.0, 71.7, 70.7, 68.8, 63.7, 56.1, 4.5. **IR** (film, cm^{-1}): 2887, 2256, 1262, 1147, 1094, 1053, 1008, 964, 926, 735 **MS:** *m/z* calcd for $C_{10}H_{11}IO_2Na$ 312.97036, found 312.96960 $[\alpha]_{20}$ = +172.2 (c = 1.0, $CHCl_3$).

Methyl (*S*,*Z*)-11-(methoxymethoxy)hexadeca-9-en-12,14-diynoate (127). A 10 mL Schlenk flask was



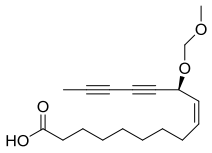
charged with Zn dust (56.1 mg, 0.86 mmol, 1.3 eq.) and anhydrous LiCl (28.0 mg, 0.66 mmol 1.0 eq.). Vacuum (0.01 mbar) was applied and the mixture was dried for 5 min at 150 °C. Once the flask had reached ambient temperature and was flushed with Ar, THF (0.3 mL) was introduced and the slurry was heated to 60 °C before 1,2-dibromethan (0.01 mL) was added. After stirring for 5 min, TMS-Cl (0.01 mL) was added followed by methyl 8-iodooctanoate **107** (187 mg, 0.66 mmol, 1.0 eq.) as a solution in THF (0.3 mL). The suspension was vigorously stirred for 5 h at 45 °C and at room temperature overnight. GC/MS revealed ~90% conversion (prolonged stirring did not further increase conversion). Stirring was stopped and the remaining Zn-dust was allowed to settle (~ 1 h) yielding a 1.0 M solution of organozinc compound.

A second Schlenk flask was charged with $Pd(PPh_3)_2Cl_2$ (3.4 mg, 0.005 mmol, 4 mol%), alkenyl iodide **126** (40.0 mg, 0.13 mmol, 1.0 eq.), anhydrous TMEDA (0.025 mL, 0.17 mmol, 1.25 eq.) and THF (0.5 mL). The resulting light yellow solution was stirred for 10 min at room temperature, then heated to 50 °C before an aliquot of the freshly prepared organozinc solution (1.0 M in THF, 0.26 mL, 0.26 mmol, 2.0 eq.) was added dropwise resulting in a color change from yellow to deep orange. The mixture was stirred for 1 h at 50 °C, then allowed to cool down to ambient temperature and quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with Et_2O (10 mL) and the organic layer was separated. The aqueous phase was extracted with MTBE (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude

material was purified by flash chromatography (SiO_2, 5% →10% EtOAc in hexane) to afford 32.8 mg (75%) of the title compound.

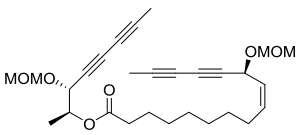
^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.67 – 5.58 (m, 1H), 5.50 – 5.42 (m, 1H), 5.14 (dt, *J* = 8.7, 1.1 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.66 (s, 3H), 3.37 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.15 – 2.06 (m, 2H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.38 (t, *J* = 6.6 Hz, 2H), 1.34 – 1.25 (m, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.1, 134.5, 125.8, 93.2, 72.7, 70.3, 63.6, 61.1, 55.5, 51.3, 33.9, 29.0, 28.9, 28.8, 27.4, 24.7, 22.2, 13.9, 4.1. **IR** (film, cm^{-1}):2929, 2856, 1737, 1436, 1150, 1094, 1025, 923 **MS:** *m*/*z* calcd for $C_{19}H_{28}O_4Na$ 343.18793, found 343.18798 **$[\alpha]_{20}$** = +45.1 (c = 1.0, $CHCl_3$).

(*S*,*Z*)-11-(Methoxymethoxy)hexadeca-9-en-12,14-diynoic acid (128). A solution of LiOH (0. 5 M in water, 2 mL, 1.0 mmol, 9.1 eq.) was added to a solution of methyl-ester **127** (34.0 mg, 0.11 mmol, 1.0 eq.) in THF/MeOH (2:1, 4 mL). The mixture was stirred at room temperature for 4 h until complete consumption of starting ester as indicated by TLC. The solution was carefully acidified with aq. HCl (3.0 N) and diluted with Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure affording 30 mg (89%) of the title compound as a pale yellow oil which was directly used for the next step.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.63 (dtd, *J* = 10.7, 7.5, 1.1 Hz, 1H), 5.47 (ddt, *J* = 10.4, 8.6, 1.5 Hz, 1H), 5.14 (dt, *J* = 8.6, 1.1 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.14 – 2.06 (m, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.68 – 1.59 (m, 2H), 1.42 – 1.27 (m, 7H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 179.0, 134.7, 126.0, 93.4, 77.2, 72.8, 70.5, 63.8, 61.3, 55.6, 33.8, 29.1, 28.9, 28.9(2C), 27.5, 24.6, 4.3 **IR** (film, cm^{-1}):2928, 2855, 1707, 1150, 1093, 1025, 922 **MS:** *m*/*z* calcd for $C_{18}H_{25}O_4$ 305.17603 found 305.17584 **$[\alpha]_{20}$** = +33.6 (c = 1.0, $CHCl_3$).

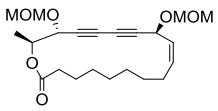
(2*S*,3*R*)-3-(Methoxymethoxy)octa-4,6-diyn-2-yl (S,Z)-11-(methoxymethoxy)hexadeca-9-en-12,14-diynoate (129). Et_3N (0.02 mL, 0.14 mmol, 1.5 eq.) and Yamaguchi-reagent (29.4 mg, 0.12 mmol, 1.25 eq.) were added at 0 °C to a solution of acid **128** (29.0 mg, 0.095 mmol, 1.0 eq.) in toluene (1 mL). The mixture was stirred at this temperature until TLC indicated complete conversion of starting material. A solution of alcohol **124** (17.1 mg, 0.094 mmol, 1.0 eq.) in toluene (1 mL) and DMAP (5.7 mg 0.047 mmol, 0.5 eq.) were added and the mixture was stirred at ambient temperature for 2 h. The reaction was quenched at 0 °C with aq. HCl (1.0 N, 5 mL) and diluted with EtOAc (10 mL). The aqueous phase



was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 10% → 20% Et_2O in hexane) yielding 34 mg (79 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.63 (dtd, *J* = 10.7, 7.5, 1.1 Hz, 1H), 5.46 (ddt, *J* = 10.3, 8.7, 1.5 Hz, 1H), 5.14 (dt, *J* = 8.7, 1.1 Hz, 1H), 5.07 (qd, *J* = 6.5, 4.0 Hz, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9, 0.6 Hz, 2H), 4.44 (dd, *J* = 4.0, 1.1 Hz, 1H), 3.37 (d, *J* = 2.0 Hz, 6H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.14 – 2.06 (m, 2H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.65 – 1.58 (m, 2H), 1.37 (t, *J* = 6.4 Hz, 2H), 1.35 – 1.26 (m, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.1, 134.9, 126.1, 94.4, 93.5, 77.3, 77.2, 72.9, 71.9, 70.6, 70.5, 68.1, 63,9 63.7, 61.3, 55.8, 55.8, 34.5, 29.4, 29.2, 29.1, 29.1, 27.7, 25.0, 15.4, 4.4, 4.4, 1.2. **IR** (film, cm^{-1}):2928, 2855, 1707, 1150, 1093, 1025, 922 **MS:** *m*/*z* calcd for $C_{28}H_{38}O_6Na$ 493.25662, found 493.25606 **$[\alpha]_{20}$** = -6.5 (c = 0.5, $CHCl_3$).

(12*S*,17*R*,18*S*,*Z*)-12,17-Bis(methoxymethoxy)-18-methyloxacyclooctadeca-10-en-13,15-diyn-2-one (130). Cyclization was done according to **GP-1:** Substrate **129** (10 mg, 0.021 mmol, 1.0 eq.), 5 Å MS (45 mg), **C5** (7.6 mg, 0,007 mmol, 35 mol%), toluene (2.7 mL), 3 h, 60 °C. The crude material was purified by flash chromatography (SiO_2 10% EtOAC in hexane) yielding 3.1 mg (39%) of the title compound. Reaction performed at 110 °C on the same scale delivered 2.7 mg (33%) of desired product.

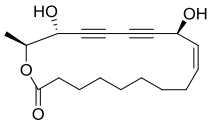


Procedure 2: A solution of ligand **L1** (9.7 mg, 0.011 mmol) and catalyst **C7** (6.5 mg, 0.01 mmol) in toluene (1 mL) was vigorously stirred for 10 min, to give a clear brown stock solution of the active catalyst (0.01 mmol/mL) which has to be used within ca 30 - 40 min before it turns dark.

A 25 mL Schlenk flask was charged with 5 Å MS (65 mg). The flask was evacuated and the molecular sieves were dried for 5 min (350°C, heat gun). The flask was backfilled with Ar and substrate **129** (15.0 mg, 0.031 mmol, 1.0 eq.) was introduced as a solution in toluene (3.4 mL). After stirring for 1 h at room temperature, the flask was immersed into an oil bath at 60 °C and an aliquot of the catalyst stock solution (0.01 mmol/mL in toluene, 0.62 mL, 0.0062 mmol, 20 mol%) was added. The mixture was stirred at 60 °C for 45 min before it was allowed to cool down to room temperature and filtrated through a pad of SiO_2, which was rinsed with EtOAc (30 mL). The solvent was evaporated and the crude material was directly loaded on column. Purification by flash chromatography (SiO_2, 10% EtOAC in hexane) yielded 9.7 mg (78%) of the title compound. Reaction performed at 110 °C on a 0.0149 mmol scale delivered 9.1 mg (75%) of the title compound.

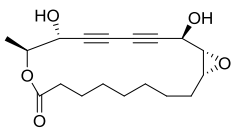
^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.59 (tdd, *J* = 10.1, 5.8, 1.1 Hz, 1H)**,** 5.53 – 5.44 (m, 1H), 5.19 (d, *J* = 8.0 Hz, 1H), 5.07 – 5.00 (m, 1H), 4.90 (d, *J* = 6.9 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.61 (dd, *J* = 6.9, 5.6 Hz, 2H), 4.28 (dd, *J* = 7.2, 0.9 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.39 – 2.23 (m, 2H), 2.20 – 2.08 (m, 2H), 1.75 – 1.42 (m, 4H), 1.41 – 1.28 (m, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.0, 134.6, 126.5, 94.5, 93.7, 75.8(2C), 70.7, 70.5, 69.6, 69.1, 61.7, 56.1, 55.8, 35.5, 29.7, 29.6, 28.8, 28.7, 28.1, 25.5, 17.6. **IR** (film, cm^{-1}): 2932, 2857, 1738, 1151, 1098, 1027 **MS:** *m*/*z* calcd for $C_{22}H_{32}O_6Na$ 415.20942, found 415.20911 $[\alpha]_{20}$ = -61.9 (0.7, $CHCl_3$).

(12*S*,17*R*,18*S*,*Z*)-12,17-Dihydroxy-18-methyloxacyclooctadeca-10-en-13,15-diyn-2-one (130b). A solution of bis-MOM-diol **130** (9.0 mg, 0.023 mmol, 1.0 eq.) in EtOH (1 mL) was treated with aq. HCl (3.0 N, 0.04 mL, 0.12 mmol, 5.0 eq.) at 70 °C for 4 h. Since TLC revealed incomplete conversion, additional aq. HCl (3.0 N, 0.04 mL, 0.12 mmol, 5.0 eq.) was added and stirring continued for 6 h at 70 °C. The mixture was allowed to cool down to ambient temperature, before it was neutralized with sat. aq. $NaHCO_3$ (10 mL) and diluted with Et_2O (10 mL). The aqueous layer was extracted with MTBE (3 x 5 mL), the combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 40% → 50% Et_2O in pentane) to give 4.4 mg (64%) of the title compound as a colorless oil. Small amounts of unreacted starting material were recovered and resubjected to MOM-cleavage under the same conditions.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.59 – 5.46 (m, 2H), 5.27 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.92 (qd, *J* = 6.5, 4.6 Hz, 1H), 4.39 – 4.29 (m, 1H), 3.17 (d, *J* = 8.1 Hz, 1H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.16 – 2.10 (m, 1H), 1.75 – 1.56 (m, 2H), 1.41 – 1.18 (m, 11H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.6, 133.6, 128.6, 79.0, 77.3, 74.2, 70.3, 69.1, 67.0, 59.1, 35.5, 29.7, 29.6, 28.8(2C), 28.2, 25.6, 17.5 **IR** (film, cm^{-1}): 3383, 2929, 2856, 1713, 1262, 1046 **MS:** *m*/*z* calcd for $C_{18}H_{24}O_4Na$ 327.15659, found 327.15668 $[\alpha]_{20}$ = + 61.2 (c = 0.5, $CHCl_3$).

Ivorenolide A (32). *m*-CPBA (8.6 mg, 0.055 mmol, 5.0 eq.) was added at 0 °C to a solution of olefin **130b** (3.4 mg, 0.011 mmol, 1.0 eq.) in of CH_2Cl_2 (1 mL). The mixture was stirred for 30 min at 0 °C, followed by stirring for 6 h at ambient temperature until TLC showed complete conversion of starting material. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and the organic layer was separated. The aqueous layer was extracted with MTBE (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the obtained crude material was

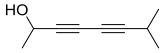


purified by flash chromatography (SiO_2, 30% → 40% → 50% MTBE in pentane) to afford 2.5 mg (74%) of the title compound as white crystals.

^{1}H NMR (600 MHz, C_5D_5N): δ = 8.27 (s, (br) 2H, OH), 5.44 (dq, *J* = 8.4, 6.2 Hz, 1H), 4.79 – 4.67 (m, 2H), 3.51 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.09 (ddd, *J* = 10.1, 4.3, 3.0 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.01 – 1.95 (m, 1H), 1.85 – 1.76 (m, 1H), 1.56 – 1.50 (m, 1H), 1.48 (d, *J* = 6.2 Hz, 3H), 1.43 (ddd, *J* = 11.6, 9.3, 6.2 Hz, 2H), 1.37 – 1.20 (m, 7H) **^{13}C NMR** (151 MHz, C_5D_5N): δ = 172.9, 81.3, 78.5, 72.8, 70.3, 68.7, 65.5, 62.2, 61.1, 57.0, 35.0, 30.0, 29.8, 29.1, 28.6, 26.2, 25.6, 17.7. **IR** (film, cm^{-1}): 3394, 2928, 2856, 1735, 1458, 1260, 1046, 797 **MS:** *m/z* calcd for $C_{18}H_{24}O_5Na$ 343.15156, found 343.15159 **$[\alpha]_{20}$** = +39.2 (0.2, MeOH).

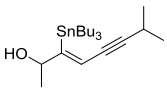
4.6. Preliminary studies

7-Methylocta-3,5-diyn-2-ol (245). Prepared according to **GP-2**: bromo alkyne **244** (900 mg, 6.0 mmol, 1.0 eq.), aq. $BuNH_2$ (30% in water, 10 mL), CuCl (60 mg, 0.6 mmol, 10 mol%), 3-methylbut-1-yne **243** (408 mg, 6.0 mmol, 1.0 eq.). Flash chromatography (SiO_2, 10% Et_2O in pentane) yielded 670 mg (81%) of the title compound.



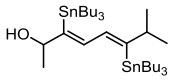
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (qd, *J* = 6.6, 0.9 Hz, 1H), 2.63 (pd, *J* = 6.9, 0.9 Hz, 1H), 1.90 (s, broad, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 87.0, 77.9, 69.1, 63.6, 58.8, 24.1, 22.4(2C), 21.1. **IR** (film, cm^{-1}): 2975, 2935, 1719, 1366, 1317, 1233, 1155, 1104, 1076, 1019 **MS:** *m/z* calcd for $C_9H_{12}O$ 136.08886, found 136.08882.

(*Z*)-7-Methyl-3-(tributylstannyl)oct-3-en-5-yn-2-ol (246). A 10 mL Schlenk flask was charged with complex **C8b** (3.0 mg, 0.01 mmol, 5 mol%) and freshly degassed CH_2Cl_2 (1 mL). Diyne **245** (27.1 mg, 0.2 mmol, 1.0 eq.) was added in one portion and the mixture was stirred for 5 min before Bu_3SnH (0.062 mL, 0.23 mmol, 1.15 eq.) dissolved in CH_2Cl_2 (1 mL) was added via syringe pump over the course of 1 h. After complete addition the mixture was further stirred for 10 min before the solvent was removed under reduced pressure and the obtained crude material was directly loaded on column (SiO_2, 0.5% EtOAc in hexane) to yield 62.8 mg (74%) of the title compound.



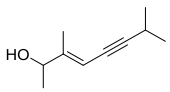
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (dd, *J* = 2.1, 1.3 Hz, J_{Sn-H} = 111.8, 1H), 4.41 (qdd, J = 6.3, 3.5, 1.2 Hz, 1H), 2.68 (pd, *J* = 6.9, 2.1 Hz, 1H), 1.58 – 1.48 (m, 6H), 1.38 – 1.27 (m, 6H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 6H), 1.09 – 1.03 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.5, 118.1, 97.3, 79.8, 74.9, 29.3(3C), 27.6(3C), 23.9, 22.9, 21.3, 13.9 (3C), 12.4, 10.7(3C) **^{119}Sn NMR** (149 MHz, $CDCl_3$): δ = -49.38 **IR** (film, cm^{-1}): 2956, 2924, 2871, 2854, 1463 **MS:** *m/z* calcd for $C_{21}H_{40}OSnNa$ 451.19948, found 451.19926.

(3*Z*,5*Z*)-7-Methyl-3,6-bis(tributylstannyl)octa-3,5-dien-2-ol (247).



