Max-Planck-Institut
für Kohlenforschung

technische universität
dortmund

Totalsynthese von Belizentrin Methylester

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Ein enantiodivergenter Zugang zu chiralen Allenen

Dissertation

Zur Erlangung des akademischen Grades eines
Doktors der Naturwissenschaften
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Der Fakultät für Chemie und Chemische Biologie
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1. Berichterstatter: Prof. Dr. Alois Fürstner
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Die vorliegende Arbeit entstand unter der Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Jänner 2015 bis November 2018 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits veröffentlicht:

Felix Anderl, Sylvester Größl, Conny Wirtz, Alois Fürstner: "Total Synthesis of Belizentrin Methyl Ester: Report on a Likely Conquest"
Angew. Chem. Int. Ed. **2018**, *57*, 10712–10717;

Die praktischen Arbeiten erfolgten zum Teil in Zusammenarbeit mit Dr. Sylvester Größl, Pascal Ortsack (Kapitel 4), Karin Radkowski und Dr. Macarena Corro Moron (Kapitel 5). Die beschriebenen Ergebnisse bilden eine vollständige Darstellung dieser gemeinsamen Arbeiten. Die von diesen Mitarbeitern alleinverantwortlich erzielten Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

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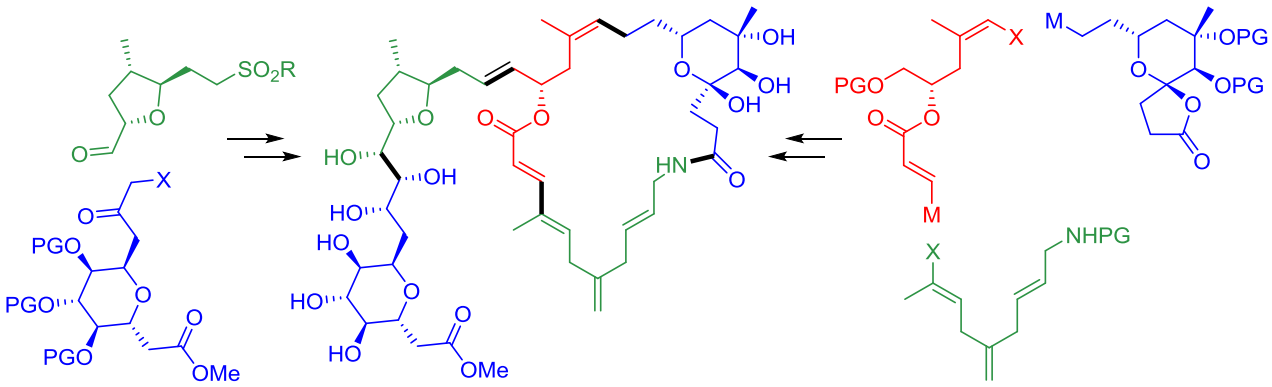
Inhalt:

Die Synthese von Naturstoffen ist seit fast 200 Jahren eine Kerndisziplin der organischen Chemie. Dabei bieten komplexe natürliche Moleküle immer neue Herausforderungen für Chemiker und verlangen dadurch neue Lösungen. Besonders marine (Mikro-)Organismen haben sich als eine ergiebige Quelle verschiedenster chemisch wie auch biologisch interessanter Naturstoffe erwiesen.

Die vorliegende Arbeit behandelt hauptsächlich die Totalsynthese von Belizentrin Methylester. Die Stammverbindung Belizentrin wurde 2014 aus dem Dinoflagellaten *Prorocentrum belizeanum* isoliert. Schon während der Isolierung hat sich diese Verbindung als sehr instabil gezeigt, was sich auch im Lauf unseres Syntheseprojektes bestätigte. Im Zuge dessen fanden wir aber auch, dass der entsprechende Methylester noch immer empfindlich, aber ausreichend stabil ist. Schließlich gelang eine sehr konvergente Totalsynthese dieser Verbindung.

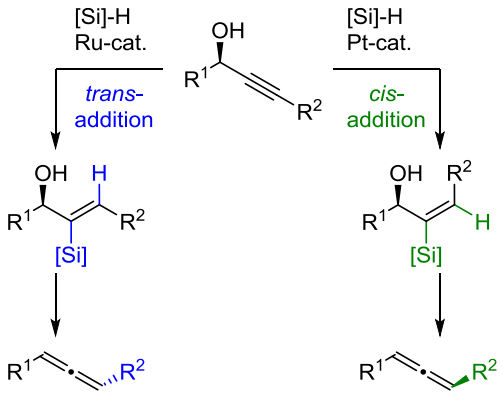


Diese Synthese wurde in Zusammenarbeit mit Dr. Sylvester Größl durchgeführt, der die polyhydroxyierte Seitenkette hergestellt hat. Seine Beiträge sind an den entsprechenden Stellen gekennzeichnet. Die Schlüsselschritte in der Synthese des makrozyklischen Teiles des Moleküls waren zwei Palladium-katalysierte Kreuzkupplungen um drei Fragmente zu verbinden, gefolgt von der intramolekularen Aminolyse eines Spirolactons um den Makrolactam-Ring zu schließen. Anschließend wurden Makrozyklus und Seitenkette nach wenigen Schutzgruppen- und Redox-Manipulationen durch eine *E*-selektive Julia-Kocienski Olefinierung zusammen gefügt. Globale Entschützung lieferte schließlich den zuvor genannten Belizentrin Methylester.

Zusätzlich dazu wurde eine enantiodivergente Methode zur Synthese chiraler Allene ausgehend von propargylischen Alkoholen entwickelt. Dieses Projekt wurde in Zusammenarbeit mit Karin Radkowski und Dr. Macarena Corro-Moron verfolgt.

Sowohl als Strukturelement in Naturstoffen und pharmazeutisch relevanten Verbindungen als auch als Intermediate in der organischen Synthese spielen Allene eine interessante Rolle. Sie zeigen axiale Chiralität und besitzen vielfältige Reaktivität, vor allem gegenüber Übergangsmetallen. Diese Eigenschaften machen sie zu nützlichen (Zwischen-) Produkten.

Verschiedene Strategien sind beschrieben worden, um propargylische Alkohole in Allene zu überführen und viele dieser Methoden sind stereospezifisch, so dass die stereogene Information des chiralen Alkohols auf das Allen übertragen werden kann. Ein Nachteil der bekannten Methoden besteht darin, dass aus einem Enantiomer des Ausgangsmaterials nur ein Enantiomer des Produkts zugänglich ist. Da man die Enantiomere von Allenen als geometrische Isomere an einer Doppelbindung betrachten kann, bot sich die Möglichkeit, beide Enantiomere durch stereospezifische Bildung der „zweiten“ Doppelbindung ausgehend von „*E*/*Z*“-isomeren Vorläufern zu erreichen.

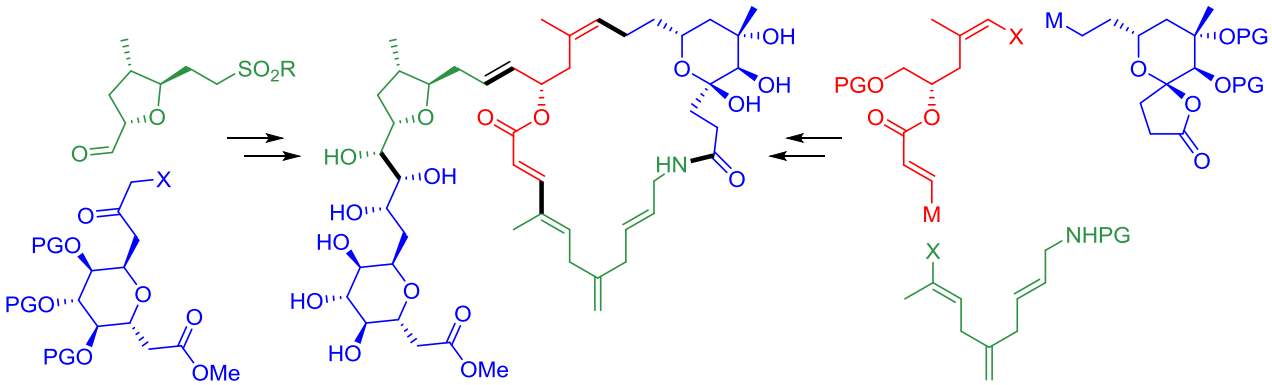


Als geeignete Intermediate dafür erwiesen sich Alkenylsilane, die durch *cis*- bzw. *trans*-selektive Hydrosilylierung von propargylischen Alkoholen zugänglich sind. Diese Verbindungen gehen in Gegenwart einer geeigneten Base und einer $Cu^{(I)}$ Quelle eine Brook Umlagerung ein, der eine stereospezifischen Eliminierung zum Allen folgt. Dadurch sind beide Enantiomere eines Allenes ausgehend von nur einem Enantiomer eines propargylischen Alkohols zugänglich. Diese Methode wurde erfolgreich an einer Auswahl propargylischer Alkohole erprobt.

Abstract:

The synthesis of natural products has been a core discipline of organic chemistry for almost 200 years. Complex molecules offer boundless challenges for synthetic chemists and demand new solutions. Marine (micro-) organisms have proven to be an especially rich source of various chemically as well as biologically interesting natural products.

The present thesis describes the total synthesis of belizentrin methyl ester. The parent compound belizentrin was isolated from the dinoflagellate *Prorocentrum belizeanum* in 2014. Already during the isolation, belizentrin proved to be a very unstable compound; this was corroborated during our campaign towards its synthesis. We also found that the corresponding methyl ester was sufficiently stable, albeit still sensitive. Our efforts eventually resulted in a highly convergent total synthesis of this compound in a longest linear sequence of 19 steps.



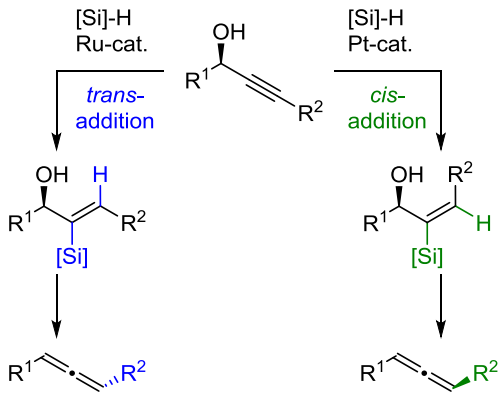
This work was conducted in collaboration with Dr. Sylvester Größl, who synthesized the polyhydroxyated sidechain; his contributions are acknowledged and described in the relevant sections of the following thesis.

The key steps during the synthesis of the macrocyclic portion of the molecule were two palladium catalyzed cross coupling reactions to assemble three fragments, followed by the intramolecular aminolysis of a spirolactone to close the macrolactam ring. After a few protecting group and redox manipulations, the macrocycle and the sidechain were connected by an *E*-selective Julia-Kocienski olefination. Finally, global deprotection yielded the aforementioned belizentrin methyl ester.

Additionally, an enantiodivergent approach to chiral allenes starting from propargylic alcohols was developed. This project was conducted in collaboration with Karin Radkowski and Dr. Macarena Corro Moron.

Chiral allenes play an interesting role as structural element in both natural products and synthetic pharmaceutical agents. Furthermore, they are valuable synthetic intermediates.

Different strategies for the stereospecific conversion of propargylic alcohols to allenes have been reported. The concept harnesses the stereochemical information of chiral propargylic alcohols to construct chiral allenes. A drawback of the known methods is that one enantiomer of the starting alcohol leads to only one enantiomer of the product allene. As the enantiomers of allenes can be viewed as geometrical isomers at one of the double bonds, we envisioned that the stereospecific construction of the "second" double bond from "*E*/*Z*"-isomeric precursors would provide access to both enantiomers of the allene in question.



We found isomeric alkenylsilanes, which were accessed via the *cis*- or *trans*-selective hydrosilylation of propargylic alcohols, to be suitable precursors. In the presence of a base and a $Cu^{(I)}$ source, these compounds undergo a facile and stereospecific Brook rearrangement with consecutive elimination to produce allenes. Due to the stereocontrolled hydrosilylation, both enantiomers of an allene are accessible from a single enantiomer of the starting alcohol. This method has been successfully tested on a selection of propargylic alcohols.

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Total Synthesis of Belizentrin Methyl Ester

&

An Enantiodivergent Approach To Chiral Allenes

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1 Introduction

Natural products were for a long time the only source of biologically active compounds available to mankind. In the course of the 19th century scientists have established that the active ingredients of many ill-defined natural materials (*e.g.* opium resin, cinchona bark etc.) were chemically well-defined entities. [1, 2] Subsequent to their isolation, chemists sought to determine the structure of these compounds. However due to lack of modern spectroscopic methods, chemical degradation to already known materials was the major method to gain insight into the chemical structure at the time. Ultimately armed with the knowledge of structural elements within the molecule of interest, one could then attempt to reconstruct the original compound synthetically. The comparison of such a synthetic material, which had been prepared by known and reliable chemical methods, with the natural compound would either corroborate or disprove a proposed structure. Two representative milestones in the development of chemical synthesis were the synthesis of the alkaloid coniine by Ladenburg and the syntheses of several hexoses by Fischer at the end of the 19th century. [3, 4, 5] These spectacular achievements mark the beginning of truly rational design of synthesis as well as deduction of fundamental structural and theoretical insights from the experimental results. From the turn of the century onwards more and more complex and demanding compounds have been synthesized; these endeavors must be seen in the light of the preparative and analytical tools available at this time.

With the advent of spectroscopic methods, chemical degradation techniques gradually lost their importance but remained an auxiliary tool in structure determination. In contrast, the partial synthesis and total synthesis from known materials retained importance as it allowed not only to establish the structure of a natural product firmly, but also to obtain this material and its artificial analogues at will, independent of the natural source. The development of the field was accelerated by the pharmacological interest in certain compounds and ultimately led to achievements whose impact were not restricted to the scientific community alone. The broad use of synthetic or semi-synthetic drugs (*e.g.* aspirin, salvarsan, atebrin, β-lactam antibiotics, steroids, etc.) had a tremendous impact on medicine and modern society in general.

As many chemically interesting and challenging natural products also exhibit intriguing biological activities, a multidisciplinary approach is especially beneficial for the sciences involved. In this context the isolation, characterization and biological evaluation of natural products, especially secondary metabolites, have proven to be a particularly rewarding subject. Insights in the nature and mechanism of the interactions between them and their target proteins can eventually lead to the rational design of *e.g.* agrochemical- or pharmaceutical agents.

As the synthetic and analytic techniques became more and more established, the area of total synthesis also turned into a testing- and play-ground for synthetic methodology. This offers the invaluable possibility to examine new reactions or methods under realistic and demanding conditions and goes hand-in-hand with the development of new methods were they are needed. As many biologically relevant compounds present chemically fascinating and synthetically very challenging features, the struggle to overcome such obstacles has led to the development of new techniques and the acquisition of valuable knowledge. Other branches of chemistry have benefitted amply from such achievements, as for example the formulation of the "Woodward-Hoffmann" rules was inspired partially by total synthesis.[6, 7]

Finally there is, in my opinion, a psychological reason to pursue total synthesis. It offers the executing chemist, in one way or another, the naïve joy of shaping matter. From childhood on, many humans enjoy playing with different things, molding them into forms at their will. The process of building anything for the first time, regardless what it is, lets the "constructor" learn about it and in the end enjoy the pride of creation. While this holds true for childish "targets" like sandcastles or treehouses, it is in principle the same for any construction, including chemical synthesis. The intense desire to reach a certain, often self-chosen, objective can provide just as much driving force as the aforementioned scientific reasons. In this context the description of "*chemistry as a game of Lego*" appears very well phrased.[8]

2 Belizentrin

2.1 Natural Background

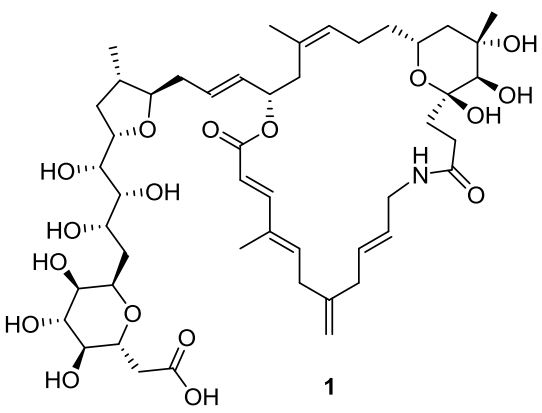
The target of our synthetic efforts, belizentrin (**1**), was isolated in 2014 by the group of Daranas from cultures of the dinoflagellate *Prorocentrum belizeanum*, native to the Indian Ocean. [9] Dinoflagellates comprise a large group of eukaryotes living in aquatic environments. They occur in both freshwater and saltwater in a multitude of shapes and forms. Their distinguishing feature is a pair of non-identical flagella which led to their name (δῖνος dinos from the Greek for "whirling", and flagellum the Latin for "whip ") and which are used for their propulsion. Some classes live in symbiosis with other organisms such as corals, sea anemones or certain jellyfishes.[10] These “living arrangements” have led in some cases to misinterpretations that the host organism was responsible for metabolites actually produced by the participating microorganism. The same misinterpretation can also occur for marine predators that ingest dinoflagellates. Be it directly or via a detour through a predator or symbiotic organism, dinoflagellates have been recognized as rich sources of biologically potent and chemically fascinating metabolites, of which the majority are of polyketide origin. Whether they are potent toxins responsible for shellfish poisoning or the toxic “red tide”, or clinically promising lead structures, the interdisciplinary investigation of these compounds, their production and mode of action has proven a rewarding topic. [11, 12, 13]

2.2 Isolation

The organism *Prorocentrum belizeanum* was suffiently productive in an artificial environment, to allow the efficient cultivation. From said large scale culture (1000 L), the labile and structurally complex metabolite was obtained in a yield of 3.1 mg. Isolation was facilitated by the nature of the producing organism: It lives on the bottom of the sea (or fermenter) therefore the isolation team was able to remove the supernatant medium easily and gather useful amounts of biomass. The cells were subjected to conventional solvent extraction, first with acetone and then with methanol. Belizentrin was found to accumulate in the methanol fractions, from which it was isolated by the means of repeated chromatography over different stationary phases. The high polarity of belizentrin rendered conventional purification by normal phase chromatography over

silica or alumina impractical, but a pre-separation on sephadex and final C 18-reversed phase HPLC purification led to the isolation of **1** in a sufficiently pure state such that its structural and biological properties could be investigated. The authors noted the tendency of **1** to decompose under seemingly innocent conditions. During the course of the isolation and purification, the molecule's very strong UV absorption, with a maximum at ~ 270 nm due to the conjugated dienoate chromophore, was an invaluable help. This property was exploited during our campaign towards **1** as means of tracing the presence and fate of minute amounts of compounds containing this moiety by HPLC and HPLC-MS.

2.3 Structural Investigation



Scheme 2.1 Proposed structure of belizentrin

With the small available quantity of **1**, the elucidation of its constitution, relative and absolute stereochemistry was undertaken. The amorphous state of the sample prevented the use of X-ray diffraction analysis; therefore spectroscopic methods were mainly employed. High resolution mass spectrometry was used to establish the empirical formula, and UV and IR spectroscopy helped to identify certain functionalities within the molecule, but NMR spectroscopy took a pivotal position in establishing the connectivity. A variety of one- and two-dimensional techniques were used to achieve this task. These measurements were unfortunately plagued by the aforementioned instability of belizentrin. Due to this rapid degradation, time consuming NMR experiments were thwarted; for example no one dimensional ^{13}C NMR spectrum could be recorded without the sample decomposing over the course of the acquisition time. Despite these obstacles, and with the aid of much more sensitive (although not as well resolved) two dimensional methods like HSQC and HMBC, ^{13}C NMR chemical shifts were deduced. Based on the collected data, it was possible to determine the connectivity and the relative stereochemistry within the sufficiently rigid 5- and 6-membered rings of the molecule. The more challenging aspect of the structure elucidation was the determination of the stereochemistry in the more flexible regions of **1**, and the eventual relative arrangement of all individually clarified fragments to each other. The available spectroscopic data could not provide

any unambiguous evidence, so the isolation team had to resort to theoretical methods. Based on calculations, the most likely relative configuration in accordance with the spectral properties was proposed. Because of the somewhat speculative nature of their deduction, the authors also pointed out that the relative stereochemistry between the sidechain and the macrocycle was arbitrarily assigned (Scheme 2.1). The determination of the absolute stereochemistry of any molecule based on NMR spectroscopy alone is hardly possible. Since the chemical degradation of this complex molecule into smaller fragments of known absolute configuration was not possible due to the scarce supply and high value of the compound, the answer to this question was left to total synthesis. In conclusion, the impressive work by the Daranas group is a remarkable testament to the power of modern analytical techniques, but also highlights the still important role of total synthesis to corroborate a molecules absolute structure.

2.4 Biological Investigation

Investigations of the biological behavior of belizentrin were prompted by the previously mentioned examples of strong biological activity exhibited by comparable metabolites. These were once more curtailed by its omnipresent instability. Despite this difficulty, *in vitro* assays revealed a strong influence on cultured neurons at nanomolar concentrations. Since these tests were conducted over a period of 24 h, the influence of concomitant decomposition of **1** on the outcome could not be judged. Because only one type of assay was included, a more reliable supply of material and the increased stability of closely related analogues would support a more thorough inspection of the biological properties and effects of belizentrin.

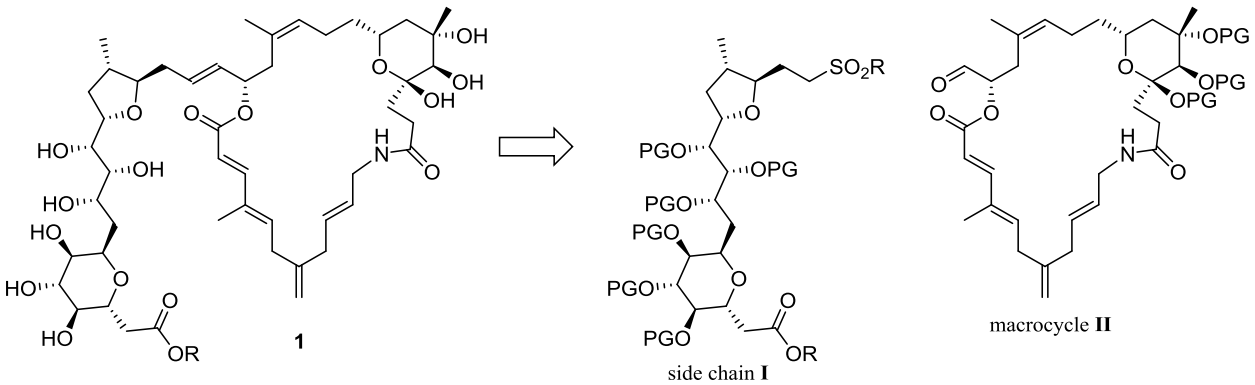
3 Retrosynthetic Analysis and Exploratory Studies

3.1 General Considerations

Due to the size and complexity of the target molecule, a wide variety of possible disconnections were envisioned. A flexible approach that would allow for modifications at different stages was desired. This is keeping with the general demand for convergent syntheses. The target molecule should be disassembled into smaller building blocks of roughly equal synthetic difficulty to achieve these goals.

3.2 Major Disconnections

Belizentrin consists of a polyhydroxyated side chain that is connected to a polyunsaturated macrocycle by a short tether, which includes an *E*-olefin. This particular C=C double bond was thought to be accessible by carbonyl olefination. This transform would bisect the molecule as desired (Scheme 3.1). Out of the plethora of reported olefination methods, the Julia-Kocienski protocol was deemed most promising.[14] This choice was based on the careful evaluation of the benefits and drawbacks of different methods. The requisite *E*-selectivity, together with the necessity to avoid excessively reducing or basic conditions, ruled out several other methods like the original Julia, Takai-Utimoto, Schlosser-Wittig or Peterson Olefination. [15, 16, 17, 18] Additionally, we were aware of some promising literature precedent for similar connections.[19, 20]

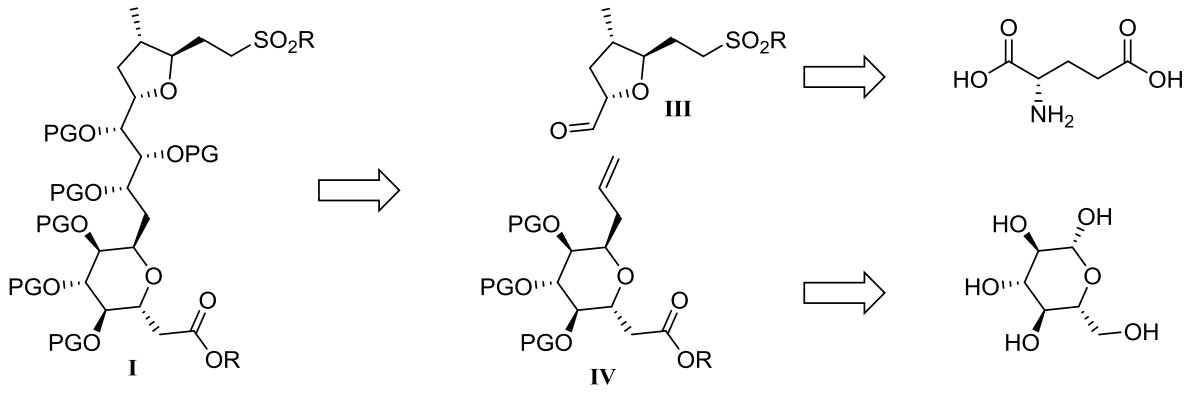


Scheme 3.1: Disconnection of side chain **I** and macrocycle **II**.

The decision as to which fragment, sidechain **I** or macrocycle **II**, should become the aldehyde-component and which should become the sulfone-component was facile; only the aldehyde

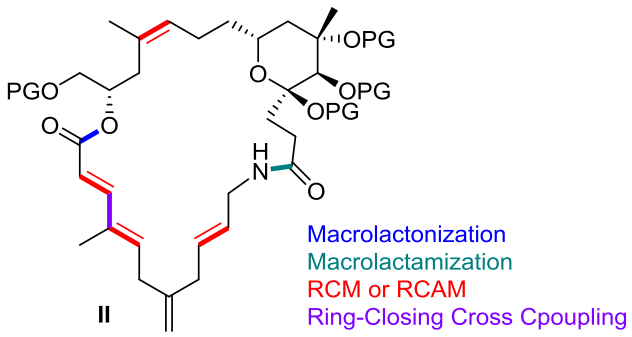
would tolerate a α-acyloxy-substituent, whereas such a group would likely be eliminated from the sulfone upon deprotonation. [21]

The sulfone-containing building block was prepared by Dr. Sylvester Größl, therefore only a brief overview is provided below (Scheme 3.2). The reader is directed to his PhD thesis for a detailed account.[22] The sidechain **I** contains a tetrahydrofuran ring and a tetrahydropyran ring, which are connected by a chain of four carbon atoms, three of which bear hydroxy groups. The two highly functionalized rings had to be constructed individually and joined afterwards with the appropriate tether for the sake of convergence. The tetrahydropyran fragment **III** was traced back to D-glucose as an inviting chiron, whereas the tetrahydrofuran fragment **IV** was traced to L-glutamic acid as a maybe less obvious chiron. These starting materials would secure the absolute stereochemistry and offer a facile construction of the required fragments.



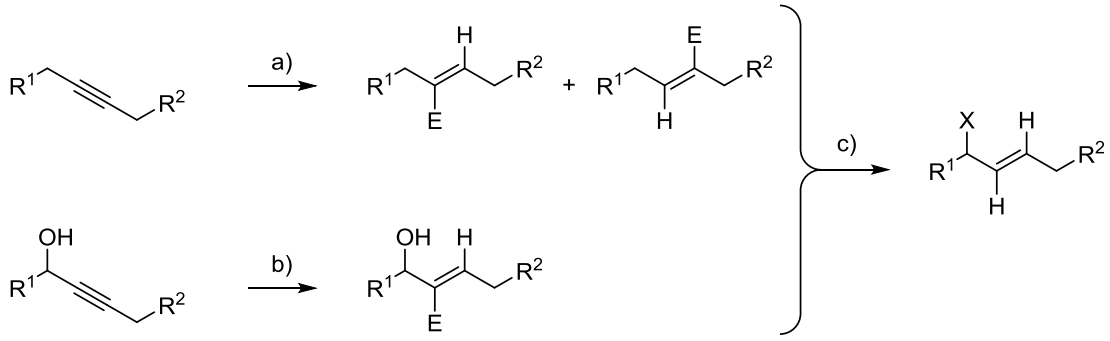
Scheme 3.2: Overview of the side chain's retrosynthetic analysis.

The synthesis of the macrocyclic aldehyde fragment **II** of belizentrin will be covered in detail. The potentially labile aldehyde functionality was traced back to an appropriately protected alcohol. The nature of that protection group had to be orthogonal to the remaining protecting groups within the rest of the macrocyclic fragment. The location and mode of the macrocyclization was not rigorously defined from the onset of the project: the presence of a lactone-, lactam- and four endocyclic olefins within the macrocycle offered several options for this crucial step (Scheme 3.3).



Scheme 3.3: Possible approaches to close the macrocycle.

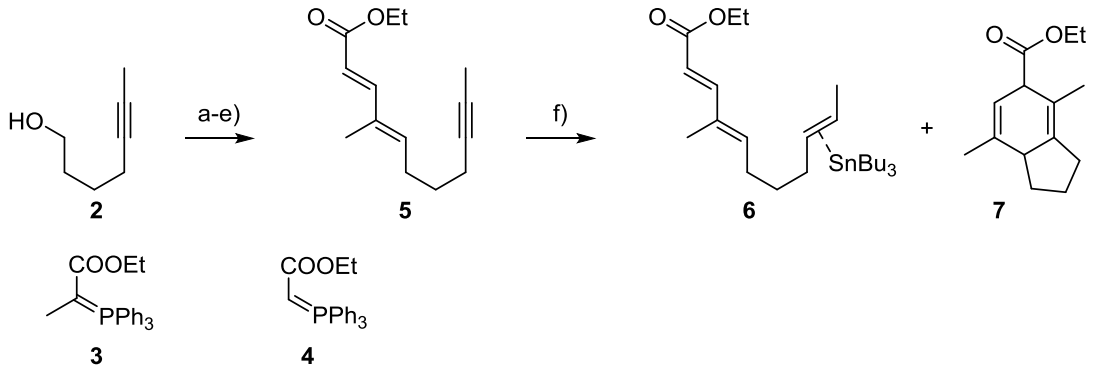
Besides macrolactonization and -lactamization, ring closing olefin- and alkyne-metathesis, as well as ring closing cross coupling were conceivable strategies. Among these possibilities, ring closing olefin metathesis (RCM) was deemed perilous due to the abundance of olefins, which could interfere with the formation of the desired ring. A macrolactonization strategy, although successfully employed in many reported syntheses, was also questionable for this particular molecule because the hypothetical seco-acid comprises a conjugated diene. [23] An activated derivative of said seco-acid, as requisite for a macrolactonization approach, would likely be rather unreactive. The scarcity of literature detailing macrolactamizations led us to demote this option. Therefore, at the outset, ring closing alkyne metathesis (RCAM) seemed to be the best choice of method for the macrocyclization step. The absence of the eponymous alkyne in the desired macrocycle, but the presence of three *E*-olefins, offered an opportunity to apply recently developed methodology for *trans*-selective hydrofunctionalization of alkynes (Scheme 3.4).[24, 25, 26, 27]



Scheme 3.4: Overall *trans*-reduction via *trans*-hydroelementation. Conditions: a) $[Cp^*Ru(MeCN)_3]PF_6$, E-H b) $[Cp^*RuCl]_4$, E-H c) $Cu[O_2PPh_2]$ for E = SnR_3; AgF for E = SiR_3

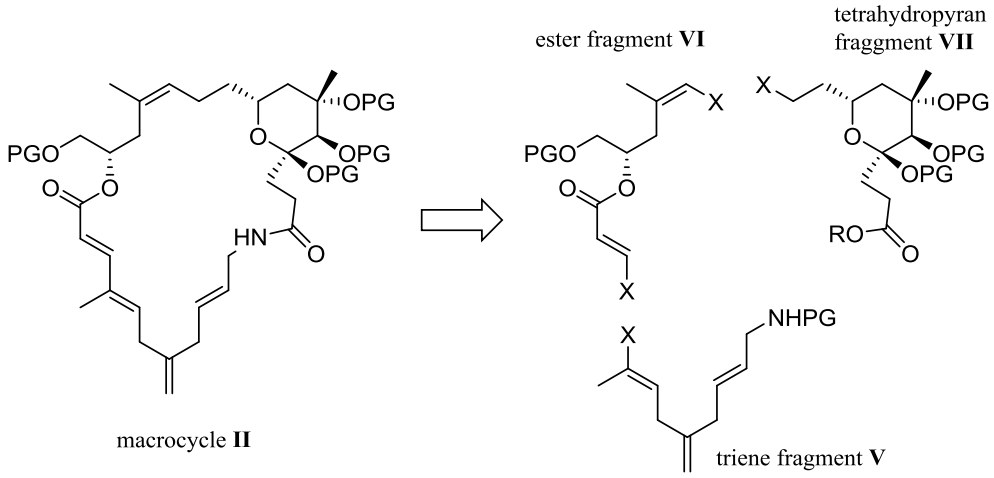
These ruthenium-catalyzed processes have shown broad functional group tolerance, with few exceptions. However, conjugated π-systems, which can ligate coordinatively unsaturated

ruthenium complexes, have been reported to be detrimental to these catalytic transformations. Nevertheless, the *E*-olefin in the "south-eastern" part of the macrocycle presented a tempting occasion to apply the RCAM/*trans*-reduction sequence. A simple model system was prepared to mimic the alkyne in the spatial vicinity of the threatening dienoate to test the viability of this concept. The attempted *trans*-hydrostannylation of dienyne **5** resulted in a low yield of the desired product **6**, and a considerable amount of **7**, which had formed as a result of a (formal) dehydro-Diels-Alder cycloaddition (Scheme 3.5). In the absence of tributyltin hydride, cycloadduct **7** was the sole product. Similar reactions have been described under $Rh^{(I)}$ catalysis.[28, 29]



Scheme 3.5: Model substrate for the prospected hydrostannation. Conditions: a) $[Cu(MeCN)_4]BF_4$ (5 mol%), 2,2'-bipyridine (5 mol%), TEMPO (5 mol%), N-methylimidazol (10 mol%), 1 atm O_2, MeCN 87% b) **3**, benzene reflux, 91% c) $LiAlH_4$, Et_2O, 87% d) MnO_2, CH_2Cl_2, 70% e) **4**, toluene, 90°C, 78% f) $[Cp^*Ru(MeCN)_3]PF_6$, Bu_3SnH, CH_2Cl_2 11% of **6** as mixture of regioisomers + **7** as major product, not rigorously quantified.

This result led us to abandon the RCAM-approach to macrocyclization. We focused on ring closing cross coupling to construct the dienoate and macrolactamization. Since both strategies require a cross coupling reaction and an amide formation, the necessary building blocks would be the same or very similar. While these disconnections led to a "southern" triene fragment **V** of the macrocycle of appropriate size, the remaining "northern" part was bigger and more complex. To address this disparity, we planned to assemble the northern fragment from two halves via another cross coupling reaction. This led to three parts, which should allow for the convergent construction of the macrocyclic portion of belizentrin (Scheme 3.6).

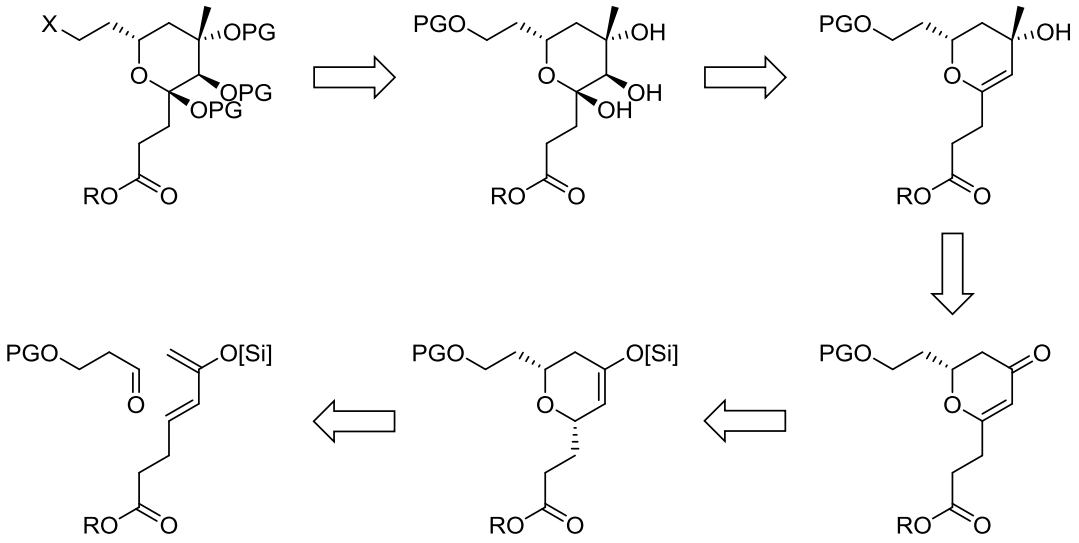


Scheme 3.6: Retrosynthetic analysis of the macrocyclic portion of belizentrin.

3.3 Building Block Retrosynthesis

3.3.1 Tetrahydropyran Fragment VII

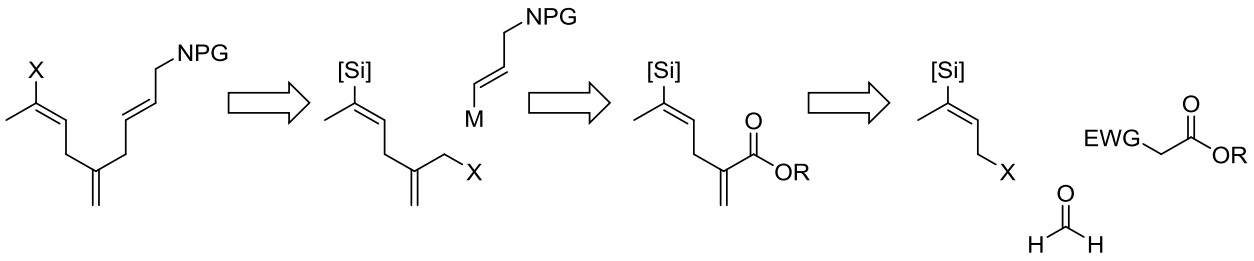
The synthesis of the highly substituted tetrahydropyran ring residing in the north-eastern corner of the macrocycle appeared to be the most ambitious task. It had to contain a carboxylic acid derivative for the envisaged amide bond formation and a handle for cross coupling to the "north-western" part **VI**. The vicinal *syn*-diol motif was traced back to an olefin via a dihydroxyation-transform to reduce complexity. The forward reaction was expected to proceed satisfactory, due to the electron rich nature of the enol ether double bond. Furthermore, the desired stereoselectivity was in good accordance with previous results on comparable cyclohexenol derivatives.[30] The adjacent methyl branch was to be installed via a 1,2-addition of a methyl nucleophile to the corresponding enone. A related methylation, while on a structurally less complex substrate, has been reported.[31] The requisite enone could in turn be traced back to a hetero-Diels-Alder cycloadduct (Scheme 3.7). The catalytic asymmetric hetero-Diels-Alder reaction has been applied successfully in numerous total syntheses and was therefore chosen as the foundation upon which to build the absolute stereochemistry of the fragment.[32, 33, 34]



Scheme 3.7: Retrosynthesis of the tetrahydropyran fragment **VII**.