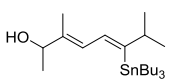
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, *J* = 10.6, 1.1 Hz, 1H), 6.66 (dd, *J* = 10.6, 1.1 Hz, 1H), 4.48 – 4.39 (m, 1H), 2.52 (pd, *J* = 6.7, 1.1 Hz, 1H), 1.56 – 1.42 (m, 12H), 1.37 – 1.27 (m, 12H), 1.25 – 1.21 (m, 3H), 1.05 – 1.00 (m, 6H), 0.89 (q, *J* = 7.2, 6.5 Hz, 30H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.4, 153.6, 139.7, 136.6, 75.6, 37.6, 29.4(3C), 29.3(3C), 24.1, 23.1, 23.1, 27.5(6C), 11.4(6C), 11.2(6C) **^{119}Sn NMR** (149 MHz, $CDCl_3$): δ = -50.21, -52.41 **IR** (film, cm^{-1}): 2955, 2922, 2870, 2853, 1462, 1376, 1070, 878 **MS:** *m*/*z* calcd for $C_{33}H_{67}OSn_2$ 719.32490, found 719.32400.

(*E*)-3,7-Dimethyloct-3-en-5-yn-2-ol (248). Stannane **246** (42.7 mg, 0.1 mmol, 1.0 eq.) was weight into a Schlenk flask, vacuum (0.01 mbar) was applied for 5 min and the flask was backfilled with Ar. The procedure was repeated two times. A second Schlenk flask was charged with $[Ph_2PO_2][NBu_4]$ (101.2 mg, 0.22 mmol, 2.0 eq), vacuum (0.01 mbar) was applied and the phosphinate was carefully fused with the Bunsen burner. The phosphinate was kept for 1 h under vacuum, the flask was backfilled with Ar and DMF (1 mL) was introduced. The solution was stirred until complete dissolution of the phosphinate. An aliquot (0.22 M in DMF, 0.5 mL, 0.11 mmol, 1.1 eq.) was added to the stannane and stirred for 5 min before $[Pd(PPh_3)_4]$ (5.8 mg, 0.05 mmol, 5 mol%) and CuTC (20.0 mg, 1.05 mmol, 1.05 eq.) were added. The mixture was stirred for 30 seconds, before MeI (21.3 mg, 0.15 mmol, 1.5 eq.) was added and stirring was continued for 1 h at ambient temperature. For work-up the solution was transferred to a separation funnel and H_2O (5 mL) and Et_2O (5 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude material was purified by flash chromatography (SiO_2, 1% EtOAc in hexane) to afford 12.7 mg (84%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (dt, *J* = 2.1, 1.2 Hz, 1H), 4.26 (qd, *J* = 6.5, 1.0 Hz, 1H), 2.71 (pd, *J* = 6.9, 2.0 Hz, 1H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.4, 105.0, 100.3, 76.8, 72.0, 23.3(2C), 21.7, 21.4, 14.8. **IR** (film, cm^{-1}): 2925, 1437, 1119, 722, 694, 541 **MS:** *m*/*z* calcd for $C_{10}H_{16}ONa$ 175.10931, found 175.10933.

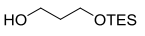
(3*E*,5*Z*)-3,7-Dimethyl-6-(tributylstannyl)octa-3,5-dien-2-ol (249). Complex **C8b** (2.2 mg, 0.007 mmol, 10 mol%) was dissolved in freshly degassed CH_2Cl_2 (0.5 mL) and enyne **248** (11.0 mg, 0.07 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min followed by addition of Bu_3SnH (0.029 mL, 0.10 mmol, 1.3 eq.) in CH_2Cl_2 (0.5 mL) via syringe pump over the



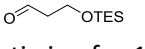
course of 1 h. After complete addition, the solution was stirred for 10 min before the solvent was removed under reduced pressure. The obtained residue was purified by flash chromatography (SiO_2, 2% Et_2O in pentane) to yield 28 mg (89%) of the desired *trans*-stannane as 10 : 1 a mixture of regioisomers (**249** : **249a**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (dd, *J* = 10.9, 1.2 Hz, J_{Sn-H} = 116.1, 1H), 5.95 (dp, *J* = 11.0, 1.4 Hz, 1H), 4.20 – 4.14 (m, 1H), 2.47 (pd, *J* = 6.8, 1.2 Hz, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.46 – 1.37 (m, 6H), 1.28 – 1.23 (m, 6H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 6H), 0.92 – 0.86 (m, 6H), 0.82 (t, *J* = 7.3 Hz, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.3, 139.8, 131.6, 125.7, 73.6, 38.4, 29.3(3C), 27.5(3C), 23.3, 23.2, 21.7, 13.8(3C), 12.4, 11.2(3C). **^{119}Sn NMR** (149 MHz, $CDCl_3$): δ = - 51.12, -54.20 **IR** (film, cm^{-1}): 2956, 2925, 2871, 1592, 1464, 1376, 1078, 670 **MS:** *m*/*z* calcd for $C_{22}H_{44}OSnNa$ 467.23103, found 467.23056.

4.7. Synthesis of the western fragment

3-((Triethylsilyl)oxy)propan-1-ol (273). TESCl (6.58 mL, 39.2 mmol, 1.0 eq.), Et_3N (8.2 mL, 58.8 mmol,  1.5 eq.) and DMAP (240 mg, 1.96 mmol, 5 mol%) were added at ambient temperature to a solution of 1,3-propanediol **272** (8.5 mL, 117 mmol, 3.0 eq.) in CH_2Cl_2 (150 mL). The mixture was stirred for 16 h at room temperature. For work up, EtOAc (30 mL) and H_2O (30 mL) were added, and the organic layer was separated and washed with H_2O (30 mL) and sat. aq. NaCl (30 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 20% Et_2O in hexane) to give 6.5 g (87%) of the title compound as a colorless oil.

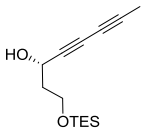
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 – 3.72 (m, 4H), 2.67 (t, *J* = 5.2 Hz, 1H), 1.78 (p, *J* = 5.6 Hz, 2H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.65 – 0.57 (m, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 62.7, 62.6, 34.3, 6.8, 4.4 **IR** (film, cm^{-1}): 2953, 2857, 1089, 1007, 740 **MS:** *m*/*z* calcd for $C_9H_{22}O_2SiNa$ 213.12818, found 213.12813.

3-((Triethylsilyl)oxy)propanal (274). Et_3N (17.3 mL, 123.2 mmol, 4.0 eq.) was added at 0 °C to a  solution of alcohol **273** (5.9 g, 30.9 mmol, 1.0 eq.) in CH_2Cl_2/DMSO (2:1, 112 mL). After stirring for 15 min at the indicated temperature, SO_3·pyridine complex (15.78 g, 99.18 mmol, 3.2 eq.) was added as a solution in DMSO (37.5 mL) to yield a 1:1 ratio of CH_2Cl_2/DMSO. The mixture was stirred at 0 °C for 3 h and at ambient temperature for 16 h. The reaction was quenched with H_2O (40 mL) and the organic layer was separated. The aqueous phase was extracted with of Et_2O (3 x 40 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced

pressure and the crude material was purified by flash chromatography (SiO_2, 20% Et_2O in pentane) yielding 4.9 g (85%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (t, *J* = 2.0 Hz, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (td, *J* = 6.1, 2.0 Hz, 2H), 0.95 (t, *J* =7.8 Hz, 9H), 0.64 – 0.55 (m, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 202.1, 57.2, 46.7, 6.8(3C), 4.4(3C). **IR** (film, cm^{-1}): 2955, 2877, 1728, 1092, 1006, 729 **MS:** *m*/*z* calcd for $C_9H_{20}O_2SiNa$ 211.11258, found 211.11248.

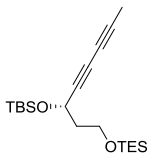
(*S*)-1-((Triethylsilyl)oxy)octa-4,6-diyn-3-ol (274b). A 25 mL Schlenk flask was charged with Ph_3P=O



(29.5 mg, 0.1 mmol, 20 mol%), (*R*,*R*)-ProPhenol (33.8 mg g, 0.05 mmol, 10 mol%) and toluene (2 mL). The solution was stirred for 5 min, before diyne **122** (80% in undecane, 0.16 g, 2.0 mmol, 4.0 eq.) and $ZnMe_2$ (1.2 M in toluene 1.3 mL, 1.59 mmol, 3.0 eq.) were added. After stirring for 1 h at room temperature the mixture was cooled to 0 °C and aldehyde **274** (100 mg, 0.053 mmol, 1.0 eq.) was added. The mixture was stirred for 16 h at 0 °C until TLC indicated complete conversion of starting material. For work up, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and the mixture was stirred for 1 h at ambient temperature until clear phase separation was observed. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 20% Et_2O in pentane) to give 112 mg (84%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (tdd, *J* = 6.4, 4.1, 1.0 Hz, 1H), 4.04 (ddd, *J* = 10.3, 8.4, 3.7 Hz, 1H), 3.82 (ddd, *J* = 10.2, 5.7, 4.3 Hz, 1H), 3.55 (d, *J* = 6.3 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.89 – 1.80 (m, 1H), 1.01 – 0.92 (m, 9H), 0.67 – 0.55 (m, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 77.0, 75.5, 70.0, 63.9, 62.5, 60.8, 38.5, 6.8(3C), 5.9, 4.3(3C) **IR** (film, cm^{-1}): 2955, 2913, 2877, 1080, 1014, 743 **MS:** *m*/*z* calcd for $C_{14}H_{24}O_2SiNa$ 275.14384, found 275.14378 $[\alpha]_{20}$ = -30.8 (c = 1.0, $CHCl_3$).

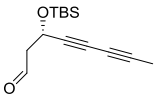
(*S*)-9,9-Diethyl-2,2,3,3-tetramethyl-5-(penta-1,3-diyn-1-yl)-4,8-dioxa-3,9-disilaundecane (275).



TBS-Cl (52 mg, 0.35 mmol, 1.3 eq.) and imidazole (35.4 mg, 0.53mmol, 2.0 eq.) were added at 0 °C to a solution of alcohol **274b** (70 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h at room temperature, before it was quenched with H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 2% Et_2O in pentane) to afford 88 mg (87%) of the title compound.

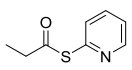
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (dtd, *J* = 7.1, 5.7, 5.1, 2.3 Hz, 1H), 3.71 (td, *J* = 6.4, 2.4 Hz, 2H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.90 – 1.80 (m, 2H), 1.01 – 0.88 (m, 18H), 0.60 (t, *J* = 7.9 Hz, 6H), 0.14 (s, 3H), 0.11 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 76.6, 69.4, 67.9, 64.1, 60.2, 58.7, 41.8, 25.9(3C), 18.3, 6.9(3C), 4.9, 4.5(3C), -4.4, -5.0. **IR** (film, cm^{-1}): 2956, 2930, 2877, 1096, 1017, 837, 778, 744 **MS:** *m/z* calcd for $C_{20}H_{38}O_2Si_2Na$ 389.23038, found 389.23026 **$[\alpha]_{20}$** = - 13.7 (c = 1.0, $CHCl_3$).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)octa-4,6-diynal (276). Oxalyl chloride (0.39 mL, 4.6 mmol, 4.2 eq.) was added at -78 °C to a solution of DMSO (0.71 mL, 10.0 mmol, 9.2 eq.) in CH_2Cl_2 (10 mL). The mixture was stirred at -78 °C for 20 min before TES-ether **275** (0.40 g, 1.1 mmol, 1.0 eq.), dissolved in CH_2Cl_2 (2 mL), was slowly added and stirring was continued at -78 °C for 20 min. The -78 °C cooling bath was replaced by a -40 °C cooling bath and the solution was stirred for 1 h between -40 °C and -30 °C. The solution was cooled to -78 °C and the reaction was quenched with Et_3N (2.27 mL, 16.4 mmol, 15.0 eq.) and allowed to warm to ambient temperature. The reaction was diluted with H_2O (10 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with sat. aq. $CuSO_4$ (2 x 10 mL), sat. aq. NaCl (15 mL), H_2O (15 mL) and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 5% Et_2O in pentane) to yield 210 mg (76%) of the title compound as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (t, *J* = 2.1 Hz, 1H), 4.90 (ddd, *J* = 7.1, 4.7, 1.1 Hz, 1H), 2.79 (ddd, *J* = 16.4, 7.0, 2.2 Hz, 1H), 2.68 (ddd, *J* = 16.4, 4.7, 2.0 Hz, 1H), 1.95 (d, *J* = 1.0 Hz, 3H), 0.87 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 200.0, 78.0, 74.6, 70.9, 63.6, 58.7, 51.3, 25.8(3C), 18.2, 4.5, -4.4, -5.1. **IR** (film, cm^{-1}): 2955, 2930, 2857, 1728, 1254, 1093, 837, 780 **MS:** *m/z* calcd for $C_{14}H_{22}O_2SiNa$ 273.12807, found 273.12813 **$[\alpha]_{20}$** = -39.2 (c = 1.0, $CHCl_3$).

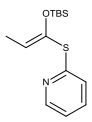
S-(Pyridin-2-yl) propanethioate (297). Propionyl chloride **117** (1.17 mL, 13.5 mmol, 1.0 eq.) and Et_3N (2.15 mL, 15.5 mmol, 1.1 eq.) were added at ambient temperature to a solution of 2-mercaptopyridine **296** (1.5 g, 13,5 mmol, 1.0 eq.) in THF (20 mL). The resulting thick slurry was stirred for 30 min and the formed precipitate was filtered off. The filtrate was collected and washed with sat. aq. $NaHCO_3$ (50 mL). The solvent was removed under reduced pressure and 2.01 g (89%) of the title compound were obtained as a yellow oil which was used directly for the next step.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.55 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.67 (td, *J* = 7.7, 1.9 Hz, 1H), 7.54 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 3H) **^{13}C NMR** (101

MHz, $CDCl_3$): δ = 197.4, 151.6, 150.5, 137.2, 130.3, 123.5, 37.7, 9.5 **IR** (film, cm^{-1}): 2980, 1703, 1572, 1562, 1449, 1420, 1082, 1011, 922, 764 **MS:** *m*/*z* calcd for $C_8H_{10}NOS$ [M + H] 168.04792, found 168.04776.

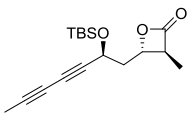
(*E*)-2-((1-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)thio)pyridine (295). A 25 mL Schlenk flask was



charged with LiHMDS (647 mg, 4.0 mmol 1.15 eq.), TBS-Cl (600 mg, 4.0 mmol, 1.15 eq), DMF (0.77 mL, 9.7 mmol, 3.0 eq.) and THF (10 mL). The reaction mixture was cooled to -78 °C before pyridyl thioester **297** (538 mg, 3.2 mmol, 1.0 eq.) was added dropwise. The mixture was stirred for 2 h at -78 °C before it was quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to yield 826 mg (91%) of the title compound as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.42 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.54 (ddd, *J* = 8.1, 7.4, 1.9 Hz, 1H), 7.32 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.00 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 5.45 (q, *J* = 6.8 Hz, 1H), 1.73 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.5, 149.5, 140.3, 136.6, 121.7, 119.7, 118.1, 25.8(3C), 18.2, 12.5, -4.2(2C) **IR** (film, cm^{-1}): 2930, 2858, 1635, 1574, 1450, 1418, 1308, 1254, 1137, 1116, 1069, 862, 839 **MS:** *m*/*z* calcd for $C_{14}H_{23}NOSSiNa$ 304.11633, found 304.11618.

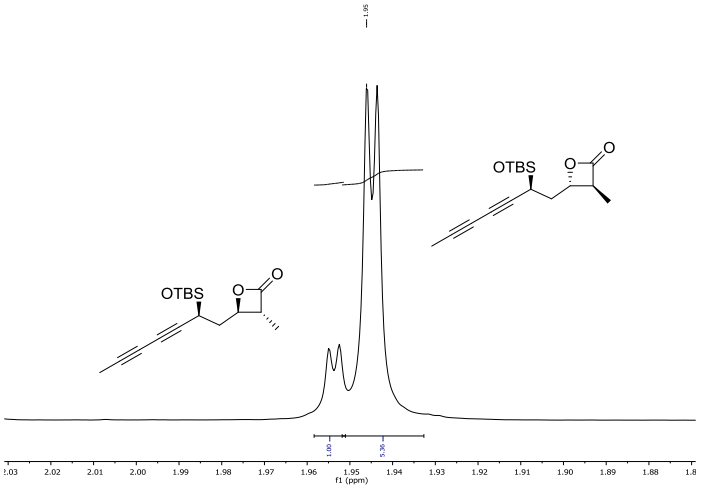
(3*S*,4*S*)-4-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)hepta-3,5-diyn-1-yl)-3-methyloxetan-2-one (291a).



A 25 mL Schlenk flask was charged with anhydrous $ZnCl_2$ (327 mg, 2.35 mmol, 2.0 eq.). The flask was evacuated (0.01 mbar) and the $ZnCl_2$ was carefully fused (heat-gun, 350°C). After reaching ambient temperature the flask was backfilled with Ar and the procedure was repeated before CH_2Cl_2 (10 mL) was introduced. The suspension was stirred for 15 min before ketene acetal **295** (388 mg, 1.38 mmol, 1.15 eq.) was added neat via syringe. The cloudy grey suspension was stirred for 15 min before a solution of aldehyde **276** (300 mg, 1.2 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was introduced. The mixture was stirred for 3 h at ambient temperature, which led to a color change from grey to dark orange. The reaction was quenched with aq. pH~7 buffer (10 mL) and diluted with Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with H_2O (15 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 1% → 2% → 4% → 8% Et_2O in pentane) yielding 205 mg (62%, d.r. 5.1 : 1.0) of an inseparable mixture of *trans*-diastereoisomers and less than 5% of *cis*-isomers.

trans-Diastereoisomers

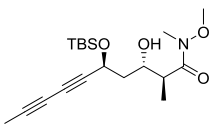
^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.61 – 4.57 (m, 1H), 4.39 (ddd, *J* = 7.5, 5.8, 4.0 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.25 – 2.06 (m, 2H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.42 (d, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.9, 77.8, 75.8, 74.9, 70.6, 63.6, 59.6, 51.3, 42.7, 25.9(3C), 18.3, 12.5, 4.5, -4.4, -5.0. **IR** (film, cm^{-1}): 2955, 2931, 2858, 1827, 1254, 1117, 1095, 1068, 835, 780 **MS:** *m*/*z* calcd for $C_{17}H_{26}O_3SiNa$ 329.15448, found 329.15434 **$[\alpha]_{20}$** = -45.1 (c = 1.0, $CHCl_3$).



cis-Isomers

^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.80 (ddd, *J* = 8.8, 6.5, 4.3 Hz, 1H), 4.56 (tdd, *J* = 6.2, 2.0, 1.0 Hz, 1H), 3.81 (qd, *J* = 7.8, 6.5 Hz, 1H), 2.15 – 2.03 (m, 2H), 1.95 (d, *J* = 1.0 Hz, 3H), 1.30 (d, *J* = 7.8 Hz, 3H)**,** 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.2, 77.8, 74.7, 72.3, 71.1, 63.7, 60.8, 47.9, 39.1, 25.9(3C), 18.3, 8.7, 4.5, -4.5, -5.0. **IR** (film, cm^{-1}): 2955, 2930, 2857, 2258, 1828, 1256, 1092, 836, 779 **MS:** *m*/*z* calcd for $C_{17}H_{26}O_3SiNa$ 329.15448, found 329.15434 **$[\alpha]_{20}$** = -45.1 (c = 1.0, $CHCl_3$).