3.3.2 Triene Fragment V

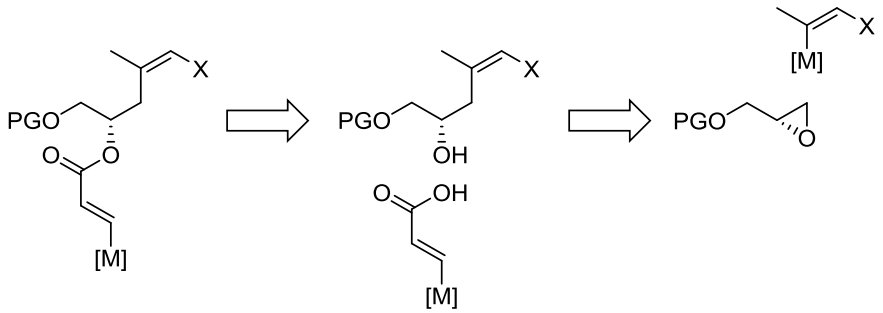
The doubly skipped triene present in this fragment, containing an *exo*-methylene motif with a potential tendency to migrate into conjugation, rendered its construction a synthetic challenge. The triene was traced to a diene via allylic cross coupling. This step would benefit from the symmetry of the required allylic electrophile, which rendered ipso- and allylic-substitution degenerate. The requisite nucleophile could be derived from N-protected propargylamine via hydrometalation. The allylic electrophile on the other hand was traced to an enoate. The preparation of closely related enoates had been reported via the alkylation of a β-keto ester and subsequent Knoevenagel-condensation with formaldehyde.[35] This strategy seemed very promising and was therefore adopted in the forward synthesis (Scheme 3.8).



Scheme 3.8: Retrosynthesis of the triene fragment **V**.

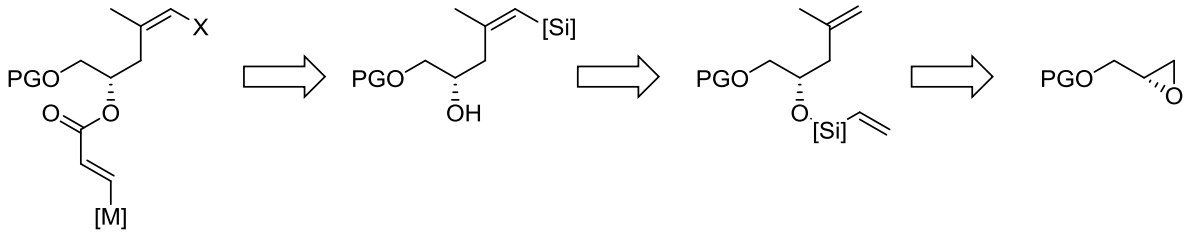
3.3.3 Ester Fragment VI

This fragment had to contain two orthogonal functionalities for cross coupling reactions and a suitably protected alcohol. These elements were arranged around a single stereogenic center in the form of a secondary ester. The ester linkage offered an inviting point to divide this building block into smaller units. Suitable boron and tin derivatives of acrylic acid were known and available in few steps. The required chiral mono-protected 1,2-diol motif could be derived from protected glycidol, which is a commercially available in both enantiomeric forms. The concise assembly of said alcohol component would be possible, if the epoxide ring could be opened with an appropriate nucleophile (Scheme 3.9).



Scheme 3.9: Schematic retrosynthesis of the ester fragment **VI**.

The necessary nucleophile should contain a handle for the downstream connection to the tetrahydropyran fragment **VII** while securing the correct geometry of the triple substituted olefin. Additionally it must be reactive enough to ensure efficient epoxide opening. Any organolithium- or Grignard -reagent would provide the required reactivity, but these reagents can be difficult to prepare in stereoselective manner. An approach to circumvent this issue would be to separate the tasks of opening the epoxide and setting the correct double bond geometry into different steps. This strategy would start with an epoxide-opening using a plain isopropenyl moiety followed by the stereoselective installation of a silyl group as handle for later functionalization. A conceivable way to install the silyl group was a C—H activation/silylation directed by the proximal hydroxy group, but ring-closing olefin metathesis with a tethered alkenylsilane appeared more promising (Scheme 3.10). Precedent from the group of Denmark showed that alkenylsilanes with a well-defined geometry, which are not accessible via hydrosilylation, can be accessed by RCM.[36, 37, 38]

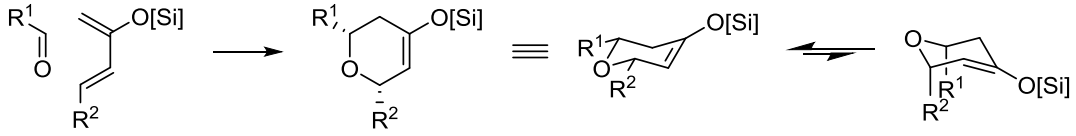


Scheme 3.10: Retrosynthesis of the ester fragment **VI** based on RCM.

4 Synthetic Work

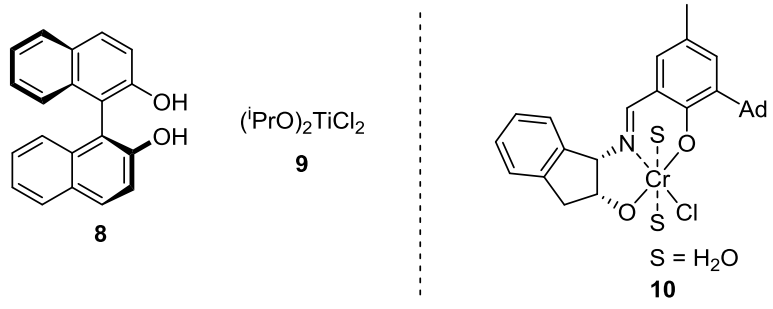
4.1 Tetrahydropyran Fragment VII

As outlined above, an asymmetric catalytic hetero-Diels-Alder (HDA) reaction was chosen to construct the tetrahydropyran ring found in fragment **VII** (Scheme 4.1). This type of cycloaddition between an aldehyde and a silyloxy diene should deliver both substituents to the 2- and 6-position in an equatorial fashion, and additionally install a silyl enol ether as a useful handle for further functionalization.



Scheme 4.1: Generic HDA reaction between an aldehyde and a 2-silyloxydiene.

Different chiral catalysts have been developed for asymmetric hetero-Diels-Alder reactions between aldehydes and electron-rich dienes. The vast majority are chiral Lewis acids, which are thought to activate the aldehyde component through coordination to the oxygen atom and consequential lowering of its LUMO, the C=O π* molecular orbital. It deserves mentioning that also other catalysts, such as chiral Brønsted acids, are capable of comparable aldehyde activation and asymmetric induction. From a synthetic perspective, the systems of Keck based on $Ti^{(IV)}$ (**8** + **9),** and Jacobsen based on $Cr^{(III)}$ (**10**), are especially popular (Scheme 4.2).[32, 39] Both have been used extensively in the synthesis of complex targets, highlighting their impressive performance, functional group tolerance and reliability. [34]

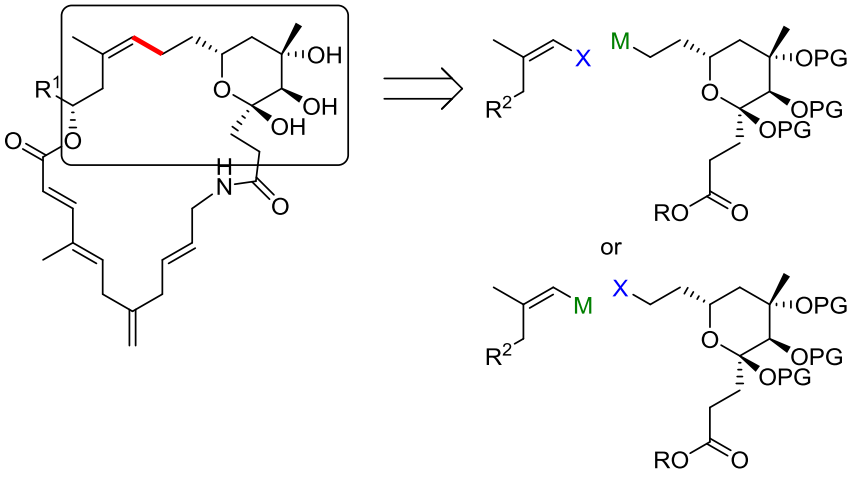


Scheme 4.2 Representative examples for a Ti- and a Cr-based catalytic system for asymmetric HDA reactions.

The $Ti^{(IV)}$ catalysts are usually prepared *in situ* from the desired ligand and an appropriate metal precursor.[39] In the case of BINOL and several derivatives thereof, they are commercially available. Their $Cr^{(III)}$ counterparts on the other hand offer an advantage, as they are neither air nor moisture sensitive and can be pre-formed and stored without loss of activity or selectivity.

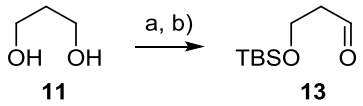
The downside of these complexes is that the requisite chiral ligand has to be prepared in a three-step sequence.[30]

The exact method for connecting the "north-western" part and the "north-eastern" parts had yet to be decided. Since the connection was planned to be between an sp^2- and an sp^3-hybridized carbon atom, a Pd-catalyzed cross coupling reaction appeared to be a promising method to construct the "northern" fragment of the macrocycle (Scheme 4.3). In this scenario, the sp^2-hybridized carbon atom on the western side should carry a halide to serve as the electrophile, and the sp^3-hybridized carbon atom would need to be a suitable nucleophile. To effect transmetalation and ensure functional group tolerance, an organoboron- or organozinc-species seemed suitable. The former could be introduced via hydroboration of a terminal olefin, whereas the latter could be formed via insertion of zinc into an alkyl halide. Furthermore, such an alkyl halide could also be used as electrophilic reaction partner, if the aforementioned polarities were reversed.[40]



Scheme 4.3 Conceivable modes to couple the tetrahydropyran **VII** fragment and the ester fragment **VI**.

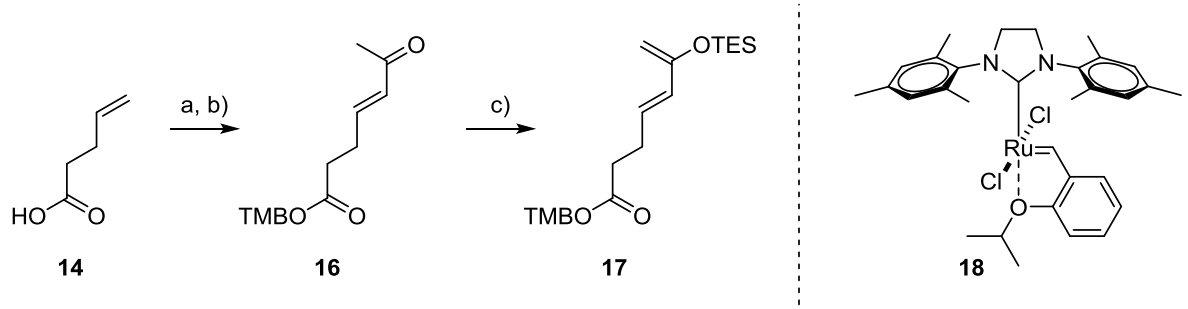
In an effort to remain flexible at this stage, a TBS-protected alcohol was chosen as masked surrogate for either an alkyl halide or a terminal olefin. The reported aldehyde **13** was therefore synthesized in two straightforward steps and was isolated in good yield (Scheme 4.4).



11 **13**

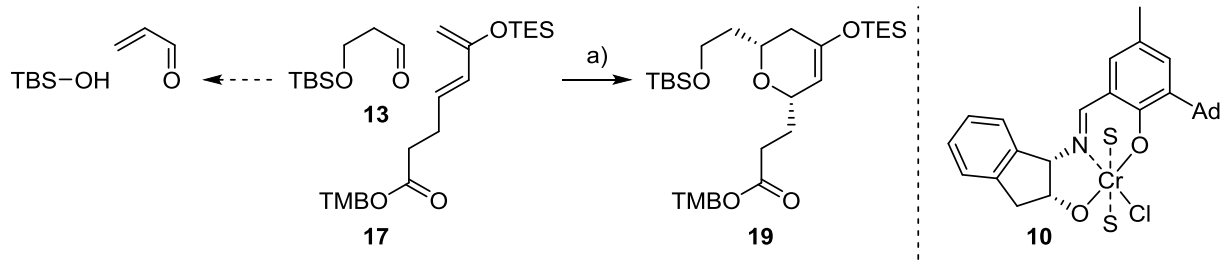
Scheme 4.4: Synthesis of aldehyde **13**. Conditions a) TBSCl, Et_3N, CH_2Cl_2, 91%; b) $[Cu(MeCN)_4]BF_4$ (4.5 mol%), 2,2'-bipyridine (4.5 mol%), TEMPO (4.5mol%), N-methylimidazol (9mol%), 1 atm O_2, MeCN 99%.

An electron-rich silyloxy-diene was required as the second component for the HDA-reaction. The carboxyl-terminus, that should form the (macro-) lactam functionality at a later stage, was introduced as the corresponding ester. A benzyl-ester seemed appropriate for its eventual cleavage and also rendered the resulting intermediates less volatile. A 3,4,5-trimethoxybenzyl (TMB) ester was deemed optimal for adjusting the polarity of subsequent intermediates, in order to facilitate the chromatographic separations. The desired silyloxy-diene **17** was prepared via esterification of acid **14** through the corresponding acid chloride, a very efficient olefin cross metathesis, and finally silylation with TESOTf and Et_3N (Scheme 4.5).



Scheme 4.5: Synthesis of the silyloxy diene **17**. Conditions: a) $(COCl)_2$ neat, then TMBOH, DMAP, K_2CO_3, CH_2Cl_2, 91% b) 3-buten-2-one, **18 (**0.1 mol%), CH_2Cl_2 reflux, 96% c) TESOTf, Et_3N, Et_2O, 89%.

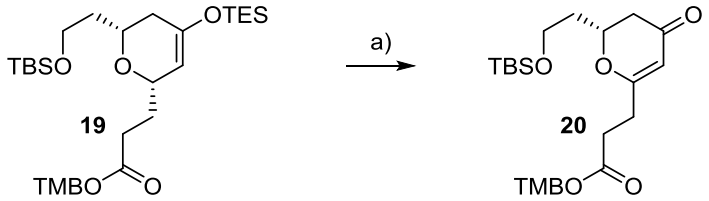
The HDA-reaction was conducted according to Jacobsen's protocol, which produced the desired product **19** in high enantiomeric excess and good yield (Scheme 4.6). These conditions deserve some discussion, because they are somewhat unconventional: The reaction had to be conducted in the absence of solvent, but rather in the presence of powdered molecular sieves, in order to proceed with high enantioselectivity. This combination formed a paste with a very thick consistency, which severely impaired stirring when the reaction was conducted on a small scale. This problem could be overcome by using the more readily available aldehyde component **13** as a diluent. A moderate excess of the aldehyde was also required to achieve complete conversion of the diene, because the β-silyloxy-aldehyde tended to decompose slowly under the reaction conditions. Its degradation was attributed to a Lewis acid catalyzed retro-Michael reaction (or E_1cB elimination) of *tert*-butyldimethylsilanol. Regardless of these minor practical issues, the reaction delivered the desired cycloadduct on multi-gram scale in good yield and very reliable 95 – 96% *ee*.



Scheme 4.6: Asymmetric hetero-Diels-Alder reaction of **13** and **17**. Conditions: a) **10** (9 mol%), 4 Å MS, neat, 76%, ≥95% *ee*.

In the next step, the silyl enol ether functionality within cycloadduct **19** had to be converted into an enone. Several methods for this kind of transformation have been described, most notably Pd-mediated and -catalyzed reactions, as well as hypervalent iodine-mediated oxidations. [41, 42, 43, 44, 45]At this early stage of the synthesic sequence, a catalytic reaction was desirable, therefore the variations of the originally stoichiometric Saegusa oxidation were considered. Among them, protocols that employed molecular oxygen as the terminal oxidant were deemed most attractive.

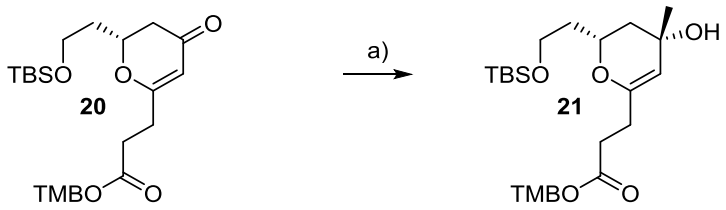
Initial tests revealed that palladium$^{(II)}$-acetate under an atmosphere of oxygen could serve as catalyst, on the condition that pure DMSO was used as solvent (Scheme 4.7). The role of DMSO as a ligand for palladium during similar aerobic oxidation reactions has been recognized.[46] The addition of co-solvents reduced the catalyst lifetime and consequently the turnover number. Therefore, rather longer reaction times, due to low solubility of the lipophilic starting material in neat DMSO, were preferred over initially faster but incomplete reactions. Product **20** was obtained cleanly and in good yield. Attempts to lower the catalyst loading below 10 mol% resulted in even longer reaction times and the onset of hydrolysis of the silyl enol ether as a competing side reaction.



Scheme 4.7: Catalytic Saegusa oxidation of **19**. Conditions: a) $Pd(OAc)_2$ (10 mol%), 1 atm O_2, DMSO, 78 %.

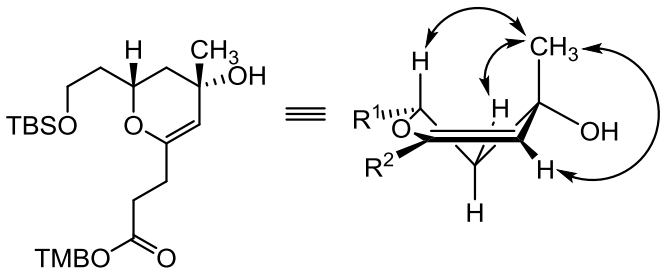
Enone **20** set the stage for the introduction of the methyl branch at the 4-position of the tetrahydropyran ring. Based on a closely related example published by Trost *et al*., the incoming methyl nucleophile was expected to approach preferentially along an axial trajectory.[31] This fits the general trend that small, reactive nucleophiles attack cyclohexanone derivatives preferentially

along an axial trajectory, while sterically demanding nucleophiles follow an equatorial trajectory.[47] In Trost's case, the addition of methyllithium to a somewhat simpler enone resulted in the formation of the desired product in 20:1 *d.r.* and 80% yield. The naïve attempt to apply the same conditions to our enone resulted in the indiscriminate methylation of the ketone and the ester. After some experimentation we found that the use of methylmagnesium chloride at low temperature resulted in the clean 1,2-addition to the enone without the ester interfering (Scheme 4.8).



Scheme 4.8: Substrate-controlled Grignard addition to **20**. Conditions: a) MeMgCl, THF, −65°C, 77%.

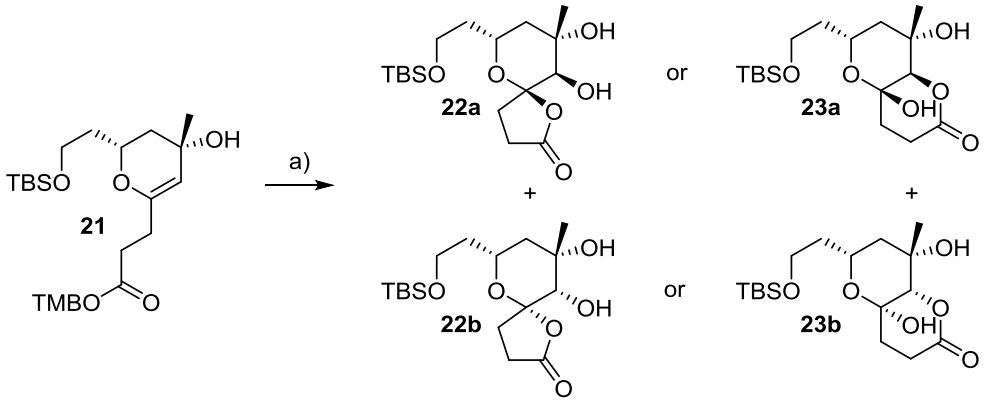
It was noted that an excess of the Grignard reagent had to be employed to achieve full conversion. This result might be understood as a consequence of the aggregation state of the organometallic species at low temperature. To prevent the addition to the ester functionality, the excess of methylmagnesium chloride had to be destroyed before allowing the mixture to reach ambient temperature. The obtained allylic tertiary alcohol was found to be very acid-sensitive and had to be handled carefully. It was isolated as a single diastereomer and the predicted stereochemistry was corroborated by NOE correlations between the axial proton at 6-position and the newly introduced methyl group (Scheme 4.9).



Scheme 4.9: Selected NOE correlations in **21** drawn in half-chair conformation.

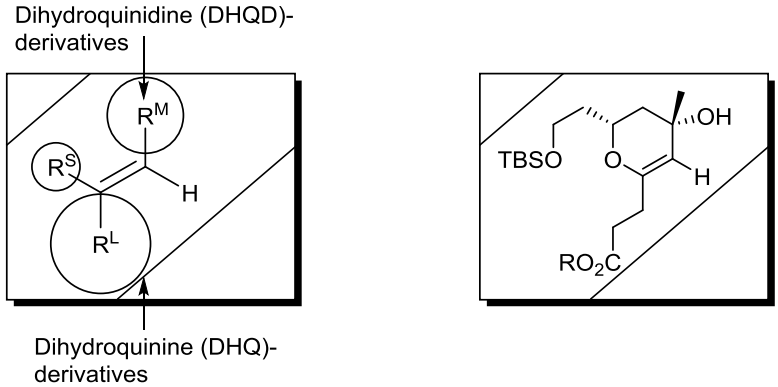
Two more stereocenters had to be constructed to complete the decoration of the tetrahydropyran ring. The *syn*-dihydroxyation of the only olefin in the molecule was expected to fulfill this task. Kishi's rule predicts that osmium tetroxide approaches a cyclic allylic alcohol from the face

opposite to the already existing OH group, presumably due to electrostatic repulsion of the oxygen atoms of OsO_4 and the hydroxy group.[30] In the projected case, this course would result in the desired selectivity for the target motif. However, when enol ether **21** was exposed to a catalytic amount of $K_2OsO_4 \bullet 2H_2O$ in the presence of NMO as the stoichiometric oxidant, an almost equimolar ratio of two isomers was formed. Furthermore, it turned out that the 3,4,5-trimethoxybenzyl ester was lost for both isomeric products during the reaction. This was the result of one of the newly created OH-groups forming a lactone, thereby expulsing the alcohol component of the ester. While the isomers of the product were separable by flash chromatography, there was still uncertainty about the stereochemistry and the connectivity of the products (Scheme 4.10).



Scheme 4.10: Possible isomers of the products from the dihydroxyation/lactonization. Conditions: a) $K_2OsO_4 \bullet 2H_2O$ (10mol%), NMO, acetone aq..

The obvious lack of substrate control offered an opportunity for catalyst control, in particular Sharpless' system was deemed promising.[48] As a trisubstituted olefin, the substrate could be fitted well the empirical mnemonic (Scheme 4.11):



Scheme 4.11: Empirical model for Sharpless' asymmetric dihydroxyation and its application to **21**.

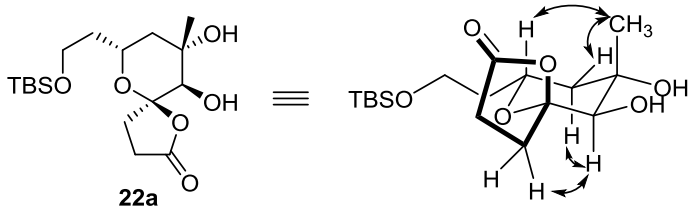
Under slightly modified Sharpless conditions (3mol% $K_2OsO_4 \bullet 2H_2O$, 7.5mol% $DHQD_2Phal$) one major product was obtained in a pleasing ~ 15:1 *d.r.*. The diastereomers were separable by flash chromatography and the major isomer was isolated in good yield. Based on the above schematic representation, the $DHQD_2Phal$ ligand produces either of the desired diastereomers **22a** or **23a**.

With the pure material in hand, the exact structure had to be elucidated and the stereochemistry confirmed. It was not obvious from the one- and two-dimensional ^{1}H and ^{13}C NMR spectra whether the 5-membered isomer **22** or 6-membered isomer **23** of the lactone had formed. The C=O ^{13}C NMR chemical shift of the product was inconclusive because it resonated in between that of γ-butyrolactone and δ-valerolactone. Comparison of the C=O stretching frequency of the obtained lactone with literature data for γ-butyrolactone and δ-valerolactone (Table 4.1) suggested product **22** to be a 5-membered lactone. [49]

Table 4.1: Comparison of the ^{13}C shifts and IR stretching frequency of the carbonyl group.

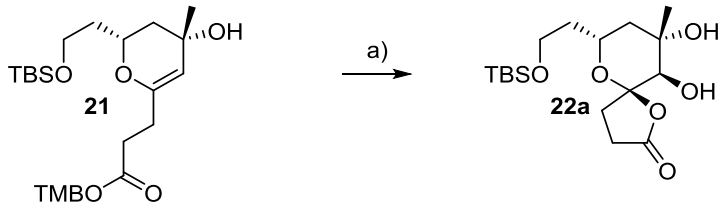
entry	compound	δ ^{13}C=O [ppm]	ν C=O [cm^{-1}]
1	γ-butyrolactone	178.0	1770
2	δ-valerolactone	171.4	1730
3	**22a**	175.3	1765

The predicted stereochemistry was corroborated by NOE experiments. The recorded data supported, among other correlations, the spatial proximity between the two axial protons "below" the tetrahydropyran ring, which indicated the introduction of the hydroxy groups from "above" the THP ring (Scheme 4.12).



Scheme 4.12: Selected NOE correlations in **22a**.

Based on these data, the course of the reaction was established to be as follows (Scheme 4.13):



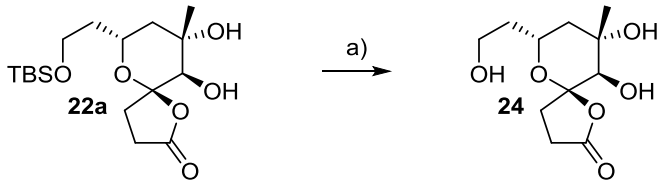
Scheme 4.13: Successful ligand-controlled dihydroxyation of **21**. Conditions: a) $K_2OsO_4 \bullet 2H_2O$ (3 mol%), $DHQD_2Phal$ (7.5 mol%), $[K_3Fe(CN)_6]$, $MeSO_2NH_2$, $^tBuOH/H_2O$ 1:1, 76%.

The spontaneous lactonization of the initial dihydroxyation product, although surprising at first sight, turned out to be advantageous for several reasons. It did not only render an extra step to remove the ester protecting group obsolete, but also locked the potentially labile anomeric OH group in the desired axial position. Additionally, there was literature precedent showing that γ-butyrolactone derivatives can be successfully opened with amines to produce the corresponding γ-hydroxy amides.[50, 51] This possibility spoke for macrolactamization as way to close the 25-membered ring.

At this stage, all stereogenic centers within the tetrahydropyran fragment have been set. Next, either an olefin as prerequisite for a hydroboration/Suzuki coupling sequence had to be introduced, or an alkyl halide formed to allow the formation of an organozinc species for a Negishi coupling. At this point the alkyl Suzuki variant was preferred, because it appeared more robust.

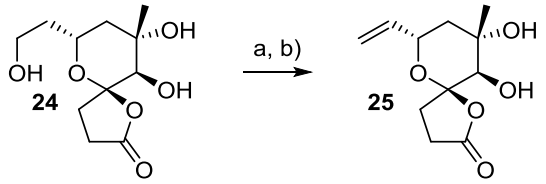
4.1.1 The Precursor for Suzuki Coupling

To install the necessary olefin in **25**, the TBS-protected primary alcohol dad to be eliminated. After the straightforward deprotection with TBAF, triol **24** was obtained in nearly quantitative yield (Scheme 4.15). To isolate **24** successfully, it was crucial to avoid an aqueous workup, which led to severe losses of this very hydrophilic material.



Scheme 4.14: TBS-deprotection of **22a**. Conditions: a) TBAF, THF, 94%.

The elimination to the olefin was achieved by the selenoxide method developed by Grieco.[52] To this end, the primary alcohol was selectively converted into a (2-nitrophenyl)seleno-ether by a Mitsunobu-type reaction. The seleno-ether intermediate was directly used for the elimination step. Oxidation of the crude intermediate to the corresponding selenoxide was conducted with *m*-CPBA at low temperature; upon warming up to ambient temperature, the labile compound eliminated via an E_i mechanism to give the desired olefin **25** (Scheme 4.15). Mechanistically, this reaction parallels the Cope elimination, elimination of sulfoxides, Chugaev elimination, and ester pyrolysis. [53]



Scheme 4.15: Elimination of water from **24**. Conditions: a) 2-NO_2-PhSeCN, Bu_3P, THF b) *m*-CPBA, then Et_3N, CH_2Cl_2/THF, −78°C→ rt, 62 – 82%

The resulting olefin **25** was the first solid intermediate in the synthetic sequence, and crystals of **25** suitable for X-ray diffraction analysis were grown via vapor diffusion. The resulting solid state structure unambiguously confirmed the relative and absolute stereochemistry and supported the assignement based on IR and NMR spectroscopy (Figure 4.1).

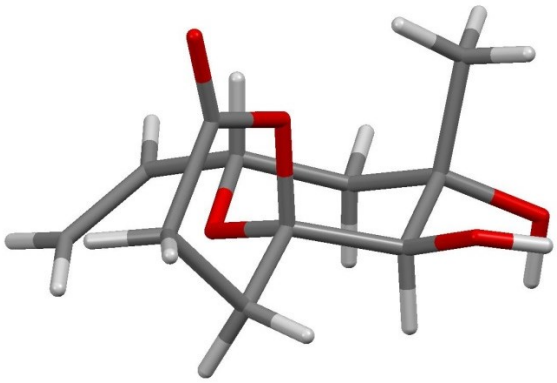
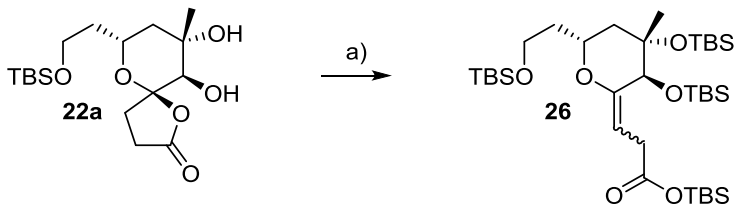


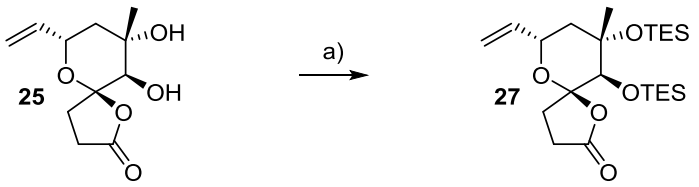
Figure 4.1 3-Dimensional structure of **25**.

The last step to complete the precursor for Suzuki coupling was the protection of the two vicinal hydroxy groups. It was not only desirable to shield the alcohol functionalities from chemical reactions, but also to adjust the polarity of the molecule in order to improve the practical handling of subsequent intermediates. Silyl protecting groups were chosen for this purpose to allow global deprotection together with other silyl ether within the side chain at the end of the total synthesis. TBS or TES groups were considered best suited for this task, because they offer a good balance of stability and ease of removal. Due to the spatial arrangement of the two alcohols, a reaction of diol **25** with TESCl or TBSCl resulted in a mixture of isomeric mono-silylated intermediates, but no bis-silylated product was obtained. In contrast, treatment of **22a**, as a model, with TBSOTf resulted in the silylation of both OH groups, but also led to the undesired opening of the lactone ring (Scheme 4.16).



Scheme 4.16: Attempted TBS protection of **22a**. Conditions: TBSOTf, lutidine, CH_2Cl_2, 0°C.

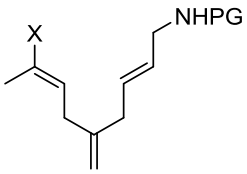
This reactivity was rationalized by the pronounced Lewis acidic character of silyl triflates. The problem was overcome by the addition of silver nitrate as a halophilic promotor to the reaction of TESCl and diol **25**.[54, 55] This combination led to clean formation of bis-TES ether **27** without any noticeable side reactions (Scheme 4.17).



Scheme 4.17: TES-protection of **25**. Conditions: a) TESCl, $AgNO_3$, DMAP, pyridine/DMF 1:1, 76 %.

This protection completed the preparation of tetrahydropyran fragment **27** in an overall yield of up to 22% over 10 steps. The fragment was adorned with an olefin for the upcoming hydroboration and subsequent Suzuki coupling, and was adequately protected to ensure its compatibility with the projected chemical manipulations. Furthermore, all required stereocenters were set and confirmed unequivocally. The synthesis of this building block relied on asymmetric catalysis, providing the desired intermediate **27** in ≥ 95% *ee*. Consequently, this approach could give access to the opposite enantiomer with the same ease, if necessary.

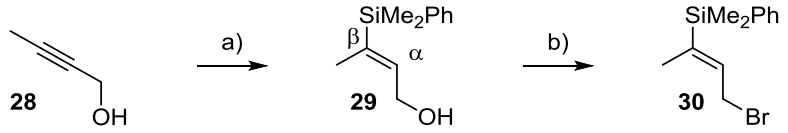
4.2 Synthesis of the Triene Fragment V



Scheme 4.18 Triene fragment

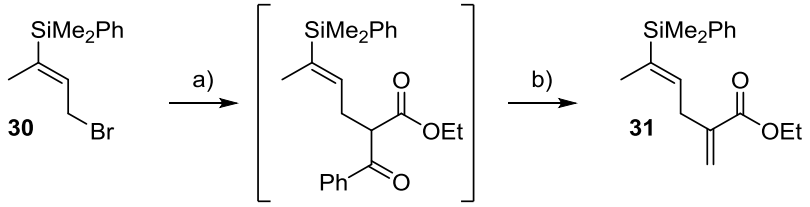
The southern part of the macrocycle shows a high degree of unsaturation: three of the six olefinic double bonds present in the target molecule are located in this region. Each of these three olefins is separated by one methylene unit from the next one (Scheme 4.18). This doubly skipped arrangement is fragile and potentially prone to double bond migration.

The synthesis of this part began with the installation of a alkenylsilane as a masked surrogate of a alkenyl halide for later cross coupling with the ester fragment. This was achieved via a highly regio- and stereoselective silyl-metalation of 2-butyn-1-ol **28**. The reaction yielded the β-silylated allylic alcohol **29** with high regioselectivity (α:β ~ 1:19). [56, 57] Said process is complementary to the platinum catalyzed hydrosilylation of propargylic alcohols, which preferentially yields the proximal isomer. Alcohol **29** was converted into the corresponding bromide **30** via the Appel method (Scheme 4.19).[58, 59]



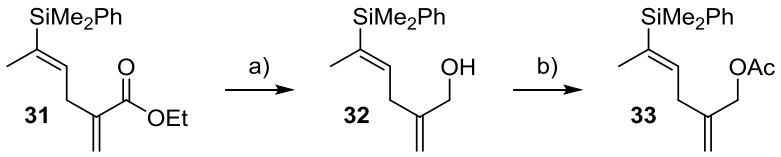
Scheme 4.19: Synthesis of bromide **30**. Conditions: a) $PhMe_2SiLi$, $AlEt_3$, CuCN (4 mol%), THF 0°C, 90%; b) CBr_4, PPh_3, CH_2Cl_2, 96%

To attach a suitable allylic electrophile for the upcoming cross coupling, a literature procedure was adopted.[35] This sequence began with the smooth mono-alkylation of ethyl benzoylacetate with bromide **30**, followed by a Knoevenagel-condensation with paraformaldehyde to give **31** after the loss of a benzoate anion. It was crucial to conduct the second step under strictly anhydrous conditions, as the resulting ester was prone to hydrolysis under the reaction conditions. With appropriate precautions, the two-step sequence was clean and high yielding (Scheme 4.20).



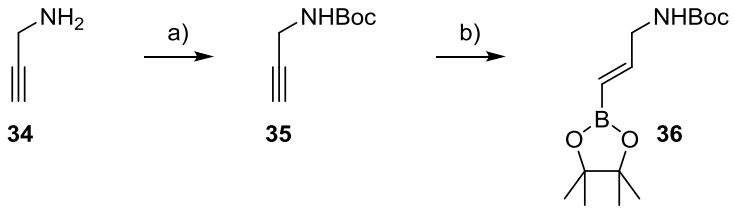
Scheme 4.20: Synthesis of acrylate **31**. Conditions: a) ethyl benzoylacetate, DBU, toluene b) $(CH_2O)_n$, K_2CO_3, THF reflux, 77%.

Enoate **31** was reduced to the corresponding allylic alcohol **32**, which was acetylated to yield **33** (Scheme 4.21). With this material in hand, the stage was set for the allylic cross coupling.



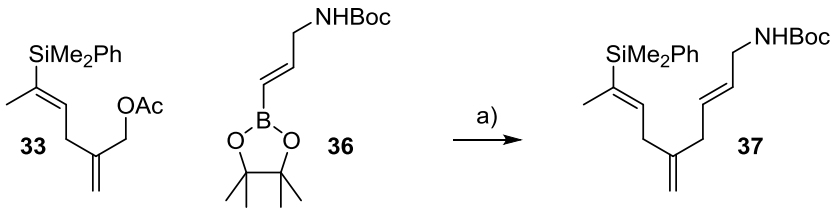
Scheme 4.21: Synthesis of acetate **33**. Conditions: a) Dibal-H, CH_2Cl_2/Et_2O, 0°C b) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 94%.

Pinacol boronate **36** was selected as coupling partner. It was prepared from propargyl amine **34**, which was initially Boc-protected. Compound **35** in turn was subjected to a dicyclohexyl borane catalyzed hydroboration with pinacol borane to yield **36** (Scheme 4.22). These conditions were adapted from a protocol for the analogous hydroboration of THP-protected propargyl alcohol. [19]



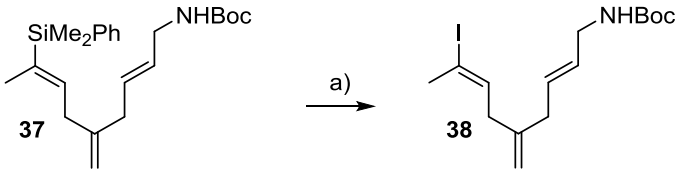
Scheme 4.22: Synthesis of pinacol boronate **36**. Conditions: a) Boc_2O, CH_2Cl_2, quant.; b) PinBH, Cy_2BH (10 mol%), THF, 40 – 50°C, 99%.

The coupling of **33** and **36** was effected in good yield (Scheme 4.23).[60] This protocol furnished **37** very cleanly without any sign of double bond isomerization or migration.



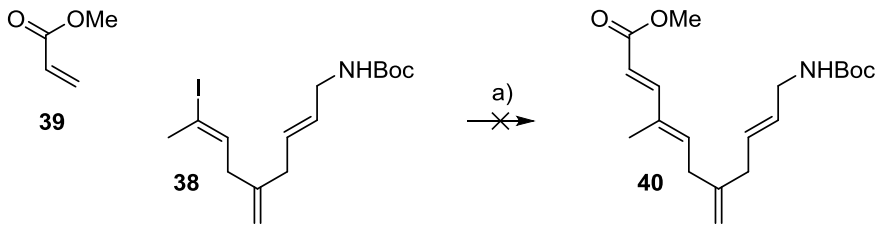
Scheme 4.23: Coupling of **33** and **36**. Conditions: a) KF, $(TFP)_2PdCl_2$ (2.7 mol%), MeOH, 90% TFP = tri(2-furyl)phosphine.

In preparation for the coupling with the ester fragment, the dimethylphenylsilyl-moiety had to be exchanged for a suitable leaving group. Since alkenyl iodides are known to be very reactive in cross coupling reactions, an iodo-desilylation was envisaged. This transformation was achieved in a straightforward manner by following a literature procedure (Scheme 4.24).[61] As this method relied on 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent in order to improve the reaction rate and stereospecificity, we expected that the acidic properties of HFIP might have caused partial Boc-deprotection, which can be accountable for a certain decrease of the yield.