(2*S*,3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-N-methoxy-N,2-dimethyldeca-6,8-diynamide



(302a). A 100 mL Schlenk flask was charged with freshly dried (two times azeotroped with benzene) N,O-dimethylhydroxylamin-hydrochlorid (267 mg 2.74 mmol, 2.0 eq.) and CH_2Cl_2 (20 mL). The solution was cooled to 0 °C and $AlMe_3$ (2 M in toluene, 1.37 mL, 2.74 mmol, 2.0 eq.) was added dropwise. The mixture was stirred for 30 min at 0 °C and then for 30 min at room temperature. The solution was cooled to 0 °C, before the mixture of lactones **292a**/**b** (420 mg, 1.37 mmol, 1.0 eq.), dissolved in anhydrous CH_2Cl_2 (4 mL), were

slowly added. The cooling bath was removed and the mixture was stirred at room temperature for 3 h before the reaction was quenched with sat. aq. Na/K-tatrate (20 mL). The mixture was further stirred for 1 h until clean phase separation was observed. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude material (SiO_2, 20% → 30% EtOAc in hexane) yielded 395 mg (78%) of the desired isomer (**302a**) and 56 mg (11%) of the undesired isomer (**302b**).

major-Isomer (**302a**)

^{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** (101 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, cm^{-1}): 2956, 2929, 2857, 1641, 1462, 1389, 1252, 1089, 996, 838, 811, 780 **MS:** *m/z* calcd for $C_{19}H_{33}NO_4SiNa$ 390.20767, found 390.20711 $[\alpha]_{20}$ = -44.6 (c = 1.0, $CHCl_3$).

minor-Isomer (**302b**)

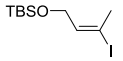
^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.69 (t, *J* = 7.5 Hz, 1H), 3.88 (dtd, *J* = 9.3, 6.0, 3.8 Hz, 1H), 3.71 (s, 3H), 3.58 (d, *J* = 6.5 Hz, 1H), 3.20 (s, 3H), 2.98 – 2.90 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.89 – 1.83 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H) **^{13}C NMR** (101 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, cm^{-1}): 2956, 2930, 2857, 1639, 1463, 1389, 1253, 1082, 994, 868, 836, 779 **MS:** *m/z* calcd for $C_{19}H_{33}NO_4SiNa$ 390.20767, found 390.20711 $[\alpha]_{20}$ = -51.9 (c = 1.0, $CHCl_3$).

(*E*)-3-Iodobut-2-en-1-ol (300). Bis-(cyclopentadienyl)titanium-(IV)-dichloride (0.57 g, 2.30 mmol, 6 mol%) was added at 0 °C portionwise to a solution of *i*-BuMgBr (2 M in Et_2O, 53.0 mL, 106 mmol, 2.6 eq.) in Et_2O (60 mL). The mixture was stirred at 0 °C for 10 min before a solution of 2-butyn-1-ol **300** (3.0 mL, 40.1 mmol 1.0 eq.) in Et_2O (12 mL) was added dropwise. The solution was warmed to ambient temperature and stirred for 4 h until complete consumption of starting material was observed by TLC. The mixture was cooled to -78 °C and stirred vigorously while iodine (35.1 g, 138 mmol, 3.4 eq.) was added in small portions. The solution was warmed to 0 °C and stirred for 1 h prior to quenching with sat. aq. NH_4Cl (30 mL). The mixture was diluted with Et_2O (60 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with

Et_2O (3 x 30 mL). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (50 mL) and dried over $MgSO_4$. The crude material was purified by flash chromatography (SiO_2, 5% Et_2O in pentane) to yield 3.6 g (3.2 g, 45% calculated by NMR purity) of the title compound contaminated with *trans*-crotyl alcohol, which was best removed in the next step.

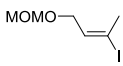
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (tq, *J* = 6.9, 1.5 Hz, 1H), 4.05 (dq, *J* = 7.0, 0.9 Hz, 2H), 2.43 (dd, *J* = 1.6, 0.8 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.8, 98.4, 59.8, 28.1 **IR** (film, cm^{-1}):3300, 2917, 1638, 1424, 1376, 1218, 1095, 1059, 99 **MS:** *m*/*z* calcd for C_4H_7OI 197.95434, found 197.95416.

(*E*)-*tert*-Butyl((3-iodobut-2-en-1-yl)oxy)dimethylsilane (298b). Alcohol **301** (1.1 g, 5.5 mmol, 1.0 eq.) was dissolved in THF (15 mL), followed by addition of imidazole (0.74 g, 11.0 mmol, 2.0 eq.) and TBS-Cl (0.87 g, 5.8 mmol, 1.05 eq.) at 0 °C. The mixture was stirred for 16 h at room temperature before the reaction was quenched with H_2O (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with sat. aq. $Na_2S_2O_3$ (20 mL) and with H_2O (20 mL). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 5% Et_2O in pentane) to yield 1.17 g (68%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (ddt, *J* = 6.5, 5.0, 1.5 Hz, 1H), 4.12 (dq, *J* = 6.5, 0.9 Hz, 2H), 2.41 (dd, *J* = 1.6, 0.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.8, 96.1, 60.8, 34.3, 28.2, 26.0(3C), -5.1(2C) **IR** (film, cm^{-1}): 2928, 2856, 1255, 1086, 1040, 833 **MS:** *m*/*z* calcd for $C_{10}H_{22}IOSi$ [M + H] 313.04789, found 313.04847.

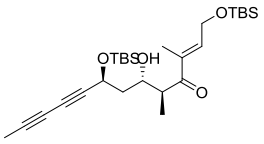
(*E*)-3-Iodo-1-(methoxymethoxy)but-2-ene (298a). This compound was prepared analogously to **298b** using alcohol **301** (300 mg, 1.5 mmol, 1.0 eq.), MOM-Cl (217 mg, 2.7 mmol, 1.8 eq.) and *i*-Pr_2Net (0.57 mL, 3.3 mmol, 2.2 eq.) in CH_2Cl_2 (10 mL). The mixture was stirred overnight and standard work-up procedure was performed. The crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to afford 235 mg (64%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (tq, *J* = 7.0, 1.5 Hz, 1H), 4.61 (s, 2H), 4.00 (dd, *J* = 7.1, 0.9 Hz, 2H), 3.37 (s, 3H), 2.45 (dt, *J* = 1.6, 0.8 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.1, 99.4, 95.5, 63.7, 55.5, 28.2 **IR** (film, cm^{-1}): 2932, 1638, 1377, 1150,1099, 1027, 981, 946, 918 **MS:** *m*/*z* calcd for $C_6H_{11}O_2INa$ 264.96969 found 264.96960.

Preparation of the *ate*-complex of $CeCl_3$·2LiCl

A Schlenk flask was charged with anhydrous $CeCl_3$ (1.54 g, 6.2 mmol) and anhydrous LiCl (0.53 g, 12.5 mmol) before THF (17.5 mL) was introduced. The mixture was stirred at ambient temperature for 2 d, before activated 4 Å MS was added. The insoluble solids were allowed to precipitate for 1 d yielding a ca 0.35 M clear solution of $CeCl_3$·2LiCl which was stored under Ar.

(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 (301). 

Et_2O (6 mL) was placed into a Schlenk flask, cooled to -78 °C and freshly titrated *t*-BuLi (2.25 M in pentane, 1.9 mL, 4.3 mmol, 10.0 eq.) was added carefully. The solution was stirred for 10 min at -78 °C before a solution of alkenyl iodide **298b** (707 mg, 2.25 mmol, 5.2 eq.) in Et_2O (3 mL), was added dropwise over 15 min. The solution was stirred for 15 min at -78 °C, then transferred to a -78 °C cold solution of $CeCl_3$·2LiCl (0.35 M in THF, 6.5 mL, 2.3 mmol, 5.3 eq.) causing an immediate color change to deep orange. The mixture was stirred for 45 min at -78°C before a solution of Weinreb amide **302a** (160 mg, 0.43 mmol, 1.0 eq) in THF (2 mL) was added dropwise over 15 min. The mixture was stirred for 45 min at -78 °C, the cooling bath was removed and the mixture was immediately transferred to a vigorously stirred, cold (0 °C) biphasic mixture of aq. HCl (30 mL, pH~ 3-4) and Et_2O (30 mL). After stirring for 5 min the organic layer was separated, the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over $MgsO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 5% → 10% EtOAc in hexane) to afford 80 mg (38%) of the title compound and 101 mg (58%) of recovered Weinreb amide **302a**.

^{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** (101 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, cm^{-1}): 2955, 2930, 2857, 1663, 1463, 1254, 1103, 1061, 1006, 836, 778 **MS:** *m/z* calcd for $C_{27}H_{48}O_4Si_2Na$ 515.29883, found 515.29834 **$[\alpha]_{20}$** = -12.3 (c = 0.5, $CHCl_3$).

(*R*)-MTPA-Ester: (*S*)-*α*-Methoxy-*α*-trifluoromethyl phenylacetic acid chloride (3.5 mg, 0.014 mmol, 2.0 eq.) was added to a solution of alcohol **301** (3.5 mg, 0.007 mmol, 1.0 eq.) and pyridine (0.002 mL, 0.021 mmol, 3.0 eq) dissolved in CH_2Cl_2 (0.3 ml). The mixture was stirred for 16 h at room temperature and quenched with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL),

the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 5% Et_2O in pentane) yielding 4.1 mg of desired product as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 – 7.47 (m, 2H), 7.43 – 7.38 (m, 3H), 6.96 – 6.91 (m, 1H), 5.46 (ddd, *J* = 9.4, 5.3, 2.1 Hz, 1H), 4.47 – 4.34 (m, 2H), 4.32 (ddd, *J* = 10.0, 3.1, 1.1 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.52 (d, *J* = 1.3 Hz, 3H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.98 – 1.82 (m, 2H), 1.68 (d, *J* = 1.2 Hz, 3H), 0.92 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H).

(*S*)-MTPA-Ester: Compound was prepared analogously using (*R*)-*α*-methoxy-*α*-trifluoromethyl phenylacetic acid chloride as the reagent. Reaction was conducted on the same scale as described above.

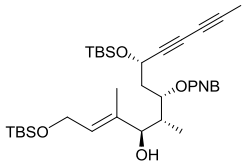
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.53 – 7.46 (m, 2H), 7.44 – 7.37 (m, 3H), 6.98 – 6.92 (m, 1H), 5.45 (ddd, *J* = 9.0, 5.4, 2.3 Hz, 1H), 4.48 – 4.34 (m, 2H), 4.21 (ddd, *J* = 9.7, 3.3, 1.1 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.50 (d, *J* = 1.1 Hz, 3H), 1.92 (d, *J* = 1.0 Hz, 3H), 1.90 – 1.78 (m, 2H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.10 (s,3H), 0.10 (s, 3H), 0.07 (s, 3H).

(9*S*,10*S*,12*S*,*E*)-10-Hydroxy-7,9,14,14,15,15-hexamethyl-12-(penta-1,3-diyn-1-yl)-2,4,13-trioxa-14-silahexadec-6-en-8-one (301b). Alkenyl iodide **299a** (14.5 mg, 0.06 mmol, 3.0 eq.) was dissolved in Et_2O (0.6 mL) and the solution was cooled to -78 °C. The solution was stirred for 5 min before freshly titrated *t*-BuLi (1.89 M in pentane, 0.063 mL, 0.12 mmol, 6.0 eq.) was added dropwise and stirring was continued for 1 h at -78°C. In a second flask the mixture of lactones **292a/b** (6 mg, 0.02 mmol, 1.0 eq.) were dissolved in Et_2O (0.2 mL) and the solution was cooled to -78 °C. The alkenyllithium solution was added dropwise in two batches to the solution of the lactones . After complete addition, the mixture was stirred for 45 min at -78 °C before the reaction was quenched with sat. aq. NH_4Cl (5 mL). The mixture was allowed to reach room temperature and the organic phase was separated. The aqueous layer was extracted with Et_2O (3 x 5 mL), the combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude material by flash chromatography (SiO_2, 10% → 20 % Et_2O in pentane) yielded 3.6 mg (36%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (td, *J* = 5.5, 1.4 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.68 (s, 2H), 4.33 (dt, *J* = 5.4, 1.2 Hz, 2H), 4.06 (dtd, *J* = 10.3, 5.9, 2.1 Hz, 1H), 3.40 (s, 3H), 3.31 (p, *J* = 6.9 Hz, 1H), 3.20 (d, *J* = 5.6 Hz, 1H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.84 (ddd, *J* = 14.0, 8.1, 2.1 Hz, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.70 (ddd, *J* = 13.8, 10.2, 3.3 Hz, 1H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.2, 139.4, 137.5, 96.5, 77.1, 72.2, 70.6, 69.8, 64.9, 61.0, 55.6, 44.4, 42.9, 25.9(3C), 18.3, 15.5, 11.9, 4.5, 1.2, -4.5, -5.1 **IR** (film, cm^{-1}): 1151, 1099, 1041, 838, 811, 780 **MS:** *m/z* calcd for $C_{23}H_{38}O_5SiNa$ 445.23839, found 445.23807 $[\alpha]_{20}$ = -33.9 (c = 1.0 $CHCl_3$).

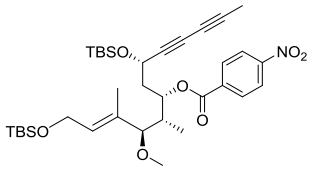
(5*S*,7*S*,8*R*,9*R*,*E*)-9-Hydroxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-yl 4-nitrobenzoate (303). A 10 mL Schlenk flask was charged with Sm metal (36.08 mg, 0.24 mmol) and a solution of diiodomethane (0,017 mL, 0.21 mmol) in THF (1.5 mL) was added. The resulting solution was stirred at 0 °C in the dark for 45 min yielding a dark blue 0.1 M solution of SmI_2.



Ketone **301** (45.1 mg, 0.09 mmol, 1.0 eq.) was dissolved in THF (0.4 mL) and *p*-nitrobenzaldehyde (55.2 mg, 0.36 mmol, 4.0 eq.) was added at -10 °C. The mixture was stirred for 10 min before an aliquot of the freshly prepared SmI_2 (0.1 M in THF, 0.95 mL, 0.095 mmol, 1.05 eq.) was added dropwise, resulting in the formation of a deep orange solution. The solution was stirred for 3 h at -10 °C until complete conversion of the starting material as indicated by TLC. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), diluted with EtOAc (10 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude material was purified by flash chromatography (SiO_2, 8% → 10% → 15% → 20% Et_2O in pentane) yielding 41 mg (70%) of the title compound as a pale yellow oil.

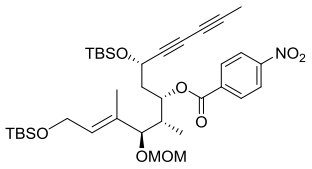
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.32 – 8.27 (m, 2H), 8.24 – 8.19 (m, 2H), 5.64 (t, *J* = 6.3 Hz, 1H), 5.24 (q, *J* = 6.2 Hz, 1H), 4.44 (t, *J* = 6.5 Hz, 1H), 4.24 (qd, *J* = 13.0, 6.1 Hz, 2H), 3.93 (t, *J* = 4.4 Hz, 1H), 2.15 – 2.10 (m, 3H), 2.00 (d, *J* = 3.5 Hz, 1H), 1.88 (d, *J* = 0.9 Hz, 3H), 1.67 – 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** (101 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, cm^{-1}): 2955, 2929, 2857, 1723, 1530, 1471, 1348, 1277, 1101, 1014, 837, 779, 720 **MS:** *m/z* calcd for $C_{34}H_{53}NO_7Si_2Na$ 666.32538, found 666.32528 $[\alpha]_{20}$ = -7.5 (c = 1.0 $CHCl_3$).

(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 4-nitrobenzoate (304). A 25 mL Schlenk flask was charged with Proton-sponge® (177.1 mg, 0.83 mmol, 9.0 eq.) and powdered 4 Å MS (80 mg). A solution of alcohol **304** (60.0 mg, 0.093 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added and the suspension was cooled to 0 °C. Me_3OBF_4 (96.1 mg, 0.65 mmol, 7.0 eq.) was added in one portion and the mixture was stirred at room temperature for 3 h. For work-up, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude material was purified by column chromatography (SiO_2, 5% EtOAc in hexane) to afford 42 mg (69%) of the title compound as a colorless oil and 4.1 mg (7%) of recovered **303**.