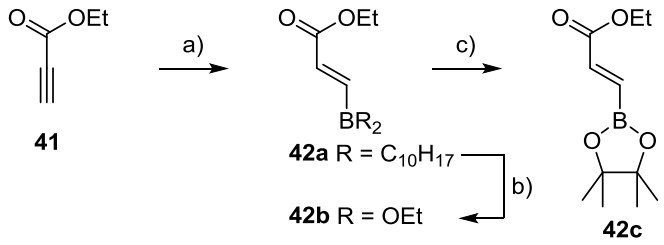
Scheme 4.24: Iodo-desilylation of **37**: Conditions: a) NIS, lutidine, HFIP, 0 °C, 75% HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

This last step completed the southern triene fragment **38** and set the scene for the subsequent connection with the ester fragment. Up to this point, the suspected tendency to double bond migration of the triene system did not manifest itself. To test which kind of nucleophilic coupling partner on the ester fragment would be best, different candidates were considered. The most straightforward and most elegant way to achieve the fragment coupling would have been a Heck reaction between alkenyl iodide **38** and an acrylate. This reaction was tested under the mild conditions developed by Jeffery (Scheme 4.25).[62] Alkenyl iodide **38** was consumed completely, but no desired product was formed.



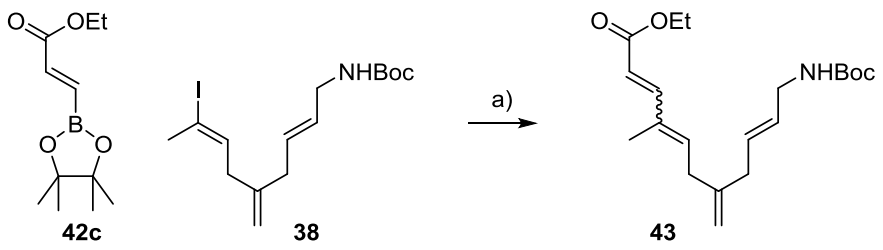
Scheme 4.25: Attempted Heck reaction of **38** and methyl acrylate **39**. Conditions: a) $Pd(OAc)_2$ (14 mol%), Bu_4NBr, $NaHCO_3$, DMF.

Next, boronic ester **42c** was prepared via hydroboration of ethyl propiolate **41** with racemic diisopinocampheylborane, followed by the *in situ* oxidation of the resulting product **42a** with acetaldehyde to yield the corresponding diethyl boronate **42b**. Subsequent addition of pinacol furnished the more stable pinacol boronate **42c** (Scheme 4.26).[63]



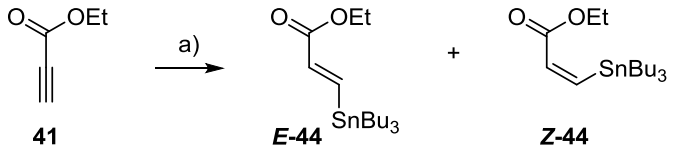
Scheme 4.26: Synthesis of pinacol boronate **42c**. Conditions: a) BH_3•SMe_2, **(±)-**α-pinene, THF, b) acetaldehyde, THF; c) pinacol, THF, 37% overall yield.

Suzuki coupling of **38** with **42c** under mild conditions delivered the coupling product **43** in fair yield (Scheme 4.27). The target tetraene **43** was obtained as an inseparable mixture of geometrical isomers, which precluded this coupling method from further use (Scheme 4.27). A comparable case of *E*/*Z*-isomerization during Suzuki coupling in the construction of an electron-poor conjugated triene has been reported recently.[64]



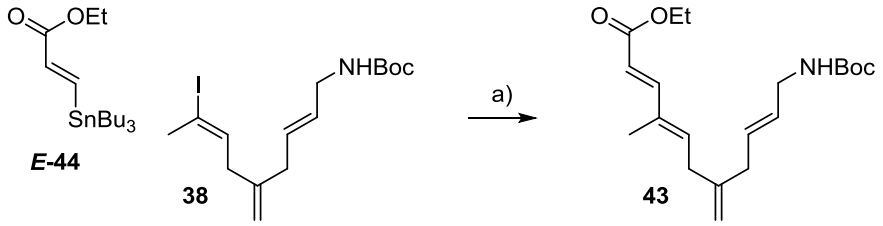
Scheme 4.27: Suzuki-coupling of **38** and **42c**. Conditions: a) $[Pd(dppf)Cl_2]•CH_2Cl_2$ (10 mol%), $AsPh_3$ (20 mol%), K_3PO_4, DMF/H_2O, 67%.

In order to apply even milder conditions, a Stille coupling was investigated as alternative. The required β-stannylated acrylate **44** was available via radical hydrostannylation of ethyl propiolate **41**. This reaction produced a roughly equimolar mixture of the desired ***E*-44** and ***Z*-44**. The geometrical isomers were well separable by flash chromatography and the reaction proved scalable (Scheme 4.28).[65]



Scheme 4.28: Synthesis of stannane ***E*-44**. Conditions: a) Bu_3SnH, AIBN (6 mol%), toluene, 80°C, 45% of ***E*-44**+ 40% of ***Z*-44**.

The subsequent Stille cross coupling reaction of **38** and ***E*-44** proceeded cleanly to give the desired tetraene **43** as a single isomer (Scheme 4.29). The moderate yield in this model reaction could be explained by the choice of a ligand-free palladium catalyst, which may result in premature deactivation to yield palladium black.



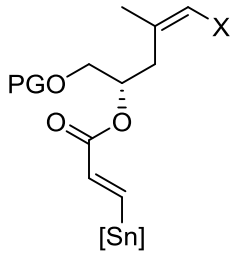
Scheme 4.29: Coupling of **38** and ***E*-44**. Conditions: a) $PdCl_2(MeCN)_2$ (20 mol%), DMF, 57%.

In conclusion triene fragment **38** was prepared in up to 42% overall yield over 8 steps. These include *syn*-selective silyl-metalation and hydroboration to secure the double bond geometry of the two endocyclic olefins. The key carbon—carbon bond formations included the alkylation of a

β-keto ester, a Knoevenagel condensation and an allylic Suzuki cross coupling reaction. Finally the requisite alkenyl iodide was installed via iodo-desilylation at the end of the sequence. A Stille coupling reaction allowed the connection of the triene fragment with a model of the ester fragment. Initial concerns that the resulting tetraene system might be prone to undergo an intramolecular Diels-Alder reaction turned out to be unjustified, at least under the conditions employed so far. Double bond migration did not cause any problems either, despite the newly introduced electron withdrawing ester functionality.

4.3 Synthesis of the Ester Fragment VI

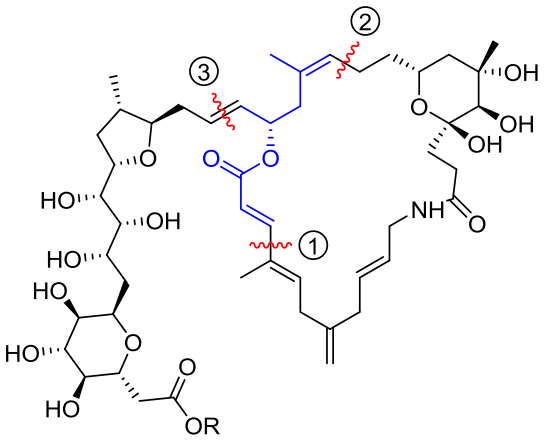
4.3.1 The "tethered RCM Approach"



Scheme 4.30 The ester fragment

The ester fragment of the macrocycle holds a very central position within the target molecule (Scheme 4.30 and 4.31), containing a single stereocenter and a *Z*-configurated trisubstituted olefin. In addition to these structural elements, the installation of suitable functionalities for further connections with the triene fragment, the tetrahydropyran fragment and finally the side chain was required. The individual coupling reactions would need to either be orthogonal to each other or the respective reactive sites would have to be masked temporarily to avoid interferences.

To keep the synthetic sequence as convergent as possible, we envisaged to first attach the triene fragment via a Stille reaction. To set the scene for this transformation, the installation of an alkenylstannane was required.



Scheme 4.31 Planned connections of the ester fragment to other fragments:

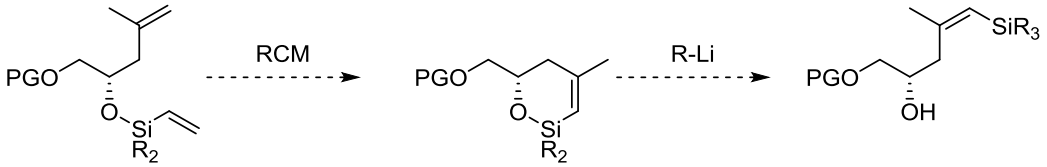
1. Stille coupling with the triene fragment
2. Suzuki or Negishi coupling with the tetrahydropyran fragment
3. Julia coupling to the side chain

Since we also planned to connect the tetrahydropyran fragment to the ester fragment via another cross coupling reaction (see section 3.2), the requisite alkenyl halide in the ester fragment might interfere with the prospected Stille coupling. To prevent this issue, we decided to conceal the alkenyl halide as an alkenylsilane.

We intended to carry the requisite aldehyde for the pivotal Julia-Kocienski olefination with the side chain during the synthetic sequence masked as a suitably protected primary alcohol. This mandated use of a protecting group, which could be cleaved selectively over the silyl ethers installed on the tetrahydropyran fragment. A TES-group or PMB-group appeared adequate. The

protection of enantiopure commercial (*R*)-glycidol with either of them was reported in the literature. [66, 67]

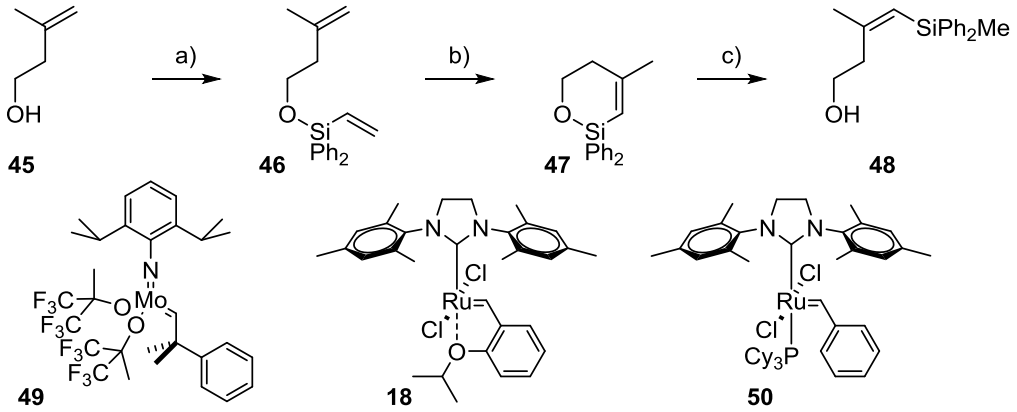
We initially planned to construct an alkenylsilane with the desired *Z*-geometry via ring closing olefin metathesis (RCM) of a tethered precursor, followed by cleavage of the oxygen—silicon bond by a carbon nucleophile (Scheme 4.32).



Scheme 4.32: Planned construction of a *Z*-alkenylsilane via RCM.

A model system was used to test the feasibility of this approach. Treating commercial 3-methyl-3-buten-1-ol (**45**) with chloro(diphenyl)vinylsilane yielded metathesis precursor **46**, which was then subjected to different RCM conditions.

Table 4.2 Ring-closing metathesis of **46**. Conditions: a) chloro(diphenyl)vinylsilane, Et_3N, cat. DMAP, THF, 95%; b) see table; c) MeLi, THF, −78°C, 97%.

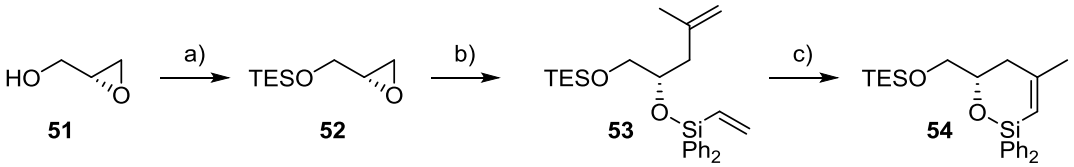


entry	catalyst (mol%)	solvent, temperature	conversion(yield)
1	**49** (7)	benzene, 80 °C	45%
2	**18** (10)	benzene, 80 °C	52%
3	**18** (10)	benzene, 60 °C	29%
4	**18** (10)	toluene, 100 °C	66%
5	**18** (10)	toluene, 111 °C	87%
6	**18** (10)	xylene, 144 °C	95%
7	**18** (10)	mesitylene, 165 °C	93% (64%)

During these exploratory studies, we found that the desired RCM was possible but required rather harsh conditions and high catalyst loadings to proceed efficiently (Table 4.2). The reluctant cyclization of the present system **46** was rationalized as a consequence of the sterically demanding environment surrounding both olefins involved. The resulting cyclic silyl ether **47** reacted smoothly with methyllithium to yield the acyclic alkenylsilane **48**.

Next, this sequence was applied to the actual substrate. The required metathesis precursor was prepared starting from (*R*)-glycidol **51**. The alcohol functionality was protected with a fairly labile TES-group to give **52**. The epoxide was then opened with isopropenylmagnesium bromide, catalyzed by copper(I) iodide. The resulting magnesium alkoxide was treated with chloro(diphenyl)alkenylsilane to give RCM precursor **53**.

Table 4.3: RCM-Approach to the north-western part. Conditions: a) TESCl, imidazole, cat. DMAP, CH_2Cl_2 80-92%; b) i isopropenylmagnesium bromide, CuI (10 mol%), THF ii chloro(diphenyl)vinylsilane, DMAP, 60%; c) see table.



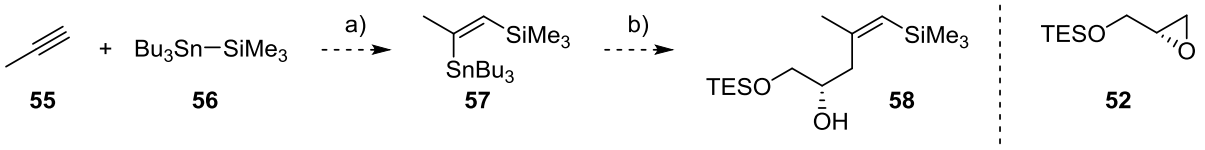
entry	catalyst (mol%)	solvent, temperature	conversion (yield)
1	**18** (10)	toluene, 111 °C	60%
2	**18** (20)	toluene, 111 °C	79% (47 %)
3	**18** (5+5+5)	toluene, 111 °C	78%
4	**18** (5+5+5+5)	toluene, 111 °C	97%
5	**50** (10)	benzene, 80 °C	27%
6	**50** (10)	toluene, 111 °C	32%

In the actual system however, even higher catalyst loadings had to be employed to drive the reaction to useful conversions (Table 4.3). The increased steric bulk due to the TES-ether might be responsible for the reduced reactivity or even more reluctant ring formation compared with **46**. Because of the high loading of expensive catalysts on a fairly early stage of the synthetic sequence, this approach was deemed too inefficient and was not pursued any further.

4.3.2 The "Alkyne-Metalation-Approach"

To find a more robust and scalable way to secure the alkenylsilane geometry, it was necessary to re-design the route. The possibility to use an alkyne and build up the olefin geometry via stereoselective addition was deemed promising.

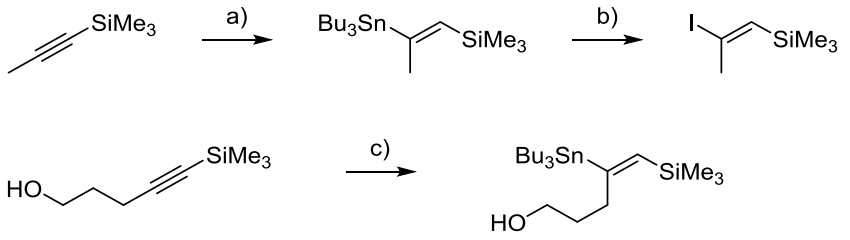
In this context, the silyl-stannylation of terminal alkynes was considered. Several reports have been published that describe the regioselective palladium-catalyzed *syn*-addition of silicon-tin reagents to terminal alkynes.[68, 69] In all reported cases the silicon substituent was delivered preferentially to the terminal- and the tin substituent to the internal position. The application of this reaction to propyne (**55)** would potentially lead to intermediate **57**. It might allow opening of epoxide **52** to access the desired secondary alcohol **58** in only two steps (Scheme 4.33).



Scheme 4.33: Attempted silylstannation of propyne. Conditions: a) $Pd(dba)_2$ (5 mol%), $P(OEt)_3$ (10 mol%), 1 atm propyne, THF; b) prospected epoxide opening.

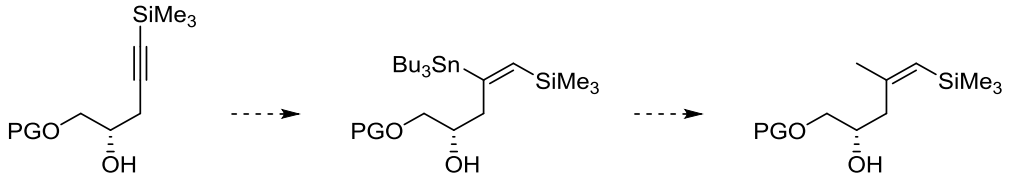
As ambient or higher temperatures are required for this silyl-stannylation reaction, the volatile nature of propyne renders it a problematic substrate. Conducting the reaction at room temperature under an atmosphere of propyne (Scheme 4.33) afforded only traces of desired product **57**, as judged by ^{1}H NMR spectroscopy.

Along the same lines we considered a regioselective hydrometallation of silyl capped alkynes that would deliver the newly introduced metal to the distal position with respect to the silicon substituent. While a Ru-catalyzed hydrostannylation yielded the undesired proximal regioisomer, a Mo-catalyzed approach to β-stannyl-alkenylsilanes has been reported (Scheme 4.34). [24, 70, 71, 72, 73] The resulting alkenylstannanes could be a versatile foothold for further functionalization. The required catalyst [Mo(η^3-allyl)Br(CO)$_2$(CH$_3$CN)$_2$] **59** is accessible in one step from molybdenumhexacarbonyl and allyl bromide. [73]



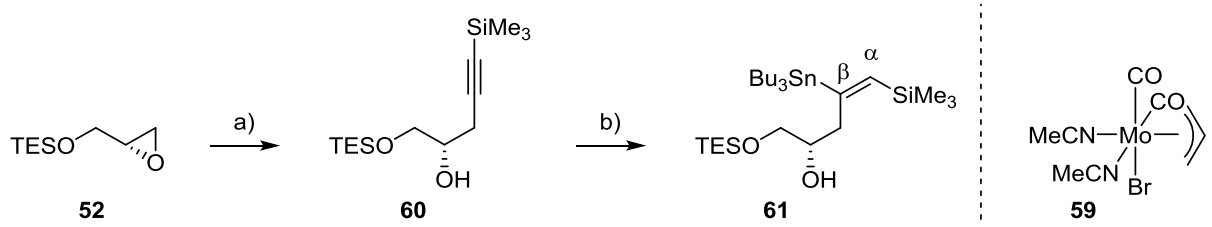
Scheme 4.34: Molybdenum-catalyzed hydrostannation of silyl-capped alkynes. Conditions: a) Bu_3SnH, [Mo(η^3-allyl)$Br(CO)_2(CH_3CN)_2$] (10 mol%), THF; b) I_2, CH_2Cl_2, 81% over both steps c) Bu_3SnH, [Mo(η^3-allyl)$Br(CO)_2(CH_3CN)_2$] (4 mol%), THF, 76%.

Since the addition of the Sn—H bond across the alkyne occurred strictly in a *syn*-fashion, the stannyl substituent would be delivered to a position where it could be employed in a methyl-Stille coupling to furnish the desired trisubstituted olefin **58** (Scheme 4.35).



Scheme 4.35: Envisaged application of the Mo-catalyzed hydrostannation to the north-western part.

To prepare the appropriate starting material for the hydrostannylation/methylation sequence the TES protected glycidol **52** was opened with lithium TMS-acetylide in the presence of BF_3•OEt_2. The subsequent Mo-catalyzed hydrostannylation delivered the expected β-regioisomer **61** as the sole product (Scheme 4.36).

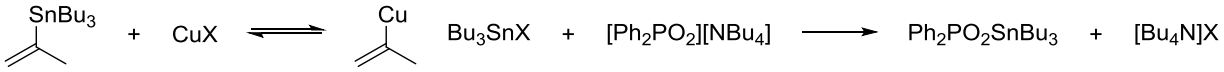


52 **60** **61** **59**

Scheme 4.36: Synthesis of stannane **61**. Conditions: a) Me_3Si-CCH, *n*-BuLi, BF_3•OEt_2, THF −78°C, 86%; b) Bu_3SnH, **59** (5 mol%), THF, 62%.

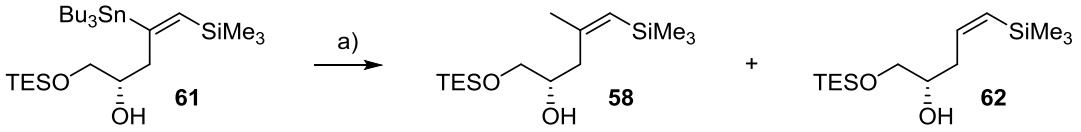
A protocol for the subsequent methylation of alkenylstannanes derived from propargylic alcohols has been developed earlier by our group. [25] This method was based on a modified Stille coupling in the presence of CuTC and $[Ph_2PO_2][NBu_4]$. These reagents are thought to form an organocopper intermediate via transmetalation of the alkenylstannane to $Cu^{(I)}$ and subsequent sequestration of the Bu_3Sn moiety as the phosphinate $[Ph_2PO_2]$—$SnBu_3$ (Scheme 4.37). Since the

transmetalation step is reversible, the removal of the tributyltin species shifts the equilibrium to the product side. The resulting alkenylcopper intermediate serves as more reactive nucleophile in the subsequent transmetalation to $Pd^{(II)}$. These conditions have led to fast and productive reactions in several applications.[74]



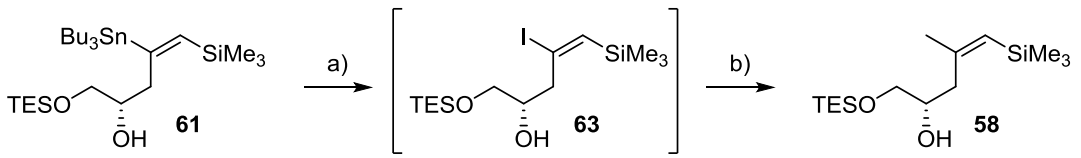
Scheme 4.37 Rational for the beneficial influence of $Cu^{(I)}$ salts and $[Ph_2PO_2][NBu_4]$.

The introduction of a methyl group via this approach has also been shown to proceed efficiently in the absence of a palladium catalyst, because the alkenylcopper intermediate can react with methyl iodide directly. Both, a palladium-catalyzed and a palladium-free protocol have been described by our group.[75]Exposure of the stannane **61** to methyl iodide under these conditions produced the desired product **58**, but was accompanied by substantial amounts of the disubstituted olefin **62** as inseparable byproduct, resulting from proto-destannylation (Scheme 4.38). This side product was formed presumably via protonation of the organocopper intermediate by the proximal OH group.



Scheme 4.38: Attempted methyl-Stille reaction of **61**. Conditions: a) MeI, CuTC, $[Ph_2PO_2][NBu_4]$, $Pd(PPh_3)_4$ (5 mol%), DMF.

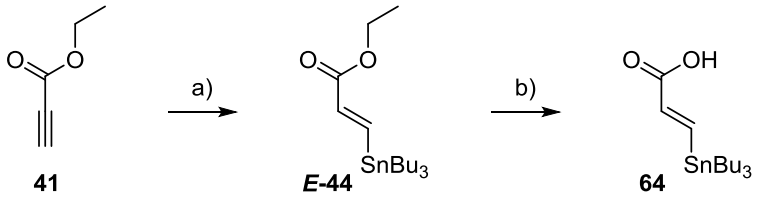
To overcome this issue, a detour was taken. Stannane **61** was first converted into alkenyl iodide **63**, which was treated with lithium dimethylcuprate *in situ* (Scheme 4.39). It was found to be crucial to use the intermediate alkenyl iodide **63** directly because it appeared to decompose upon attempted isolation/purification, presumably via (formal) elimination of Me_3SiI. This two-step/one-pot protocol delivered the desired product **58** in good yield.



Scheme 4.39: Synthesis of **58**. Conditions: a) I_2, THF, 0°C; b) Me_2CuLi, THF/Et_2O, −78°C, 71%.

4.3.3 Esterification

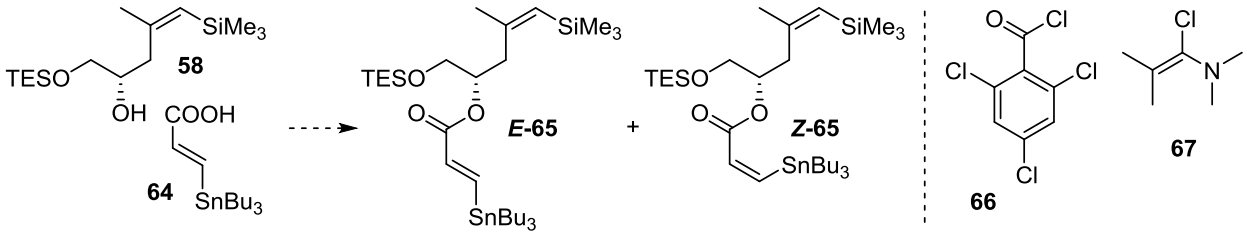
To complete the fragment, the β-tributylstannyl propenoate remained to be installed. The required *E*-β-tributylstannyl acrylic acid **64** was synthesized in two steps following a literature protocol. The sequence started with the free radical hydrostannylation of ethyl propiolate **41** to give the ester ***E*-44** as described earlier (see section 4.2), followed by saponification to produce the free acid **64** (Scheme 4.40).[65, 76]



Scheme 4.40: Synthesis of stannane **64**. Conditions: a) Bu_3SnH, AIBN (6 mol%), toluene, 80°C, 45% ***E*-44** + 40% ***Z*-44**; b) LiOH, THF/MeOH/H_2O, 89%.

The formation of the seemingly trivial ester linkage turned out to be more challenging than expected. Most of the examined protocols were plagued by the inherently low reactivity of the sterically encumbered secondary alcohol **58** as well as of most activated derivatives of the electron rich and bulky acid **64**. Partial *E* → *Z* isomerization of the β-tributylstannyl acryl moiety at some stage of the reaction reduced the productivity even further. Various conditions were tested, but none of them gave a satisfactory outcome (Table 4.4).

Table 4.4: Attempted esterification of **58** and **64**. Conditions: see table.



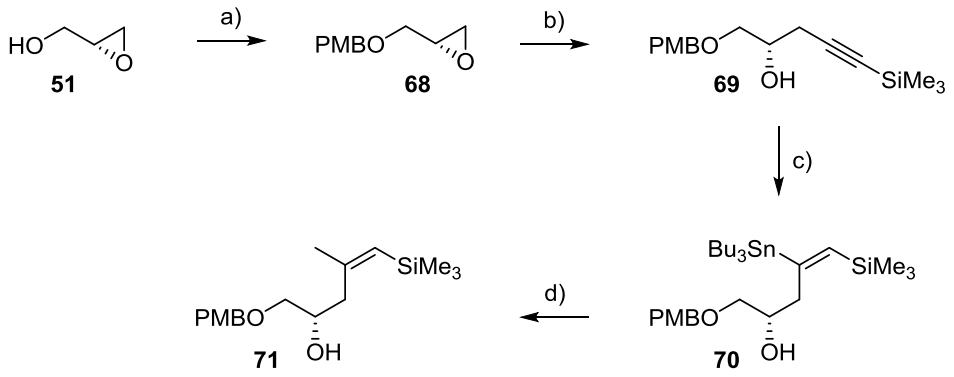
entry	conditions	result
1	**58**, **64**, DCC, DMAP	24% of the *Z*-isomer
2	**58**, **64**, EDC, DMAP	no desired product
3	**64**, **66**, Et_3N, then **58**, DMAP	traces of product
4	**58**, **64**, PPh_3, DEAD	no desired product
5	**58**, acroyl chloride, Et_3N, DMAP	69% of the corresponding acrylate
6	**64**, **67**, then **58**, Et_3N, DMAP	decomposition of the alkenylstannane
7	**64**, $(COCl)_2$, then **58**, Et_3N, DMAP	decomposition of the alkenylstannane
8	**64**, PPh_3, CCl_4, then **58**, Et_3N, DMAP	decomposition of the alkenylstannane

The use of different carbodiimides as coupling reagents uniformly resulted in low yields of the corresponding *Z*-isomer ***Z*-65** accompanied by the respective N-acyl-ureas (entries 1, 2). The Yamaguchi method via a mixed anhydride yielded only traces of the desired product (entry 3). Mitsunobu esterification, although it would have led to the opposite enantiomer, did not yield any product (entry 4).

The observation that alcohol **58** could cleanly be acylated with acroyl chloride (entry 5), led to the attempts to form an acid chloride derived from **64**. Neither Ghosez' reagent **67**, oxalyl chloride nor a reagent formed from triphenylphosphine and carbon tetrachloride gave any reactive intermediate, leading instead to the decomposition of acid **64** (entries 6 – 8).

The failure to synthesize this particular ester was attributed mainly to the steric bulk surrounding the OH functionality in alcohol **58**. As probably a very reactive acylating agent (like an acyl chloride) would be required to drive the reaction forward, we sought alternative pathways as such a reagent could not be prepared from acid **64**.

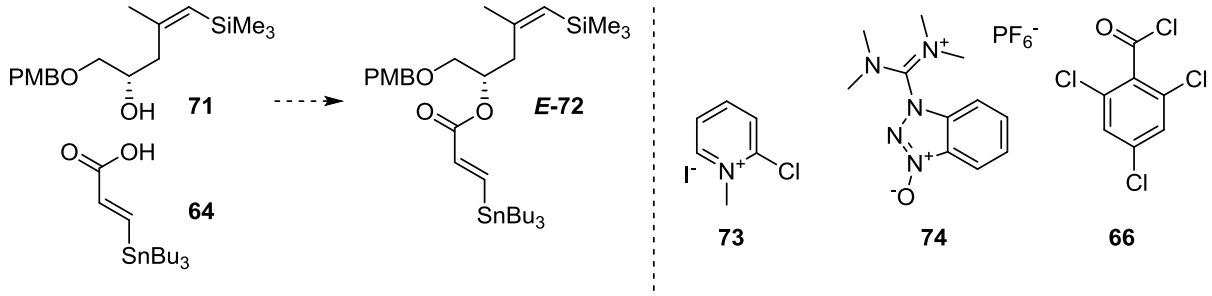
One way to overcome this problem was to reduce the steric congestion in the alcohol component. The single variable position to do so was the protecting group of the primary alcohol position in **58**. The only silyl ether protecting group smaller than TES would have been TMS, but the primary TES-ether has already been quite labile and the TMS-analogue would be impracticable. Therefore a slim protecting group, which could be cleaved selectively over the silyl ethers located in the tetrahydropyran fragment, was sought. An ester protecting group was ruled out, due to concerns over the possibility of cleaving it cleanly in the presence of the targeted macrolactone. Additionally any useful blocking group had to provide certain stability against strong Lewis acids, such as BF_3•OEt_2, required in the epoxide opening step. For this reason, acetals such as MOM- MEM- or SEM-groups appeared risky. This led us to consider substituted benzyl ethers. Among them, PMB is arguably the most popular one. It should be susceptible to selective cleavage under mildly oxidizing conditions.[77] Despite some concern, whether these cleavage conditions would be compatible with a conjugated, albeit electron-poor diene, we have found encouraging literature precedent for that scenario in a similar environment.[78] For these reasons the PMB group was selected.



Scheme 4.41: Synthesis of **71**. Conditions: a) PMB-Cl, NaH, DMF, 87%; b) Me_3SiCCH, *n*-BuLi, BF_3•OEt_2, THF −78°C, 92%; c) Bu_3SnH, $[Mo(\eta^3allyl)Br(CO)_2(CH_3CN)_2]$ (5 mol%), THF, 69%; d) I_2, THF, 0°C; then Me_2CuLi, THF/Et_2O, −78°C, 77%.

The PMB protected analog of TES-ether **58** was prepared by an almost identical four step sequence (Scheme 4.41). With this material in hand, the reluctant esterification step was revisited (Table 4.5).

Table 4.5: Esterification of **64** and **71**. Conditions: see table.



entry	conditions	result
1	**64**, **71**, DCC, DMAP	38% ***E*-72** + 23% ***Z*-72**
2	**64**, **71**, **73**, Et_3N	no desired product
3	**64**, **71**, **74**, DBU	no desired product
4	**64**, **66**, Et_3N, then **71**, DMAP	67% ***E*-72** + 19% ***Z*-72**

The reactions in the PMB-series proceeded cleaner and faster than those of the TES analogue. Already the Steglich esterification worked much better (entry 1) and finally the Yamaguchi method produced useful yields of desired ***E*-72**, but still considerable amounts of the *Z*-isomer were obtained as side product (entry 4). Nevertheless, this material could be recycled to alcohol

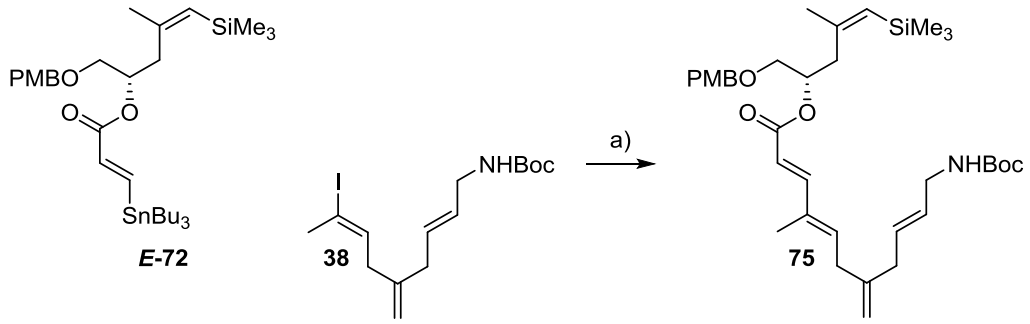
71 via alkaline saponification. The extent of the geometric isomerization depended on the loading of DMAP. Empirically, 2.5mol% of DMAP was found to produce the best results.

In conclusion, ester fragment **72** was accessed in up to 28% overall yield over 5 steps. The absolute stereochemistry of this fragment was based on commercial enantiopure (*R*)-glycidol. The geometry of the trisubstituted alkenylsilane was established via regio- and stereoselective molybdenum-catalyzed hydrostannylation. Finally a surprisingly challenging esterification was achieved by Yamaguchi's method. The building block was decorated with a alkenylstannane for the upcoming connection to the triene fragment via Stille reaction, as well as with a alkenylsilane, which could be subsequently converted into a suitable alkenyl halide for the next cross coupling reaction with the tetrahydropyran fragment.

4.4 Connecting the Triene Fragment V and the Ester Fragment VI

The successful and scalable syntheses of fragments **38** and ***E*-72** permitted the subsequent investigation of the fragment coupling. Although the aforementioned model (Scheme 4.29) Stille reaction using $PdCl_2(MeCN)_2$ as catalyst had generated the desired coupling product in 57% yield, there was room for improvement. The influence of various ligands, additives, and (co-) solvents on Stille coupling reactions has been thoroughly studied and reviewed.[79]

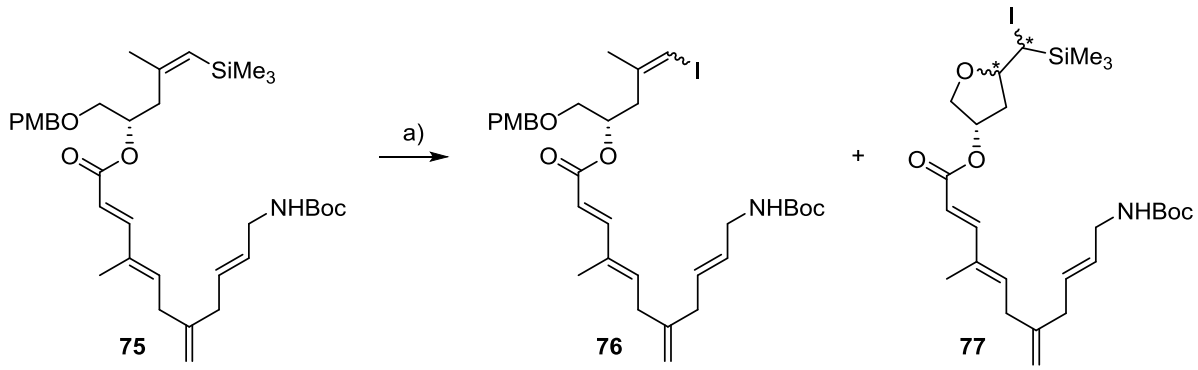
Indeed, after some experimentation, the use of preformed $Pd(AsPh_3)_4$ as a catalyst for the Stille coupling of fragments **38** and ***E*-72** resulted in a dramatic improvement in the isolated yield of product **75**.[80] After optimization, the product was obtained in 89% yield as a single isomer (Scheme 4.42). The beneficial influence of triphenylarsine can be rationalized by the weaker σ-donation of arsine lone pair of electrons than the phosphine analogue. This results in a more facile dissociation of the $AsPh_3$ ligands, to generate the catalytically active, coordinatively unsaturated palladium species. Moreover, the resulting lower electron density at the palladium center is believed to accelerate the transmetalation of the alkenylstannane nucleophile.



Scheme 4.42: Fragment coupling of **38** and ***E*-72**. Conditions: a) $Pd(AsPh_3)_4$ (10 mol%), DMF, 89%.

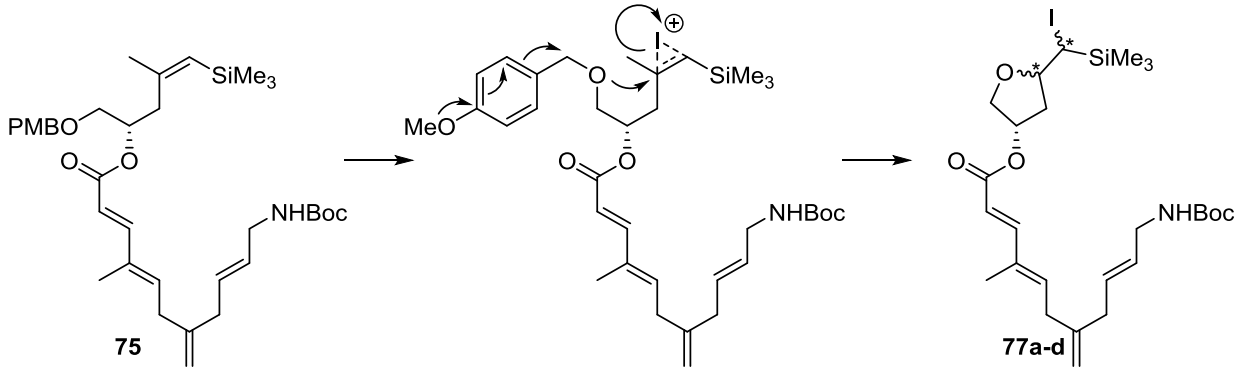
It was then planned to convert the trimethylsilyl group in **75** into the corresponding alkenyl iodide **76** in preparation for the next fragment coupling. This operation was not without precedent, but due to the high degree of unsaturation in **75** the projected iodo-desilylation was deemed challenging. It is of note that the previous iodo-desilylation of **37** during the synthesis of the triene fragment in the southern part of the target macrocycle, which already contained three double bonds, had proceeded cleanly. Therefore similar conditions were chosen for the initial tests.

Unfortunately, the desired isomer of the alkenyl iodide ***Z*-76** was only obtained in low yield, accompanied by its *E*-isomer as well as several other side products, which were difficult to remove by flash chromatography. These byproducts were identified by HPLC-MS as four diastereomeric products which likely resulted from an iodo-etherification pathway (Scheme 4.43).



Scheme 4.43: Attempted iodo-desilylation of **75**. Conditions: a) NIS, lutidine, HFIP, 0°C, 25-30%.

This side reaction appeared to proceed through the attack of the PMB-ether on an iodonium-intermediate, causing the loss of a PMB cation and the formation of a tetrahydrofuran ring. The creation of two new stereogenic centers with a lack of selectivity led to all four isomeric products **77a-d** (Scheme 4.44).