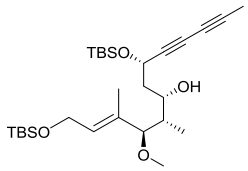
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.31 – 8.26 (m, 2H), 8.22 – 8.17 (m, 2H), 5.55 (dd, *J* = 6.8, 4.8 Hz, 1H), 5.16 (ddd, *J* = 10.9, 4.3, 2.0 Hz, 1H), 4.44 – 4.38 (m, 1H), 4.34 (dd, *J* = 13.2, 7.1 Hz, 1H), 4.19 (ddd, *J* = 13.3, 4.8, 1.3 Hz, 1H), 3.24 (d, *J* = 7.6 Hz, 1H), 3.18 (s, 3H), 2.26 – 2.17 (m, 1H), 2.11 (ddd, *J* = 15.0, 10.9, 4.4 Hz, 1H), 1.96 (ddd, *J* = 14.3, 8.9, 2.0 Hz, 1H), 1.86 (d, *J* = 0.9 Hz, 3H), 1.66 (q, *J* = 1.0 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.08 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.8, 150.5, 135.9, 133.1, 130(2C).7, 129.7, 123.5(2C), 87.7, 76.1, 73.6, 69.8, 63.6, 60.1, 59.8, 56.3, 38.6, 38.0, 25.9(3C), 25.7(3C), 18.3, 18.0, 11.6, 10.1, 4.2, -4.6, -5.1, -5.1, -5.2 (1C mising) **IR** (film, cm^{-1}): 2956,2929, 2857, 1724, 1530, 1276, 1259, 1091, 1015, 835, 807, 777 **MS:** *m/z* calcd for $C_{35}H_{55}NO_7Si_2Na$ 680.34088, found 680.34093 $[\alpha]_{20}$ = -11.4 (0.75 $CHCl_3$).

(5*S*,7*S*,8*S*,9*R*,*E*)-9-(Methoxymethoxy)-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 (304b). A solution of alcohol **304** (6.2 mg, 0.009 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was cooled to 0 °C, before *i*-Pr_2NEt (0.031 mL, 0.18 mmol, 20.0 eq.) and MOM-Cl (7.1 mg, 0.09 mmol, 10.0 eq.) were added. The cooling bath was removed and the mixture was stirred at room temperature for 18 h before the reaction was quenched with sat. aq. NH_4Cl (5 mL) and the mixture was diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude material was purified by flash chromatography (SiO_2, 4% EtOAc in hexane) to yield 6.0 mg (93%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.31 – 8.26 (m, 2H), 8.22 – 8.17 (m, 2H), 5.57 (td, *J* = 5.7, 4.9, 1.5 Hz, 1H), 5.12 (ddd, *J* = 10.9, 4.2, 2.0 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.46 – 4.40 (m, 2H), 4.32 (ddd, *J* = 13.3, 7.2, 0.8 Hz, 1H), 4.17 (ddd, *J* = 13.2, 4.7, 1.3 Hz, 1H), 3.72 (d, *J* = 8.8 Hz, 1H), 3.37 (s, 3H), 2.33 (ddd, *J* = 8.8, 4.5, 2.4 Hz, 1H), 2.18 – 2.08 (m, 1H), 1.99 – 1.90 (m, 1H), 1.86 (d, *J* = 1.0 Hz, 3H), 1.71 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 9H), 0.07 (s, 6H), 0.05 (s, 3H), -0.08 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.0, 150.6, 136.0, 132.8, 131.3, 130.8(2C), 123.7(2C), 93.3, 82.4, 76.1, 73.2, 69.9, 63.7, 60.1, 59.8, 56.1, 38.2, 37.5, 26.1(3C), 25.8(3C), 18.4, 18.1, 11.6, 10.8, 4.4, -4.5, -5.0, -5.0, -5.2 (one carbon of diyne underneath $CDCl_3$) **IR** (film, cm^{-1}): 2954, 2930, 2857, 1724, 1530, 1347, 1277, 1098, 1033, 837, 778, 720 **MS:** *m*/*z* calcd for $C_{36}H_{57}NO_8Si_2Na$ 710.35138, found 710.35150 **$[\alpha]_{20}$** = - 21.2 (0.4 $CHCl_3$).

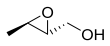
(5*S*,7*S*,8*S*,9*R*,*E*)-9-Methoxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-ol (305). Benzoate **304** (42.1 mg, 0.064 mmol, 1.0 eq.) was dissolved in THF/MeOH (1:1, 1.5 mL) and K_2CO_3 (14.2 mg, 0.10 mmol, 1.6 eq.) was added at 0 °C. The cooling bath was removed and the mixture was stirred at ambient temperature for 6 h. The solvent was removed under reduced pressure and the crude material was directly purified by flash chromatography (SiO_2, 10% → 20% Et_2O in pentane) to yield 23 mg (71%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.50 (tt, *J* = 6.2, 1.3 Hz, 1H), 4.73 (ddd, *J* = 7.2, 3.5, 1.1 Hz, 1H), 4.27 (ddt, *J* = 6.0, 2.9, 0.9 Hz, 2H), 3.88 (tdd, *J* = 6.6, 4.5, 2.2 Hz, 1H), 3.61 (d, *J* = 4.7 Hz, 1H), 3.36 (d, *J* = 4.4 Hz, 1H), 3.24 (s, 3H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.86 – 1.69 (m, 3H), 1.56 (s, 3H), 0.90 (s, 18H), 0.89 (m, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.07 (s, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 133.4, 127.8, 86.9, 77.0, 76.2, 70.5, 69.9, 64.0, 61.7, 60.0, 56.9, 42.2, 41.0, 26.1(3C), 25.9(3C), 18.5, 18.2, 13.3, 11.0, 4.5, -4.5, -5.0(2C), -5.2 **IR** (film, cm^{-1}): 2929, 2857, 1463, 1255, 1061, 940, 835, 776, 665 **MS:** *m*/*z* calcd for $C_{28}H_{52}O_4Si_2Na$ 531.32944, found 531.32964 **$[\alpha]_{20}$** = - 5.1 (c = 0.2, $CHCl_3$).

4.8. Synthesis of the eastern fragment

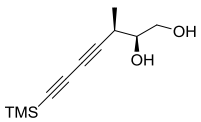
((2*R*,3*R*)-3-Methyloxiran-2-yl)methanol (267). A jacketed Schlenk flask was charged with 4 Å MS (2 g) and CH_2Cl_2 (100 mL). D-(-)-diisopropyl tartrate (702 mg, 3.0 mmol, 6 mol%) and Ti(*i*-PrO)$_4$ (568 mg, 2 mmol, 4 mol%), were added and the mixture was cooled to -20 °C. A solution of *trans*-crotyl alcohol **268** (19 : 1 *trans/cis*, 3.6 g, 50 mmol, 1.0 eq.) in CH_2Cl_2 (12.5 mL) was added and the suspension was stirred for 30 min, followed by addition of TBHP (5.5 M in decane, 13.63 mL, 75 mmol, 1.5 eq.). The mixture was stirred at -20 °C for 16 h, before the reaction was quenched with dimethylsulfide (7.3 mL, 100 mmol, 2.0 eq.). Stirring was continued for 10 h at room temperature



and the mixture was filtered through a short pad of Celite®. Purification via flash chromatography (SiO_2, 20% Et_2O in pentane) yielded 3.44 g (78%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (ddd, *J* = 12.6, 5.6, 2.5 Hz, 1H), 3.61 (ddd, *J* = 12.6, 7.2, 4.4 Hz, 1H), 3.04 (qd, *J* = 5.3, 2.3 Hz, 1H), 2.89 (dt, *J* = 4.7, 2.4 Hz, 1H), 2.02 (ddd, *J* = 8.6, 6.3, 2.6 Hz, 1H), 1.33 (d, *J* = 5.2 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 61.8, 59.7, 52.1, 17.2 **IR** (film, cm^{-1}): 3405, 1451, 1383, 1102, 1037, 988, 864 **MS:** *m/z* calcd for $C_4H_8O_2Na$ 111.04178 found 111.04165 **$[\alpha]_{20}$** = + 42.3 (1.0 $CHCl_3$).

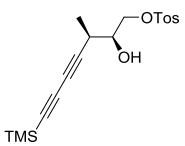
(2*S*,3*R*)-3-Methyl-7-(trimethylsilyl)hepta-4,6-diyne-1,2-diol (306b). A 25 mL Schlenk flask was



charged with TMS-diyne **74** (550 mg, 4.5 mmol, 3.0 eq.) and toluene (8 mL). The solution was cooled to -78 °C and *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol, 2.6 eq.) was added. Stirring was continued for additional 30 min and the -78 °C cooling bath was replaced with a 0 °C cooling bath. Et_2AlCl (0.9 M in toluene, 4.4 mL, 4.0 mmol, 2.6 eq.) was added and the mixture was stirred for 30 min before a solution of epoxide **267** (132 mg, 1.5 mmol, 1.0 eq.) in toluene (2 mL) was added dropwise. The reaction was left to proceed overnight at ambient temperature before it was quenched with aq. HCl (1.0 N, 5 mL) and the mixture was diluted with Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, 30% → 40% Et_2O in pentane) yielded 210 mg (67%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (ddd, *J* = 10.8, 6.2, 3.0 Hz, 1H), 3.70 (ddd, *J* = 11.1, 6.9, 4.3 Hz, 1H), 3.61 (ddt, *J* = 7.0, 5.3, 3.5 Hz, 1H), 2.69 (p, *J* = 7.0 Hz, 1H), 2.37 (s, broad, 1H, OH), 1.89 (s, broad, 1H, OH), 1.27 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 87.9, 85.1, 79.9, 74.6, 67.9, 64.7, 30.3, 16.6, -0.3(3C) **IR** (film, cm^{-1}): 3358, 2960, 1251, 844, 760 **MS**: *m/z* calcd for $C_{11}H_{18}O_2SiNa$ 233.09672, found 233.09683 **$[\alpha]_{20}$** = +9.6 (c = 0.4, $CHCl_3$).

(2*S*,3*R*)-2-Hydroxy-3-methyl-7-(trimethylsilyl)hepta-4,6-diyn-1-yl4-methylbenzenesulfonate (307b).

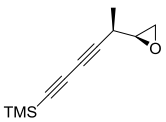


Bu_2SnO (20 mg, 0.081 mmol, 10 mol%) was added to a stirred solution of diol **307b** (180 mg, 0.86 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). The mixture was stirred for 5 min before Et_3N (0.13 mL, 0.95 mmol, 1.1 eq.) and Tos-Cl (180 mg, 0.95 mmol, 1.1 eq.) were added and the reaction was left to proceed overnight at room temperature. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the layers were separated. The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was

removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 5% → 15% EtOAc in hexane) to afford 250 mg (80%) of the title compound as colorless oil.

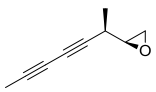
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 – 7.78 (m, 2H), 7.40 – 7.34 (m, 2H), 4.29 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.08 (dd, *J* = 10.5, 6.4 Hz, 1H), 3.72 (dtd, *J* = 11.0, 6.0, 3.0 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.46 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.19 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.3, 132.5, 130.1(2C), 128.2(2C), 87.7, 85.5, 78.7, 72.4,72.0, 68.3, 30.0, 21.8, 16.5, -0.3(3C) . **IR** (film, cm^{-1}): 2960, 1361, 1251, 1190, 1176, 960, 846, 555 **MS:** *m/z* calcd for $C_{18}H_{24}O_4SSiNa$ 387.10565, found 387.10568 **$[\alpha]_{20}$** = +32.2 (c = 0.5, $CHCl_3$).

Trimethyl((*R*)-5-((*S*)-oxiran-2-yl)hexa-1,3-diyn-1-yl)silane (265b). DBU (0.19 mL, 1.3 mmol, 2.0 eq.) was added at 0 °C to a stirred solution of tosylate **307b** (240 mg, 0.68 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL). The mixture was stirred for 6 h at room temperature before H_2O (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (1% Et_2O in pentane) to yield 95 mg (75%) of the title compound as a volatile colorless liquid.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (ddd, *J* = 6.4, 3.8, 2.5 Hz, 1H), 2.79 (dd, *J* = 4.8, 3.8 Hz, 1H), 2.68 (dd, *J* = 4.8, 2.5 Hz, 1H), 2.49 (p, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 3H), 0.19 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 87.8, 85.2, 78.3, 67.6, 54.5, 46.4, 30.0, 17.5, -0.3(3C) **IR** (film, cm^{-1}): 2961, 2935, 2227, 2108, 1251, 909, 839, 760 **MS**: *m/z* calcd for $C_{11}H_{16}OSi$ 192.09720, found 192.09704 **$[\alpha]_{20}$** = + 4.2 (c = 0.3, $CHCl_3$).

(*S*)-2-((*R*)-Hepta-3,5-diyn-2-yl)oxirane (265c). NBS (231 mg, 1.3 mmol, 1.3 eq.) and $AgNO_3$ (25.4 mg, 0.15 mmol, 15 mol%) were added to a stirred solution of **265** (168 mg, 1.0 mmol, 1.0 eq.) in acetone (6 mL). The mixture was stirred at room temperature in the dark for 2 h. After cooling to 0 °C, the reaction was quenched with H_2O (10 mL) and the mixture was diluted with Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude bromo alkyne was directly used in the next step.



Prepared according to **GP-2**: Crude bromo alkyne (130 mg, 0.73 mmol, 1.0 eq.), aq. $BuNH_2$ (30% in water, 4 mL), CuCl (6.9 mg, 0.07 mmol, 10 mol%), liquid propyne (0.1 mL). The crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to yield 41 mg (40%) of the title compound as a volatile liquid.

^{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** (101 MHz, $CDCl_3$): δ = 75.3, 74.9, 67.6, 64.1, 54.7, 46.4, 29.9, 17.7, 4.3 **IR** (film, cm^{-1}): 2982, 2932, 1722, 1455, 1258, 1073, 1025, 922, 882, 828 **MS**: *m/z* calcd for $C_9H_{10}O$ 134.07333, found 134.07317 **$[\alpha]_{20}$** = + 59.7 (c = 0.5 $CHCl_3$).

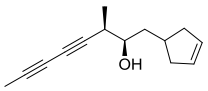
4-Iodocyclopent-1-ene (309). A 50 mL flask was charged with triphenylphosphine (1.62 g, 6.18 mmol, 1.3 eq.), imidazole (420 mg, 6.18 mmol, 1.3 eq.) and CH_2Cl_2 (15 mL). After stirring for 5 min the solution was cooled to 0 °C. Iodine (1.56 g, 6.18 mmol, 1.3 eq.) was added in three portions every 5 min. Stirring was continued for 15 min at 0 °C, before a solution of alcohol **309** (400 mg, 4.75 mmol, 1.0 eq.), in CH_2Cl_2 (2 mL) was added with a syringe pump over the course of 45 min. The mixture was stirred overnight and diluted with pentane (50 mL) which resulted in the formation of large amounts of precipitate. The precipitate was filtered off and the procedure was repeated yielding 750 mg (81%) of the desired product as a light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, *J* = 0.8 Hz, 2H), 4.54 (tt, *J* = 6.8, 4.4 Hz, 1H), 3.03 – 2.80 (m, 4H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 129.6(2C), 46.7(2C), 22.9 **IR** (film, cm^{-1}): 2826, 1428, 1200, 1126, 896, 730 **MS:** *m/z* calcd for C_5H_7I 193.95940 found 193.95925.

(2*R*,3*R*)-1-(Cyclopent-3-en-1-yl)-3-methyl-5-(trimethylsilyl)pent-4-yn-2-ol (264). A solution of freshly prepared cyclopent-3-enylmagnesiumbromide (1.3 M in Et_2O, 4.0 mL, 5.22 mmol, 1.8 eq.) was added at -40 °C to a stirred suspension of CuI (552 mg, 2.9 mmol, 1.0 eq.) in THF (20 mL). The mixture was stirred for 30 min, while the suspension turned from light grey to dark grey. A solution of epoxide **265** (500 mg, 2.9 mmol, 1.0 eq.) in THF (3.5 mL) was added dropwise and the solution was stirred for 2 h between -40 °C and -30 °C. The reaction was quenched with sat. aq. NH_4Cl (15 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to yield 620 mg (87%) of the title compound as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 – 5.62 (m, 2H), 3.65 – 3.55 (m, 1H), 2.64 – 2.40 (m, 4H), 2.08 – 1.93 (m, 2H), 1.72 (d, *J* = 5.7 Hz, 1H), 1.61 (ddd, *J* = 8.0, 4.8, 3.0 Hz, 2H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.15 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 130.2, 129.7, 108.8, 86.9, 73.2, 40.3, 39.7, 38.6, 34.4, 34.3, 15.6, 0.3 (3C) **IR** (film, cm^{-1}): 3360, 3054, 2959, 2932, 2165, 1249, 1055, 839, 759 **MS:** *m*/*z* calcd for $C_{14}H_{24}OSiNa$ 259.14885, found 259.14886 **$[\alpha]_{20}$** = + 16.1 (*c* =0.4, $CHCl_3$).

(2*R*,3*R*)-1-(Cyclopent-3-en-1-yl)-3-methylocta-4,6-diyn-2-ol (312). NBS (266 mg, 1.5 mmol, 1.2 eq.)

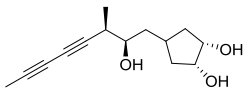


and $AgNO_3$ (20 mg, 0.12 mmol, 10 mol%) were successively added in the dark to a solution of TMS-alkyne **264** (300 mg, 1.26 mmol, 1.0 eq.) in acetone (7 mL). The solution was stirred for 2 h before it was diluted with Et_2O/pentane (2:3, 30 mL). The organic layer was washed three times with H_2O (10 mL) and the solvent was carefully removed under reduced pressure. The crude bromo alkyne was directly used in the next step.

Prepared according to **GP-2**: Crude bromo alkyne (306 mg, 1.26 mmol, 1.0 eq.), aq. $BuNH_2$ (30% in water, 6 mL), CuCl (11.2 mg, 0.12 mmol, 10 mol%), liquid propyne (0.1 mL). The crude material was purified by flash chromatography (SiO_2, 10% Et_2O in pentane) to yield 140 mg (60% over two steps) of the title compound.

^{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** (101 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, cm^{-1}): 3393, 2931, 2842, 1451, 1070, 1038, 971 **MS:** *m*/*z* calcd for $C_{14}H_{18}ONa$ 225.12475, found 225.12498 **$[\alpha]_{20}$** = + 9.2 (c =0.4, $CHCl_3$).