Scheme 4.44: Proposed mechanism of the THF ring formation.

To address this issue, the reaction conditions were examined more closely. Both pathways leading to the desired alkenyl iodide **76** and to the tetrahydrofuran side products **77a-d** were thought to involve the same iodonium intermediate. At that point, either a trimethylsilyl-cation is expelled, or the neighboring PMB-ether participates in the reaction. If it was possible to accelerate the departure of the Me_3Si^+ moiety, the former path should prevail. On the other hand,

it would also help to delay the attack of the PMB ether. The use of a polar, coordinating solvent was expected to stabilize a trimethyl silyl cation; indeed, there were reported examples describing the use of acetonitrile or chloroacetonitrile in similar reactions.[81] A screening of different conditions revealed that the selectivity could be substantially improved, although at the cost of a longer reaction time (Table 4.6).

Table 4.6: Iodo-desilylation of **75**. Conditions: all reactions were conducted in the presence of 2 equiv. lutidine and 1.5 equiv. NIS, solvent and temperature: see table. Conversion and product ratios were determined by HPLC-MS. Discrepancies between the sum of the assigned products and the conversion arose from other unidentified side products.

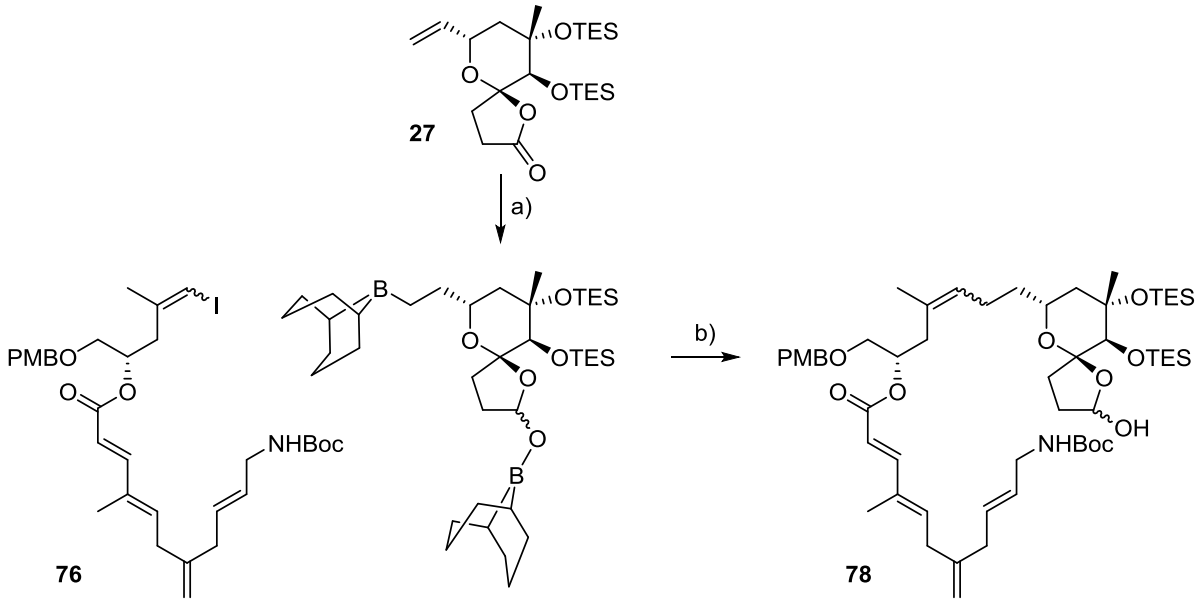
entry	solvent	temp. [°C]	***Z*-76**:***E*-76:77**	Conversion (yield ***Z*+*E*-76**)
1	HFIP	0	43:17:37	100%
2	$ClCH_2CN$:EtOAc 2:1	0	18:10:7	38%
3	MeCN	-20	22:3:10	37%
4	MeCN	-10	72:12:9	95%
5	MeCN	0	77:13:7	98%
6	MeCN	0	67:11:6	85% (67%)
7	EtCN	0	62:14:13	91%

This improvement provided a reliable access to the alkenyl iodide **76** in a satisfactory yield. The geometrical isomers could not be separated at this stage, but the ratio of ~ 5-6:1 in favor of the desired *Z*-isomer was deemed acceptable.

4.5 Connecting the Polyene Fragment with the Tetrahydropyran Fragment

4.5.1 The Suzuki Coupling Approach

The tetrahydropyran fragment **27**, which contained a terminal olefin as prerequisite for a hydroboration/Suzuki coupling sequence, had to be connected to alkenyl iodide **76** (Scheme 4.45). This type of fragment coupling was well established in complex molecule synthesis.[82, 83]

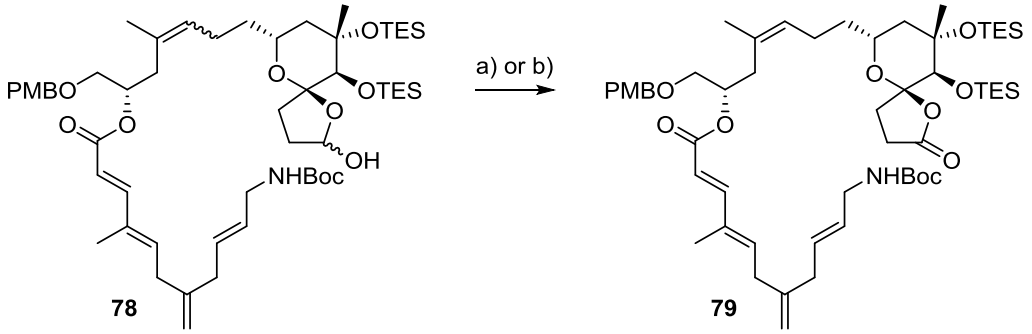


Scheme 4.45: Hydroboration and Suzuki-coupling of **27** and **76**. Conditions: a) 9-BBN, then H_2O, THF; b) $[Pd(dppf)Cl_2]\bullet CH_2Cl_2$ (20 mol%), $AsPh_3$, Cs_2CO_3, THF/DMF, 63%.

The crucial carbon—carbon bond formation worked very well, but the reaction was plagued by other features. Due to the partial geometrical isomerization over the course of the iodo-desilylation reaction, substrate **76** and the resulting product **78** were a mixture of *E*/*Z*-isomers. Furthermore, lactone **27** was reduced to the corresponding lactol during the hydroboration reaction. This led to a product mixture consisting of two diastereomeric lactols, which were interconverting during flash chromatography, of both geometrical isomers (Scheme 4.45). The resulting mixture rendered the characterization at this stage very difficult.

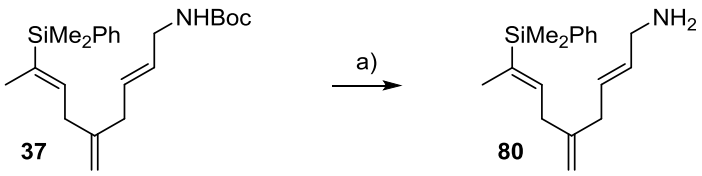
It was not possible to suppress the undesired lactone reduction during hydroboration of **27** by control of the reaction stoichiometry or temperature. The described mixture of isomeric products **78** was re-oxidized to the corresponding lactone **79** in an effort to reduce the complexity. At this point, the geometrical isomers resulting from the iodo-desilylation were finally separable by

careful flash chromatography. Both a stoichiometric and the usual catalytic protocol for a Ley oxidation were employed to oxidize the lactol diastereomers **78**, and both led to comparable results (Scheme 4.46).



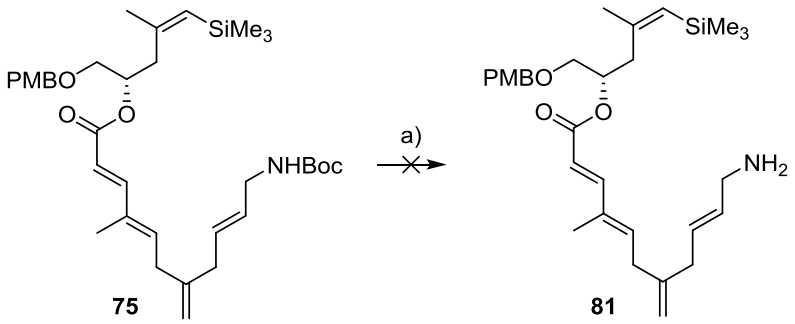
Scheme 4.46: Oxidation of lactol **78**. Conditions: a) $[Pr_4N][RuO_4]$, CH_2Cl_2, 52%; b) $[Pr_4N][RuO_4]$ (20 mol%), NMO, MeCN, 47%.

With the macrolactamization within reach, only the amine deprotection was left to be addressed. Since the standard methods for cleaving N-Boc groups use strong Brønsted acids, which would likely also cleave the TES ethers in **79**, it was planned to exploit Lewis acids instead.[84] Intermediate **37** was used as a model substrate to test the Lewis acid-mediated N-Boc deprotection. Compound **37** was treated with three equivalents of anhydrous zinc bromide in CH_2Cl_2 at room temperature, which cleanly furnished the corresponding amine **80** (Scheme 4.47); at 0 °C, no reaction occurred.



Scheme 4.47: Boc-deprotection of **37**. Conditions: $ZnBr_2$, CH_2Cl_2, quant.

However, when the slightly more complex compound **75** was subjected to the identical conditions, it resulted in the formation of a complex mixture. Among other side reactions, the cleavage of the PMB-ether was observed, but no desired product **81** could be isolated (Scheme 4.48).

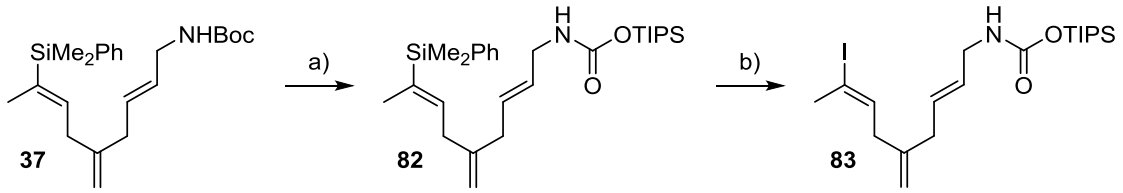


Scheme 4.48: Attempted Boc-deprotection of **75**. Conditions: a) $ZnBr_2$, CH_2Cl_2.

It has also been shown that Boc groups can be cleaved by various silyl triflates, followed by mild aqueous workup. This type of reaction would be conceptually similar to the cleavage mediated by other Lewis acids, with the difference that after loss of a *tert*-butyl cation, a silyl carbamate is formed. The stability of this silyl carbamate towards hydrolysis depends heavily on the nature of the silyl substituent. Although such a method was a tempting alternative, it had been noticed earlier that the lactone ring in **22a** was cleaved by silyl triflates (TBSOTf) as well (Scheme 4.16).

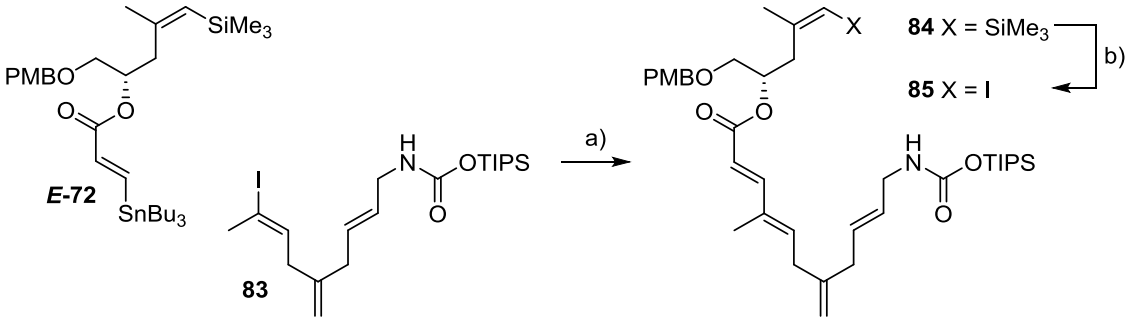
The failure to remove the Boc-group necessitated a change in the protecting group strategy. The desired protecting group should shield the amine similarly to the Boc-group, which had endured all reaction conditions so far, but should be selectively removable under mild conditions. Any blocking group that would need either acidic or alkaline hydrolysis or hydrogenolysis was ruled out due to expected incompatibility with the functional groups found in rest of the molecule. After a careful literature survey, the triisopropylsilyl-oxy-carbonyl (Tsoc-) group was selected. It offers good stability to acids, bases, oxidizing and reducing agents, but is susceptible to fluoride.[85] As a further advantage, it was possible to convert a Boc- into a Tsoc-group by treatment with TIPSOTf (*vide supra*). [132] This possibility allowed the remaining Boc-protected material to be used, which otherwise would have been lost.

The question remained at which stage the Boc-group was best converted into its fluoride-labile counterpart. It had to happen after the potassium fluoride-promoted Suzuki coupling to form the triene fragment. For the sake of convergence, a good opportunity would be before the connection of the triene and the ester fragments. Therefore, Boc-derivative **37** was treated with TIPSOTf, which led to the clean and high yielding formation of the corresponding Tsoc-protected amine **82**. This product was transformed into the alkenyl iodide **83** in analogy to its Boc-congener (Scheme 4.49).



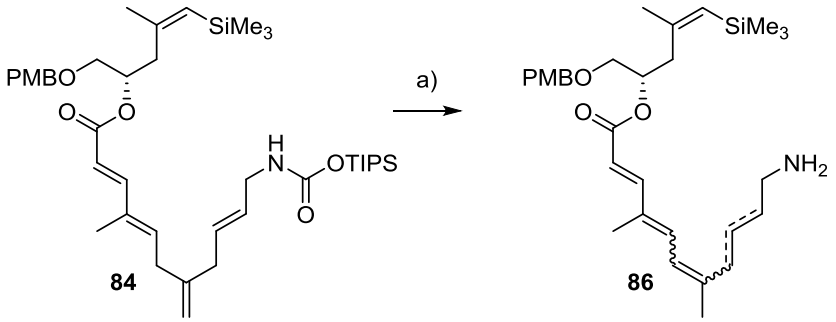
Scheme 4.49: Synthesis of Tsoc-derivative **83**. Conditions: a) TIPSOTf, lutidine, CH_2Cl_2 0°C, 89%; b) NIS, lutidine, HFIP, 0°C, 66%; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

From this point onward, the synthesis proceeded in an analogous fashion to the sequence described for the Boc-series. The Stille-type fragment coupling and the following iodo-desilylation performed well, giving rise to alkenyl iodide **85**, which was now ready for the installation of the tetrahydropyran fragment (Scheme 4.50).



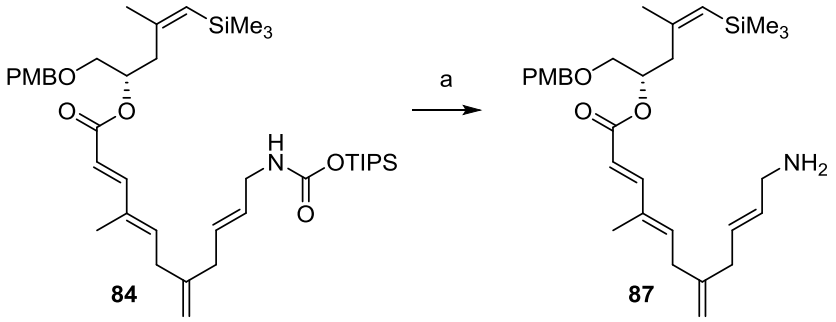
Scheme 4.50: Synthesis of alkenyl iodide **85**. Conditions: a) $Pd(AsPh_3)_4$ (10 mol%), DMF, 79%; b) NIS, lutidine, MeCN, 0°C, 69%, *Z*:*E* ~ 5:1.

Before that, however, the cleavage of the new protecting group was tested. The conditions reported in the literature involved TBAF in THF. In the case of this particular system, TBAF was found to be incompatible with the base-sensitive doubly skipped tetraene motif of **84**. Upon treatment with TBAF at 0 °C, a colorless solution of compound **84** immediately turned intensely yellow and the ^{1}H NMR spectrum indicated that the olefinic system had changed dramatically. This observation was attributed to the migration of one or both isolated olefins into conjugation with the dienoate system (Scheme 4.51).



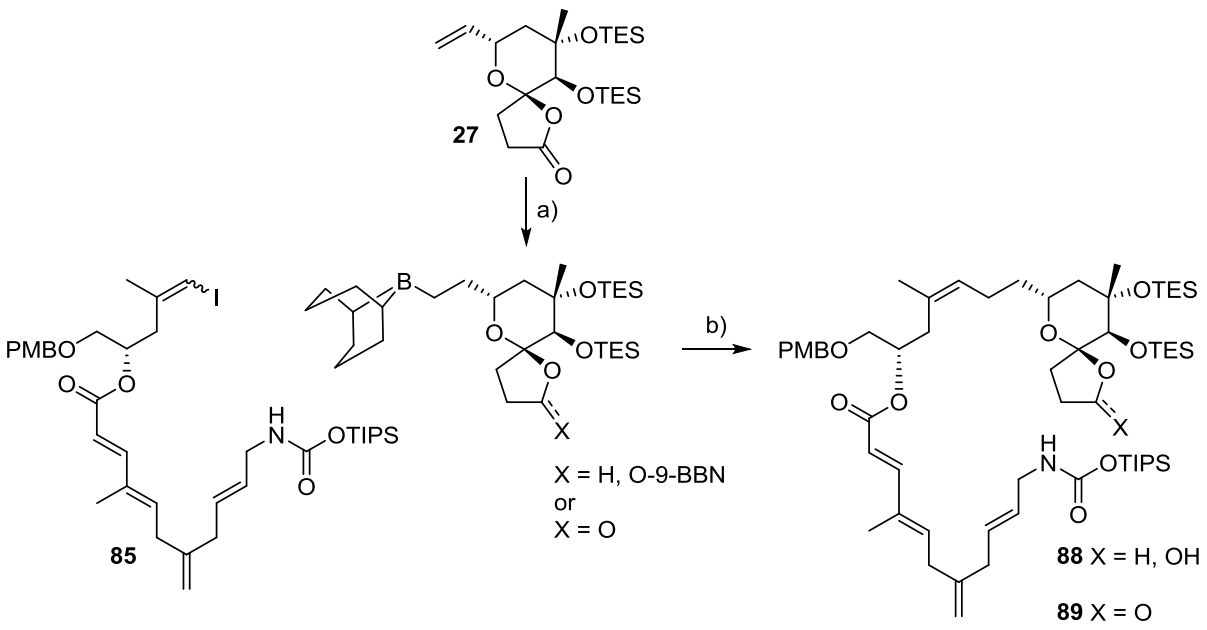
Scheme 4.51: TBAF induced decomposition of **84**. Conditions: TBAF, THF, 0°C.

This problem was overcome by switching the fluoride source from the relatively basic TBAF to hydrogen fluoride pyridine complex (Olah's reagent), which brought about clean and quantitative removal of the Tsoc-group within minutes (Scheme 4.52).



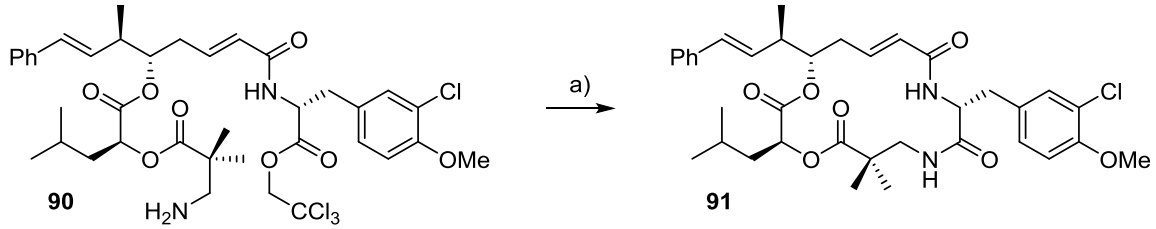
Scheme 4.52: Tsoc-deprotection of **84**. Conditions: a) HF•pyridine, THF, 0°C, quant..

The Suzuki coupling to attach the tetrahydropyran fragment was carried out under the previously established conditions, but this time a mixture of the desired lactone and the expected lactol was obtained. This outcome might have been the result of only partial reduction during hydroboration or of aerobic re-oxidation of the lactol during the workup or purification. After a somewhat tedious separation, the lactone **89** was obtained in low yield (Scheme 4.53).



Scheme 4.53: Hydroboration and Suzuki-coupling of **27** and **85**. Conditions: a) 9-BBN, then H_2O, THF; b) $[Pd(dppf)Cl_2]•CH_2Cl_2$ (20 mol%), $AsPh_3$, Cs_2CO_3, THF/DMF, **88** 14%; **89** 11%.

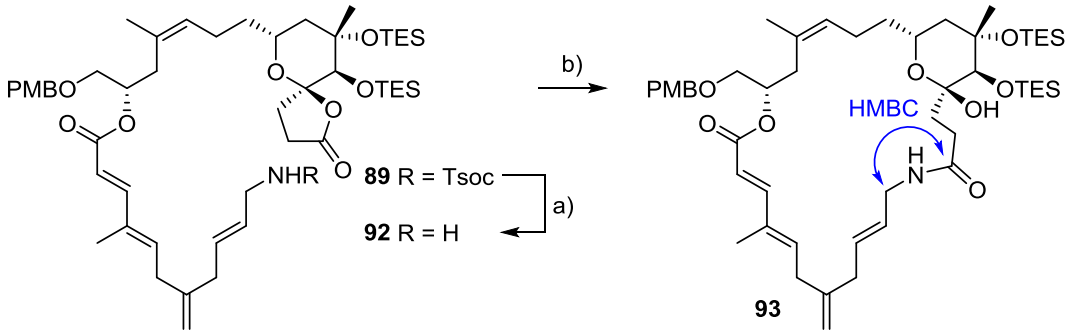
Although only a small amount of **89** was available, the pivotal macrolactamization could be tested. Gratifyingly, the removal of the Tsoc-group of **89** proceeded cleanly, despite the presence of the two TES ethers, which were unperturbed under the employed reaction conditions. The deprotection proceeded so cleanly that no further purification beyond an aqueous workup was required. The available literature on the intramolecular aminolysis of esters or lactones was somewhat limited, but one report by an Eli Lilly group gave an invaluable hint.[86] In this report, a trichloroethyl ester in **90**, which had initially been introduced as a protection group, served as an electrophile in the macrolactamization *en route* to the cryptophycin intermediate **91** (Scheme 4.54).



Scheme 4.54: Macrolactamization via aminolysis. Conditions: a) 2-pyridone, toluene 0.02 M, 80%.

This impressive cyclization was conducted on 575 g scale. While slightly unconventional, this approach had been chosen by Eli Lilly chemists to avoid the use of expensive peptide coupling reagents, which would have led to purification issues on such a scale.

When crude amine **92** was subjected to similar conditions, the desired macrocycle **93** was indeed obtained (Scheme 4.55). The identity of this important compound was established and confirmed by (high resolution) mass spectrometry and NMR spectroscopy. In addition to the correct mass (that was the same as the mass of the isomeric acyclic amine), an HMBC correlation between the methylene group next to the nitrogen atom and the amide carbon atom supported the successful amide-bond formation.

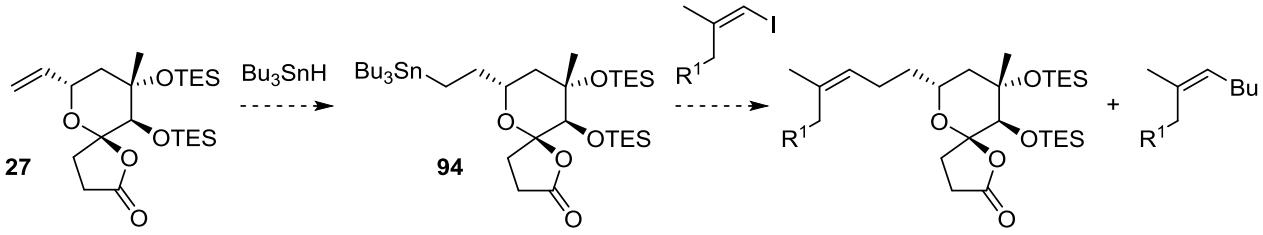


Scheme 4.55: Tsoc-deprotection and macrolactamization of **89**. Conditions: a) HF•pyridine, THF, 0°C; b) 2-pyridone, benzene, 80°C 0.001 M, ~ 20%.

It was relieving to find that the strategy of macrolactamization via intramolecular aminolysis was viable, but several issues in the synthetic sequence had yet to be addressed to render it efficient. The yield of the macrocyclization was disappointingly low and was the most important problem to solve. To gain better insight into the pitfalls and possible improvements of this reaction, a more efficient material supply had to be established. The major bottleneck appeared to be the Suzuki coupling, which produced a troublesome mixture of the lactol diastereomers together with varying amounts of the corresponding lactone. An alternative method for fragment coupling had to be found without sacrificing the convergence of the route.

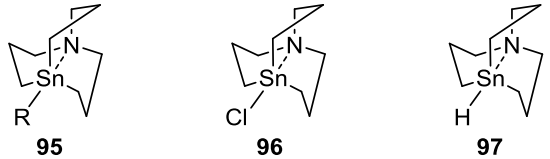
4.5.2 Alternative Cross Coupling Approach

The lessons learned from the Suzuki approach discussed in the previous section were taken into account for the re-design and improvement of the fragment coupling strategy. The cross coupling reaction itself has worked well, but the main disadvantage was the concomitant reduction of the lactone over the course of the hydroboration reaction. Therefore, we opted to keep the palladium catalyzed cross coupling strategy, while employing a different method to generate the nucleophile. This nucleophile should be an organometallic species, which will transmetalate readily to palladium$^{(II)}$ and can also be generated cleanly without affecting the lactone or any other component of the tetrahydropyran fragment. The fact that an sp^3-hybridized carbon atom had to be delivered to a $Pd^{(II)}$ center limited the choice of suitable organometallic reagents. Alkyl stannanes could be easily prepared in an analogous fashion to the aforementioned alkyl borane via hydrostannylation of **27** with *e.g.* tributyltin hydride (Scheme 4.56). These compounds, however, show a limited tendency to transfer an unactivated alkyl group to palladium$^{(II)}$. Furthermore, the tetravalent nature of tin would lead to unfavorable statistics for the transfer of the desired alkyl group rather than *e.g.* a butyl group.



Scheme 4.56 Hypothetical hydrostannantion/Stille coupling sequence

One elegant solution to some of these problems in Stille cross coupling reactions has been developed by Vedejs *et al.* in the form of stannatranes (Scheme 4.57). The rigid architecture of these entities aligns the nitrogen lone pair to overlap with the σ* antibonding orbital of the tin—carbon bond of the transferable group. This interaction weakens the tin—carbon bond and renders it suitable for transmetalation.[87, 88]

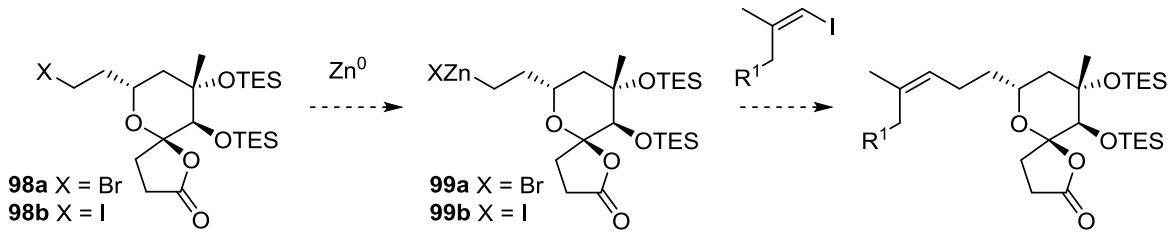


Scheme 4.57: Stannatrane derivatives.

Unfortunately, this method was not applicable for our synthesis because stannatrane-derivatives of the type **95** have so far only been prepared from the corresponding commercially available tin chloride **96** and a more reactive organometallic species, usually lithium- or magnesium alkyls. The hypothetical tin hydride **97**, which might have been useful in hydrostannation, has not yet been described and its synthesis was not investigated.

Hydrozirconation was also considered, as the resulting alkyl zirconocene derivatives constitute useful synthetic intermediates. Due to the reducing properties of zirconium hydrides, issues similar to those arising from hydroboration were deemed likely.[89]

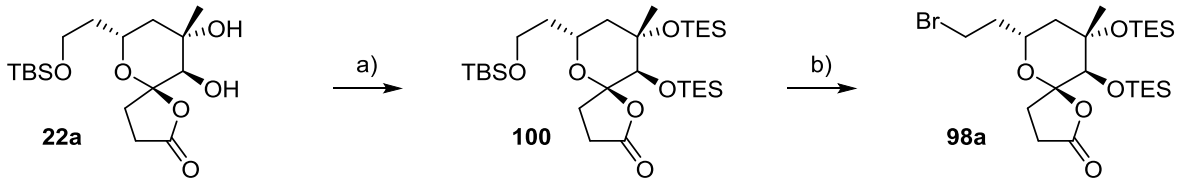
This led to the examination of organozinc species as suitable nucleophiles. In contrast to the more polar organolithium or -magnesium compounds, organozinc compounds have been shown to be compatible with esters and appropriately protected amines. The Negishi reaction has been employed, although not as frequently as Suzuki or Stille reactions, for fragment coupling in total synthesis.[90, 91] An intermediate like **99** was required to perform the desired Negishi coupling for the present synthesis (Scheme 4.58).



Scheme 4.58: Envisaged zinc insertion/Negishi coupling sequence.

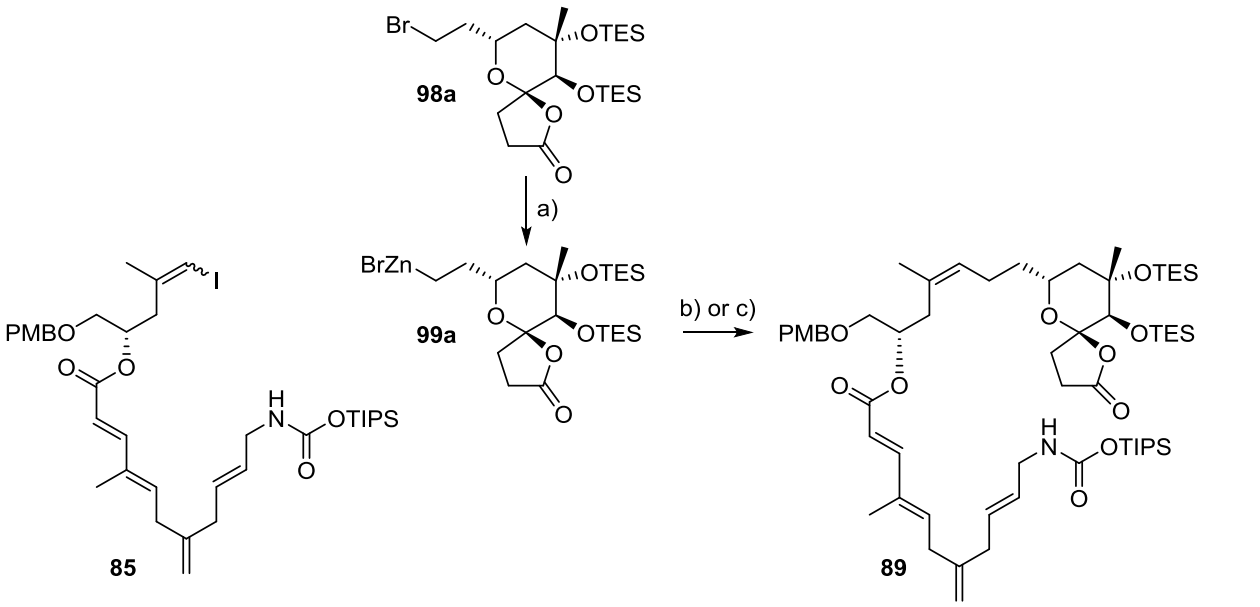
The most straightforward approach to such a species seemed the insertion of zinc into the corresponding alkyl halide **98**. In order to prepare this material, the synthesis of the tetrahydropyran fragment had to be altered slightly, but it seemed possible to acquire either alkyl iodide **98b** or bromide **98a** without too much difficulty. The alkyl iodide would likely be the more reactive compound, while the analogous alkyl bromide would be more stable. Since there was good precedent for the successful use of alkyl bromides in the formation of functionalized organozinc compounds, the bromide was targeted first.[92, 93] Should the zinc insertion into the alkyl bromide fail, it could still be "upgraded" to the corresponding iodide via Finkelstein reaction.

The digression from the original route, leading to alkyl bromide **98a**, started from intermediate **22a**. After TES protection, the fully silylated compound **100** was exposed to triphenylphosphine dibromide, which cleanly converted the primary TBS ether, in the presence of the two more hindered TES ethers, into the desired bromide **98a** (Scheme 4.59).[94]



Scheme 4.59: Synthesis of bromide **98a**. Conditions: a) TESCl, $AgNO_3$, DMAP, DMF/pyridine 1:1, 76%; b) Ph_3PBr_2, CH_2Cl_2, 0°C, 89%.

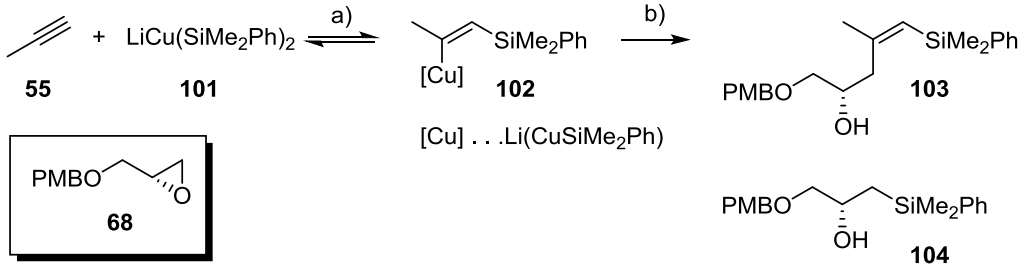
When bromide **98a** was allowed to react with a moderate excess of Rieke zinc in DMF at ambient temperature, it smoothly produced the expected alkylzinc bromide **99a**.[95] The progress of the zinc insertion was followed semiquantitatively via GC-MS. The desired Negishi coupling was first attempted in the presence of $Pd(PPh_3)_4$, the prototypical catalyst for countless cross coupling reactions. We reasoned that a $Pd^{(II)}$ pre-catalyst would consume two equivalents of the precious organozinc reagent to be reduced to the catalytically active $Pd^{(0)}$ catalyst. Therefore, it seemed better to employ a $Pd^{(0)}$ complex directly, to avoid wasting any **99a**. However, $Pd(PPh_3)_4$ showed low catalytic activity; the reaction required prolonged stirring at 60 °C and the desired product **89** was obtained in only 28% yield. The Pd/dppf catalyst system, as had been demonstrated in the previous Suzuki approach (Scheme 4.53), was well suited to promote this closely related cross coupling under mild conditions. Experiments were then undertaken to pre-reduce $[Pd(dppf)Cl_2]$, in the hope of generating a more efficient palladium$^{(0)}$ catalyst. We found that a very active (pre-) catalyst could be obtained by reducing $[Pd(dppf)Cl_2 \bullet CH_2Cl_2]$ with manganese dust in the presence of two equivalents of triphenylarsine as stabilizing ligand and DMF as solvent. Manganese was selected because it has been reported to be rather unreactive towards alkenyl halides.[96] The progress of the reduction was easily monitored due to the indicative color change from bright orange to intense purple. The resulting (pre-) catalyst solution was used directly in the cross coupling reaction, giving rise to a faster reaction and an improved yield of 70% (Scheme 4.60). The exact nature of said (pre-) catalyst has not yet been established. However, this method allowed for the synthesis of reasonable quantities of macrocyclization precursor **89**.



Scheme 4.60: Zinc insertion in **98a** and Negishi coupling with **85**. Conditions: a) Rieke zinc, DMF; b) $Pd(PPh_3)_4$ (21 mol%), DMF 60°C, 28%; c) $[Pd(dppf)Cl_2]•CH_2Cl_2$ (20 mol%), $AsPh_3$, Mn, DMF/THF, 70%.

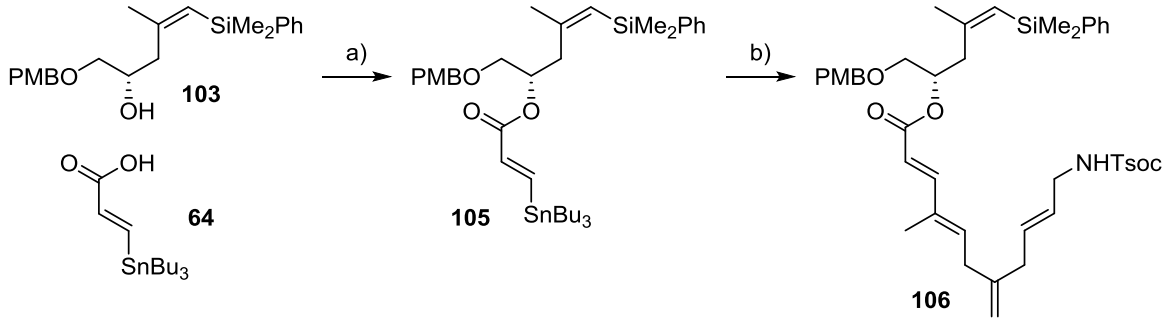
4.5.3 A Short Cut to the Ester Fragment

In parallel to the improvement on the above mentioned fragment coupling, a minor advance was realized in the sequence leading to the ester fragment. While it had previously taken 5 steps to acquire the fragment ***E*-72** in the correct geometry, a conceptually more elegant and shorter route was found. The same PMB-protected epoxide **68**, which had previously served as the chiral starting material, was now opened with alkenyl cuprate **102**. This reagent was produced *in situ* by the silyl-cupration of propyne. Due to the excellent regioselectivity and clean *syn* fashion of the silyl-cupration, the organocopper reagent was formed as a single isomer.[97, 98] The major drawback of this reaction was its reversibility. An excess of silyl cuprate **101** with respect to propyne would have been needed to achieve clean consumption of the alkyne. However, it was not practical to employ this reagent in excess because **101** itself was also able to react with epoxide **68**, leading to β-silyl alcohol **104**. Therefore, an excess of **101** needed to be avoided. The use of excess propyne to ensure complete consumption of **101** was prohibited by the acidic nature of the terminal alkyne. The sp hybridized C—H bonds of terminal alkynes have been shown to protonate alkenyl cuprates.[97] Due to these limitations, a ratio of propyne **55** and **101** as close as possible to 1:1 was desired. This was difficult to achieve, since propyne is very volatile, but it could be manipulated as a stock solution in THF at low temperature with sufficient accuracy. When this solution of propyne was mixed with a solution of **101** at −78 °C, the insertion product **102** was formed, and it was possible to open epoxide **68** in the presence of boron trifluoride diethyl etherate at the same temperature. It was important to maintain low temperature throughout the reaction because **102** could have partially lost propyne at higher temperatures, reverting to **101**. The additional activation of the epoxide allowed the desired reaction to proceed efficiently (Scheme 4.61).



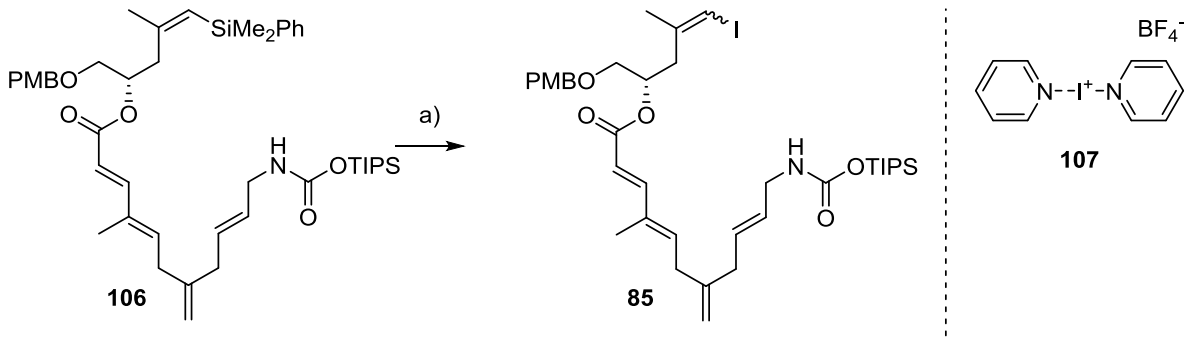
Scheme 4.61: Silylcupration/epoxide opening approach to **103**. Conditions: a) THF, −78°C; b) epoxide **68**, BF_3•OEt_2, THF, −78°C, 51%.

The major drawback of this transformation was the concomitant formation of the β-silyl alcohol **104**, via direct attack of **101** on the epoxide, but the desired compound **103** could be separated from **104** by careful flash chromatography. This slight inconvenience was outweighed by the reduction in the number of steps and (subjective) gain in elegance. It was now possible to assemble the ester fragment **105** in only three operations. The esterification with β-tributylstannyl acrylic acid **64** and the subsequent Stille coupling with the triene fragment **83** proceeded smoothly, in a similar fashion to the closely related trimethylsilyl-derivative, to give **106** (Scheme 4.62).



Scheme 4.62: Assembly of **106**. Conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **103**, DMAP (2.5 mol%), 0°C → RT, 63% b) **83**, $Pd(AsPh_3)_4$ (6 mol%), DMF, 82%.

At this point, a minor change was required to achieve the iodo-desilylation of **106**. It was discovered that the newly synthesized dimethylphenylsilyl-derivative **106** was more reluctant towards this reaction than its trimethylsilyl-congener **84**. This finding was attributed to the more electron withdrawing nature of a phenyl-substituent on silicon which renders the departure of a formal silyl cation less favorable. The lower reactivity of the alkenylsilane was matched with Barluenga's iodinating reagent **107**, which is more reactive than NIS (Scheme 4.63).[99] Its use led to yields of **85** comparable to those obtained from the trimethylsilyl variant, albeit in a slightly worse *Z*:*E* ratio of ~ 3:1.



Scheme 4.63 Iodo-desilylation of **106**. Conditions: a) **107**, MeCN, −20°C, 62 %, (*Z*:*E* ~ 3:1).

The subsequent Negishi coupling of **85** with the tetrahydropyran fragment **99a** proceeded as described earlier, completing the synthesis of macrolactamization precursor **89** in 10 steps as the longest linear sequence. The successful route of **89** was heavily reliant on the convergent assembly of three "prefabricated" fragments via robust palladium catalyzed cross coupling reactions. Difficulties regarding the compatibilities of various functional groups and protecting groups present in this advanced intermediate were eventually overcome by careful choice of reagents and conditions. All employed reactions were scalable and provided access to **89** in useful quantities (0.37 g on the single largest scale).

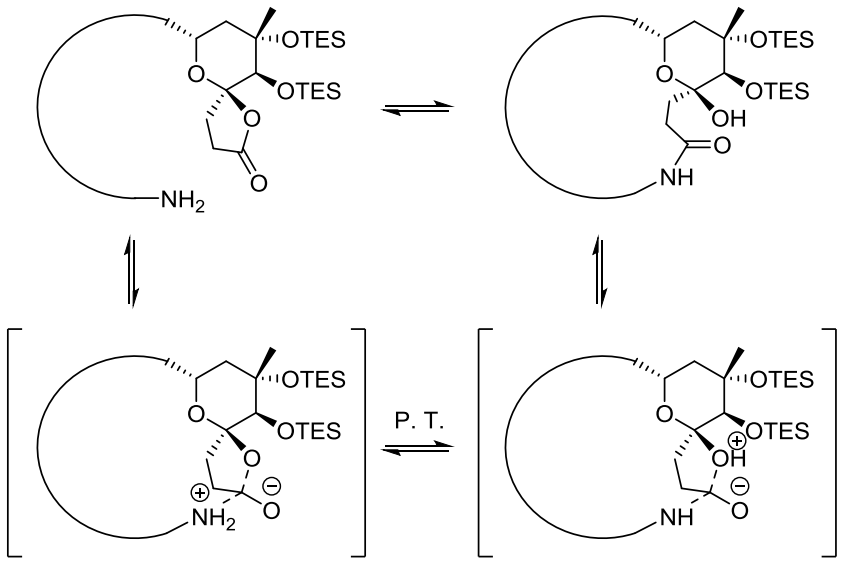
4.6 Optimization of the Macrocyclization

Now that the supply chain up to the cyclization precursor **89** was secured, the crucial macrolactamization could be inspected in more detail. Initially different solvents were tested, instead benzene, which had been employed in the first place, but none of them showed any improvement.

In the next step, several promotors were examined that had shown activity in similar reactions. Several (thio)urea-type organocatalysts did not lead to any product formation.[100] Lewis acids like lithium bistriflimide or Otera's catalyst produced some product, but also significant amounts of side products.[50, 101] Finally, compounds structurally related to 2-pyridone like 2-mercaptopyridine and 8-hydroxyquinoline were tested but did not bring about any improvement.

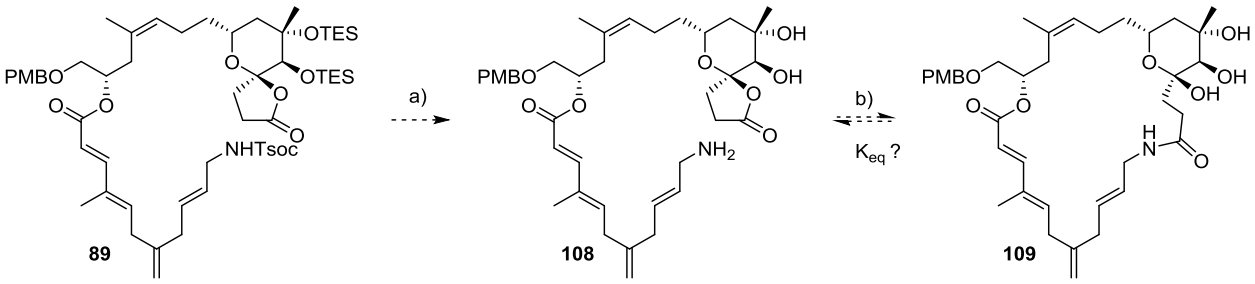
As the intermolecular aminolysis of γ-butyrolactones is well established, we speculated that this pathway might occur as detrimental side reaction.[50, 51] In the present case, this would lead to oligomerization. In line with this notion, it was found to be crucial to maintain the free acyclic amine **92** (Scheme 4.55) after deprotection in dilute solution, rather than attempting to isolate it in neat form. This seemingly minor variation increased the yield of the desired macrocycle **93** from 20 – 25% to well reproducible 45 – 50%.

Another important feature of the macrolactamization step was that it never proceeded to completion, but halted at 60 – 65% conversion as determined by HPLC-MS. Although puzzling at first, this behavior was then understood as result of an equilibrium between acyclic amine **92** and the desired macrocycle **93**.[102] To test this hypothesis, isolated macrocycle **93** was subjected to the conditions of the cyclization reaction, which yielded the same equilibrium mixture between closed and opened form. While we had naively expected that the very strong amide bond would be a sufficient driving force for the macrocyclization step, this proved incorrect for the present situation. One possible rational for this equilibrium might be the spatial proximity of the newly formed amide functionality and the "anomeric" hydroxy group within the macrocycle. This would allow the OH group to attack the otherwise poorly electrophilic amide carbonyl to eventually re-open the macrolactam (Scheme 4.64).



Scheme 4.64: Rationalization of the aminolysis equilibrium. P. T. = proton transfer.

A possible way to alter the position of the equilibrium would have been to remove the protecting groups on the neighboring alcohols (Scheme 4.65). This approach was not pursued because of the expected very high polarity of the proposed intermediate **108** which would render an aqueous workup after the removal of the Tsoc- and TES-groups very challenging and probably low-yielding.



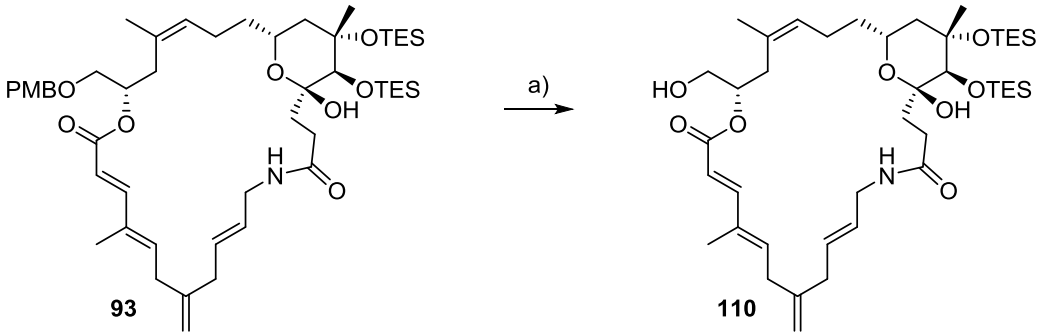
Scheme 4.65: Hypothetical preparation and macrocyclization of a deprotected analogue. Conditions: a) HF aq. then NaOH aq.; b) 2-pyridone, toluene, 90 °C.

In the light of the complex macrocyclic framework that has been constructed, the route so far seemed acceptably efficient. The yield of the unconventional macrolactamization compares reasonably well with other methods to assemble rings of this size.[103]

4.7 Connection to the Side Chain

With the complete macrocycle in hand, the attachment of the side chain came finally into reach. To approach the decisive fragment coupling, the PMB protected alcohol had to be converted into an aldehyde.

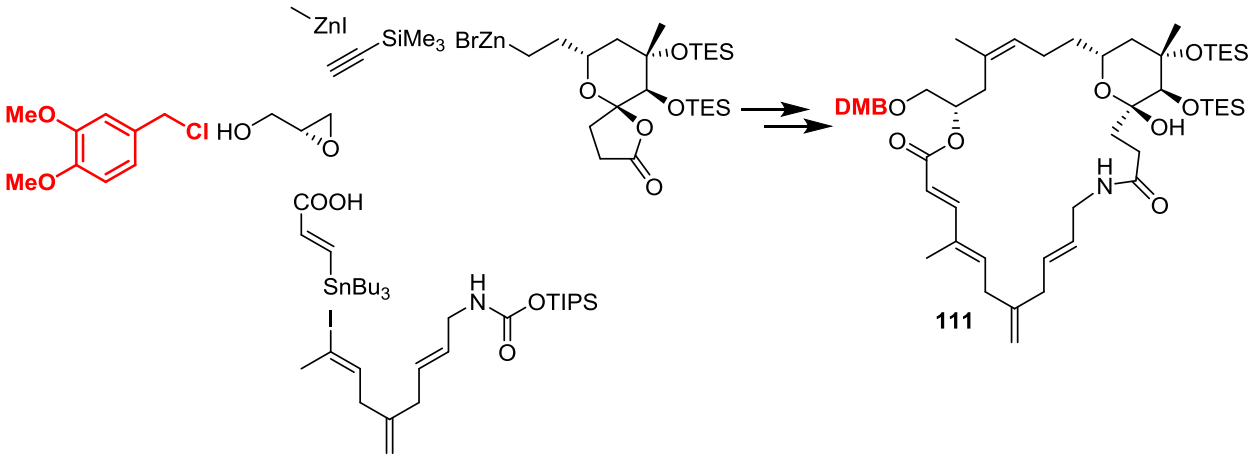
The cleavage of the PMB group turned out to be more challenging than expected. In contrast to seemingly very promising literature examples, the described conditions led only to traces of the desired product.[78] A survey of reported condition for similar deprotections led eventually to the use of trityl tetrafluoroborate as suitable reagent, while all other conditions tested failed to deliver the product (Scheme 4.66).[104] Despite the modest yields (44-52%) the crucial alcohol **110** was obtained.



Scheme 4.66: PMB-deprotection of **93**. Conditions: a) $Ph_3C^+BF_4^-$, CH_2Cl_2, 0°C, 44-52%.

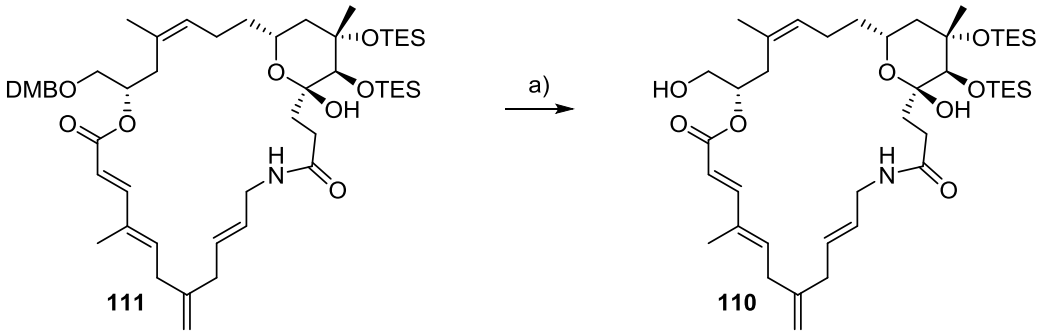
The troublesome deprotection was largely attributed to the exceptional lability of the tetraene system. Indeed, as long as the intermediates had been acyclic and therefore not subject to any ring strain, their tendency to isomerize or decompose was only moderate. However, the oxidizing and/or Lewis acidic conditions necessary for the cleavage of a PMB-ether were not well tolerated by the more sensitive cyclic molecule.

To improve the yield, a different protecting group was considered. Since the PMB-group had served well throughout the whole sequence so far, it was desirable to retain its positive qualities. This led to the inspection of the 3,4-dimethoxybenzyl group, which would be more susceptible to oxidative cleavage and Lewis acid mediated cleavage.[77, 104] This might allow the cleavage reaction to outcompete detrimental side reactions. The DMB-analogue **111** corresponding to the PMB-ether **93** was synthesized via a very similar sequence (Scheme 4.67).



Scheme 4.67: Synthesis of DMB-analogue **111**. Conditions: see experimental section.

The preparation was entirely uneventful, but the expected improvement in the deprotection step did not manifest itself. While the cleavage reaction under conditions used for the corresponding PMB-ether **93** proceeded faster, the isolated yield of **110** remained similarly low (Scheme 4.68).

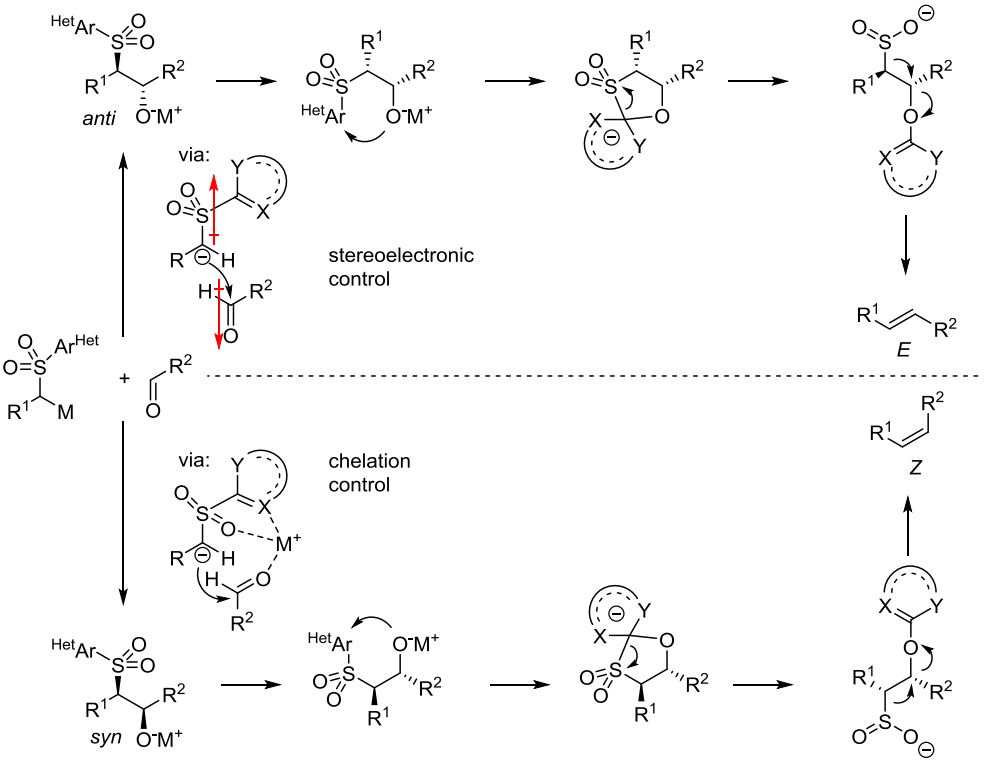


Scheme 4.68: DMB-deprotection. Conditions: a) $Ph_3C^+BF_4^-$, CH_2Cl_2, 0°C, 39% + 20% recovered starting material.

Moreover, a side product arising from transfer of a DMB moiety to another molecule of the starting material was formed, which co-eluted with free alcohol **110** during flash chromatography and was therefore difficult to remove. This side reaction had not been noticed in the case of the PMB analogue **93**. Other methods for the removal of DMB-ethers (DDQ, PIDA) were to no avail.

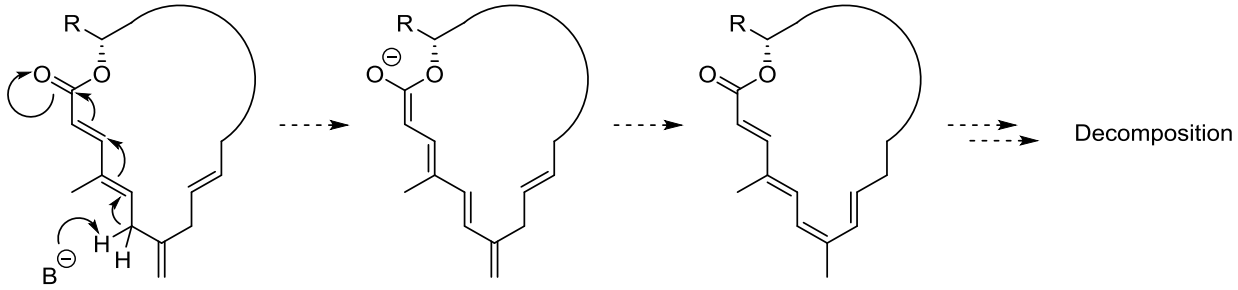
Alcohol **110** was oxidized to the corresponding aldehyde **112** under Parikh-Doering conditions.[105] To reduce the risk of epimerization of the stereocenter adjacent to the carbonyl group, the aldehyde was used in the next step without chromatographic purification. This set the stage for the pivotal Julia-Kocienski olefination. This type of reaction has been used multiple

times to construct olefinic double bonds with good *E*-selectivity in complex molecules.[20, 106, 107] In contrast to the original Julia protocol, which requires a three step sequence, the Kocienski modification allowes for the convenient one pot execution. It has been shown that the degree of stereoselectivity dependes highly on the nature of the base, particularly the metal ion, as well as on the solvent. The general trend, although not without exceptions, indicates that poorly coordinating cations and/or polar solvents lead to high *E*-selectivity. This finding has been rationalized through the influence of metal coordination on the diastereoselectivity of the attack of the metalated sulfone on the carbonyl compound. While chelation of a coordinating metal ion can arrange the heteroaryl sulfone and the aldehyde oxygen in spatial proximity and favor the *syn*-adduct, dipole-repulsion in the absence of chelation leads predominantly to the *anti*-adduct. This step dictates the later double bond geometry because the following Smiles-rearrangement and elimination steps are stereospecific (Scheme 4.69). However, in some cases the initial nucleophilic addition to the carbonyl component can be reversible. This leads to a more complex mechanistic picture.



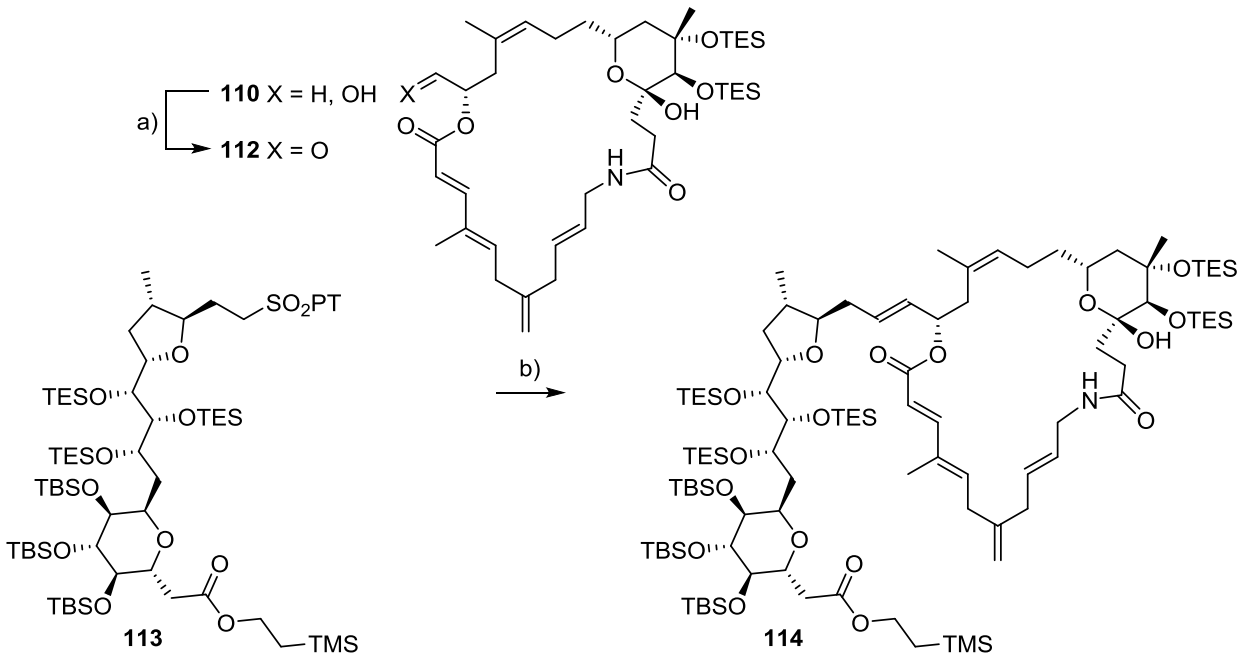
Scheme 4.69: Simplified rational for the stereochemical outcome of the Julia-Kocienski-olefination.[156]

Sulfone **113** (prepared by Dr. Sylvester Größl, see his PhD thesis for details[22]) was deprotonated with LiHMDS and the resulting anion was reacted with aldehyde **112**; disappointingly however no desired product was formed. This outcome was explained again by the lability of the doubly skipped tetraene motif: It seemed likely that the bis-allylic positions next to the exo-methylene moiety could be deprotonated by the lithiated sulfone. This hypothesis was supported by the appearance of an intense yellow color upon the addition of the aldehyde to the lithiated sulfone, reminiscent of the decomposition of **84** due to TBAF mentioned earlier (Scheme 4.70).



Scheme 4.70: Possible bases-mediated decomposition of the polyene system.

Therefore a way to attenuate the basicity of the metalated sulfone was sought to overcome this problem. Based on the experience gathered in the Negishi coupling during the construction of the macrocyclization precursor, it was reasoned that an organozinc species might be compatible with the sensitive polyene. The treatment of the lithiated sulfone with a zinc salt was expected to give the analogous zinc derivative via transmetalation. This should exhibit a more covalent character than the lithium derivative, and therefore be less basic. Indeed, the sequential addition of LiHMDS, zinc chloride and finally aldehyde **112** to sulfone **113** led to the highly desired product **114** (Scheme 4.71). To the best of our knowledge, zincated sulfones have not yet been employed in Julia-type olefination reactions. Their application might significantly expand the scope of said olefination protocol to base sensitive substrates.



Scheme 4.71: Julia-Kocienski fragment coupling. Conditions: a) SO_3•pyridine, DMSO, DIPEA, CH_2Cl_2, −20°C; b) LiHMDS, $ZnCl_2$ then **112**, −40°C → RT, DMF:DMPU 3:1, over two steps 25-30%. PT = (1-phenyl-1H-tetrazol-5-yl)

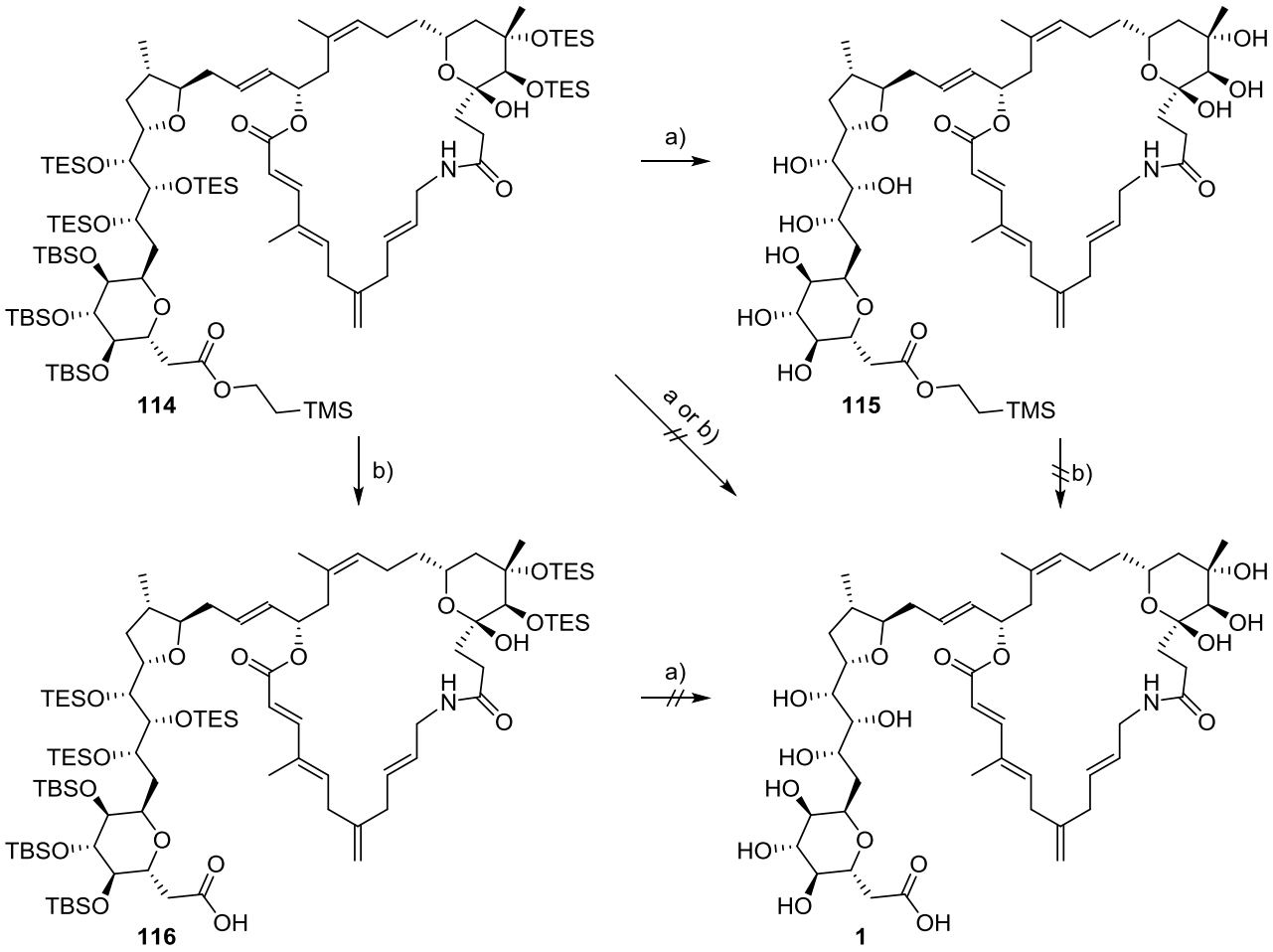
Despite the success in joining the two halves of the target molecule, the yield was low (25-30%). A positive feature of the reaction was that the excess sulfone could be recovered unchanged after each run. This allowed the investigation of the influence of the stoichiometry on the reaction outcome. Unfortunately, the use of up to three equivalents of the metalated sulfone with respect to the aldehyde led only to a minor improvement in yield. Additionally, other additives (Et_2Zn, $CeCl_3$ and Me_3SiCl) instead of zinc chloride were tested without positive effect on the reaction yield.

It is of note that the present modification of the Julia-Kocienski olefination allowed for the connection of two very elaborate and delicate fragments. In contrast to the typical protocols involving alkali metal bases (LiHMDS, NaHMDS, KHMDS etc.) alone, the transmetalation to a more electronegative metal like zinc rendered the reaction milder and more tolerant. The reduced basicity of the resulting reagent might be useful in other occasions but the present one to further expand the scope of the Julia-Kocienski reaction to base sensitive substrates. Moreover, in the aforementioned classical protocols the metallated sulfone component, which exhibits at least formally a carbenoid character, can undergo undesired side reactions. These can not only reduce the yield of the product olefin, but also hamper the recovery of any unreacted sulfone, which is beneficial in the cases of precious material like ours. The present zinc derivate of sulfone **113** was

found to be stable at ambient temperature and the unreacted parent sulfone could be recovered efficiently. Finally it is worth mentioning that the high *E*-selectivity of the reaction was unperturbed by the presence of $Zn^{(II)}$, an outcome that can be attributed to the highly polar solvent system, which attenuates the Lewis acidity.

4.8 End Game

Despite the low yield of the fragment coupling, the complete framework of belizentrin was now assembled. The only remaining task was the complete removal of the silyl protecting groups. It should be pointed out here that various intermediates along the synthetic sequence were sensitive to bases, particularly TBAF. Furthermore, the highly polar and hydrophilic character of the desired product **1** forbade an aqueous workup, calling for a reagent that could be removed by other means. We envisaged that aqueous HF in acetonitrile would satisfy the prerequisites of this demanding operation. Indeed, this reagent proved very efficient in cleaving all eight silyl ethers; however, the TMSE ester was unreactive.



Scheme 4.72: Attempted deprotections. Conditions: a) HF aq. MeCN b) TASF, DMF.

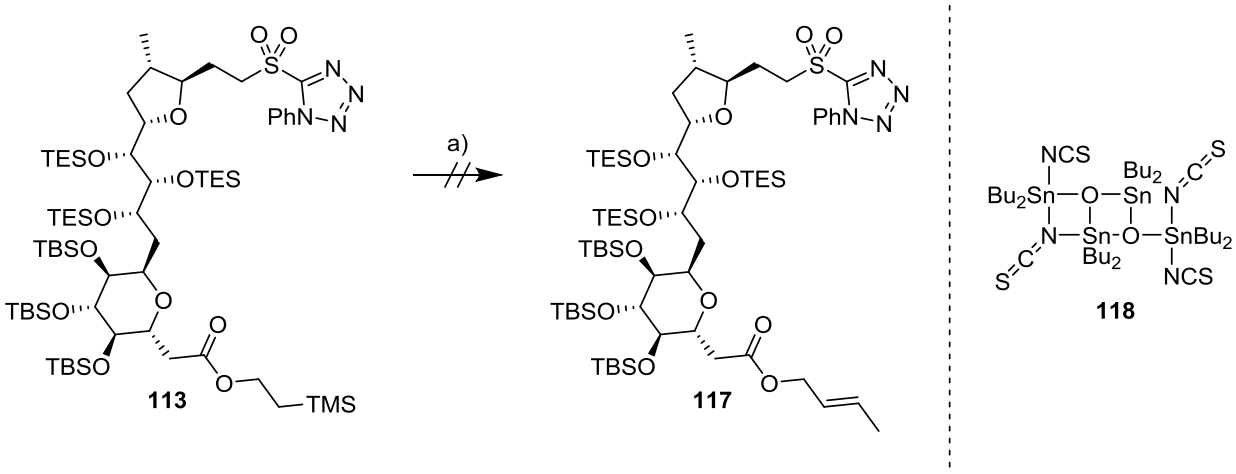
Increasing the reaction times led to the slow formation of unidentified side products, while no cleavage of the reluctant ester was observed. TASF has been successfully used as a milder substitute for TBAF for the cleavage of TMSE esters in several cases.[108, 109] In a preliminary

experiment on an early intermediate of the sidechain, we have been able to employ TASF in order to remove a TMSE ester in the presence of three TBS groups. (see Dr. Sylvester Größl's PhD Thesis for details[22]) Encouraged by this result, we considered two strategies: (i) complete deprotection by TASF and (ii) stepwise selective deprotection of the TMSE ester with TASF, followed by deprotection of the remaining silyl ethers with HF. When fully protected **114** was exposed to an excess of TASF in DMF, only decomposition was observed. Therefore, in the stepwise approach, the treatment of **114** with ~ 10 eq. of TASF produced indeed a more polar product with the expected mass for free acid **116** carrying still the other silyl ethers, as judged by HPLC-MS. Unfortunately, this conversion was not entirely clean but rather plagued by the formation of different by-products, some of them probably arising from further desilylation, while others could not be identified. However this partial success allowed the subsequent deprotection of the silyl ethers with HF to be tested. When the crude mixture containing tentative **116** was exposed to aqueous HF in acetonitrile, it again led to complete loss of the material. The order of steps was reversed and the otherwise deprotected TMSE ester **115** was subjected to TASF, but this led again to the loss of the material (Scheme 4.72).

These results indicated that otherwise still protected acid **116** was stable, at least for a short time, even in the presence of TASF, but on the other hand completely deprotected **1** and/or partially protected intermediates were decomposed in the presence HF. This was contrasted by the previous finding that otherwise deprotected ester **115** had survived the action of HF for several hours. Based on these observations we conclude that both ester **115** and protected acid **116** were sufficiently robust to withstand the respective deprotection conditions for some time, while fully deprotected **1** is highly unstable under these conditions. We reiterate here that the isolation team had described belizentrin **1** also as very unstable even under neutral conditions.[9]

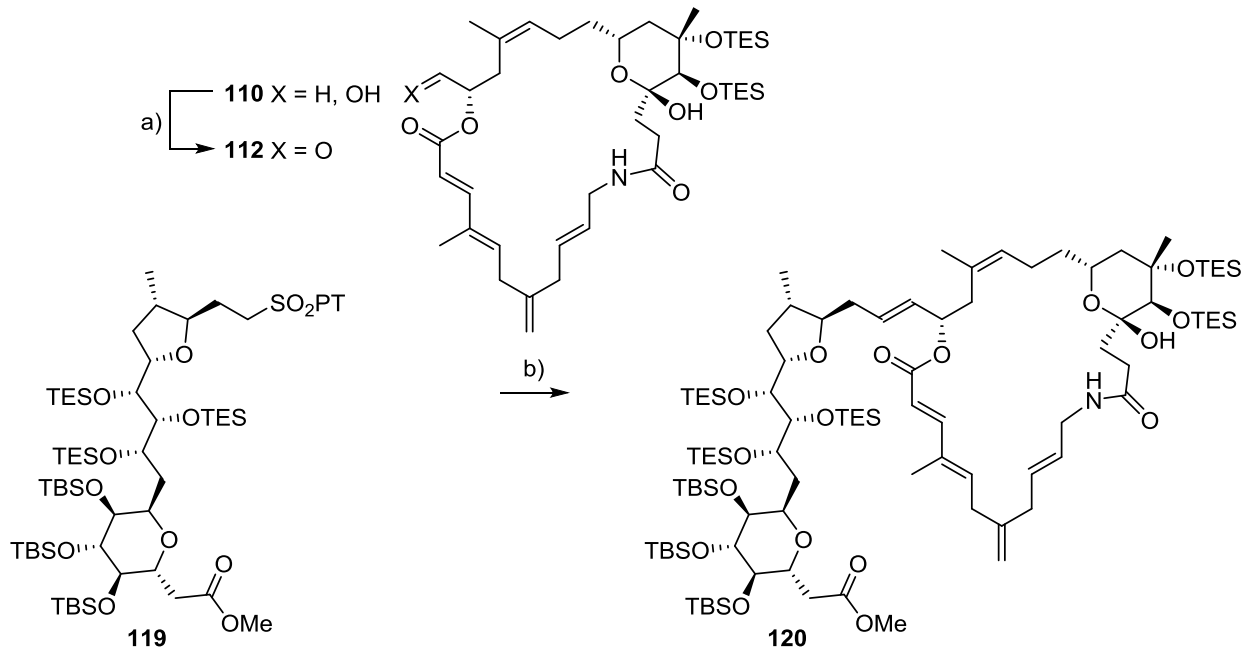
This setback mandated a seemingly minor, albeit laborious, change in the protecting group strategy. Since the TMSE ester had resisted all attempts at deprotection without damaging the desired product, we envisaged that another ester might be more cooperative. At a close inspection, it turned out that many of the "usual suspects" for the protection of a carboxylic acid held little promise of success. Alternative esters susceptible to reduction or hydrogenolysis, such as benzyl-esters, are excluded due to the abundance of olefins in the target molecule. Similarly any base sensitive ester like β-sulfonylethyl-esters or acid-sensitive esters like *tert*-butyl ester would be an unlikely candidate. An allylic ester might be susceptible to oxidative addition of

$Pd^{(0)}$ or $Ni^{(0)}$ and the resulting allyl-metal intermediate would be prone to nucleophilic attack and therefore cleavage. This seemingly mild process appeared unpractical as an allyl ester would have very little chance to prevail under the conditions of osmium catalyzed dihydroxyation during the synthesis of the side chain (see Dr. Sylvester Größl's PhD Thesis[22]). The attempt to change the troublesome TMSE ester into a crotyl ester after the dihydroxyation and subsequent TES protection was met with little success. When the TMSE ester **113** was subjected to the transesterification conditions developed by Otera, the desired crotyl ester **117** was observed by HPLC-MS, but the majority of the material had decomposed (Scheme 4.73).[101]



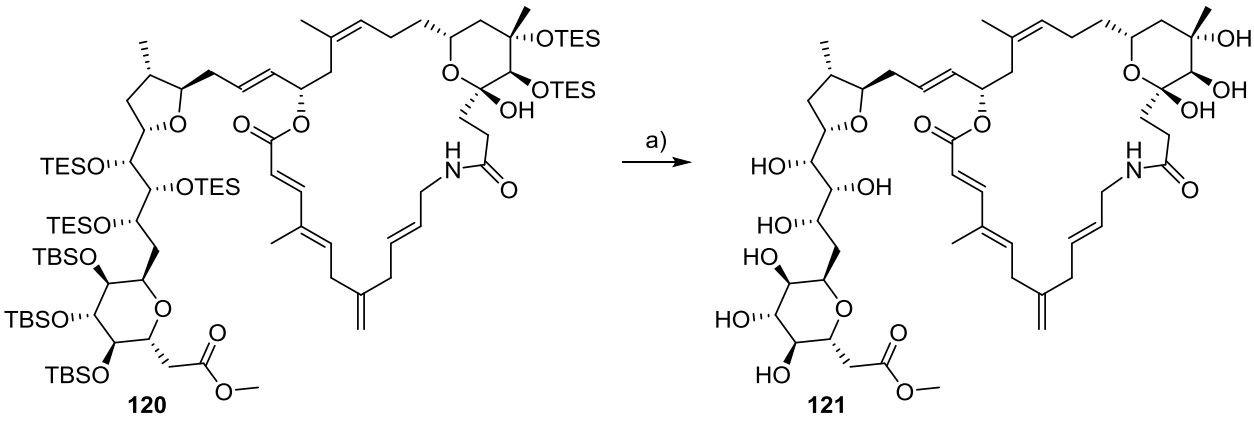
Scheme 4.73: Attempted transesterification of **113** with crotyl alcohol. Conditions: a) crotyl alcohol, **118**, toluene, 120°C.

Therefore, a methyl ester was chosen for the following reasons: (i) hydrolysis might be possible under neutral conditions *e.g.* by enzymatic hydrolysis and (ii) should the removal be not feasible, the methyl ester is as close as possible to the free acid belizentrin. This would allow for a meaningful spectroscopic comparison of our synthetic and the natural product. Sulfone **119** was prepared by Dr. Sylvester Größl via an analogous route to its TMSE counterpart **113**. The Julia-Kocienski olefination proceeded again with 25 – 30% yield to produce **120** (Scheme 4.74).