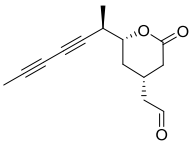
(1*R*,2*S*)-4-((2*R*,3*R*)-2-Hydroxy-3-methylocta-4,6-diyn-1-yl)cyclopentane-1,2-diol (263). NMO (140.7



mg, 1.2 mmol, 1.7 eq.) and OsO_4 (4% in water, 0.12 mL, 0.002 mmol, 4 mol%) were added successively to a stirred solution of alkene **313** (140 mg, 0.69 mmol, 1.0 eq.) in acetone/H_2O (2:1, 5 mL), which resulted in a color change to light yellow. The mixture was stirred at ambient temperature until complete conversion of the starting material was reached, as judged by TLC. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and the mixture was stirred for 30 min before it was diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried over $MgsO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 2% MeOH in EtOAc) to afford 110 mg (70%, 7.7 : 1 d.r.) of the title compound as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.04 (ddd, *J* = 4.7, 3.4, 1.6 Hz, 2H), 3.36 (ddd, *J* = 9.7, 7.0, 2.6 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.44 (tq, *J* = 7.0, 1.1 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.88 (d, *J* = 1.1 Hz, 3H), 1.61 (ddd, *J* = 13.9, 10.0, 2.6 Hz, 1H), 1.53 – 1.40 (m, 3H), 1.17 (d, *J* = 7.0 Hz, 3H) **^{13}C NMR** (101 MHz, CD_3OD): δ = 78.9, 74.8, 74.8, 74.6, 74.4, 68.2, 65.1, 43.1, 39.4, 38.2, 35.2, 32.2 17.3, 3.5 **IR** (film, cm^{-1}): 3302, 1933, 2914, 1343, 1134, 1111, 1078, 1040, 1026, 986, 882, 869, 716 **MS:** *m/z* calcd for $C_{14}H_{20}O_3Na$ 259.13021, found 259.13046 **$[\alpha]_{20}$** = + 17.1 (c =0.4, $CHCl_3$).

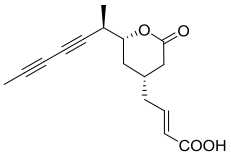
2-((2*R*,4*S*)-2-((*R*)-Hepta-3,5-diyn-2-yl)-6-oxotetrahydro-2H-pyran-4-yl)acetaldehyde (262). $NaIO_4$ (10% on SiO_2, 2.56 g, 1.2 mmol, 2.85 eq.) was added to a vigorously stirred suspension of diol **263** (100 mg, 0.42 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at ambient temperature for 20 min before it was filtered through a short pad of SiO_2. The SiO_2 was rinsed with Et_2O (50 mL) and the filtrate was evaporated under reduced pressure to yield a 1:1 mixture of anomers which were used directly for the next step.



PIDA (283 mg, 0.88 mmol, 2.1 eq.) and TEMPO (9.3 mg, 0.06 mmol, 14 mol%) were added to a solution of the anomeric mixture in CH_2Cl_2 (4 mL). The yellowish solution was cooled to 0 °C and $Yb(OTf)_3$ (20.4 mg, 0.03 mmol, 7 mol%) was added. The cooling bath was removed and the mixture was stirred at ambient temperature for 1 h. The reaction was diluted with CH_2Cl_2 (4 mL) and quenched with sat. aq. $Na_2S_2O_3$ (4 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 40% EtOAc in hexane) to yield 75 mg (76% over two steps) of the title compound as a colorless gum.

^{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** (101 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, cm^{-1}): 2918, 1724, 1385, 1235, 1082 **MS:** *m/z* calcd for $C_{14}H_{16}O_3Na$ 255.09900 found 255.09916 **$[\alpha]_{20}$** = -18.6 (c =0.35, $CHCl_3$).

(*E*)-4-((2*R*,4*R*)-2-((*R*)-Hepta-3,5-diyn-2-yl)-6-oxotetrahydro-2H-pyran-4-yl)but-2-enoic acid (255).

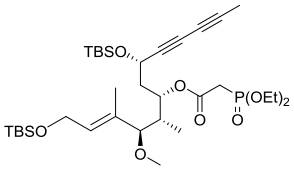


Diethylphosphonoacetic acid (12.4 mg, 0.062 mmol, 1.1 eq.) was added to a suspension containing $Zn(OTf)_2$ (43.6, 0.12 mmol, 2.0 eq.), TMEDA (7.7 mg, 0.067 mmol, 1.2 eq.), DBU (33.5 mg, 0.22 mmol, 4.0 eq.) and THF (1 mL). The suspension was cooled to 0 °C and aldehyde **262** (13 mg, 0.056 mmol, 1.0 eq.) was added. The cooling bath was removed and the suspension was stirred for 16 h at ambient temperature, while it became a clear yellow solution. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 50% MeOH in EtOAc) to give 10 mg (70%) of the title compound as a white powder.

^{1}H NMR (400 MHz, CD_3OD): δ = 6.70 – 6.59 (m, 1H), 5.90 (d, *J* = 15.6 Hz, 1H), 4.28 (ddd, *J* = 11.7, 6.2, 2.8 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.76 – 2.64 (m, 1H), 2.28 – 2.13 (m, 4H), 1.89 (d, *J* = 1.1 Hz, 3H), 1.44 – 1.28 (m, 2H) 1.24 (d, *J* = 7.1 Hz, 3H) **^{13}C NMR** (101 MHz, CD_3OD): δ = 173.5(2C), 141.5, 130.5, 83.5, 76.3, 75.5, 69.1, 64.7, 39.2, 36.6, 33.6, 32.4, 31.9, 16.8, 3.5 **IR** (film, cm^{-1}): 3377, 2919, 1719, 1655, 1544, 1418, 1252, 1171, 1033 **MS:** *m/z* calcd for $C_{16}H_{18}O_4Na$ 297.10943, found 297.10973 **$[\alpha]_{20}$** = +2.1 (c =0.1, MeOH).

4.9. Fragment assembly and RCDM

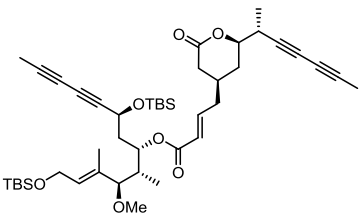
(5*S*,7*S*,8*S*,9*R*,*E*)-9-Methoxy-2,2,3,3,8,10,14,14,15,15-decamethyl-5-(penta-1,3-diyn-1-yl)-4,13-dioxa-3,14-disilahexadec-10-en-7-yl 2-(diethoxyphosphoryl)acetate (318).



Diethylphosphono acetic acid (22.1 mg, 0.11 mmol, 2.8 eq.) was added to a flask containing CH_2Cl_2 (1 mL) and 3 Å MS (beads). The solution was cooled to 0 °C before EDC·HCl (13.4 mg, 0.072 mmol, 1.8 eq.) was added and the solution was stirred for 15 min. A solution of alcohol **305** (20.1 mg, 0.039 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added, the cooling bath was removed and DMAP (1.5 mg, 0.013 mmol, 30 mol%) was introduced. The yellow solution was stirred for 8 h at ambient temperature. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (SiO_2, 10% → 15% EtOAc in hexane) to afford 25.3 mg (94%) of the title compound as a colorless oil.

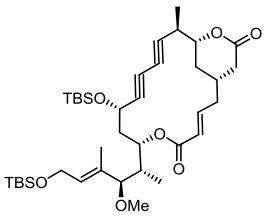
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 – 5.48 (m, 1H), 4.98 – 4.89 (m, 1H), 4.42 – 4.35 (m, 1H), 4.31 (dd, *J* = 13.2, 7.1 Hz, 1H), 4.22 – 4.09 (m, 5H), 3.19 (d, *J* = 7.0 Hz, 1H), 3.17 (s, 3H), 2.93 (dq, *J* = 21.8, 14.3 Hz, 2H), 2.10 – 2.01 (m, 1H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.89 (td, *J* = 9.2, 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** (101 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, cm^{-1}): 2955, 2929, 2856, 1735, 1471, 1463, 1255, 1090, 1048, 1024, 834, 777 **MS:** *m*/*z* calcd for $C_{34}H_{63}O_8PSi_2Na$ 709.36890, found 709.36914 **$[\alpha]_{20}$** = -10.0 (c = 0.2, $CHCl_3$).

Metathesis precursor (319). LiCl (3.8 mg, 0.09 mmol, 2.5 eq.) was added to a Schlenk flask containing a solution of phosphonate **317** (25 mg, 0.036 mmol, 1.0 eq.) in MeCN (1 mL). The mixture was stirred at ambient temperature for 20 min before DBU (6 mg, 0.039, 1.1 eq.) was added and the reaction was cooled to 0 °C. Stirring was continued for an additional 15 min before a solution of aldehyde **262** (10.5 mg, 0.045 mmol, 1.25 eq.) in THF (0.6 mL) was added. The cooling bath was removed and the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the crude material was purified via flash chromatography (SiO_2, 5% EtOAc in hexane) to yield 15 mg (54%) of title compound and 3.5 mg (12%) of recovered **317**.



^{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** (101 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, cm^{-1}): 2929, 2856, 1718, 1250, 1089, 1048, 835, 778 **MS:** *m*/*z* calcd for $C_{44}H_{68}O_7Si_2Na$ 787.43961, found 787.43958 **$[\alpha]_{20}$** = -10.0 (c =0.2, $CHCl_3$).

Macrocycle (320). Procedure 1: A solution of ligand **L1** (9.7 mg, 0.011 mmol) and catalyst **C7** (6.5 mg, 0.01 mmol) in 1 mL toluene was vigorously stirred for 10 min to give a clear brown stock solution of the active catalyst (0.01 mmol/mL) which has to be used within ca 30 - 40 min before it turns dark.

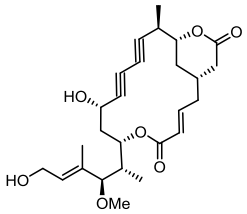


A 10 mL Schlenk flask was charged with 5 Å MS (25 mg). The flask was evacuated (0.01 mbar) and the molecular sieves were dried for 5 min (350°C, heat gun). The flask was backfilled with Ar and substrate **318** (6.0 mg, 0.0078 mmol, 1.0 eq.) was introduced as a solution in toluene (3.5 mL). After stirring for 1 h at room temperature, the flask was immersed into an oil bath at 65 °C and an aliquot of the catalyst stock solution (0.01 mmol/ mL in toluene, 0.23 mL, 0.0023 mmol, 30 mol%) was added. The mixture was stirred at 65 °C for 1.5 h. The reaction was allowed to cool to ambient temperature and filtrated through a pad of silica, which was rinsed with EtOAc (30 mL). Purification of the crude material by flash chromatography (SiO_2, 10% → 15% → 20% EtOAC in hexane) yielded 2.9 mg (50% calculated by NMR) of the title compound contaminated with an impurity from the silanol ligand.

Procedure 2: Cyclization was done according to **GP-1:** Substrate **319** (6.0 mg, 0.0078 mmol, 1.0 eq.), 5Å MS (25 mg), **C5** (2.5 mg, 0,0024 mmol, 30 mol%), toluene (3.5 mL), 1 h, 65 °C. Purification by flash chromatography (SiO_2, 10% → 15% → 20% EtOAC in hexane) yielded 3.1 mg (58%) of the title compound as a white solid.

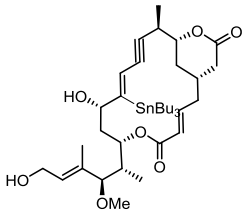
^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.84 (ddd, *J* = 15.8, 10.2, 5.7 Hz, 1H), 5.92 (d, *J* = 15.7 Hz, 1H), 5.45 (t, *J* = 6.0 Hz, 1H), 4.75 (dd, *J* = 9.3, 3.8 Hz, 1H), 4.34 – 4.28 (m, 2H), 4.21 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.02 (ddd, *J* = 11.2, 7.4, 4.0 Hz, 1H), 3.17 (s, 3H), 3.16 (d, *J* = 6.2 Hz, 1H), 2.75 (p, *J* = 7.1 Hz, 1H), 2.72 (dq, *J* = 17.6, 2.6, 1.9 Hz, 1H), 2.49 (dt, *J* = 12.1, 3.9 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.24 (dd, *J* = 17.4, 10.9 Hz, 1H), 2.09 (td, *J* = 10.0, 2.8 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.95 (q, *J* = 10.5 Hz, 1H), 1.83 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.66 (s, 3H), 1.34 – 1.29 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3, 165.6, 144.4, 134.6, 129.8, 126.3, 88.6, 82.3, 80.6, 78.7, 72.6, 69.6, 68.8, 63.2, 59.8, 56.4, 39.2, 38.0, 37.6, 36.4, 34.0, 30.7, 29.7, 26.1(3C), 25.8(3C), 18.5, 18.2, 16.6, 11.4, 9.9, -4.3, -4.8, -5.0, -5.0 **IR** (film, cm^{-1}): 2927, 2855, 1718, 1463, 1258, 1083, 837, 779 **MS:** *m/z* calcd for $C_{38}H_{62}O_7Si_2Na$ 709.39287, found 709.39263 $[\alpha]_{20}$ = +4.0 (c =0.1, $CHCl_3$).

Macrocyclic diol (321). TBAF (1.0 M in THF, 0.012 mL, 0.012 mmol, 2.8 eq.) was added at -50 °C to a solution of macrocycle **320** (3 mg, 0.0044 mmol, 1.0 eq) in THF (0.4 mL). The solution was allowed to warm to -10 °C over 2 h and maintained at this temperature for 3 h. The mixture was diluted with Et_2O (2 mL) and quenched with H_2O (2 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (SiO_2, 60% → 70% → 80% EtOAc in hexane, then 20% MeOH in EtOAc) to afford 1.4 mg (71%) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (ddd, *J* = 15.7, 10.1, 5.6 Hz, 1H), 5.93 (d, *J* = 16.1 Hz, 1H), 5.57 (dt, *J* = 5.9, 0.9 Hz, 1H), 4.78 (ddd, *J* = 9.2, 3.9, 1.2 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.26 (d, *J* = 6.6 Hz, 2H), 4.02 (ddd, *J* = 11.3, 7.4, 4.0 Hz, 1H), 3.19 (d, *J* = 8.6 Hz, 1H), 3.17 (s, 3H), 2.80 – 2.69 (m, 2H), 2.51 (ddd, *J* = 8.9, 7.4, 3.4 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.25 (dd, *J* = 17.3, 10.7 Hz, 1H), 2.15 – 1.91 (m, 6H), 1.71 (dt, *J* = 1.5, 0.8 Hz, 3H), 1.34 – 1.29 (m, 1H) 1.24 (d, *J* = 5.8 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H).

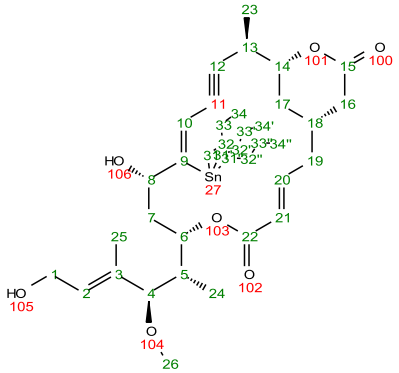
Stannane (322). A stock solution of stannane was prepared by dissolving Bu_3SnH (0.004 mL, 0.014 mmol) in freshly degassed CH_2Cl_2 (2 mL). A stock solution of catalyst was prepared by dissolving [Cp*$RuCl_4$] **C8a** (2 mg, 0.013 mmol) in freshly degassed CH_2Cl_2 (1 mL).



Diol **321** (1 mg, 0.0022 mmol, 1.0 eq.) was transferred to a Schlenk flask and dried by applying vacuum (0.01 mbar) for 15 min. An aliquot of the catalyst stock solution (0.1 mL of the prepared solution, 0.0004 mmol, 15 mol%) was added causing a color change to deep purple. The solution was stirred for 1 min before Bu_3SnH (0.4 mL of the prepared solution, 0.0025 mmol, 1.15 eq.) was added over the course of 30 min. After complete addition the reaction was further stirred for 5 min. The solvent was removed under a stream of argon and the crude material was purified by flash chromatography (SiO_2, 50% → 60% EtOAc in hexane) to afford 1.1 mg (66%) of the title compound.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.78 (ddd, *J* = 15.7, 11.0, 5.0 Hz, 1H), 5.99 (d, *J* = 3.1 Hz, $J_{Sn\text{-}H}$ = 105.6 Hz, 1H), 5.77 (d, *J* = 15.7 Hz, 1H), 5.62 (td, *J* = 6.5, 0.8 Hz, 1H), 4.73 (dd, *J* = 9.8, 3.3 Hz, 1H), 4.28 (t, *J* = 7.3 Hz, 2H), 4.08 – 4.00 (m, 1H), 3.91 – 3.85 (m, 1H), 3.21 (d, *J* = 9.1 Hz, 1H), 3.18 (s, 3H), 2.79 (ddd, *J* = 17.9, 5.4, 2.3 Hz, 1H), 2.67 – 2.62 (m, 1H), 2.61 (ddd, *J* = 14.3, 5.4, 2.8 Hz, 1H), 2.56 – 2.50 (m, 2H), 2.19 – 2.11 (m, 1H), 2.12 – 2.04 (m, 1H), 1.88 (dt, *J* = 14.9, 10.2 Hz, 1H), 1.82 – 1.74 (m, 3H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.15 – 1.04 (m, 6H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 9H) **^{119}Sn NMR** (149 MHz, $CDCl_3$): -52.1 **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 166.2, 165.4, 145.1, 137.0, 91.6, 89.1, 83.7, 81.6, 73.8, 59.0, 56.2, 39.2, 38.0, 37.0, 36.2, 34.0, 33.1, 30.3, 29.2 (3C), 27.6 (3C), 16.7, 14.1, 13.8 (3C),

11.0, 10.9 (3C), 10.2 **IR** (film, cm^{-1}): 2924, 2853, 1988, 1718, 1657, 1082 **MS:** *m*/*z* calcd for $C_{38}H_{62}O_7SnNa$ 773.34099, found 773.34090.