Scheme 4.74 Julia-Kocienski fragment coupling. Conditions: a) SO_3•pyridine, DMSO, DIPEA, CH_2Cl_2, −20°C; b) LiHMDS, $ZnCl_2$ then **112**, −40°C → RT, DMF:DMPU 3:1, over two steps 25-30%.

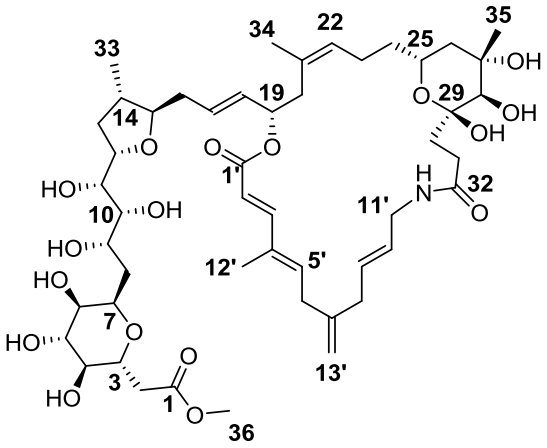
The deprotection of **120** with aqueous HF in acetonitrile cleanly removed all silyl ethers, leading to fairly pure **121**, as judged by HPLC-MS. After the reaction had reached full conversion, the remaining HF was quenched with excess of trimethylsilanol in order to convert it to the volatile trimethylsilyl fluoride (Scheme 4.75). This process allowed for the removal of the corrosive reagent prior to the final purification via preparative LC.



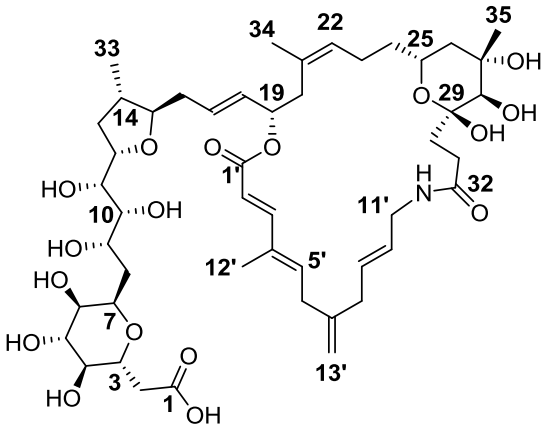
Scheme 4.75: Deprotection of **120**. Conditions: a) HF aq., MeCN, then Me_3SiOH, 36%.

To our delight, the deprotection product **121** showed good spectral agreement with the spectral data reported for the authentic natural product belizentrin **1** (Table 4.7 and Table 4.8).

Table 4.7 Comparison of the ^{13}C NMR chemical shifts of synthetic **121** and authentic belizentrin (**1**). There appeared to be a systematic drift of ~ −0.4 ppm between the reported ^{13}C NMR spectrum of **1** and the recorded ^{13}C NMR spectrum of **121**. The ^{13}C NMR chemical shifts of **1** were extracted from two dimensional HSQC and HMBC NMR spectra. Color code: $\Delta\delta \leq 0.5$ ppm; $0.5 < \Delta\delta < 1$ ppm; $\Delta\delta \geq 1$ ppm.[110]



121



1

Position	δ (ppm) Synthetic 121	δ (ppm) Natural 1	Δ δ	Δ δ −0.4 ppm
1	173.9	179.4	[-5.5]	[-5.9]
2	38.4	41.7	[-3.3]	[-3.7]
3	71.4	71.4	0.0	-0.4
4	75.3	75.6	-0.3	-0.7
5	74.7	74.5	0.2	-0.2
6	73.0	72.8	0.2	-0.2
7	74.8	76.2	-1.4	-1.8
8	30.4	29.8	0.6	0.2
9	71.5	73.3	-1.8	-2.2
10	73.5	72.8	0.7	0.3
11	75.8	76.0	-0.2	-0.6
12	80.2	78.9	1.3	0.9
13	38.3	38.2	0.1	-0.3
14	40.5	40.0	0.5	0.1
15	86.2	85.5	0.7	0.3
16	37.9	37.3	0.6	0.2
17	131.1	130.6	0.5	0.1

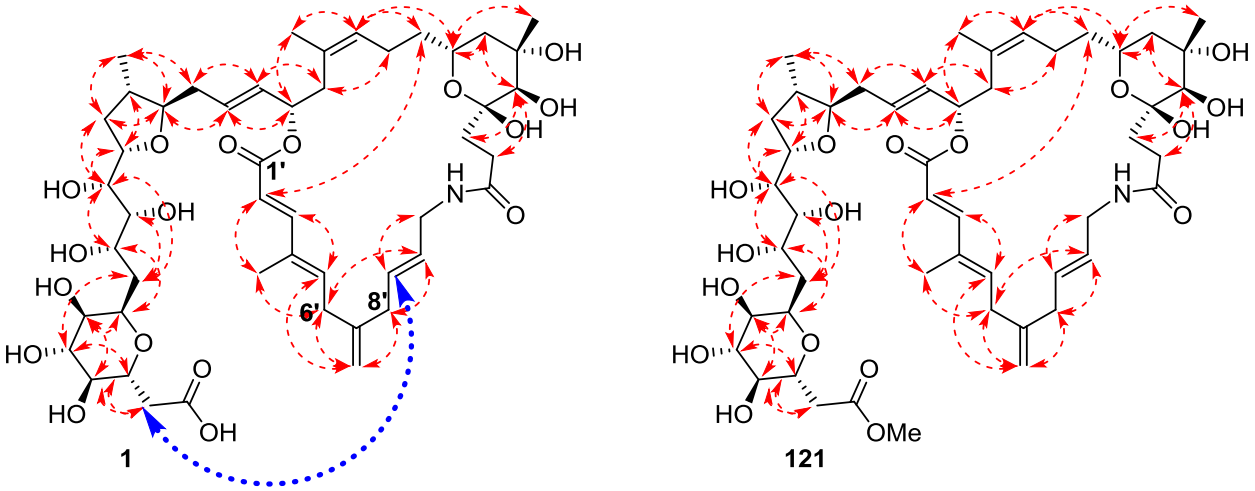
18	132.1	131.2	0.9	0.5
19	73.7	73.0	0.7	0.3
20	38.4	38.0	0.4	0.0
21	131.9	131.5	0.4	0.0
22	129.2	129.2	0.0	-0.4
23	24.8	25.5	-0.7	-1.1
24	37.0	37.0	0.0	-0.4
25	68.0	68.4	-0.4	-0.8
26	46.5	46.5	0.0	-0.4
27	72.8	72.2	0.6	0.2
28	79.4	78.8	0.6	0.2
29	98.5	97.9	0.6	0.2
30	36.6	35.8	0.8	0.4
31	31.0	30.5	0.5	0.1
32	176.3	175.7	0.6	0.2
33	16.7	16.4	0.3	-0.1
34	23.9	23.2	0.7	0.3
35	21.8	21.4	0.4	0.0
36	52.3	n.d.		
1'	168.3	167.8	0.5	0.1
2'	117.2	116.8	0.4	0.0
3'	150.7	150.1	0.6	0.2
4'	135.1	134.9	0.2	-0.2
5'	140.9	139.8	1.1	0.7
6'	36.2	35.2	1.0	0.6
7'	147.3	146.7	0.6	0.2
8'	40.6	40.1	0.5	0.1
9'	131.3	130.8	0.5	0.1
10'	129.4	129.1	0.3	-0.1
11'	41.9	41.3	0.6	0.2
12'	12.8	12.4	0.4	0.0
13'	113.1	112.4	0.7	0.3

Table 4.8 Comparison of the ^{1}H NMR chemical shifts and coupling constants of synthetic **121** and authentic belizentrin (**1**). Coupling constants were not resolved for all positions.[110]

position	Synthetic 121 δ (ppm)	Natural 1 δ (ppm)	Δδ	Synthetic 121 *J* (Hz)	Natural 1 *J* (Hz)
2a	2.87	2.67	0.20	2.9 / 15.9	4.3 / 16.7
2b	2.42	2.16	0.26	9.4 /16.7	9.4 /16.7
3	3.92	3.85	0.07	9.6 / 8.4 / 2.9	9.4 / 8.9 / 4.3
4	3.10	2.97	0.13	8.4 / 8.4	8.9 / 8.9
5	3.54	3.43	0.11	8.4 / ?	8.9 / 10.5
6	3.57	3.48	0.09	10.5 / 4.2	
7	4.05	3.94	0.11	9.8 / 4.6 / 4.6	4.2 / 10.6 / 3.1
8a	2.04	1.89	0.15		
8b	1.92	1.89	0.03		
9	3.99	3.83	0.16	6.6 / 6.6 / 2.8	8.9 / 5.7 / 3.9
10	3.52	3.48	0.04	2.8 / 4.0	2.8 / 3.9
11	3.57	3.56	0.01	4.0 / 4.5	2.8 / 5.8
12	4.12	3.97	0.15	4.5 / 5.9 /10.2	5.8 / 9.0 / 6.1
13a	2.10	2.09	0.01		
13b	1.56	1.45	0.11		
14	1.91	1.83	0.08		
15	3.50	3.38	0.12		
16a	2.35	2.23	0.12		
16b	2.20	2.14	0.06		
17	5.81	5.71	0.10		
18	5.59	5.51	0.08	15.4 / 6.9	15.3 / 9.2
19	5.45	5.36	0.09	9.5 / 6.9 / 5.1	9.2 / 8.9 /4.8
20a	2.69	2.64	0.05	9.5 / 13.7	8.9 / 14.2
20b	2.09	1.92	0.17	5.1 / 13.7	4.8 / 14.2
22	5.28	5.12	0.16	7.4 / 7.4	6.4 / 8.5
23a	2.13	2.10	0.03		
23b	2.10	1.96	0.14		
24a	1.52	1.42	0.10		
24b	1.45	1.26	0.19		

25	3.90	3.78	0.12		
26a	1.73	1.64	0.09		3.5 / 14.5
26b	1.45	1.30	0.15		10.5 / 14.5
28	3.28	3.18	0.10		
30a	2.09	1.93	0.16		
30b	1.88	1.82	0.06		
31a	2.52	2.42	0.10	15.5 / 9.1 / 6.7	
31b	2.35	2.26	0.09		
33	1.02	0.92	0.10	6,4	6.5
34	1.71	1.61	0.10		
35	1.38	1.29	0.09		
36	3.67				
2’	5.79	5.7 2	0.0 7	15,6	15.7
3’	7.27	7.17	0.10	15,6	15.7
5’	5.93	5.83	0.10	6.7 / 8.5	7.6 / 8.2
6’a	3.04	2.86	0.18	8.5 / 15.7	7.6 / 15.4
6’b	2.92	2.86	0.06	6.7 / 15.7	8.2 / 15.4
8’	2.77	2.66	0.11		
9’	5.53	5.45	0.08		6.7 / 8.0 / 15.5
10’	5.46	5.39	0.07		15.5 / 6.9 / 5.9
11’a	3.75	3.84	-0.09	15.4 / 5.1	14.9 / 6.9
11’b	3.65	3.41	0.24		14.9 / 5.9
12’	1.78	1.67	0.11		
13’a	4.84	4.75	0.09		1.3 / 1.3
13’b		4.72			

Despite small deviations of the chemical shift of a few atoms, the relative stereochemistry seemed very likely to be identical with the natural product. The careful inspection of coupling constants and NOE correlations provided an additional strong support. Since these values are related the dihedral angles, they provide valuable information about the spatial conformation. Similar *J*-values would go in line with similar conformations in the molecules in question. These in turn are likely to result from close chemical relationship. Also the pattern of NOE correlations of **121** matched that of belizentrin (**1**) very closely. The lack of a single contact in **121** was the only noticeable discrepancy (Scheme 4.76). This difference might be of significance for the discussion of the "stability" of belizentrin (*vide infra*). With respect to the relative stereochemistry of acid **1** compared to ester **121**, the absence of this signal in the case of **121** is considered a minor feature compared to the general resemblance of the spectral properties.

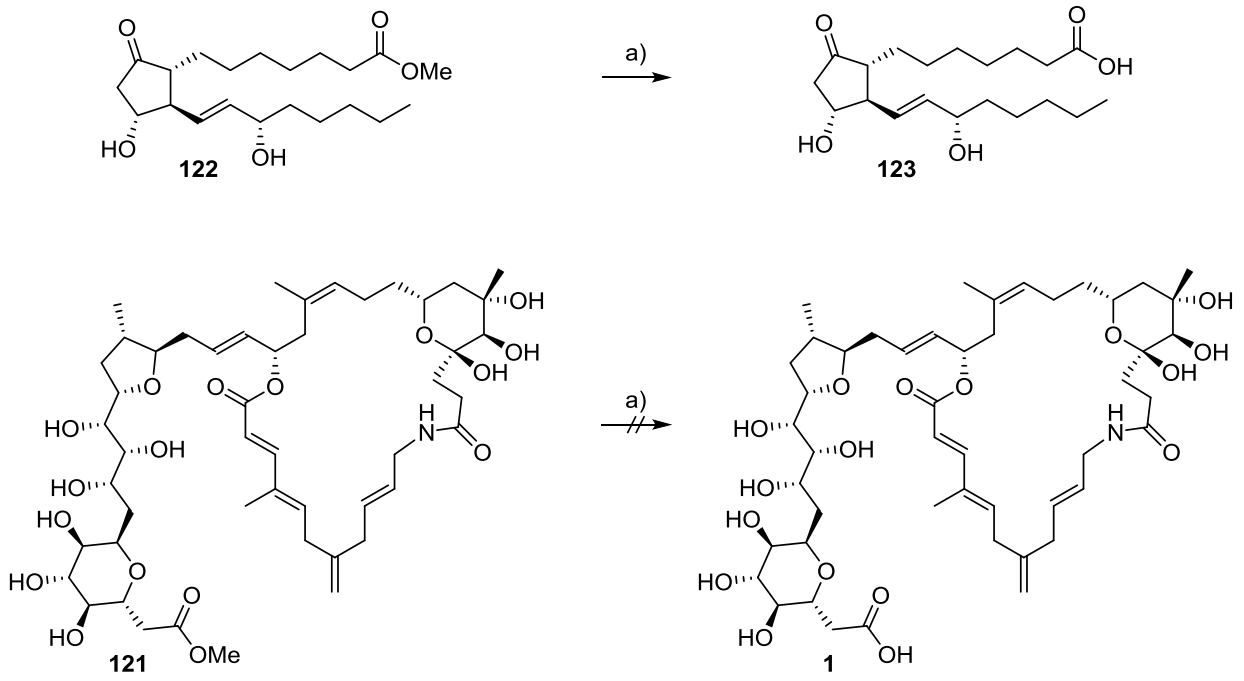


Scheme 4.76: Comparison of the respective NOE correlations in 1[9] and 121.

The absolute stereochemistry of the isolated natural product on the other hand could not be proved right or wrong at this stage, because the comparison of the optical rotation of structurally different compounds appeared doubtful. It must be mentioned though that the isolated material was laevorotatory and our synthetic sample turned out to be dextrorotatory. The influence of the methyl ester compared to the free acid was unknown; therefore no conclusive statement was possible.

The last remaining step to arrive at the proposed structure of belizentrin was to attempt an ester cleavage. Due to the aforementioned instability towards bases, alkaline saponification was ruled out. Methyl ester cleavage in the presence of trimethyltin hydroxide (Nicolaou's reagent) has

been used successfully in the synthesis of complex molecules.[20, 111] However, we envisaged that this pathway would also be of limited use as it has not been successfully on a previous intermediate *en route* to the side chain (see Dr. Sylvester Größl's PhD Thesis for details[22]). The necessity of mild conditions suggested the use of a hydrolytic enzyme as potential solution. We therefore considered the application of porcine liver esterase (PLE), as a similar strategy has been used it the synthesis of prostaglandin E1 (**123**), which also exhibits pronounced instability towards bases.[112] Unfortunately no desired product could be detected by HPLC-MS or HRMS in our case (Scheme 4.77). This result might be attributed to the higher steric demand of the tetrahydropyran ring next to the ester in **121** compared to the slim and flexible aliphatic chain in **122**.



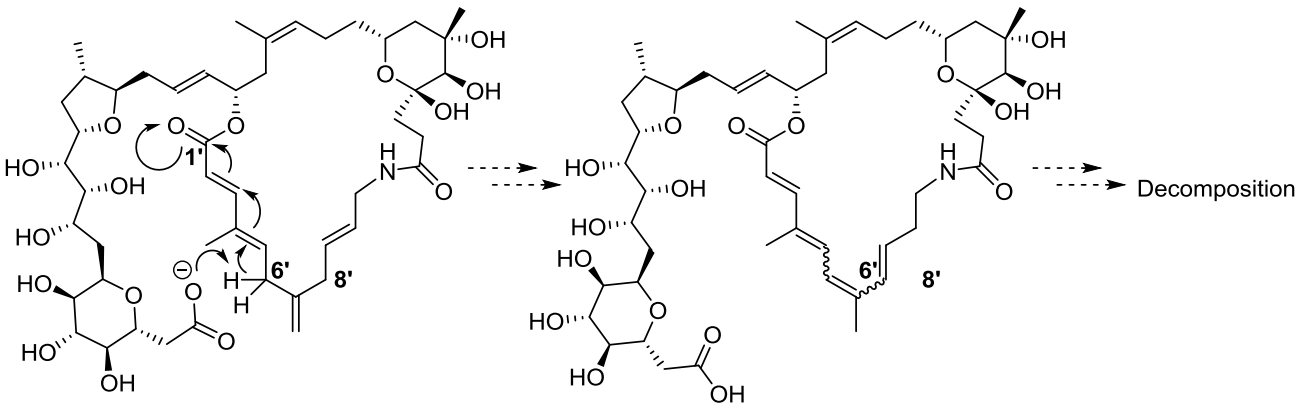
Scheme 4.77: Attempted enzymatic ester cleavage of **121**. Conditions: a) PLE, pH 7 phosphate buffer. PLE = porcine liver esterase.

At this point, no further attempts on the ester cleavage were made. With very little material available and no promising concept to remove the ester at hand, it seemed more rewarding to preserve the remaining quantity of the compound **121** for biological evaluation.

4.9 On the Stability of Belizentrin and some of its Derivatives

During the very last stage of this campaign, several intermediates came very close to the assigned structure of belizentrin. In the course of their synthesis a few pieces of valuable information considering their chemical stability were collected. Most importantly, the free acid **1**, the proposed and very likely structure of belizentrin, could not yet be observed by our means. In stark contrast the corresponding methyl ester **121** was obtained. This material proved stable in the presence of HF, throughout preparative HPLC and finally it turned out to be stable as NMR sample in deuterated methanol for more than 2 ½ month! The parent compound belizentrin (**1**) on the other hand was not even long lived enough to allow for the measurement of one-dimensional ^{13}C NMR spectra, and even the published ^{1}H NMR spectrum reveals signs of decomposition. This remarkable difference provided a very strong hint that the free carboxylic acid plays a critical role in the degradation of belizentrin. Another clue pointing at the carboxylic acid or the corresponding carboxylate as possible culprit came from the comparison of the NOE correlations in belizentrin and its methyl ester (Scheme 4.76).

While almost all of the NOE contacts appear to be identical, one contact between the methylene group adjacent to the carboxylic acid and visually very remote protons within the macrocycle is missing in the case of ester **121** (Scheme 4.76). This seems to indicate that the carboxylic acid reaches all the way to the macrocycle. In doing so, it would get in the vicinity of the sensitive methylene group (position 6' in belizentrin numbering) which breaks the conjugation between the electron-poor dienoate motif and the exo-methylene group. One could imagine the carboxylate functionality acting as a base to abstract the somewhat acidic proton from this position, leading to double bond isomerization. This might further place the next methylene group (position 8') in jeopardy, since only this site separates the remaining isolated olefin from the newly formed trienoate. It could then suffer the same fate as its neighbor, leading eventually to a fully conjugated tetraenoate, which itself might undergo follow-up transformations (Scheme 4.78). Since enolization is predominantly promoted by acids or bases the even more pronounced lability under the conditions of (attempted) deprotection fits into the picture. Alternative to the described base-catalyzed enolization also the protonation of the exo-methylene group to form a tertiary carbocation is conceivable. However, the stability of **121** in the presence of excess HF does not tell of marked acid sensitivity.



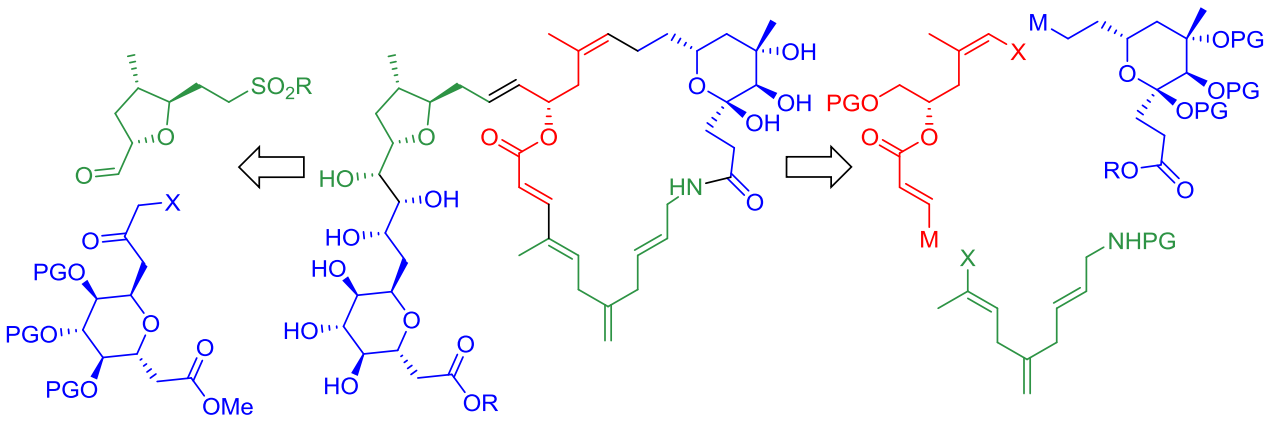
Scheme 4.78: Hypothetical mechanism of belizentrin's autocatalytic decomposition.

This hypothesis is of course speculative but would match the observed results. Additionally it would explain why the acid **116**, resulting from TASF mediated partial deprotection of **114**, did not spontaneously decompose. It seems plausible that the presence of the remaining silyl ether protecting groups rendered the side chain more rigid. This could force the whole molecule into a significantly different conformation that might preclude the carboxylate group from reaching for the methylene group 6' in the macrocycle.

4.10 Conclusion

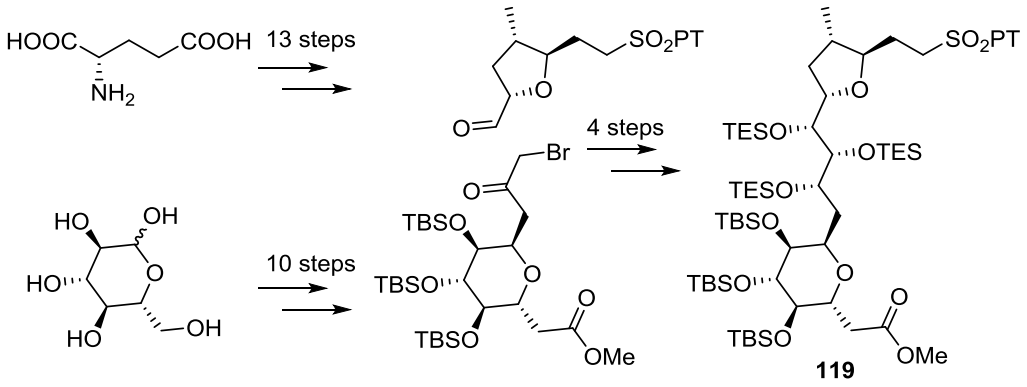
The present thesis describes a highly convergent first total synthesis of belizentrin methyl ester (**121**). In a longest linear sequence of 19 steps starting from L-glutamic acid, five building blocks were assembled to arrive at the natural product's framework. The relative and absolute stereochemistry of our synthetic material was unambiguously determined based on X-ray structure analysis and extensive NMR studies.

Belizentrin is a complex and unique natural product, which was isolated in 2014 from the marine dinoflagellate *Prorocentrum belizeanum*. It comprises a highly oxygenated side chain and an unsaturated 25 membered macrocycle, which contains macrolactone and macrolactam functionalities. These characteristics make it the first member of this class to be isolated from a dinoflagellate. Moreover, belizentrin exhibits potent neurotoxicity at nanomolar concentration.



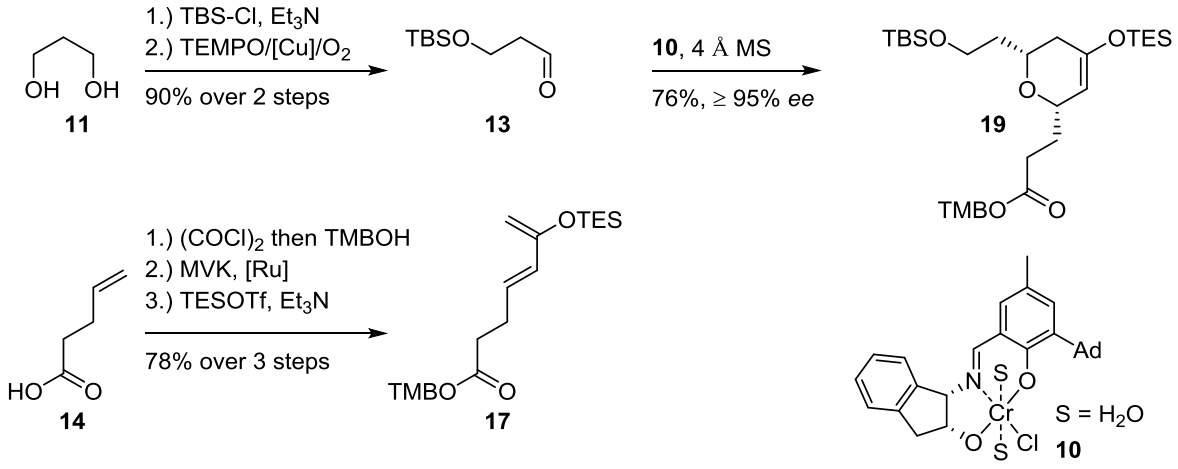
Scheme 4.79 Retrosynthetic analysis of belizentrin

In a retrosynthetic direction, we traced the molecule to two fragments representing the side chain and the macrocyclic portion (Scheme 4.79). This allowed for the convergent construction of the target. The side chain **119** was synthesized by Dr. Sylvester Größl from D-glucose and L-gutamic acid (Scheme 4.80).[22] These chiral starting materials secured the absolute stereochemistry of the fragment.



Scheme 4.80 Overview of the synthesis of the side chain.

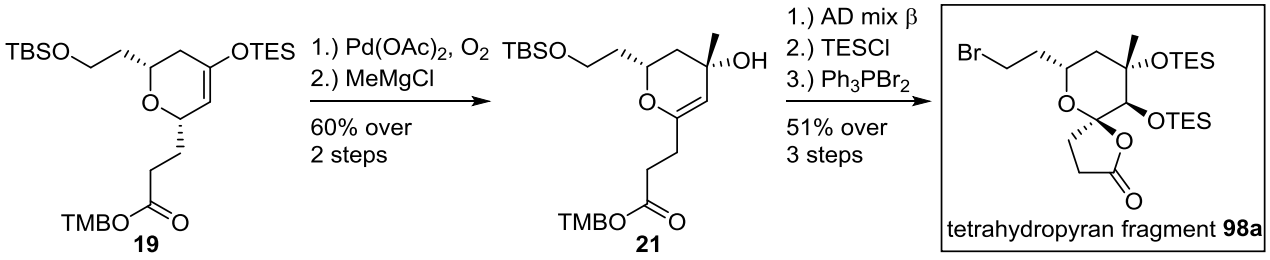
The macrocycle was assembled from three building blocks, which were synthesized as outlined below and connected in a highly convergent manner. The arguably most complex piece of the macrocycle, a densely functionalized tetrahydropyran ring decorated with four stereogenic centers, was prepared in an efficient way by focusing on transition metal catalysis. The synthetic sequence started with the construction of silyloxy diene **17** and aldehyde **13** involving a copper-catalyzed oxidation and a ruthenium catalyzed olefin cross metathesis. Said parts were then joined via an asymmetric chromium-catalyzed hetero Diels-Alder reaction to give multi-gram amounts of cycloadduct **19** in excellent optical purity (≥ 95% *ee*) and good yield (Scheme 4.81).



Scheme 4.81: Construction of the (tetrahydro)pyran framework. MVK = methyl vinyl ketone.

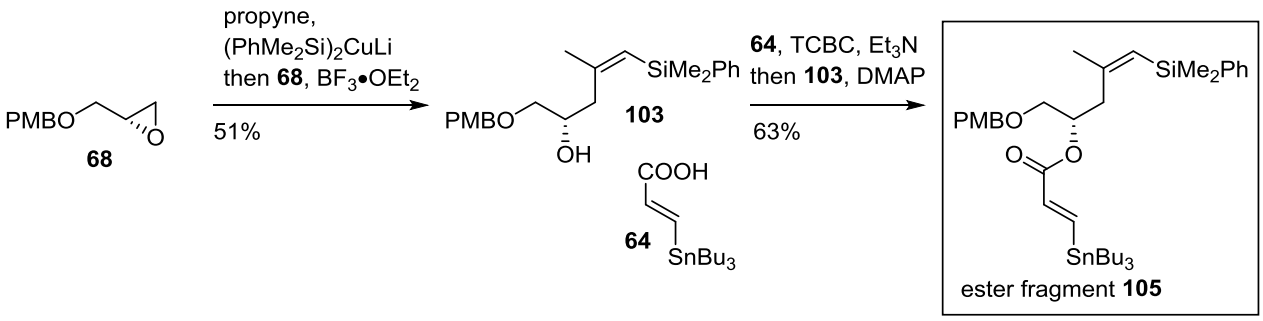
From **19** onwards, the remaining stereocenters were set in a few steps. The sequence commenced with a palladium-catalyzed Saegusa oxidation employing oxygen as terminal oxidant, delivering the expected enone cleanly. This set the stage for a substrate-controlled Grignard addition which proceeded with excellent diastereoselectivity. Finally, ligand-controlled osmium-catalyzed

dihydroxylation furnished the remaining *syn* diol motif. After two more protecting group manipulations, the fully decorated tetrahydropyran fragment **98a** was obtained in up to 18% overall yield over 9 steps starting from 4-pentenoic acid (**14**) (Scheme 4.81 and Scheme 4.82).



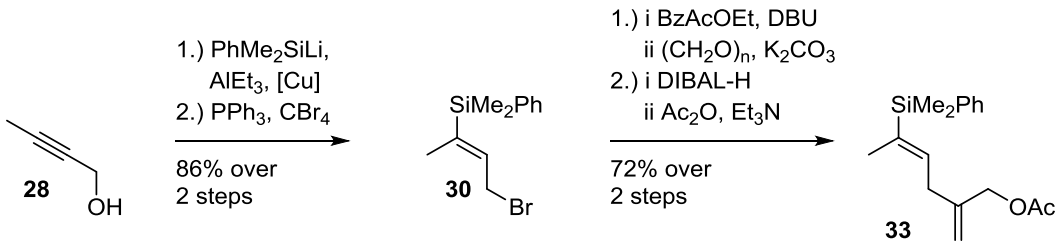
Scheme 4.82 Completion of the tetrahydropyran fragment.

The ester fragment was reached by a quite concise sequence. PMB-protected (*R*)-glycidol (**68**) was reacted with an alkenyl cuprate, which was formed *in situ* by the regio- and stereoselective silyl cupration of propyne. This protocol allowed for the rapid construction of the alcohol part **103** with complete control of double bond geometry and absolute stereochemistry. Subsequent Yamaguchi esterification with **64** yielded the complete building block **105** in only three steps starting from (*R*)-glycidol (Scheme 4.83).



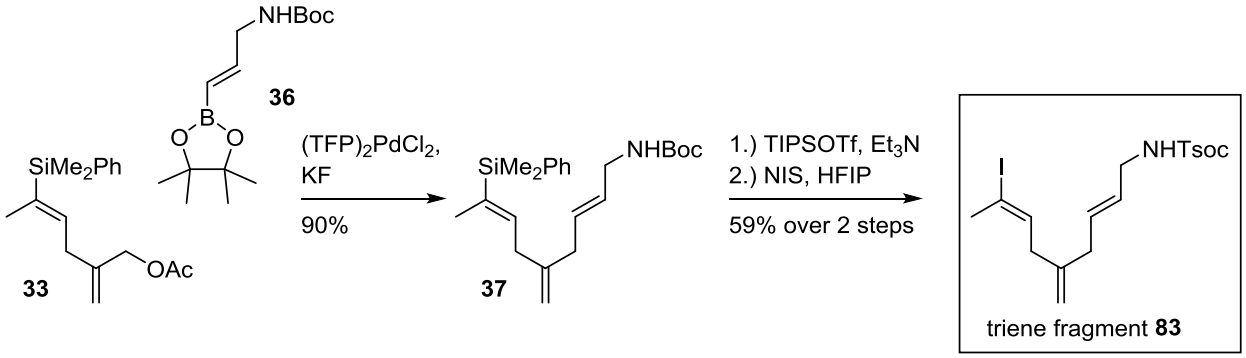
Scheme 4.83: Schematic overview of the synthesis of fragment **105**. TCBC = 2,4,6-trichlorobenzoyl chloride.

The synthesis of the triene fragment **83** started with copper-catalyzed silyl metalation of but-2-yn-1-ol (**28**). This process provided the expected alkenylsilane in excellent yield as well as regio- and stereoselectivity. Conversion of the alcohol to the corresponding bromide **30** allowed for a very practical alkylation/Knoevenagel condensation cascade. This transformation first attached said bromide to ethyl benzoylacetate; condensation with formaldehyde then installed the *exo*-methylene motif with concomitant loss of the benzoyl moiety. Reduction and acetylation of the resulting enoate provided allylic acetate **33** as electrophile for an upcoming cross coupling reaction (Scheme 4.84).



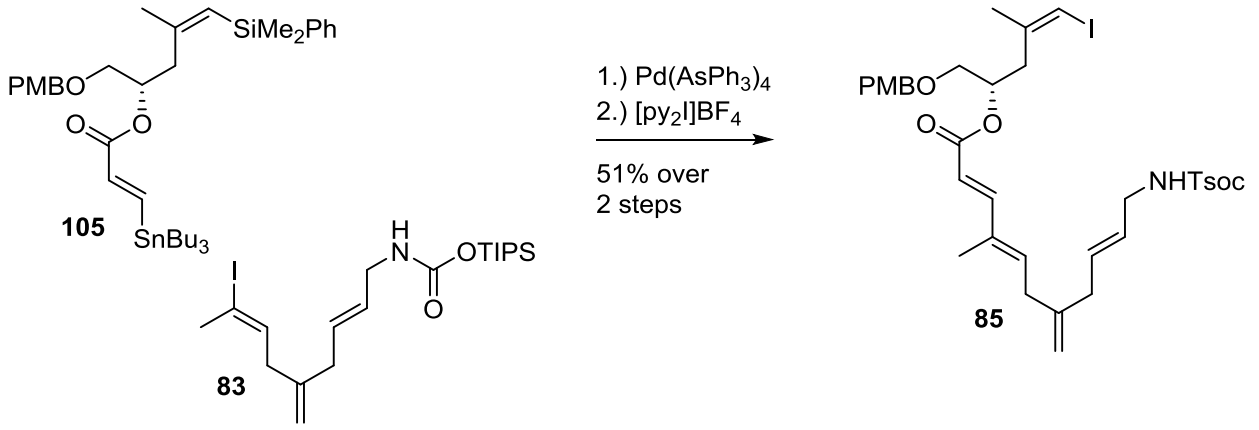
Scheme 4.84: Synthesis of the triene fragment part 1.

Suzuki coupling of **33** with a pinacol boronate **36**, which is derived from propargyl amine, smoothly delivered the doubly skipped triene scaffold. No sign of double bond migration or isomerization was observed despite the counter-thermodynamic arrangement. Protecting group exchange of the Boc-group for the more versatile Tsoc-group followed by iodo desilylation completed the triene fragment **83** in 42% overall yield over 8 steps starting from **28** (Scheme 4.85).



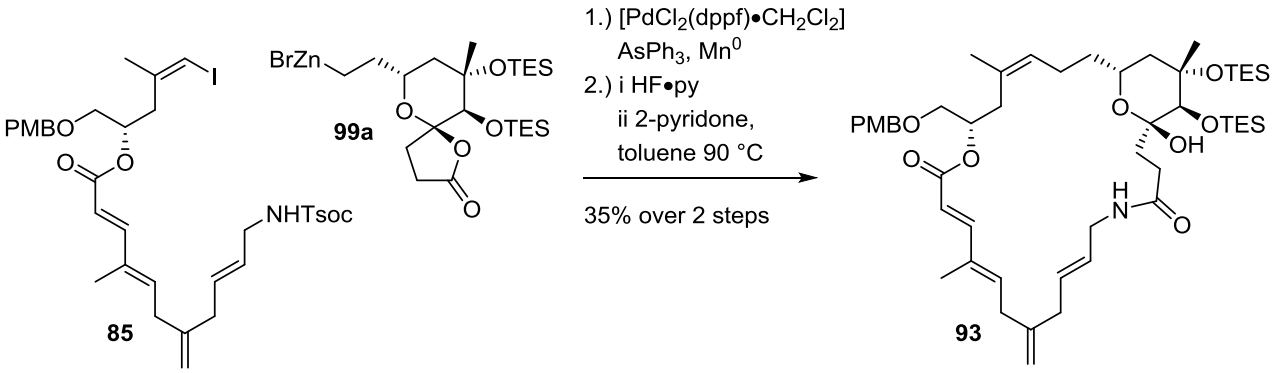
Scheme 4.85 Synthesis of the triene fragment part 2.

With a robust supply of the three building blocks established, the assembly of the macrocycle was undertaken. The two "western" parts **83** and **105** were joined by Stille coupling. Despite the inherently low reactivity of the relatively electron poor alkenylstannane **105** the desired reaction proceeded efficiently under optimized conditions. Consecutive iodo desilylation of a highly unsaturated *Z*-alkenylsilane set the stage for the next cross coupling (Scheme 4.86).



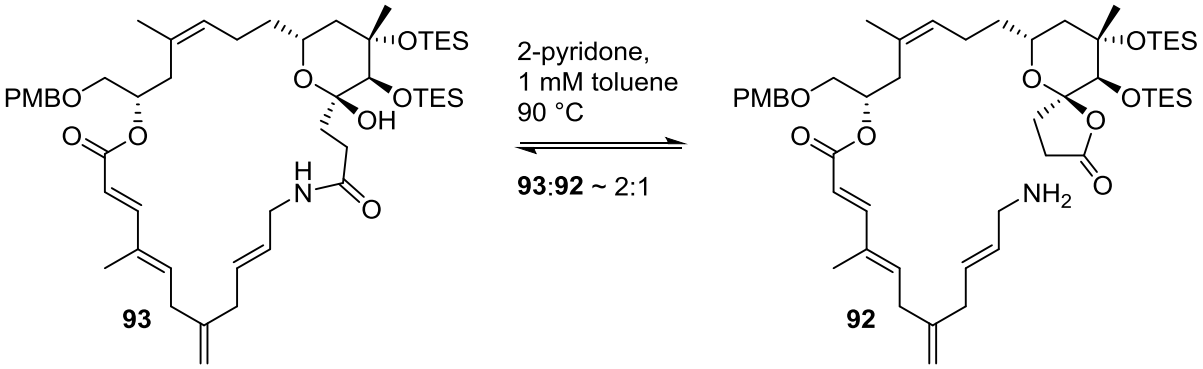
Scheme 4.86: Connection of the ester and triene fragments.