Atom	Chemical Shift	J	COSY	HSQC	HMBC
1 C	58.95			1	
H2	4.28		2	1	2, 3
2 C	128.68			2	1, 4, 25
H	5.62		1	2	4, 25
3 C	137.01				1, 25
4 C	89.10			4	2, 26, 25, 24
H	3.21	9.10(5)	5	4	2, 26, 24, 25, 5
5 C	39.21			5	4, 24
H	2.08	9.10(4)	4, 24, 6	5	
6 C	73.80			6	7a, 24
H	4.73		5, 7a, 7b	6	22, 8, 24
7 C	36.21			7b, 7a	
Ha	1.88		6, 8	7	9, 6, 8
Hb	1.79		6, 8	7	9, 8
8 C	81.58			8	10, 6, 7a, 7b
H	4.03		7a, 7b	8	10
9 C	166.19				10, 7a, 7b
10 C	119.14			10	8
H	5.99			10	9, 12, 8
11 C					
12 C	91.56				10, 23
13 C	34.03			13	23
H	2.65		14, 23	13	
14 C	83.72			14	17b, 23
H	3.89		13, 17b, 17a	14	
15 C	169.89				16a, 16b
16 C	36.96			16a, 16b	
Ha	2.79		16b, 18, 17a	16	15, 17
Hb	2.15		16a	16	15, 18, 19
17 C	33.13			17a, 17b	16a, 19a, 19b
Ha	2.61		14, 17b, 16a, 18	17	
Hb	0.97		14, 17a	17	14
18 C	30.29			18	16b
H	1.88		19b, 16a, 17a	18	
19 C	37.96			19a, 19b	21, 16b
Ha	2.53		20, 19b	19	17
Hb	1.78		20, 19a, 18	19	20, 21, 17
20 C	145.10			20	19b
H	6.78	15.70(21)	21, 19a, 19b	20	22
21 C	125.55			21	19b
H	5.77	15.70(20)	20	21	22, 19
22 C	165.39				20, 21, 6
23 C	16.65			23	
H3	1.29		13	23	12, 14, 13
24 C	10.17			24	4, 6
H3	0.98		5	24	6, 4, 5
25 C	11.01			25	2, 4
H3	1.73			25	2, 3, 4
26 C	56.24			26	4
H3	3.18			26	4
31 31' 31''C	10.93			31 31' 31''	
H2	1.09		32 32' 32''	31 31' 31''	
32 32' 32'' C	29.21			32, 32' 32''	
H2	1.56		31,33, 31', 33' 31'', 33''	32, 32' 32''	
33 33' 33'' C	27.56			33, 33', 33''	
H2	1.36		32, 34, 32', 34', 32'', 34''	33, 33', 33''	
34 34' 34'' C	13.76			34, 34', 34''	
H3	0.93		33, 33', 33''	34, 34', 34''	

6. List of abbreviations

9-BBN	9-borabicyclo(3.3.1)nonane
Ac	acetyl
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
BINOL	1,1´-bi-2-naphtol
Bn	benzyl
Br	broad
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionization
CBS	Corey-Bakshi-Shibata
CC_{50}	concentration of the compound that reduced cell viability to 50%
ConA	concavalin A
COSY	correlation spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CsA	cyclosporin A
Cy	cyclohexyl
Δ	reflux temperature
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distorsionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	*N,N*-dimethyl 4-aminopyridine
DMF	dimethylformamide
DMP	Dess-Martin Periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
d.r.	diasteromeric ratio
EDC·HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EE	ethoxy ethyl
ee	enantiomeric excess
ent	enantiomeric
ESI	electronspray ionization
Et	ethyl
g	gram

GC	gas chromatography
h	hour
IBX	2-iodoxybenzoic acid
HMBC	heteronuclear multiple quantum coherence
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single quantum coherence
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons olefination
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
l	liter
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
mol	molar
m	multiplet
Me	methyl
mg	milligram
min	minute
mL	milliliter
MOM	methoxy methyl
MTBE	*tert*-butylmethylether
Ms	methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
N	normal (mol/kg)
NBS	*N*-bromosuccinimide
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ph	phenyl
PIDA	phenyliodine-(III)-diacetate
PG	protecting group
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzoate
PPTS	pyridinium-*para*-toluenesulfonate
Pr	propyl
ProPhenol	2,6-Bis((2-(hydroxydiphenylmethyl)pyrrolidin-1-yl)methyl)-4-methylphenol
q	quartet
quant.	quantitative
RCAM	ring-closing alkyne metathesis
RCDM	ring-closing alkyne metathesis of 1,3-diyne
RCM	ring-closing (olefin)metathesis
rt	room temperature
s	singlet

sm	starting material
sat.	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tc	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl

7. Bibliography

[1] a) M. S. Butler, A. A. B. Robertson, M. A. Cooper, *Nat. Prod. Rep.* **2014**, *31*, 1612-1661; b) C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419-432.

[2] A. K. L. J. Cseke, P. B. Kaufman, S. Warber, J. A. Duke, H. L. Brielmann, *Natural Products from Plants*, 2nd. ed., Taylor & Francis, **2006**.

[3] H. Woodruff, *Science* **1980**, *208*, 1225-1229.

[4] G. L. Challis, S.-C. Tsai, *Nat. Prod. Rep.* **2014**, *31*, 1241-1241.

[5] J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2015**, *32*, 116-211.

[6] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311-335.

[7] H.-P. Lipp, C. Bokemeyer, *Pharm. Unserer Zeit* **2005**, *34*, 128-137.

[8] S. Krishna, L. Bustamante, R. K. Haynes, H. M. Staines, *Trends Pharmacol. Sci.* **2008**, *29*, 520-527.

[9] R. L. Bunch, J. M. Mcguire, Google Patents, **1953**.

[10] C. A. Townsend, Y. Ebizuka, *Natural Products Structural Diversity -I Secondary Metabolites: Organization and biosynthesis*, Elsevier, UK, **2010**.

[11] F. Wöhler, *Ann. Phys. Chem* **1828**, *12*, 253 - 256.

[12] a) A. Eschenmoser, C. Wintner, *Science* **1977**, *196*, 1410-1420; b) R. B. Woodward, *Pure Appl. Chem.* **1973**, *33*, 145.

[13] K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature* **1994**, *367*, 630-634.

[14] T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc.* **1992**, *114*, 3162-3164.

[15] a) M. J. Towle, K. A. Salvato, J. Budrow, B. F. Wels, G. Kuznetsov, K. K. Aalfs, S. Welsh, W. Zheng, B. M. Seletsky, M. H. Palme, G. J. Habgood, L. A. Singer, L. V. DiPietro, Y. Wang, J. J. Chen, D. A. Quincy, A. Davis, K. Yoshimatsu, Y. Kishi, M. J. Yu, B. A. Littlefield, *Cancer Res.* **2001**, *61*, 1013-1021; b) H. Ledford, *Nature* **2010**, *468*, 608 - 609.

[16] A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem. Int. Ed.* **2006**, *45*, 1034-1057.

[17] F. Bohlmann, T. Burkhardt, C. Zdero, *Naturally occuring acetylenes*, Academic Press, London, New York, **1973**.

[18] R. E. Minto, B. J. Blacklock, *Prog. Lipid. Res.* **2008**, *47*, 233-306.

[19] a) J. S. S. J. T. Mortensen, N. A. Sørensen, *Acta. Chem. Scand.* **1964**, *18*, 2392 - 2394; b) F. Bohlmann, K.-M. Kleine, *Chem. Ber.* **1965**, *98*, 3081-3086.

[20] M. A. E. Rodriguez, T. Nishida, S. Uehara, R. Wrangham, Z. Abramowski, A. Finlayson, G.H.N. Towers *Experentia* **1985**, *41*, 419 - 420.

[21] Y. Nakamura, N. Kawamoto, Y. Ohto, K. Torikai, A. Murakami, H. Ohigashi, *Cancer Lett.*, *140*, 37-45.

[22] N. Wang, X. Yao, R. Ishii, S. Kitanaka, *Chem. Pharm. Bull.* **2001**, *49*, 938-942.

[23] a) C. Chin, E. R. H. Jones, V. Thaller, R. T. Aplin, L. J. Durham, S. C. Cascon, W. B. Mors, B. M. Tursch, *Chem. Commun.* **1965**, 152-154; b) S. C. Cascon, W. B. Mors, B. M. Tursch, R. T. Aplin, L. J. Durham, *J. Am. Chem. Soc.* **1965**, *87*, 5237-5241.

[24] T. Kusumi, I. Ohtani, K. Nishiyama, H. Kakisawa, *Tetrahedron Lett.* **1987**, *28*, 3981-3984.

[25] a) C. Glaser, *Ber. Dt. Chem. Ges.* **1869**, *2*, 422-424; b) C. Glaser, *Ann. Chem. Pharm.* **1870**, 137 - 171.

[26] a) A. Baeyer, *Ber. Dt. Chem. Ges.* **1882**, *15*, 50-56; b) A. Baeyer, L. Landsberg, *Ber. Dt. Chem. Ges.* **1882**, *15*, 57-61.

[27] A. R. G. G. Eglington, *Chem. Ind. (London)* **1956**, 737 - 738.

[28] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320-3321.

[29] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657.

[30] a) P. C. W. Chodkiewicz, *C. R. Hebd. Seances Acad. Sci.* **1955**, 1055 - 1057; b) W. Chodkiewicz, *Ann. Chim. (Paris)* **1957**, *2*, 819 - 869.
[31] S. Lysenko, J. Volbeda, P. G. Jones, M. Tamm, *Angew. Chem. Int. Ed.* **2012**, *51*, 6757-6761.
[32] S. T. Li, T. Schnabel, S. Lysenko, K. Brandhorst, M. Tamm, *Chem. Commun.* **2013**, *49*, 7189-7191.
[33] F. Pennella, R. L. Banks, G. C. Bailey, *Chem. Commun.* **1968**, 1548-1549.
[34] A. Mortreux, M. Blanchard, *J. Chem. Soc., Chem. Commun.* **1974**, 786-787.
[35] P. Jean-Louis Hérisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161-176.
[36] T. J. Katz, J. McGinnis, *J. Am. Chem. Soc.* **1975**, *97*, 1592-1594.
[37] a) S. F. Pedersen, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *J. Am. Chem. Soc.* **1982**, *104*, 6808-6809; b) R. R. Schrock, *Acc. Chem. Res.* **1986**, *19*, 342-348; c) L. G. McCullough, R. R. Schrock, J. C. Dewan, J. C. Murdzek, *J. Am. Chem. Soc.* **1985**, *107*, 5987-5998; d) L. G. McCullough, R. R. Schrock, *J. Am. Chem. Soc.* **1984**, *106*, 4067-4068; e) M. L. Listemann, R. R. Schrock, *Organometallics* **1985**, *4*, 74-83.
[38] C. C. Cummins, *Chem. Commun.* **1998**, 1777-1786.
[39] a) A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J* **2001**, *7*, 5299-5317; b) A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453-9454.
[40] a) J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045-11057; b) J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard, A. Fürstner, *Chem. Eur. J* **2012**, *18*, 10281-10299.
[41] a) A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794-2819; b) A. Fürstner, *Science* **2013**, *341*, 1357.
[42] a) W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 6929-6933; b) K. Lehr, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 11373-11377; c) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471-13480; d) C. M. Neuhaus, M. Liniger, M. Stieger, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 5866-5870.
[43] P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh, A. Fürstner, *Chem. Eur. J* **2013**, *19*, 13047-13058.
[44] a) J. Willwacher, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 4217-4221; b) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 8739-8744; c) K. J. Ralston, H. C. Ramstadius, R. C. Brewster, H. S. Niblock, A. N. Hulme, *Angew. Chem. Int. Ed.* **2015**, *54*, 7086-7090; d) L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. Eur. J* **2013**, *19*, 4532-4537; e) A. D. Finke, J. S. Moore, in *Materials Science and Technology*, Wiley-VCH Verlag GmbH & Co. KGaA, **2006**.
[45] B. Zhang, Y. Wang, S.-P. Yang, Y. Zhou, W.-B. Wu, W. Tang, J.-P. Zuo, Y. Li, J.-M. Yue, *J. Am. Chem. Soc.* **2012**, *134*, 20605-20608.
[46] Y. Wang, Q.-F. Liu, J.-J. Xue, Y. Zhou, H.-C. Yu, S.-P. Yang, B. Zhang, J.-P. Zuo, Y. Li, J.-M. Yue, *Org. Lett.* **2014**, *16*, 2062-2065.
[47] J. M. Agbedahunsi, F. A. Fakoya, S. A. Adesanya, *Phytomedicine* **2004**, *11*, 504-508.
[48] C. A. Janeway, P. Travers, M. Walport, M. J. Shlomchik, *Immunobiology: The Immune System in Health and Disease*, 6th. ed., Garland Science Oxforshire, UK, **2004**.
[49] a) B. D. Kahan, *Nat. Rev. Immunol.* **2003**, *3*, 831-838; b) E. J. Corey, B. Czakó, L. Kürti, *Molecules and Medicine*, Wiley, New York, **2008**.
[50] a) U. Ramulu, D. Ramesh, S. Rajaram, S. P. Reddy, K. Venkatesham, Y. Venkateswarlu, *Tetrahedron Asymmetry* **2012**, *23*, 117-123; b) I. Shiina, Y.-j. Takasuna, R.-s. Suzuki, H. Oshiumi, Y. Komiyama, S. Hitomi, H. Fukui, *Org. Lett.* **2006**, *8*, 5279-5282; c) C.-J. Tang, Y. Wu, *Tetrahedron* **2007**, *63*, 4887-4906.
[51] H. Lindlar, *Helv. Chim. Acta* **1952**, *35*, 446-450.
[52] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn* **1979**, *52*, 1989-1993.
[53] L. F. Wiggins, *J. Chem. Soc.* **1946**, 13-14.

[54] S. Ghosh, T. K. Pradhan, *Synlett* **2007**, *15*, 2433-2435.
[55] a) S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 12432-12440; b) N. Kumar Bejjanki, A. Venkatesham, K. Balraju, K. Nagaiah, *Helv. Chim. Acta* **2013**, *96*, 1571-1578.
[56] B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556-557.
[57] D. K. Mohapatra, G. Umamaheshwar, R. N. Rao, T. S. Rao, S. K. R, J. S. Yadav, *Org. Lett.* **2015**, *17*, 979-981.
[58] I. Shiina, T. Mukaiyama, *Chem. Lett.* **1994**, *23*, 677-680.
[59] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.
[60] I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822-1830.
[61] J. Lee, J. S. Panek, *Org. Lett.* **2014**, *16*, 3320-3323.
[62] a) L. Fan, W. Zhao, W. Jiang, J. Zhang, *Chem. Eur. J* **2008**, *14*, 9139-9142; b) M. Turlington, Y. Du, S. G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat, L. Pu, *J. Am. Chem. Soc.* **2011**, *133*, 11780-11794.
[63] T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby, B. P. Woods, *Nature* **2012**, *490*, 208-212.
[64] P. Liu, M. J. Krische, K. N. Houk, *Chem. Eur. J* **2011**, *17*, 4021-4029.
[65] S. Kramer, J. L. H. Madsen, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 2758-2761.
[66] Y. Matsuda, S. Naoe, S. Oishi, N. Fujii, H. Ohno, *Chem. Eur. J* **2015**, *21*, 1463-1467.
[67] V. Gevorgyan, A. Takeda, M. Homma, N. Sadayori, U. Radhakrishnan, Y. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 6391-6402.
[68] I. Marek, C. Meyer, J.-F. Normant, *Org. Synth* **1997**, *74*, 194.
[69] V. Fiandanese, D. Bottalico, G. Marchese, A. Punzi, *Tetrahedron* **2004**, *60*, 11421-11425.
[70] B. M. Trost, V. S. Chan, D. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5186-5192.
[71] S. Huo, *Org. Lett.* **2003**, *5*, 423-425.
[72] A. Krasovskiy, B. H. Lipshutz, *Org. Lett.* **2011**, *13*, 3818-3821.
[73] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449-5452.
[74] S. Reber, T. F. Knöpfel, E. M. Carreira, *Tetrahedron* **2003**, *59*, 6813-6817.
[75] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040-6044.
[76] G. Seidel, A. Fürstner, *Chem. Commun.* **2012**, *48*, 2055-2070.
[77] Y. Xia, F. Qu, A. Maggiani, K. Sengupta, C. Liu, L. Peng, *Org. Lett.* **2011**, *13*, 4248-4251.
[78] M. Tsakos, E. S. Schaffert, L. L. Clement, N. L. Villadsen, T. B. Poulsen, *Nat. Prod. Rep.* **2015**, *32*, 605-632.
[79] F. Ungeheuer, A. Fürstner, *Chem. Eur. J* **2015**, *21*, 11387-11392.
[80] S. Schaubach, K. Gebauer, F. Ungeheuer, L. Hoffmeister, M. K. Ilg, C. Wirtz, A. Fürstner, *Chem. Eur. J* **2016**, *22*, 8494 - 8507.
[81] H. D. Verkruijsse, L. Brandsma, *Synth. Commun.* **1991**, *21*, 141-144.
[82] a) Z. Sato, T. Noda, Matsuda, S. Iwasaki, H. Kobayashi, J. Furukawa, S. Okuda, *Ann. Phytopathol. Soc. Jpn.* **1983**, *49*; b) H. K. S. Iwasaki, J. Furukawa, M. Namikoshi, S. Okuda, Z. Sato, I. Matsuda, T. Noda, *J. Antibiot.* **1984**, *37*, 354 - 362.
[83] a) S. Iwasaki, M. Namikoshi, H. Kobayashi, J. Furukawa, S. Okuda, *Chem. Pharm. Bull.* **1986**, *34*, 1387-1390; b) Y. K. S. Kiyoto, T. Kawakita, E. King, M. Okuhara, I. Uchida, H. Tanaka, M. Hashimoto, H. Terano, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1986**, *6*, 762 - 772.
[84] M. N. S. Iwasaki, H. Kobayashi, J. Furukawa, S. Okuda, A. Itai, A. Kasuya, Y. IItaka, Z. Sato, *J. Antibiot.* **1986**, *3*, 424 - 429.
[85] H. Kobayashi, S. Iwasaki, E. Yamada, S. Okuda, *J. Chem. Soc., Chem. Commun.* **1986**, 1702-1703.
[86] L. P. Partida-Martinez, C. Hertweck, *Nature* **2005**, *437*, 884-888.
[87] T. P. Nicholson, B. A. M. Rudd, M. Dawson, C. M. Lazarus, T. J. Simpson, R. J. Cox, *Chem. Biol.* **2001**, *8*, 157-178.
[88] J. Piel, D. Hui, N. Fusetani, S. Matsunaga, *Environ. Microbiol.* **2004**, *6*, 921-927.

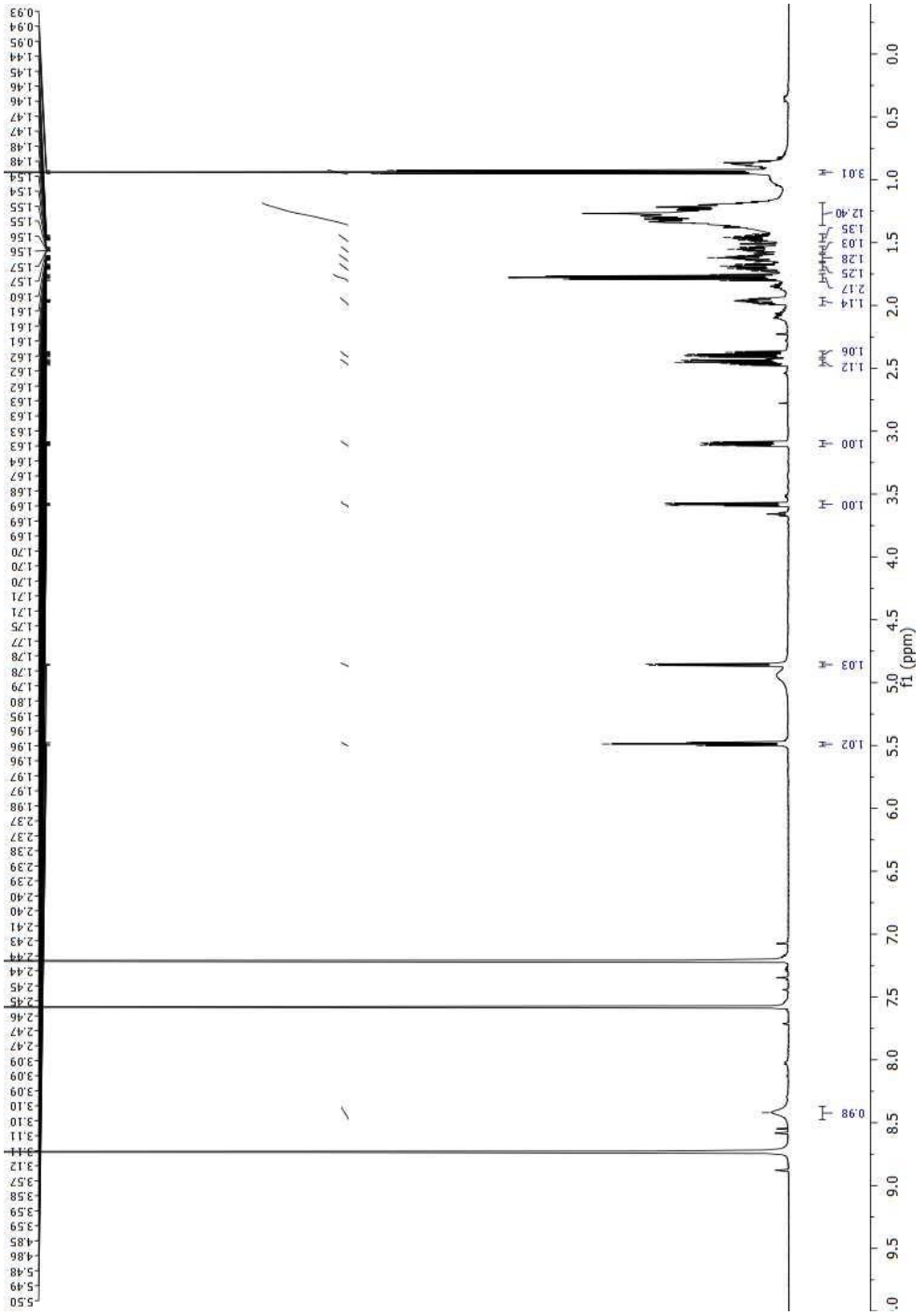
[89] K. Scherlach, L. P. Partida-Martinez, H.-M. Dahse, C. Hertweck, *J. Am. Chem. Soc.* **2006**, *128*, 11529-11536.
[90] E. Hamel, *Pharmacol. Therapeut.* **1992**, *55*, 31-51.
[91] T. Tsuruo, T. Oh-hara, H. Iida, S. Tsukagoshi, Z. Sato, I. Matsuda, S. Iwasaki, S. Okuda, F. Shimizu, K. Sasagawa, M. Fukami, K. Fukuda, M. Arakawa, *Cancer Res.* **1986**, *46*, 381-385.
[92] a) J. Hong, J. D. White, *Tetrahedron* **2004**, *60*, 5653-5681; b) H. R. Hendriks, J. Plowman, D. P. Berger, K. D. Paull, H. H. Fiebig, Ø. Fodstad, H. C. D.-v. d. Meulen, R. E. C. Henrar, H. M. Pinedo, G. Schwartsman, *Ann. Oncol.* **1992**, *3*, 755-763.
[93] a) Phase I clinical trials rhizoxin: M. A. Graham, D. Bissett, A. Setanoians, T. Hamilton, D. J. Kerr, R. Henrar, S. B. Kaye, *J. Natl. Cancer Inst.* **1992**, *84*, 494-500; b) D. Bissett, M. A. Graham, A. Setanoians, G. A. Chadwick, P. Wilson, I. Koier, R. Henrar, G. Schwartsmann, J. Cassidy, S. B. Kaye, D. J. Kerr, *Cancer Res.* **1992**, *52*, 2894-2898; c) A. W. Tolcher, C. Aylesworth, J. Rizzo, E. Izbicka, E. Campbell, J. Kuhn, G. Weiss, D. D. Von Hoff, E. K. Rowinsky, *Ann. Oncol.* **2000**, *11*, 333-338; d) J. H. Beijnen, K. P. Flora, G. W. Halbert, R. E. Henrar, J. A. Slack, *Br J Cancer* **1995**, *72*, 210-218; e) Phase II clinical trials rhizoxin: H. L. McLeod, L. S. Murray, J. Wanders, A. Setanoians, M. A. Graham, N. Pavlidis, B. Heinrich, W. W. ten Bokkel Huinink, D. J. Wagener, S. Aamdal, J. Verweij, *Br. J. Cancer* **1996**, *74*, 1944-1948; f) A. R. Hanauske, G. Catimel, S. Aamdal, W. ten Bokkel Huinink, R. Paridaens, N. Pavlidis, S. B. Kaye, A. te Velde, J. Wanders, J. Verweij, *Br. J. Cancer* **1996**, *73*, 397-399; g) S. Kaplan, A. R. Hanauske, N. Pavlidis, U. Bruntsch, A. te Velde, J. Wanders, B. Heinrich, J. Verweij, *Br. J. Cancer* **1996**, *73*, 403-405.
[94] a) R. L. Bai, G. R. Pettit, E. Hamel, *J. Biol. Chem.* **1990**, *265*, 17141-17149; b) M. Takahashi, S. Iwasaki, H. Kobayashi, S. Okuda, T. Murai, Y. Sato, *Biochimica et Biophysica Acta* **1987**, *926*, 215-223.
[95] A. S. Sullivan, V. Prasad, M. C. Roach, M. Takahashi, S. Iwasaki, R. F. Ludueña, *Cancer Res.* **1990**, *50*, 4277-4280.
[96] L. Amiri-Kordestani, G. M. Blumenthal, Q. C. Xu, L. Zhang, S. W. Tang, L. Ha, W. C. Weinberg, B. Chi, R. Candau-Chacon, P. Hughes, A. M. Russell, S. P. Miksinski, X. H. Chen, W. D. McGuinn, T. Palmby, S. J. Schrieber, Q. Liu, J. Wang, P. Song, N. Mehrotra, L. Skarupa, K. Clouse, A. Al-Hakim, R. Sridhara, A. Ibrahim, R. Justice, R. Pazdur, P. Cortazar, *Clin. Cancer Res.* **2014**, *20*, 4436-4441.
[97] A. E. Prota, K. Bargsten, J. F. Diaz, M. Marsh, C. Cuevas, M. Liniger, C. Neuhaus, J. M. Andreu, K.-H. Altmann, M. O. Steinmetz, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 13817-13821.
[98] a) S. Iwasaki, *Med. Res. Rev.* **1993**, *13*, 183-198; b) Y. O. Y. Kato, T. Imada, S. Iwasaki, N. Shimazaki, T. Kobayashi, T. Komai, *J. Antibiot.*, *1*, 66 - 75.
[99] a) M. Nakada, S. Kobayashi, M. Shibasaki, S. Iwasaki, M. Ohno, *Tetrahedron Lett.* **1993**, *34*, 1039-1042; b) M. Nakada, S. Kobayashi, S. Iwasaki, M. Ohno, *Tetrahedron Lett.* **1993**, *34*, 1035-1038.
[100] a) A. S. Kende, B. E. Blass, J. R. Henry, *Tetrahedron Lett.* **1995**, *36*, 4741-4744; b) D. R. Williams, K. M. Werner, B. Feng, *Tetrahedron Lett.* **1997**, *38*, 6825-6828; c) J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, *68*, 4215-4234; d) G. E. Keck, C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covel, M. D. McLaws, D. Krishnamurthy, V. J. Cee, *Angew. Chem. Int. Ed.* **2001**, *40*, 231-234; e) I. S. Mitchell, G. Pattenden, J. Stonehouse, *Org. Biomol. Chem.* **2005**, *3*, 4412-4431; f) J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. Nylund Kolz, B. W. Phillips, *J. Org. Chem.* **2002**, *67*, 7750-7760; g) Y. Jiang, J. Hong, S. D. Burke, *Org. Lett.* **2004**, *6*, 1445-1448; h) M.-A. N'Zoutani, N. Lensen, A. Pancrazi, J. Ardisson, *Synlett* **2005**, *2005*, 491-495.
[101] J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *Tetrahedron Lett.* **1999**, *40*, 4145-4148.
[102] a) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923; b) H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570-1576.

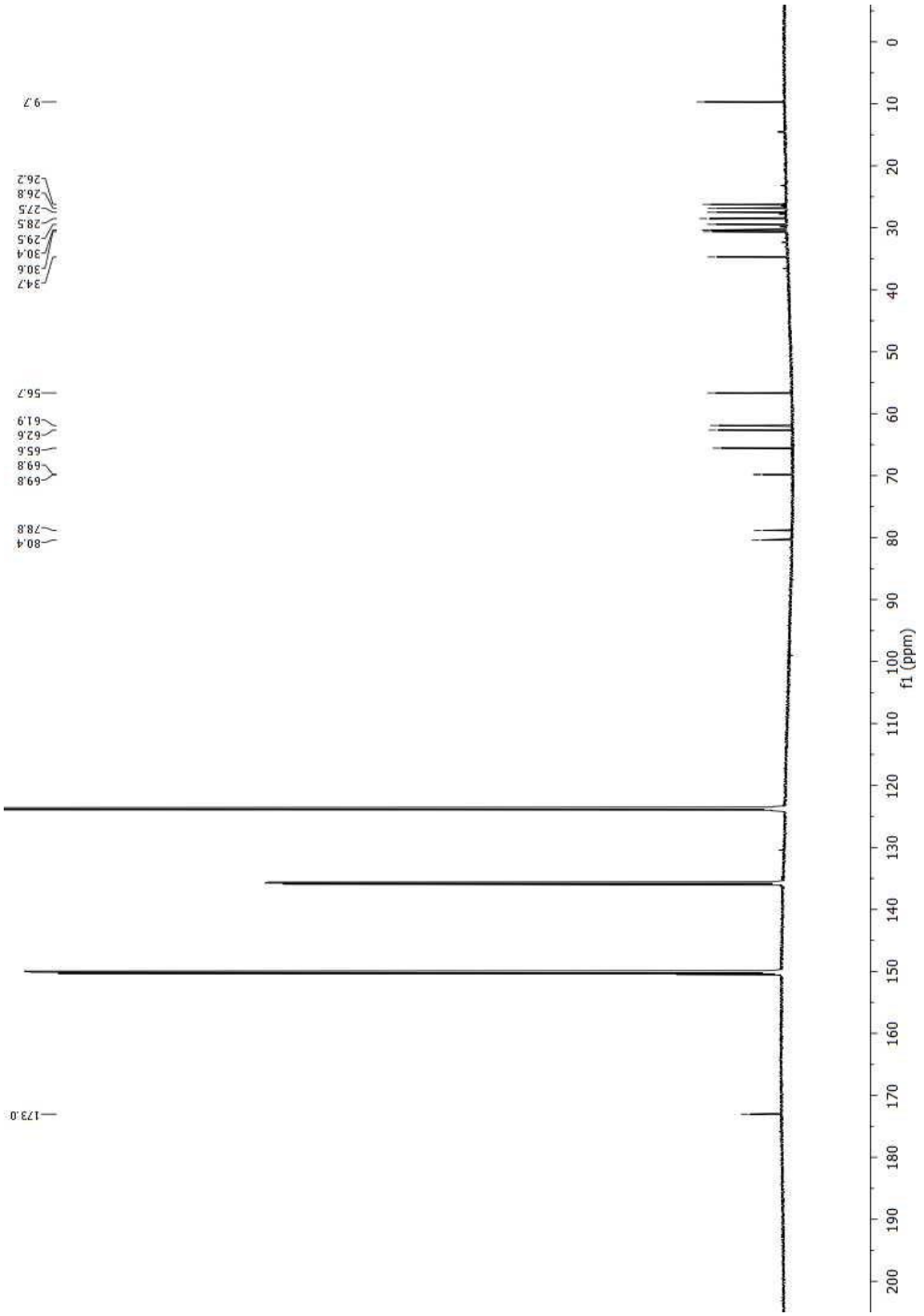
[103] a) M. Fetizon, V. Balogh, M. Golfier, *J. Org. Chem.* **1971**, *36*, 1339-1341; b) G. Tojo, M. Fernández, *Selective Oxidations of Allylic and Benzylic Alcohols in the Presence of Saturated Alcohols*, Springer US, Boston, MA, **2006**.
[104] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.
[105] a) R. F. Heck, in *Organic Reactions*, John Wiley & Sons, Inc., **2004**; b) T. Jeffery, *Tetrahedron* **1996**, *52*, 10113-10130.
[106] S. Takano, K. Inomata, K. Samizu, S. Tomita, M. Yanase, M. Suzuki, Y. Iwabuchi, T. Sugihara, K. Ogasawara, *Chem. Lett.* **1989**, *18*, 1283-1284.
[107] E. J. Corey, C. M. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
[108] M. Scheck, H. Waldmann, *Can. J. Chem.* **2002**, *80*, 571-576.
[109] A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243-251.
[110] W. M. Pearlman, *Tetrahedron Lett.* **1967**, *8*, 1663-1664.
[111] M. T. Crimmins, A. C. DeBaillie, *J. Am. Chem. Soc.* **2006**, *128*, 4936-4937.
[112] a) K. Radkowski, B. Sundararaju, A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 355-360; b) B. Sundararaju, A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 14050-14054; c) S. M. Rummelt, K. Radkowski, D.-A. Roşca, A. Fürstner, *J. Am. Chem. Soc.* **2015**, *137*, 5506-5519; d) S. M. Rummelt, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 3626-3630.
[113] a) M. Fuchs, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 3978-3982; b) S. M. Rummelt, J. Preindl, H. Sommer, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 6241-6245.
[114] S. Melnes, A. Bayer, O. R. Gautun, *Tetrahedron* **2012**, *68*, 8463-8471.
[115] B. Wrackmeyer, *Chem. Unserer Zeit* **1994**, *28*, 309-320.
[116] a) T. Kull, R. Peters, *Angew. Chem. Int. Ed.* **2008**, *47*, 5461-5464; b) T. Kull, J. Cabrera, R. Peters, *Chem. Eur. J* **2010**, *16*, 9132-9139.
[117] B. M. Trost, B. L. Ashfeld, *Org. Lett.* **2008**, *10*, 1893-1896.
[118] A. Rodríguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1999**, *40*, 5161-5164.
[119] D. H. T. Phan, B. Kim, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 15608-15609.
[120] Q. Wang, C. Wilson, A. J. Blake, S. R. Collinson, P. A. Tasker, M. Schröder, *Tetrahedron Lett.* **2006**, *47*, 8983-8987.
[121] P. Meier, F. Broghammer, K. Latendorf, G. Rauhut, R. Peters, *Molecules* **2012**, *17*, 7121.
[122] H. W. Yang, D. Romo, *J. Org. Chem.* **1997**, *62*, 4-5.
[123] H. H. K. Hirai, I. Mikoshiba, *Heterocycles* **1994**, *38*, 281 - 282.
[124] H. W. Yang, C. Zhao, D. Romo, *Tetrahedron* **1997**, *53*, 16471-16488.
[125] a) P.-Y. Yang, K. Liu, M. H. Ngai, M. J. Lear, M. R. Wenk, S. Q. Yao, *J. Am. Chem. Soc.* **2010**, *132*, 656-666; b) R. D. Richardson, G. Ma, Y. Oyola, M. Zancanella, L. M. Knowles, P. Cieplak, D. Romo, J. W. Smith, *J. Med. Chem.* **2008**, *51*, 5285-5296.
[126] C. Zhao, T. A. Mitchell, R. Vallakati, L. M. Pérez, D. Romo, *J. Am. Chem. Soc.* **2012**, *134*, 3084-3094.
[127] a) R. Annunziata, M. Cinquini, F. Cozzi, P. G. Cozzi, E. Consolandi, *Tetrahedron* **1991**, *47*, 7897-7910; b) K.-H. Suh, D.-J. Choo, *Tetrahedron Lett.* **1995**, *36*, 6109-6112.
[128] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.
[129] a) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas, O. Loiseleur, J. Genovino, C. Moessner, *Org. Biomol. Chem.* **2012**, *10*, 5861-5872; b) F. Sato, H. Ishikawa, M. Sato, *Tetrahedron Lett.* **1981**, *22*, 85-88.
[130] a) Y.-G. Suh, S.-Y. Seo, J.-K. Jung, O.-H. Park, R.-O. Jeon, *Tetrahedron Lett.* **2001**, *42*, 1691-1694; b) Y.-G. Suh, J.-K. Jung, S.-Y. Seo, K.-H. Min, D.-Y. Shin, Y.-S. Lee, S.-H. Kim, H.-J. Park, *J. Org. Chem.* **2002**, *67*, 4127-4137.
[131] a) K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem. Int. Ed.* **2000**, *39*, 2481-2483; b) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333-4339.
[132] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497-500.
[133] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449.