The use of very reactive Rieke zinc allowed for the formation of a highly functionalized organozinc reagent derived from the tetrahydropyran fragment **98a**. The following Negishi coupling mandated the use of a tailor-made catalyst system which was prepared by pre-reduction of [Pd(dppf)Cl_2•CH_2Cl_2] with manganese in the presence of $AsPh_3$ as stabilizing yet sufficiently labile ligand. Under optimized conditions the cross coupling gave rise to the desired product in reproducible ~ 70% yield. This set the scene for the pivotal macrolactamization. Removal of the somewhat uncommon but versatile Tsoc-protecting group in the presence of two TES ethers afforded the acyclic amine in high yield. Heating a dilute (~1 mM) toluene solution of this compound in the presence of 2-pyridone resulted in the crucial macrocyclization. Upon careful investigation of the reaction, we found that the acyclic amine was so reactive towards the lactone moiety that it had to be handled as dilute solution from the N-deprotection onwards in order to suppress oligomerization. With this notion in mind it was possible to obtain the cyclized product in 45 – 50% yield (Scheme 4.87).



Scheme 4.87 Synthesis of the macrocycle **93**.

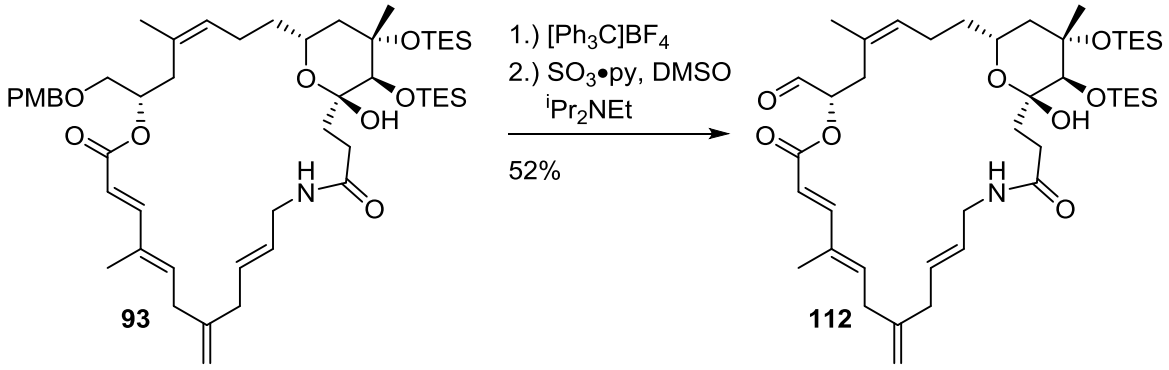
A surprising feature of the macrolactamization was its reversibility. Although a very strong amide-bond was formed, it turned out that this very bond was susceptible to cleavage, leading back to the starting spirolactone under the reaction conditions. This result was confirmed by a control experiment, in which the pure macrolactam **93** was re-subjected to the same environment and the acyclic amine **92** was observed by HPLC-MS (Scheme 4.88).



Scheme 4.88 Equilibrium of the macrolactam and acyclic amine.

This aspect notwithstanding, the method offers an underexploited alternative to methods relying on the activation of a carboxylic acid. Since the cyclization precursor and the macrocycle are isomers, no additional waste was generated. This feature, although irrelevant to small scale total synthesis, might be an asset in a different context.

With the macrocyclic portion of the target in hand, the requisite aldehyde for the envisaged Julia-Kocienski reaction had to be installed. PMB-deprotection presented a serious obstacle at first as the most common reagents for this kind of transformation (DDQ, CAN etc.) proved to be incompatible with the delicate doubly skipped tetraene motif. Migration of one or both isolated double bonds into conjugation with the dienoate would result in a considerable enthalpic gain. Moreover, this structural element appeared to contribute significantly to ring strain in the macrocycle due to the presence of three *E*-olefins which render the framework quite rigid. Therefore, its isomerization and consequent destruction would be thermodynamically favorable. Eventually the desired cleavage was realized by the action of trityl tetrafluoroborate. Consecutive Parikh-Doering oxidation provided the aldehyde **112** ready for the olefination (Scheme 4.89).



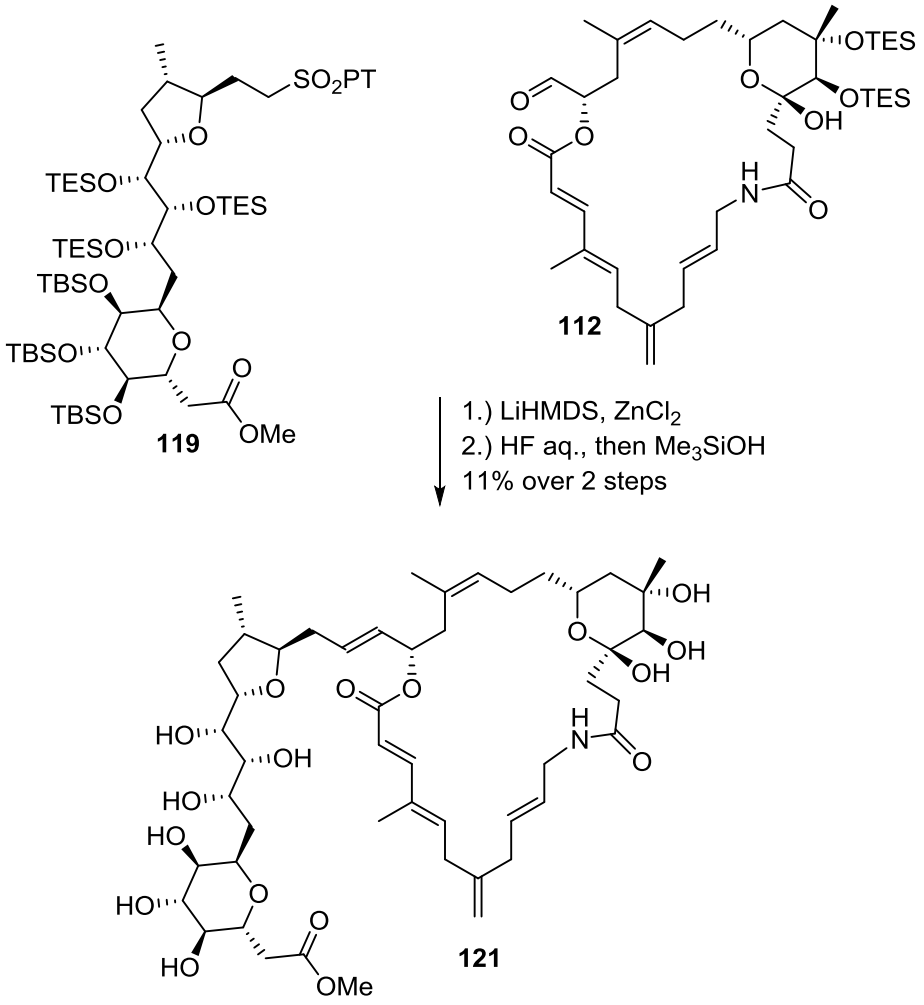
Scheme 4.89 Synthesis of aldehyde **112**.

As both components for the prospected fragment coupling, sulfone **119** and aldehyde **112**, contained C—H acidic sites apart from the methylene group adjacent to the sulfone functionality, the Julia-Kocienski olefination was far from trivial. Moreover the macrocyclic aldehyde contained a free OH group which had resisted all attempts to mask it with any protecting group. Nevertheless, the crucial connection had to be achieved.

Under typical conditions for Julia-Kocienski reactions (LiHMDS or KHMDS to metallate the sulfone) only decomposition of the aldehyde component was observed. We attributed this result to the highly basic character of the lithiated sulfone which could promote the isomerization and concomitant destruction of the tetraene system within the macrocycle. In the hope to attenuate the basicity of said metallated intermediate, while retaining its nucleophilicity, the transmetallation from lithium to a more electronegative metal that would form a more covalent bond to carbon was considered. Guided by the successful Negishi coupling in the presence of the tetraene motif earlier in the synthetic sequence, $Zn^{(II)}$ was deemed a promising candidate for this operation.

Indeed, the desired product was obtained when the initially lithiated sulfone was treated with zinc chloride prior to the addition of the aldehyde. This demanding coupling of two very elaborate and sensitive fragments proceeded in a yield of 25 – 30%. Only via the unprecedented transmetallation from lithium to zinc could the basicity of the metallated sulfone be attenuated to permit this challenging merger. This simple but effective modification might allow for the application of the very powerful Julia-Kocienski olefination to more sensitive substrates which would not be compatible under the usual conditions. It is of note in this context that the high *E*-selectivity of the transformation was unperturbed by the presence of $Zn^{(II)}$. Finally all remaining silyl ethers were cleaved with HF to produce **121** (Scheme 4.90). This reagent was found to be well tolerated by the sensitive compound, in contrast to more basic fluoride sources. Furthermore,

it was possible to trap the excess HF with Me_3SiOH in order to form only volatile and essentially neutral side products.



Scheme 4.90: Schematic overview of the fragment coupling and global deprotection.

This deprotection completed the total synthesis of belizentrin methyl ester. We were pleased to find that its ^{1}H and ^{13}C NMR spectra revealed close resemblance with the published spectra of belizentrin.[9] Moreover, the careful comparison of the coupling constants within the ^{1}H NMR spectra and NOE correlations spoke for the same (relative) stereochemistry. It deserves mentioning that the synthetic methyl ester **121** proved significantly more stable than belizentrin. This virtue allowed for the in depth spectral characterization and gave a hint at the critical role of the free carboxylic acid during the decomposition of belizentrin.

4.11 Outlook

Since the current situation is (formally) only one step away from the proposed structure of the natural product, it would be desirable to take this last step. As outlined above, due to the early introduction of any ester in this position during the synthetic sequence seemingly minor modifications demand a great deal of effort. On the other hand the knowledge that was gained in our campaign would certainly benefit the next generation that might work on this problem. If the incorporation of the doubly skipped tetraene motif into the macrocycle "primes" belizentrin and its precursors or analogues for decomposition, this event should be postponed. By reversing the order of steps – attaching the side chain before the macrocyclization – it might be possible to complete a similar synthetic sequence in significantly higher overall yield.

A further question that might be addressed eventually is the relative stereochemistry between the sidechain and the macrocycle. Despite the good spectral match of our synthetic **121** and the isolated belizentrin, some uncertainty remains. To gain deeper insight, it would be necessary to invert one half of the molecule and synthesize the corresponding diastereomer. For practical reasons, such an "inversion" could not easily be conducted on the side chain, because it is derived from the chiral pool and *e.g.* L-glucose is not an affordable starting material. In the macrocyclic portion on the other hand this operation would be possible, because its synthesis relies on asymmetric catalysis. This fragment could be easily prepared in the enantiomeric form.

Along these lines, it appears desirable to prepare the free acid derived from "our" methyl ester **121** as well as the analogous acid derived from the same side chain and an inverted macrocycle. The comparison of these two compounds with the natural material should allow the confirmation or revision of the structure of belizentrin. Synthetic work in this direction is currently underway in our group.

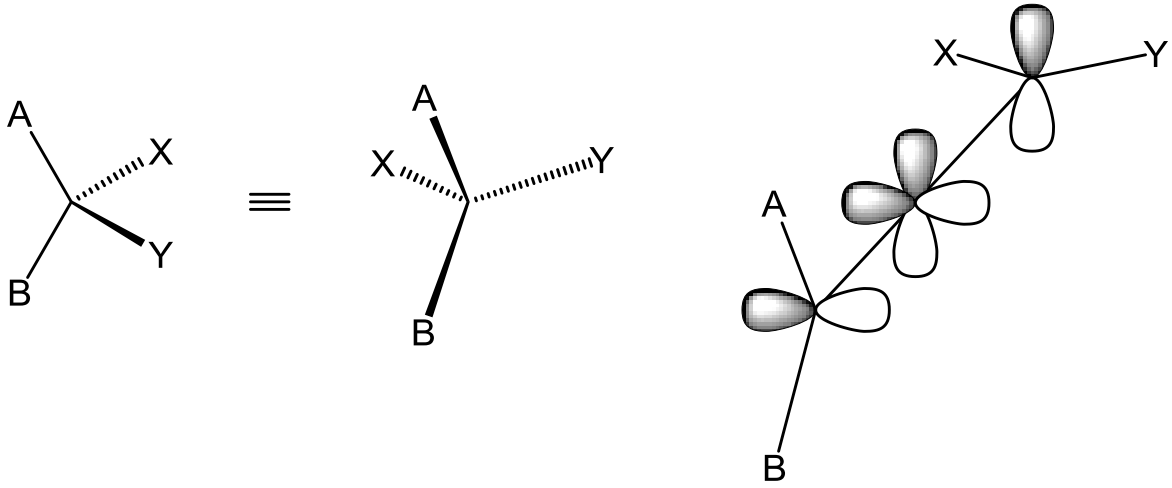
5 An Enantiodivergent Approach to Chiral Allenes

5.1 Disclaimer

This work was done in collaboration with Karin Radkowski and Dr. Maccarena Corro-Moron. Their results will be included for the sake of completeness.

5.2 Introduction

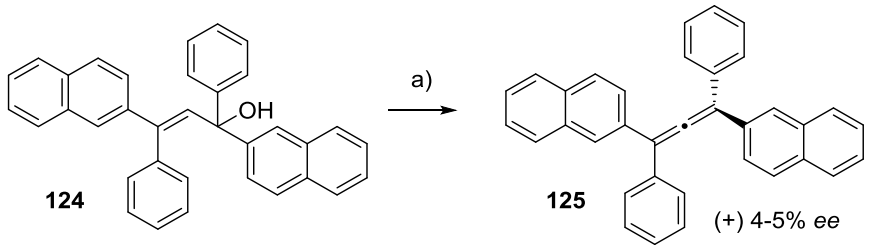
The existence of allenes, as well as of higher cumulenes, was predicted almost 150 years ago by Jacob H. van't Hoff. Beyond the prediction that such compounds could exist, he also expected cumulenes with an even number of double bonds to be chiral.[113] This can be viewed as an extension of the central chirality of an sp^3-hybridized carbon atom bearing four different substituents (Scheme 5.1).



Scheme 5.1: Relationship of central- and axial chirality in allenes.

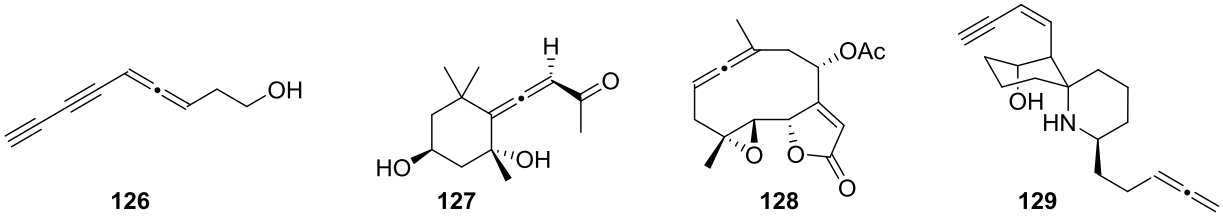
Although this hypothesis was not widely accepted in the 19th century, it remained an interesting puzzle for organic chemists. Unsuccessful attempts to deliver the experimental prove of this chirality were reported early in the 20th century.[114, 115, 116, 117, 118, 119] In 1935, some 60 years after the initial prediction of van't Hoff, it was demonstrated that optically active allenes can indeed exist.[120, 121] This was done in a very elegant way, especially given the state of organic synthesis at the time. Allene **125** was prepared by dehydration of the racemic allylic alcohol **124** with enantiopure camphorsulfonic acid. The allene was initially obtained in only 4 - 5% *ee*, but this

optical purity could be improved by repeated fractional crystallizations. In accordance with the "Wallach-rule", the racemate crystallized preferentially and could therefore be removed.[122, 123, 124] This asymmetric synthesis represented an early example of chiral Brønsted-acid organocatalysis (Scheme 5.2). The success of this work was dependent on the very high specific optical rotation of chiral allenes, allowing an asymmetric reaction to be monitored with the instrumentation available at the time.



Scheme 5.2: Asymmetric synthesis of allene **125**. Conditions: a) (+)-CSA, benzene reflux.

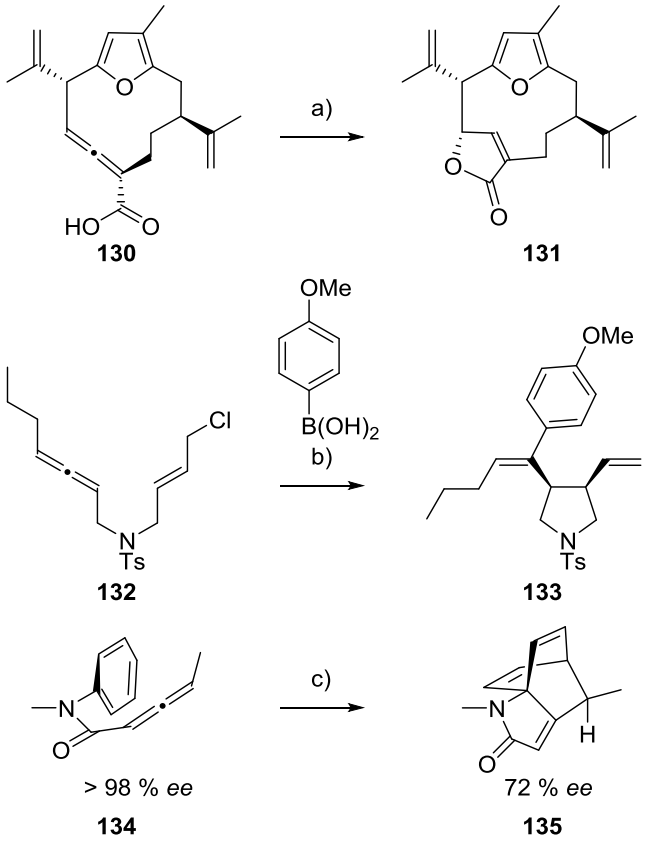
The advent of spectroscopic methods, particularly IR spectroscopy, greatly facilitated research on allenes because they generally exhibit a characteristic stretching frequency around 1950 cm^{-1}, which is an area between the carbonyl- and the alkyne-region of the IR spectrum that is typically void. With the help of this analytical tool, it became possible to detect allenes as (by-) products of reactions as well as in natural products. Until now, approximately 150 natural products containing allene functionalities have been identified. They cover a wide range in terms of complexity and stability (Scheme 5.3).[125, 126] Natural allenes occur in linear and cyclic molecules, in macrocyclic polyketides, as well as alkaloids. Such motifs have triggered the interest of organic chemists, resulting in several fascinating total syntheses. [127, 128]



Scheme 5.3: Selected naturally occurring allenes.

Furthermore, allenes have been found to undergo an impressive set of chemical reactions, most notably under transition metal catalysis.[129, 130] Among them, nucleophilic additions and cycloadditions are particularly prominent and synthetically useful. These reactions can benefit

from the chiral nature of suitably decorated allenes, resulting in diastereoselective reactions which can lead to new stereogenic centers (Scheme 5.4).

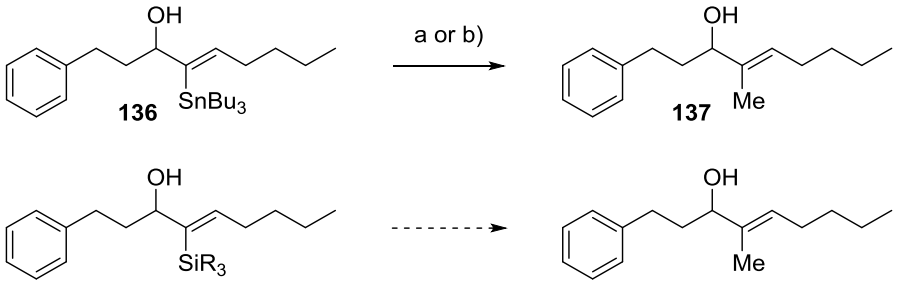


Scheme 5.4: Representantive examples of transformations of allenes. Conditions: a) $AgNO_3$ (20mol%), acetone, 68%; b) $Pd(PPh_3)_4$ (5mol%), K_3PO_4, toluene, 50°C, 82%; c) toluene, 140°C, 72%.

The π-system of the allene motif can coordinate to various transition metals. These interactions often activate the allene sufficiently such that it can undergo reactions, which are sometimes difficult to achieve with alkenes or alkynes. For example, allenes are often susceptible to nucleophilic attack, especially under the influence of π-acidic (transition-) metal catalysts. An interesting example of this type of reactivity is the late-stage formation of a butenolide moiety in the synthesis of (−)-kallolide B.[131] In a different application, one of the two allenic double bonds can participate in a metalla-ene reaction, as shown in Scheme 5.4. The allene inserts into the initially formed allyl-palladium complex, resulting in a alkenyl-palladium species, which can be intercepted by an aryl boronic acid in a Suzuki-like fashion.[132] There also exists a rare example of an uncatalyzed, thermal, dearomative [2+4] cycloaddition, the so-called Himbert reaction. The resulting polyunsaturated tricyclic product can be used to build up molecular complexity quickly.[133, 134, 135]

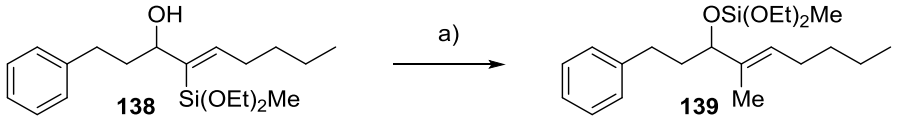
5.3 Initial Results and Motivation

As consequence of the highly regio- and stereoselctive *trans*-hydroelementation reactions developed in our group, synthetically useful follow-up chemistry was investigated.[24, 25, 26] Although the alkenylstannanes produced by this method are arguably the most versatile starting materials for further transformations, the use of the more benign silicon analogues also offers synthetic applications. To parallel the previously described methylation (methyl-Stille coupling) of alkenylstannanes, a comparable transformation of the corresponding alkenylsilanes was sought (Scheme 5.5).



Scheme 5.5: Methyl-Stille coupling and hypothetical "Hiyama-type" coupling. Conditions: a) $Pd(PPh_3)_4$ (5 mol%), CuTC, $[Ph_2PO_2][NBu_4]$, MeI, DMF, 85%; b) CuTC, $[Ph_2PO_2][NBu_4]$, MeI, DMSO, 85%.

The above mentioned Stille-type methylation likely proceeds through a alkenyl copper intermediate. It had been demonstrated that the Brook rearrangement of alkenylsilanes that contain a hydroxy group can provide an analogous alkenylcopper species.[136, 137] This was the appropriate starting point to develop the analogous methylation reaction based on alkenylsilanes. Indeed, careful investigation and optimization of this concept in our group led to suitable conditions for a one-pot Brook rearrangement/alkylation sequence (Scheme 5.6).[75]



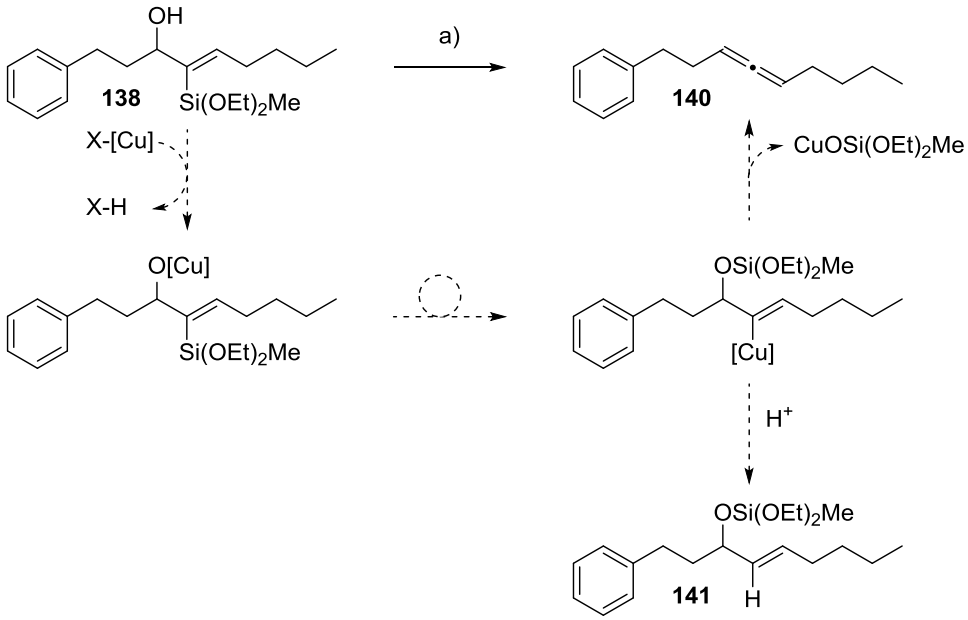
Scheme 5.6: Alkylation of alkenylsilane **138** via Brook-rearrangement. Conditions: a) CuI, LiO^tBu, MeI, DMF/ 2-methyl-THF, 91%.

During the inspection of different reaction conditions and electrophiles that are less reactive than methyl iodide, it was noticed that substantial amounts of allenes were formed in some cases. This was rationalized as product of the elimination of the silyl ether from the intermediate alkenyl copper species. In reactions with unreactive electrophiles or the absence of an electrophile, this

elimination becomes the dominant pathway. A question then arose, as to whether the allene formation could be developed into a synthetically useful transformation.

5.4 Optimization of the Allene Formation

The conditions that were previously developed for the alkylation method served as starting point to optimize the now intended allene formation. If the electrophile was simply omitted, allene **140** was formed, but it was always accompanied by side product **141** arising from the protonation of the pivotal organocopper species (Scheme 5.7).



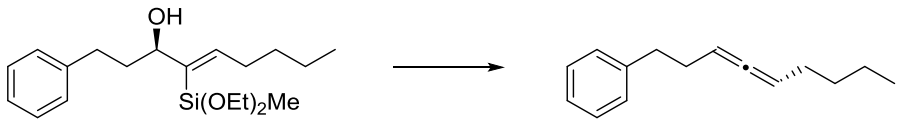
Scheme 5.7: Deliberate elimination to allene and its proposed simplified mechanism. Conditions: a) LiO^{t}Bu, CuI, THF/DMF.

The proton source was identified as the conjugate acid of the employed base, *tert*-butanol. Therefore, switching to different bases with weaker corresponding acids held the promise of suppressing this undesired pathway. It also appeared a logical move to employ an organocopper compound or a cuprate as base and copper source. With these considerations in mind, lithium dimethylcuprate was found to promote the reaction cleanly and rapidly.

With this obstacle overcome, we turned towards enantioenriched starting materials, to test whether the reaction was stereospecific (Table 5.1). Disappointingly, the reaction promoted by lithium dimethylcuprate gave rise to a completely racemic product when the alkenylsilane starting material with 95% *ee* was employed (entry 2). In sharp contrast to this result, the

"alkylation conditions" afforded the allene in a respectable 94% *ee* but only a meager 46% yield (entry 1). The use of methyl copper, which is insoluble in most solvents, instead gave variable results with up to 61% *ee* (entry 3). The inconsistency of the optical purity was ascribed to a varying degree of contamination with lithium dimethylcuprate, due to experimental difficulties (precise handling of a methyllithium solution in diethyl ether during the summer month). However, these results gave a valuable hint that reliable stoichiometry of 1:1 between the organic residue and copper might be crucial, while an excess of *e.g.* methyllithium led to the formation of a cuprate that was found to deteriorate the enantiomeric purity.

Table 5.1: Optimization of the base and copper source for the allene formation.

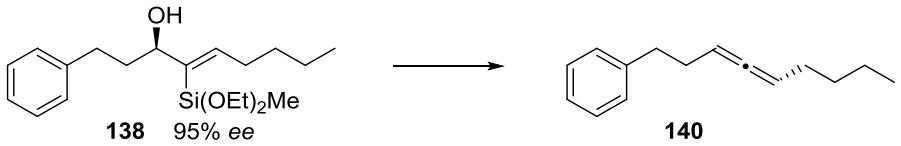


entry	Cu source	temp [°C]	yield [%]	*ee* [%]	comment
1	LiO^tBu + CuI	50	46	94	low yield
2	Me_2CuLi•LiI	−78 → RT	88	0	complete racemization
3	MeCu•LiI	−78 → RT	83	61	inconsistent results
4	MesCu	50	83	93	product contained bimesityl
5	$[Ph_3PCuH]_6$	rt	No product formed		

Finally, mesitylcopper, an isolable and thermally fairly stable organocopper compound, was found to give good and reproducible results in terms of yield and optical purity (entry 4). [138] Stryker's reagent was also tested, but its otherwise valuable mildness and low basicity prevented any productive reaction from occurring (entry 5).

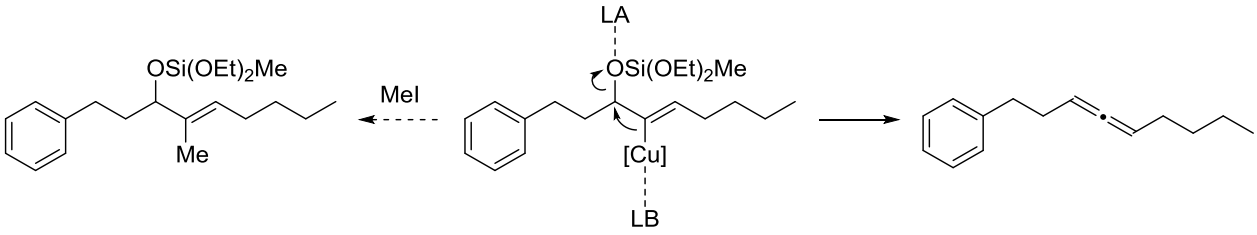
The first promising result using mesitylcopper was obtained by employing ~ 4 eq. of the reagent at 50 °C. Next, we attempted to optimize the reaction conditions by minimizing the amount and lowering the temperature. Decreasing the equivalents of mesitylcopper from 4 to 3, and from 4 to 1.5, resulted in significantly slower conversion (Table 5.2). Premature termination of the reaction resulted in diminished yield, while longer reaction times led to lower optical purity of the product. If the reaction was to be efficiently carried out with lower amounts of mesitylcopper, it was necessary to accelerate the reaction without influencing its stereospecificity.

Table 5.2: Influence of the reaction stoichiometry on the allene formation and stereospecificity.



entry	MesCu	temp.	time	yield [%]	*ee* [%]	comment
1	4 equiv.	50°C	7.5 h	62	93	
2	3 equiv.	50°C	10 h	54	85	
3	1.5 equiv.	50°C	23 h	88	n.d.	racemic sm

In consideration of the (proposed) mechanism of the allene formation, it appeared very likely that the elimination of the alkenylcopper intermediate to the allene was the rate determining step. This seemed plausible because only an accumulation of this intermediate would allow for the alkylation *(vide supra*) to proceed efficiently. It would therefore be beneficial to accelerate the elimination of this species (Scheme 5.8). This might be realized by either "pushing", *i.e.* increasing electron density at Cu with a suitable donor ligand, or "pulling", *i.e*. activating the leaving group with a Lewis acid.

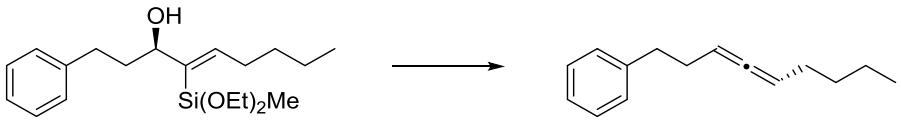


Scheme 5.8: Hypothetical influence of Lewis basic or acidic additives.

It had been reported that the addition of triethyl phosphite to a related alkoxy alkenylcopper compound increased the rate and stereospecificity of a similar allene formation.[139] Based on this report, we also tested triethyl phosphite as an additive. Its use did indeed speed up the reaction significantly at 50 °C, but also led to a decrease in yield of the allene product due to undesired side reactions. The optical purity, however, was barely affected by this change. The increased reaction rate allowed the transformation to be conducted at lower temperatures. At ambient

temperature, in the presence of 1.5 equivalents of mesitylcopper and 1.5 equivalents of triethyl phosphite, the desired allene was formed in 89% *ee* but only 56% yield (Table 5.3).

Table 5.3: Influence of triethyl phosphite as additive for the allene formation.



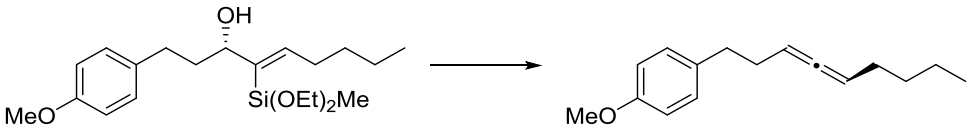
138 95% *ee* **140**

entry	MesCu	additive	temp.	time	yield[%]	*ee* [%]	comment
1	3 eq.	$P(OEt)_3$, 3.0 equiv.	50°C	1 h	n.d.	89	complex mixture
2	3 eq.	$P(OEt)_3$, 3.0 equiv.	rt	1 h	n.d.	87	
3	1.5 eq.	$P(OEt)_3$, 1.5 equiv.	rt	8 h	56	89	

Because the additional ligand accelerated the desired reaction but also promoted side reactions, we then turned to testing Lewis acidic additives. Out of the plethora of conceivable Lewis acids, magnesium chloride was deemed a suitable starting point (Table 5.4). One reason for this decision was that magnesium halides were an inevitable side product of the formation of mesitylcopper from a copper salt and a Grignard reagent.[138] If these would exhibit a positive effect on allene formation, one could perhaps form a mesitylcopper-magnesium halide reagent *in situ* and avoid the time-consuming purification of mesitylcopper.

At the same time, we changed the substrate from **138** to its *p*-methoxy derivative **142**, to render the corresponding allene product **143** slightly more polar than **140** in hopes of improving its chromatographic purification without influencing the relevant chemical properties.

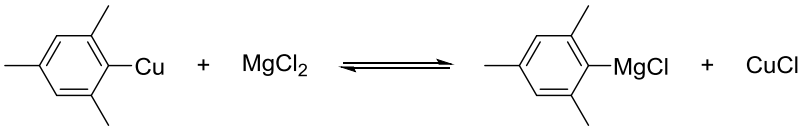
Table 5.4: The influence of stoichiometry and magnesium chloride as additive.



142 96% *ee* **143**

entry	MesCu [equiv.]	additive [equiv.]	temp. [°C]	time	yield [%]	*ee* [%]	comment
1	3.3 eq.	$MgCl_2$	rt	40 min	38	91	
2	1.5 eq.	$MgCl_2$	rt	55 min	46	92	
3	2.9 eq.	$MgCl_2$	0	5 h	13	92	
4	1.5 eq.	$MgCl_2$	rt	3 h	57	91	
5	1.5 eq.	$MgCl_2$	rt	5 h	78	89	inverse
6	**1.5 eq.**	**$MgCl_2$**	**rt**	**1.5 h**	**78**	**91**	**inverse**
7	1.5 eq.	$MgCl_2$	rt	2 h	70	88	inverse

During these experiments, the starting material was added to a solution of mesitylcopper and magnesium chloride. We were pleased to find that the Lewis acid shortened the reaction time even at ambient temperature without affecting the optical purity, but the yields were disappointingly low. However, when the order of addition was changed, and the solution of magnesium chloride was added to a pre-stirred solution of mesitylcopper and the starting material, the yield increased markedly. We reasoned, that there might be an equilibrium between mesitylcopper + magnesium chloride and mesitylmagnesium chloride + copper(I) chloride (Scheme 5.9). During the synthesis of the mesitylcopper, this equilibrium has to be shifted by the precipitation of the magnesium salts with dioxane.

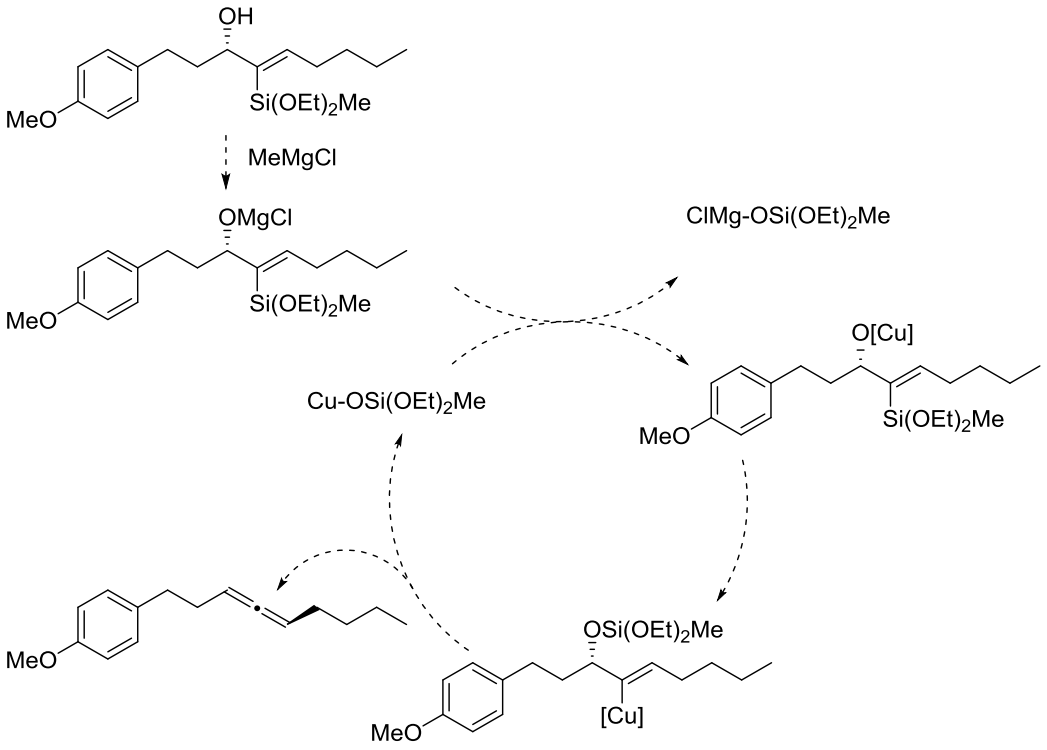


Scheme 5.9: Hypothetical equilibrium of the reagents.

The more basic and nucleophilic Grignard reagent might undergo undesirable side reactions with either the starting material or the product (or even both). This obstacle was overcome simply by changing the order of the addition. When the starting material was added to mesitylcopper alone, the hydroxy group could be deprotonated to form a copper alkoxide and inert mesitylene. As shown before, the productive elimination under these conditions was slow, but consecutive addition of magnesium chloride increased the reactions rate significantly. This allowed us to employ only 1.5 eq. of mesitylcopper and 1 eq. of magnesium chloride to drive the reaction to completion within 1.5 h.

Next, we tried to render the reaction catalytic in copper. It appeared possible that a copper silanolate, which was eliminated during the allene formation, could re-form the presumed copper alkoxide in the presence of a suitable base. Since magnesium chloride had shown a beneficial influence, we tested methylmagnesium chloride as stoichiometric base.

Table 5.5: Hypothetical catalytic cycle for the elimination.