[134] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
[135] T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1982**, *23*, 3597-3600.
[136] Sergei I. Kozhushkov, R. Langer, Dmitrii S. Yufit, Judith A. K. Howard, H. Schill, D. Demus, K. Miyazawa, A. de Meijere, *Eur. J. Org. Chem.* **2004**, *2004*, 289-303.
[137] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973-1976.
[138] J. K. Cha, W. J. Christ, Y. Kishi, *Tetrahedron Lett.* **1983**, *24*, 3943-3946.
[139] J. K. Cha, W. J. Christ, Y. Kishi, *Tetrahedron* **1984**, *40*, 2247-2255.
[140] J.-M. Vatèle, *Synlett* **2006**, *2006*, 2055-2058.
[141] D. J. Schauer, P. Helquist, *Synthesis* **2006**, 3654-3660.
[142] B. M. Trost, W. M. Seganish, C. K. Chung, D. Amans, *Chem. Eur. J* **2012**, *18*, 2948-2960.
[143] T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protocols* **2007**, *2*, 2451-2458.

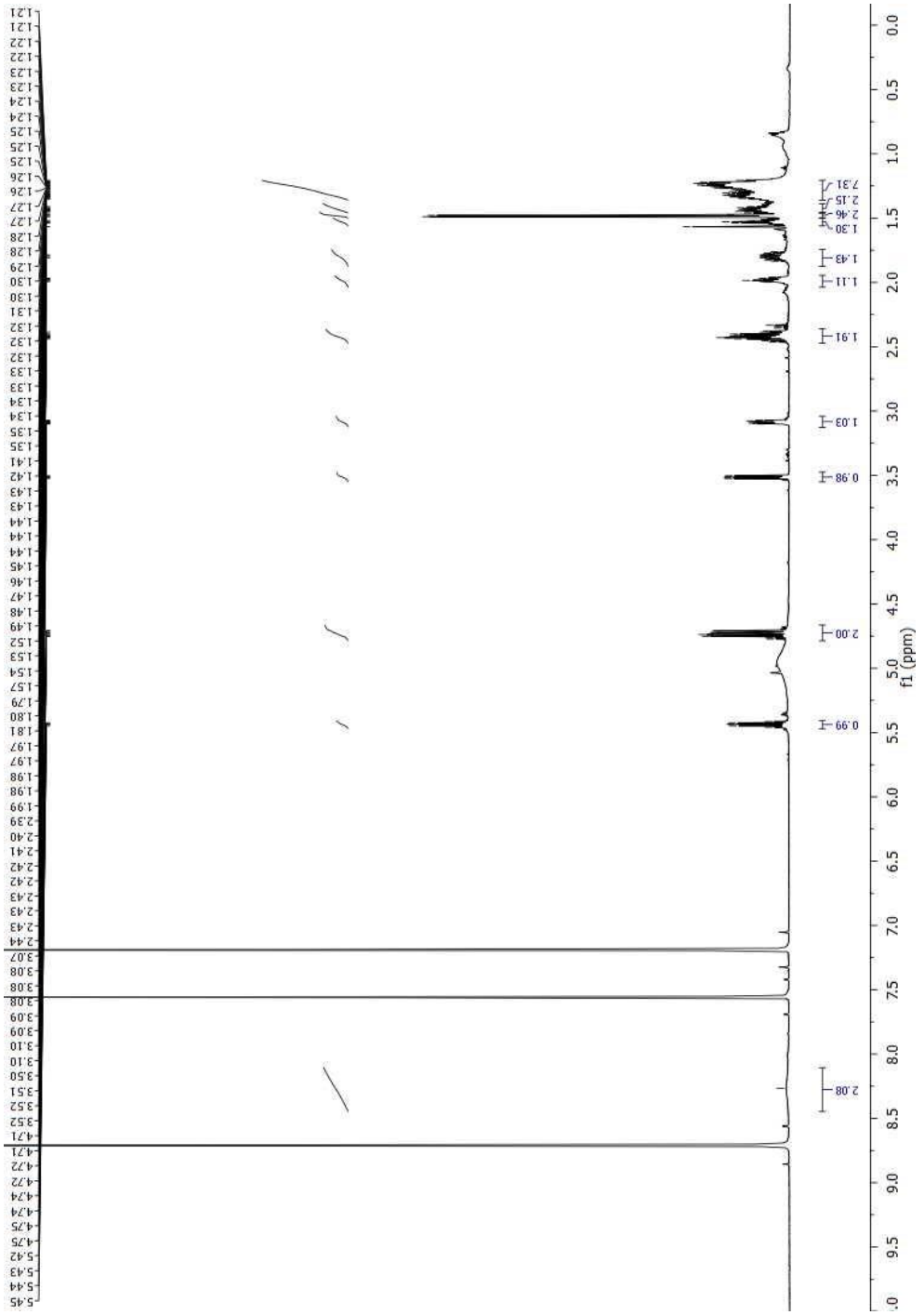
8. Appendix

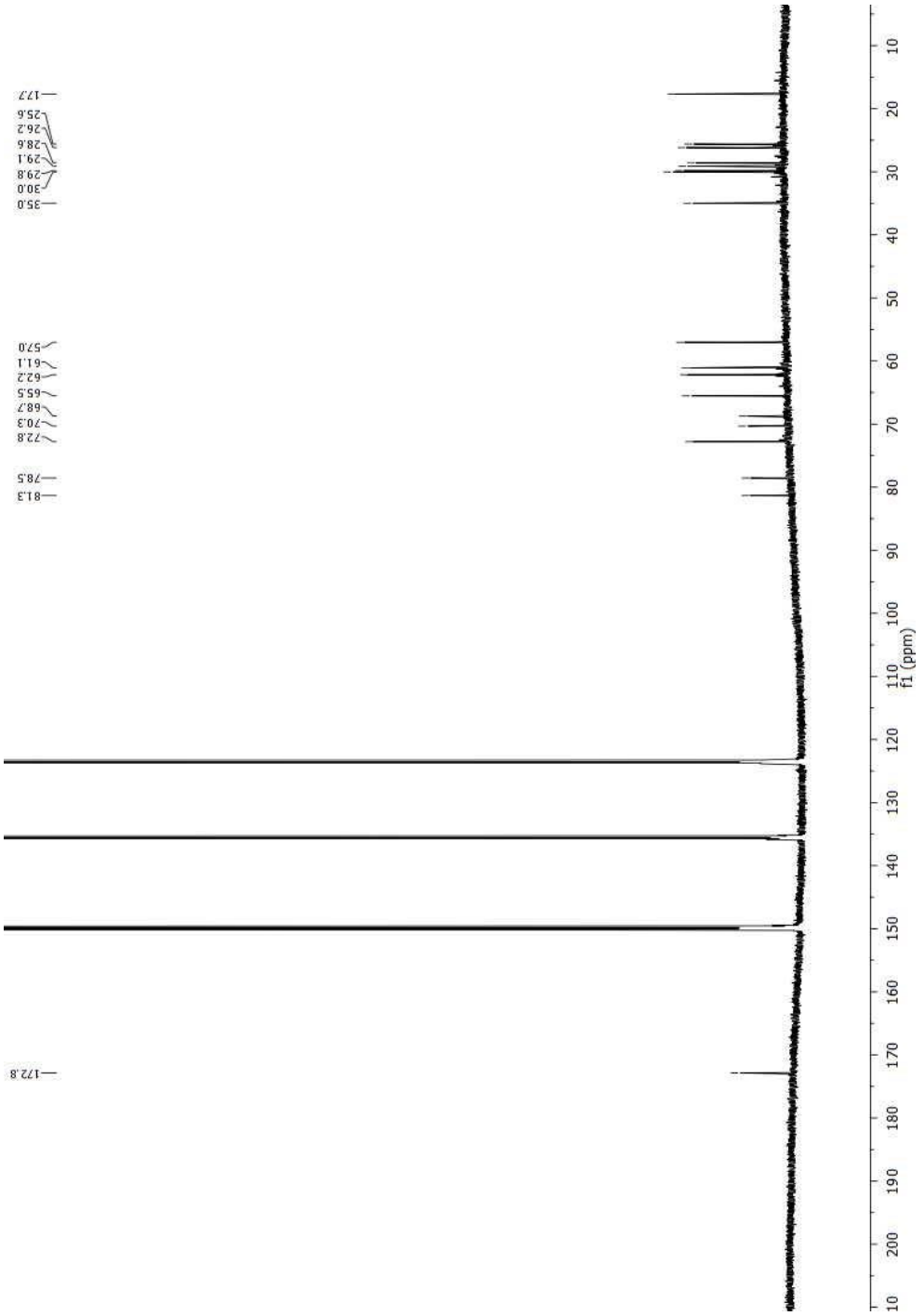
8.1 Spectra of synthetic ivorenolide B



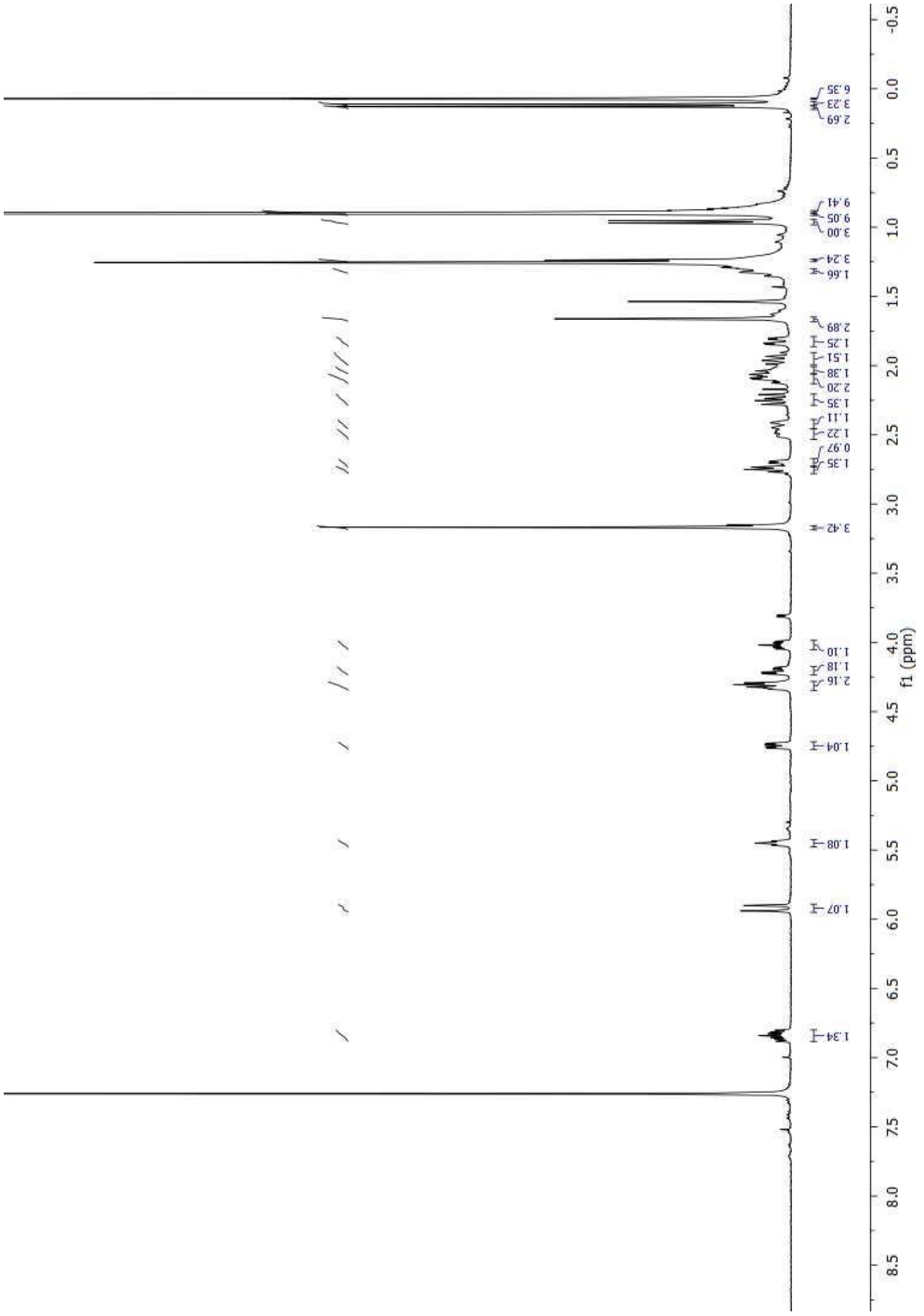

9.7
26.2
26.8
27.5
28.5
29.5
30.4
30.6
34.7
56.7
61.9
62.6
65.6
69.8
69.8
78.8
80.4
173.0
f1 (ppm)

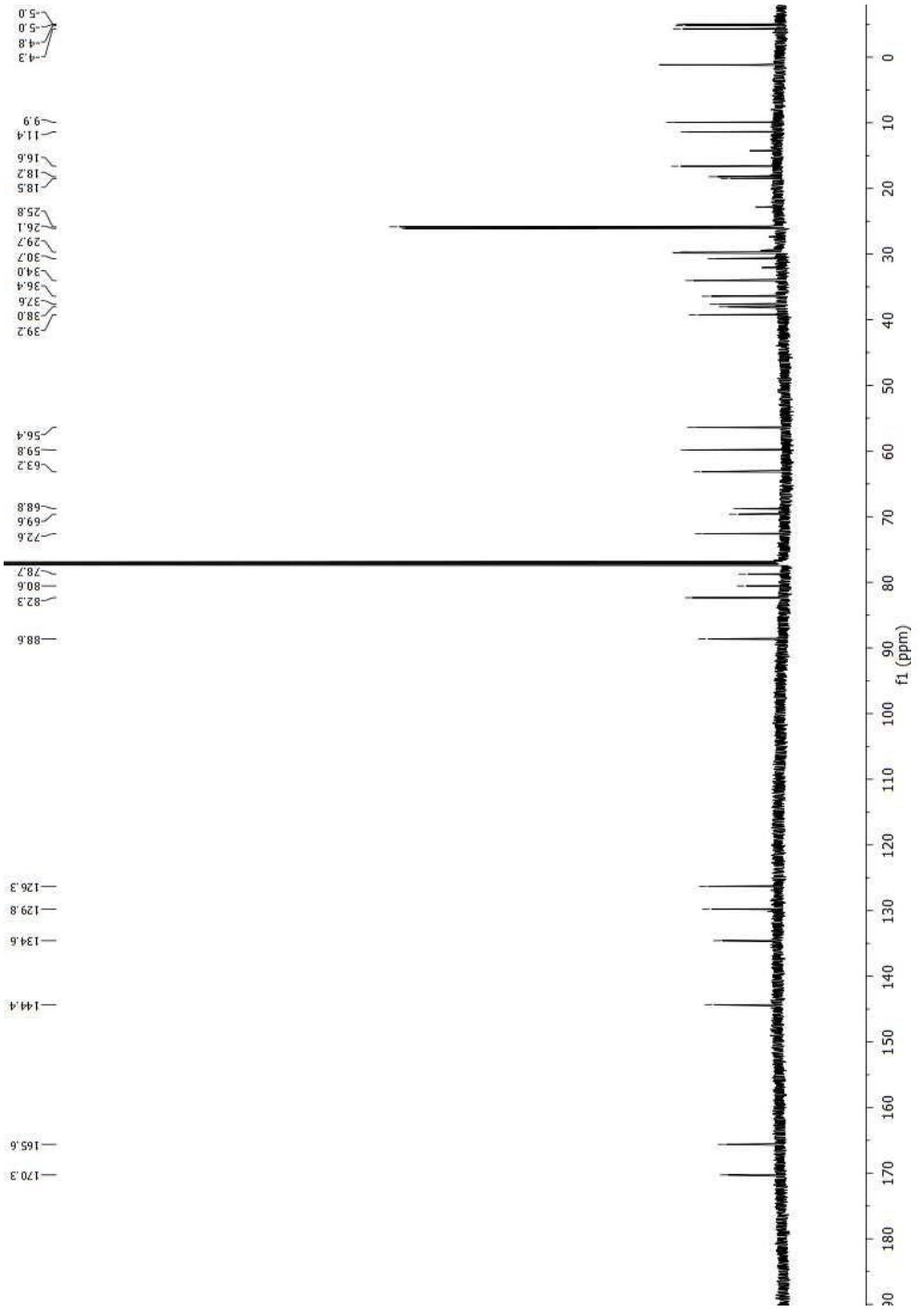
8.2 Spectra of synthetic ivorenolide A




172.8
81.3
78.5
72.8
70.3
68.7
65.5
62.2
61.1
57.0
35.0
30.0
29.8
29.1
28.6
26.2
25.6
17.7
f1 (ppm)

8.3 Spectra of macrocycle 320




-5.0
-5.0
-4.8
-4.3
9.9
11.4
16.6
18.2
18.5
25.8
26.1
29.7
30.7
34.0
36.4
37.6
38.0
39.2
56.4
59.8
63.2
68.8
69.6
72.6
78.7
80.6
82.3
88.6
126.3
129.8
134.6
144.4
165.6
170.3
f1 (ppm)