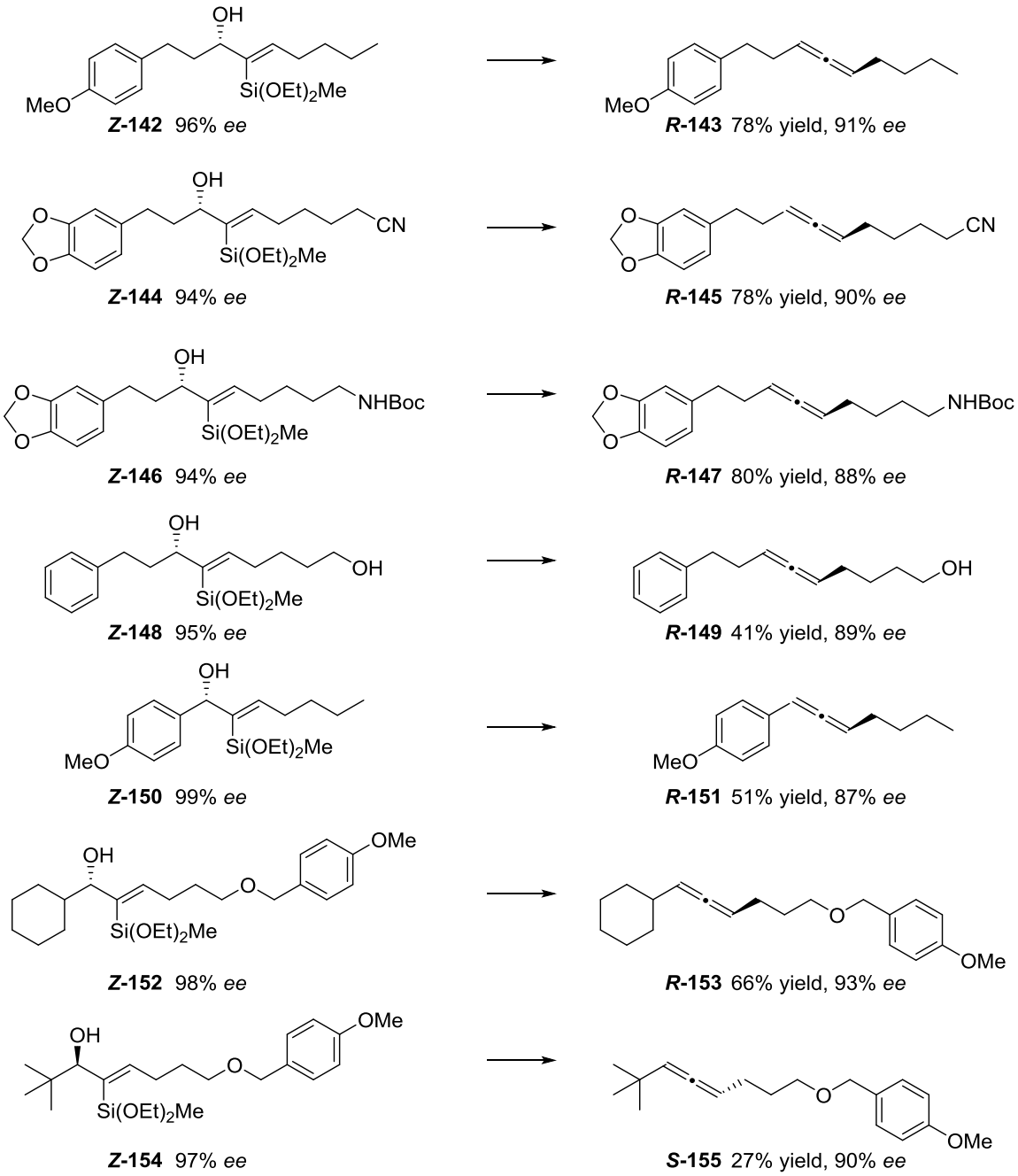
entry	MeMgCl [equiv.]	MesCu [equiv.]	additive	temp.	time	yield [%]	*ee* [%]
1	1.2	none	none	rt	22 h	< 9	91
2	1.1	0.1	none	rt	5.5 h	24	92
3	1.2	0.23	none	rt	5 h	32	91
4	2.0	0.35	none	rt	5 h	35	90
5	1.0	0.1	1.0 equiv. $MgCl_2$	rt	2h 20 min	26	92

This concept relied on the fast deprotonation of the hydroxy group by the Grignard reagent to prevent it from causing side reactions. Unfortunately, only low yields and 2 - 3 turnovers with respect to copper were obtained. A control reaction in the absence of any copper source revealed that a very slow but stereospecific background reaction occurred. The additional supplement of magnesium chloride, in case any magnesium silanolate would be not sufficiently Lewis acid, did not improve the efficiency.

5.5 Scope of the Allene Formation

With promising, albeit stoichiometric, reaction conditions for our standard substrate in hand, the next step was to test whether the reaction was generally applicable. Several alkenylsilanes, decorated with different functional groups, were prepared and tested (

Scheme 5.10).

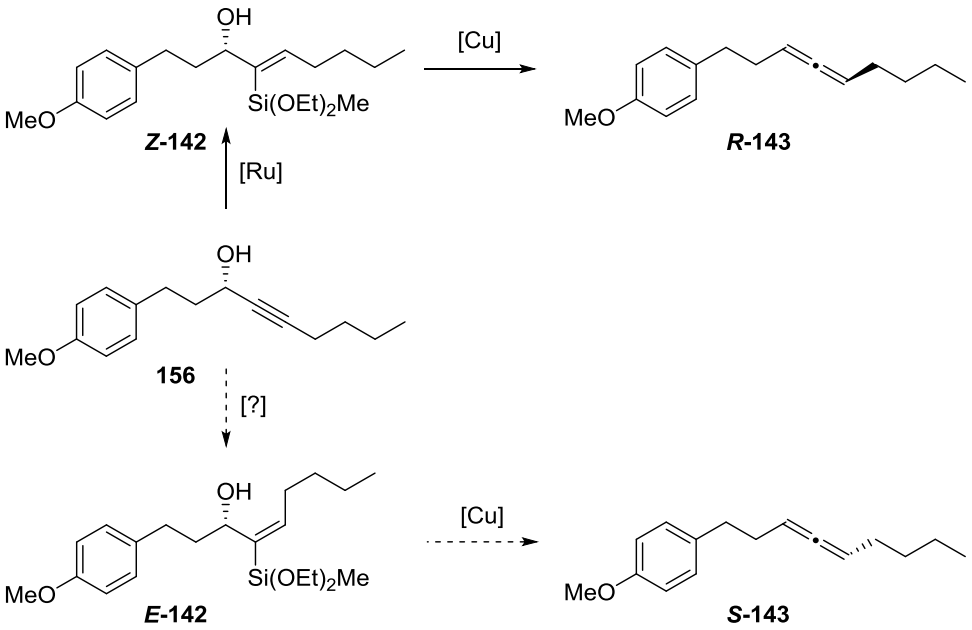


Scheme 5.10: Scope of the allene formation. Conditions: MesCu, 0°C → RT, then $MgCl_2$, THF.

We have found that different functionalities such as nitrile or Boc-protected amine were well tolerated, but there were also limitations. The presence of an unprotected primary alcohol resulted, despite the use of an increased amount of mesitylcopper, in a rather low yield of the desired product. This might be the consequence of a nucleophilic attack of a (copper-) alkoxide on the nascent allene. Also the direct vicinity of an aryl group somewhat lowered yield and stereospecificity. In terms of steric effects, the change from the linear alkyl chain to cyclohexyl or even *tert*-butyl group next to the newly formed allene motif led to a reduced yield, although the optical purity was still appreciable.

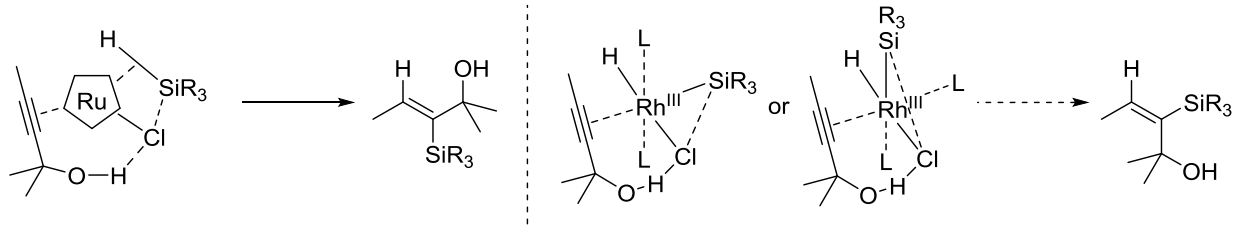
5.6 Enantiodivergence

Spurred by the results described above, we considered the possibility of rendering the transformation enantiodivergent. The enantiomers of an allene can be viewed as geometrical isomers differing at one double bond. Based on the working hypothesis that the elimination step proceeded in a strict "*anti*"-fashion (Scheme 5.7), inversion of the double bond geometry should result in the opposite enantiomer of the allene. To test this idea, an access to the isomeric *E*-alkenylsilanes was required (Scheme 5.11).



Scheme 5.11: Possible access to both enantiomers of an allene from a single enantiomer of a propargylic alcohol.

In contrast to the well-established hydroxy-directed *trans*-hydrosilylation of propargylic alcohols, the same level of regioselectivity in *cis*-hydrosilylation has not yet been achieved. As hydrogen bonding is capable of directed hydrosilylation in ruthenium-catalyzed *trans*-hydroelementation, we sought to apply the same steering effect to a catalyzed reaction that is known to yield the *cis* isomer. We therefore turned our attention to rhodium-chloride-catalysts, which are known to promote *cis*-hydrosilylation.[140, 141, 142, 143, 144] It seemed plausible that the chloride ligand might stay bound to the metal center throughout the reaction and therefore dictate the pre-arrangement of ligands in the metal coordination sphere to lead to the desired regioselectivity. A simplified picture of an octahedral (d 6) $Rh^{(III)}$ complex bearing the silyl- and hydride-ligand *cis* to each other (as result of a concerted oxidative addition) and the propargylic alcohol bound through the π-system as well as the hydroxy group illustrates the presumed analogy to the well-studied Ru-system. Whether the hydride-, silyl- and alkyne-ligands would be arranged in a facial or meridional fashion might depend on the additional ancillary ligands L but either way should lead to the same (major) product (Scheme 5.12).



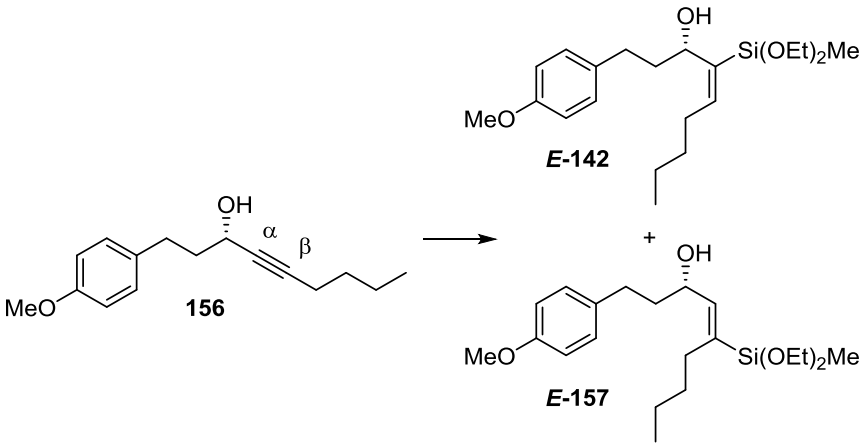
Scheme 5.12: Rational for the ruthenium-catalyzed regioselective *trans*-hydrosilylation and hypothetical rhodium-catalyzed *cis*-hydrosilylation.

Unfortunately, after screening $[(cod)RhCl]_2$ alone or in combinations with various phosphine ligands, we found no particularly promising regioselectivity. Furthermore these reactions were in all cases rather slow at ambient temperature.

Next, we opted to investigate platinum catalysts, which serve as the system of choice in *cis*-hydrosilylation, since the discovery of Speier's (pre-) catalyst (H_2PtCl_6).[145] Several cases are known in which free or protected propargylic alcohols were converted with moderate to good regioselectivity into the proximal alkenylsilane via Pt-catalysis.[146] In good accordance to these reports, we found that the reaction of **156** with methyldiethoxysilane catalyzed by $(cod)PtCl_2$ quickly led to complete conversion. The reaction started after a short induction period (visible due to color change from colorless to golden yellow) and gave the isomeric alkenylsilanes ***E*-142**

and ***E*-157** in a ratio of ~ 7:1. These isomers were easily separable by flash chromatography. To test whether the presence of chloride in the (pre)catalyst had any influence on the regioselectivity we also tested $Pt(dba)_3$ as catalyst. In this case no induction time was observed, but the regioselectivity was unchanged. This would comply with the Chalk-Harrod mechanism involving a $Pt^{(0)} – Pt^{(II)}$ cycle, therefore requiring a $Pt^{(0)}$ species as active catalyst.[147] To further improve the regioselectivity, several solvents were screened, which revealed a qualitative correlation between solvent polarity and regioselectivity (Table 5.6). An exception from the trend was the reaction in pentane, which led to somewhat lower regioselectivity than that in dichloromethane or toluene.

Table 5.6: Pt-catalyzed hydrosilylation of **156**. Conditions: H-Si(OEt)$_2$Me, Pt(dba)$_3$ (0.1 – 0.5 mol%), solvent.

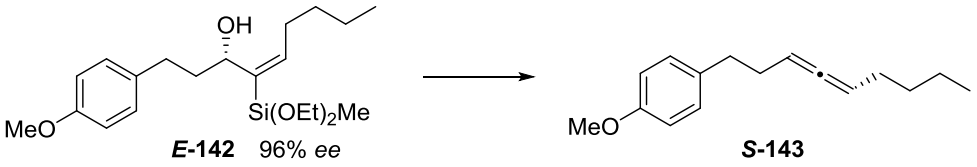


solvent	α:β
toluene	**11:1**
dichloromethane	6.8:1
pentane	5.3:1
THF	2.7:1
DMF	1:1

Since the regioisomers were easily separable by flash chromatography, the achieved selectivity was deemed sufficient for our purpose. These hydrosilylation conditions were applicable to most propargylic alcohols examined. This allowed us to move on to the allene forming step. Treatment of silane ***E*-142** with mesitylcopper without any additives at 50 °C led indeed to the expected allene with an optical rotation of opposite sign to that of allene ***R*-143**. However the yield and *ee* for this unoptimized protocol were modest (67% and 73% *ee* respectively). This result prompted us to attempt a similar optimization as described above for the isomeric silane. At first, several solvents were screened, but it turned out that the influence was minimal in most cases. Consequently additives were considered, and in this case we were pleased to find that triethyl phosphite was a very suitable promotor: it increased the reaction rate and allowed us to conduct

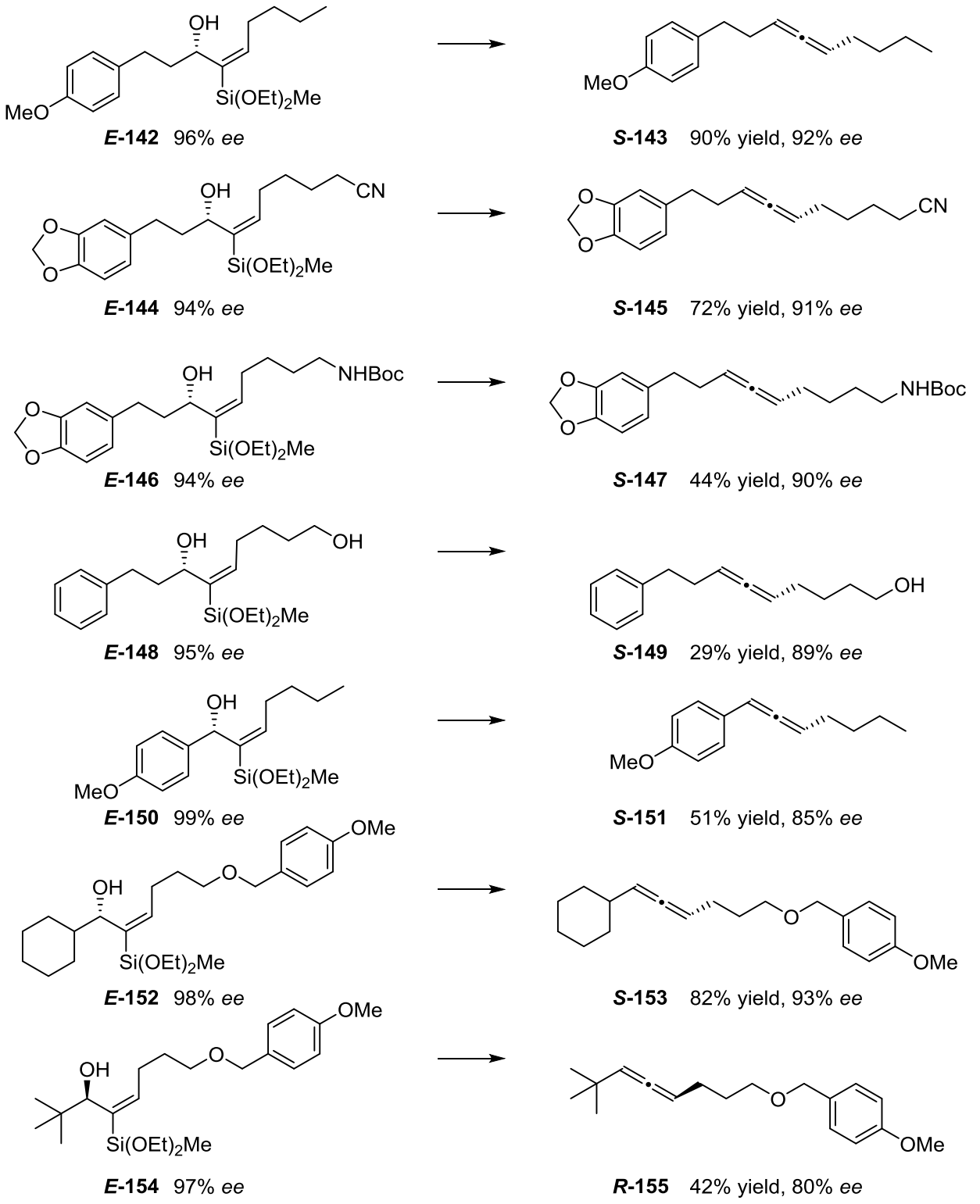
the reaction at ambient temperature or even below. Lower temperature and shorter reaction times were correlated with an increase in optical purity (Table 5.7).

Table 5.7: Optimization of the allene formation from the *E*-alkenylsilane.



entry	MesCu [equiv.]	additive [equiv.]	solvent	temp [°C]	time	yield [%]	*ee* [%]
1	3.3	none	THF	50	5 h	67	73
2	2.8	none	dioxane	50	3.5 h	66	78
3	2.5	none	DME	50	3.5 h	63	76
4	3.4	none	toluene	50	3.5 h	57	57
5	3.3	none	benzene	50	3.5 h	63	77
6	3.1	none	hexane	50	3.5 h	72	81
7	2.7	none	acetonitril	50	4.5 h	56	64
8	3.9	none	DMF	50	4.5 h	13	17
9	3.3	$P(OEt)_3$ 6.5.	THF	rt	1 h	n.d.	89
10	**3.3**	**$P(OEt)_3$ 6.5**	**THF**	**0**	**1 h**	**90**	**92**
11	3.3	$P(OEt)_3$ 6.5	THF	−20	1 h	n.d.	91

With these promising condition established, we studied the substrate scope of the transformation. The same set of propargylic alcohols was converted to the isomeric *E*-alkenylsilanes and finally to the enantiomeric allenes. In general, these stereoisomeric alkenylsilanes followed similar trends as the corresponding *Z*-isomers (Scheme 5.13).



***E*-142** 96% *ee* → ***S*-143** 90% yield, 92% *ee*

***E*-144** 94% *ee* → ***S*-145** 72% yield, 91% *ee*

***E*-146** 94% *ee* → ***S*-147** 44% yield, 90% *ee*

***E*-148** 95% *ee* → ***S*-149** 29% yield, 89% *ee*

***E*-150** 99% *ee* → ***S*-151** 51% yield, 85% *ee*

***E*-152** 98% *ee* → ***S*-153** 82% yield, 93% *ee*

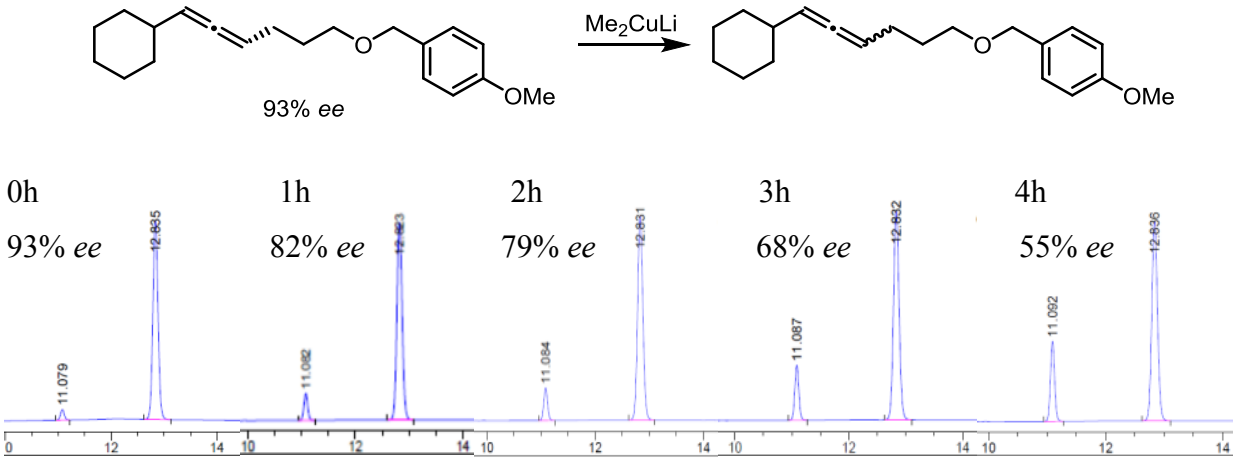
***E*-154** 97% *ee* → ***R*-155** 42% yield, 80% *ee*

Scheme 5.13: Scope of the allene formation from *E*-alkenylsilanes. Conditions: MesCu, $P(OEt)_3$, THF, 0°C.

5.7 Mechanistic Considerations and Comparison of the *E*- and *Z*-Alkenylsilanes

At the first glance it appeared to be very likely that the geometrical isomers of alkenylsilanes should yield the opposite enantiomers of the product allene via the described Brook rearrangement/elimination sequence. This expectation was based on the naïve assumption that both isomers would behave (more or less) in the same way throughout this sequence. During the reaction optimization, it became apparent that they behaved similar, albeit a few differences could also be noted.

The transformations of both isomeric series of alkenylsilanes had in common that, under optimized conditions, they proceeded fairly fast and under mild conditions. They also shared the drawback that the optical purity deteriorated by roughly 5% from the enantioenriched starting material during the reaction. It was difficult to determine whether this loss resulted from a competing reaction pathway leading to the opposite enantiomer or racemic product, or alternatively from racemization of the product allene under the above conditions. It has been reported that various organic and inorganic copper species are capable of partially or fully racemizing enantioenriched allenes.[148, 149] This racemization has been explained as result of a reversible single electron reduction of the allene in question, which would result in an allylic radical anion that is configurationally unstable.

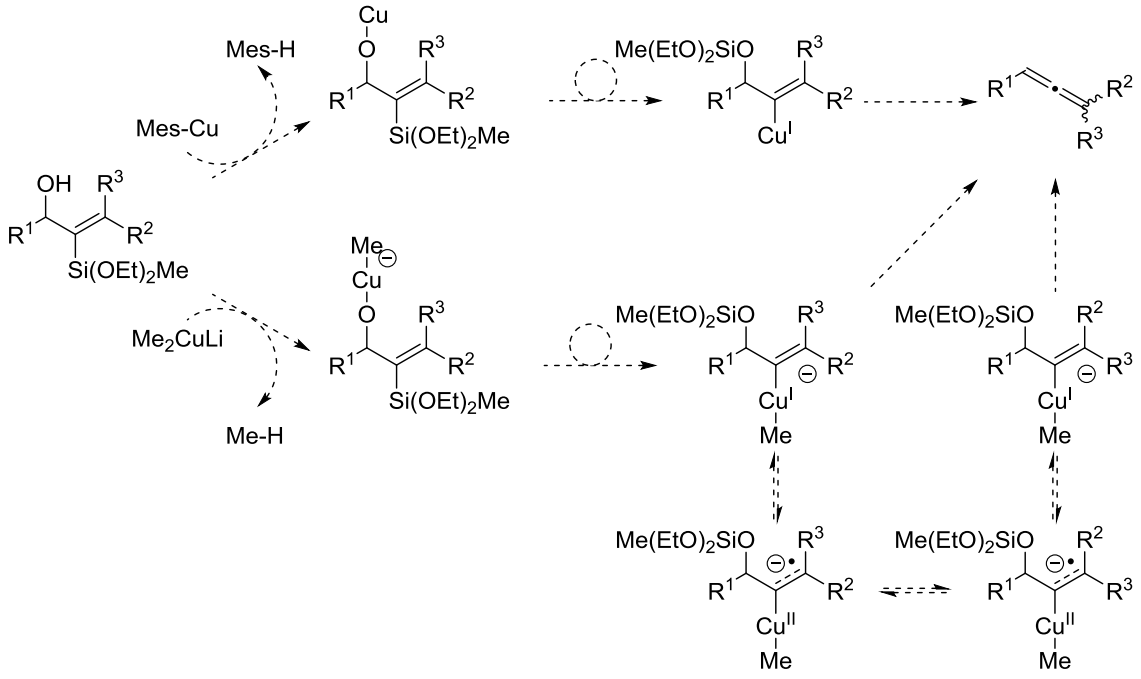


Scheme 5.14: Qualitative racemization experiment with lithium dimethylcuprate; chiral HPLC traces.

This property is at least part of the problem concerning our methodology, as we have observed no stereospecificity when the reaction was promoted by lithium dimethylcuprate (Table 5.1). A control experiment proved that lithium dimethylcuprate did gradually racemize a preformed

allene but the rate was much too slow to account for the complete loss of chiral information observed during the reaction of a alkenylsilane to the allene (Scheme 5.14).

This observation indicated that also a different pathway for racemization was likely to operate, at least in the reactions carried out with lithium dimethylcuprate. In this case, it would be plausible that a mixed cuprate results from the Brook rearrangement. Such a species is likely to act as stronger reducing agent than the analogous alkenylcopper species (Scheme 5.15).

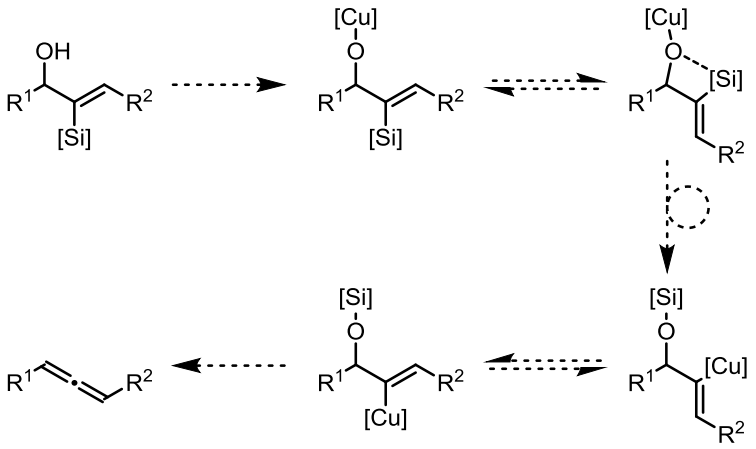


Scheme 5.15: Comparison organocopper vs. cuprate reagents in the allene formation.

The intermediacy of an electron-rich cuprate bound directly to the central carbon of the future allene in the course of the reaction might facilitate racemization via single electron reduction. This notion is in line with the much higher stereospecificity observed when using mesitylcopper, which should give rise to a neutral alkenylcopper intermediate.

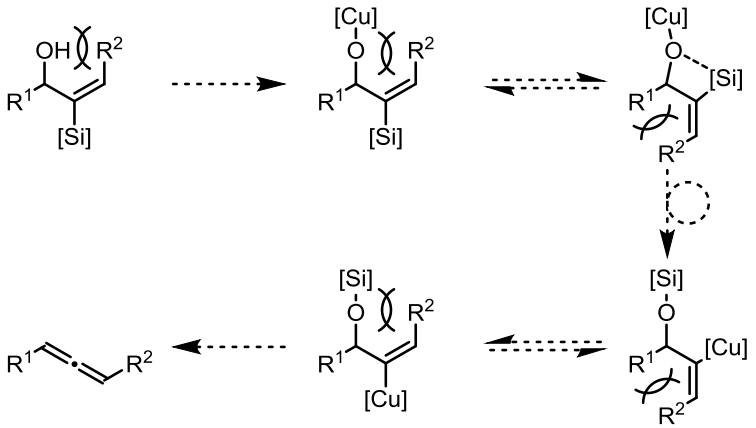
This argument offers a probably oversimplified explanation for the observed results. It must be emphasized here that, more often than not, organocopper compounds exist in solution as aggregates, which renders a discussion of their behavior difficult.[150]

The differences between the geometrical isomers of the alkenylsilanes, resulting from *cis*- or *trans*-hydrosilylation become apparent when one considers the conformations of the tentative intermediates.



Scheme 5.16: Proposed mechanism of the allene formation from *Z*-alkenylsilanes.

In the case of *Z*-alkenylsilanes, the initially formed copper alkoxide can easily rotate into a conformation which allows the silicon atom to interact with the oxygen atom, in order to undergo a Brook rearrangement. Subsequently, the alkenylcopper species can again rotate freely to position the silanolate leaving group in an anti-periplanar fashion with respect the carbon—copper bond, which should entail facile elimination. Throughout this sequence, the molecule would never be forced to adopt an especially unfavorably conformation (Scheme 5.16). The isomeric *E*-alkenylsilanes and the analogous intermediates resulting from them on the other hand would suffer from an unfavorable 1,3-allylic strain, assuming that the reaction proceeds via a comparable mechanism. This raises the question as to whether the *E*-alkenylsilanes follow the same mechanism as their *Z*-analogues or a different pathway (Scheme 5.17).

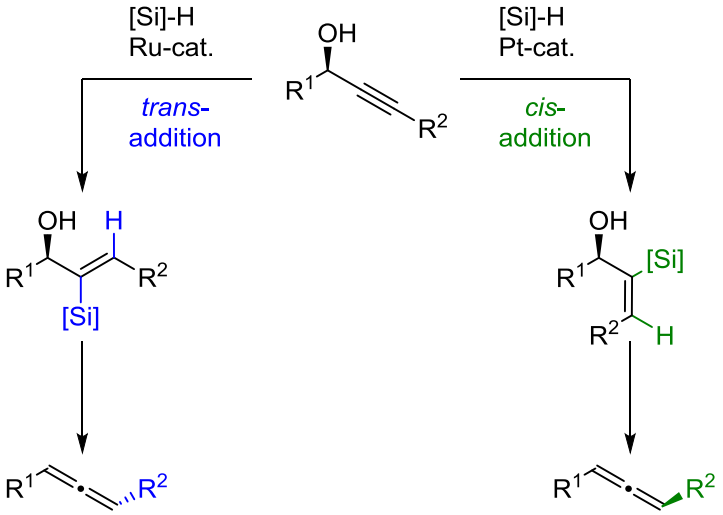


Scheme 5.17: proposed mechanism of the allene formation from *E*-alkenylsilanes.

The observed overall stereochemical outcome fits these mechanistic proposals, but in depth studies would be required to determine whether competitive mechanistic pathways are operational.

5.8 Conclusion

This section describes an enantiodiveregent method to convert enantioenriched propargylic alcohols into allenes with good stereospecificity. The sequence consists of a stereo- and regioselective hydrosilylation, which proceeds in a stereodivergent fashion, depending on the choice of catalysts, followed by a stereospecific Brook rearrangement/ elimination cascade. The method is applicable to various functionalized substrates. Nevertheless, while studying the reaction scope, we have also encountered limitations. Since a plethora of well-established methods for the conversion of propargylic alcohols to chiral allenes is known in the literature, the synthetic utility of this protocol appears limited. On the other hand, it has a certain conceptual charm; our initial idea that geometrical isomers of alkenylsilanes would result in opposite enantiomers of allenes turned out to be correct. Furthermore, the dual role of the Brook rearrangement to produce an organometallic species as well as an appropriate leaving group in the correct position is noteworthy. Under carefully tuned conditions, the resulting metalated intermediate could be either alkylated or eliminated at will.[75] In this context the investigation of the allene formation can also give insights into how this reaction could be suppressed if alkylation or any other type of reactivity of the organocopper intermediate is desired.



Scheme 5.18 Schematic overview of the enantiodivergent allene formation.

5.9 Outlook

In order to improve the efficiency of the described allene formation, several issues need to be addressed; (i) the practicality and handling of the alkenyl(methyldiethoxy)silanes (ii) the stereospecificity of the allene formation (iii) the functional group tolerance. It would be desirable, to exchange the diethoxy(methyl)silyl-group for a different silyl-group. Despite its utility in the Brook rearrangement/elimination, the derived alkenylsilanes are not very stable to flash chromatography likely because of partial hydrolytic cleavage of the ethoxy-residues on the silicon atom and consequent loss of material. Initial experiments in this direction led us to investigate dimethyl(pentafluorophenyl)silane as a substitute. It was found suitable for the hydrosilylation step, but not yet satisfactory in the Brook rearrangement/elimination step. The stereospecificity and functional group tolerance of the elimination have still room for improvement. The stereospecificity might be influenced by the choice of organocopper reagent, leaving group or additives. The tolerance towards certain functionalities on the other hand might be inherently limited by the reactive nature of a alkenylcopper intermediate, which is likely to intercept many acidic or oxidizing motifs. This limitation is shared with virtually all allene syntheses which rely on organocopper intermediates.

6 Experimental Section

6.1 General

All reactions were carried out under Ar in flame-dried glassware unless H_2O was used as a (co-) solvent or otherwise noted. The following solvents and organic bases were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene); hexane, toluene (Na/K), N-ethyldiisopropylamine, CH_2Cl_2, (CaH_2); 1,4-Dioxane, DMF, DMSO, MeCN, NEt_3 and pyridine were dried by an adsorbtion solvent purification system based on molecular sieves. All other commercially available compounds (ABCR, Acros Organics, Alfa Aesar, Aldrich, TCI) were used as received.

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

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

NMR Spectra were recorded on Bruker AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ([D_3]-Acetonitrile: $\delta_H \equiv 1.94$ ppm, $\delta_C \equiv 118.26$ ppm $CDCl_3$: $\delta_H \equiv 7.26$ ppm, $\delta_C \equiv 77.16$ ppm; C_6D_6: $\delta_H \equiv 7.16$ ppm, $\delta_C \equiv 128.06$ ppm; CD_2Cl_2: $\delta_H \equiv 5.32$ ppm, $\delta_C \equiv 54.0$ ppm; [D_6]-DMSO: $\delta_H \equiv 2.50$ ppm, $\delta_C \equiv 39.52$ ppm). Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet; hept: heptet, m: multiplet. The abbreviation "br" indicates a broad signal. ^{13}C NMR spectra were recorded in [^1H]-decoupled mode and the values of chemical shifts are rounded to one position after decimal point. All spectra from the 500 MHz and 600 MHz spectrometers were acquired by the NMR department under guidance of Dr. Christophe Farès at the Max-Planck-Institut für Kohlenforschung.

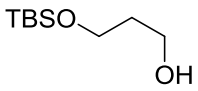
IR spectra were recorded on Alpha Platinum ATR (Bruker) at room temperature, wavenumbers are given in cm^{-1}.

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).

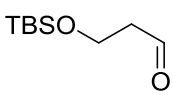
Optical rotations were measured with a Krüss Optronics P 8000-T polarimeter at a wavelength of 589 nm. They are given as specific optical rotation with exact temperature, concentration (c /(10 mg/mL)) and solvent.

6.2 Total Synthesis of Belizentrin Methyl Ester

3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol (12): A solution of *tert*-butyldimethylsilyl chloride (48.9 g, 324 mmol) in CH_2Cl_2 (150 mL) was added to a stirred solution of 1,3-propanediol (49.0 mL, 678 mmol) and triethylamine (50.0 mL, 359 mmol) in CH_2Cl_2 (500 mL) at 0 °C. The mixture was allowed to reach room temperature. The mixture was stirred for 23 h before the reaction was quenched with saturated aqueous $NaHCO_3$ solution (150 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x80 mL). The combined organic layers were washed with water (150 mL) and saturated aqueous NaCl solution (150 mL), dried over sodium sulfate, and concentrated under reduced pressure. The red crude material was distilled *in vacuo*. The pure product was collected after a small forerun at 93 - 95 °C / 10 - 12 mbar as colorless oil (53.5g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (t, *J* = 5.6 Hz, 2H), 3.82 – 3.76 (m, 2H), 2.57 (brs, 1H), 1.78 (tt, *J* = 6.1, 5.2 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.1, 62.7, 34.3, 26.0, 18.3, −5.3. IR (neat): 2953, 2929, 2857, 1472, 1389, 1361, 1254, 1081, 1006, 960, 939, 832, 773, 721, 662, 512 cm^{-1}. HRMS (ESI): m/z calculated for $C_9H_{22}O_2SiNa$ [M+Na$^+$]: 213.12813, found 213.12814.



3-((*tert*-Butyldimethylsilyl)oxy)propanal (13): 2,2′-Bipyridyl (715 mg, 4.58 mmol, 4.5 mol%), $[Cu(MeCN)_4]BF_4$ (1.44 g, 4.58 mmol, 4.5 mol%), TEMPO (716 mg, 4.58 mmol, 4.5 mol%) and N-methylimidazol (0.73 mL, 9.1 mmol, 9 mol%) were added to a stirred solution of compound **12** (19.2 g, 101 mmol) in MeCN (500 mL). The resulting reddish-brown solution was stirred vigorously under O_2 atmosphere for 3 h. At this point, the mixture had turned blue. The mixture was diluted with water (500 mL) and extracted with pentane (7x100 mL). The combined organic layers were dried over sodium sulfate and carefully concentrated under reduced pressure. The crude aldehyde was obtained as red liquid (20 g, 99 %). The product was found to be 94% pure [^{1}H NMR] and was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.1 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.60 (td, *J* = 6.0, 2.1 Hz, 2H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 57.5, 46.6, 25.9, 18.3, -5.3. IR (neat): 2955, 2930, 2886, 2857, 2728, 1727, 1472, 1389, 1362, 1254, 1212, 1094, 1006, 970, 939, 832, 775, 680, 568, 529 cm^{-1}. HRMS (ESI): m/z calculated for $C_9H_{21}O_2Si_1$ [M+H$^+$]: 189.13053, found 189.13024.

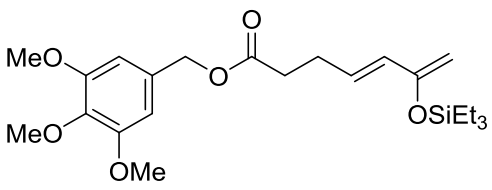


3,4,5-Trimethoxybenzyl pent-4-enoate (15): Oxalyl chloride (2.8 mL, 33 mmol) was added slowly to 4-pentenoic acid **14** (3.2 mL, 31 mmol) at 0 °C. The orange-brown mixture was stirred vigorously and was allowed to reach room temperature. After 4 h the evolution of gas had ceased, the turbid crude acid chloride was dissolved in CH_2Cl_2 (30 mL) and the resulting solution was cooled to 0 °C again. 4-Dimethylamino pyridine (37 mg, 0.3 mmol), potassium carbonate (6.22 g, 45 mmol) and 3,4,5-trimethoxybenzyl alcohol (4.8 mL, 30 mmol) were added and the mixture was allowed to reach room temperature. After 18 h triethylamine (1.0 mL, 7.2 mmol) was added and the mixture was stirred for 1 h. Then the reaction was quenched with water (30 mL), the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2x30 mL), the combined organic layers were dried over sodium sulfate and concentrated und reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 4:1) yielded the product as a colorless oil (7.58 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.18 – 4.90 (m, 4H), 3.87 (s, 6H), 3.84 (s, 3H), 2.50 – 2.45 (m, 2H), 2.44 – 2.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 153.5, 138.1, 136.7, 131.7, 115.7, 105.6, 66.6, 61.0, 56.3, 33.7, 29.0, 14.4. IR (neat): 3078, 2940, 2839, 1732, 1641, 1591, 1507, 1459, 1421, 1378, 1331,1235, 1154, 1123,1044, 1004, 960, 915, 824, 781, 696, 639, 583, 527 cm^{-1}. HRMS (ESI): m/z calculated for $C_{15}H_{20}O_5Na$ [M+Na$^+$]: 303.12029, found: 303.12025.

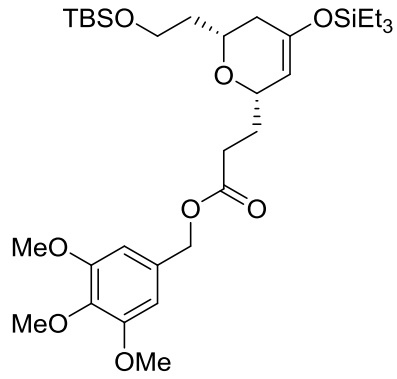
3,4,5-Trimethoxybenzyl (*E*)-6-oxohept-4-enoate (16): Hoveyda-Grubbs II catalyst (44 mg, 70 µmol, 0.1 mol%) was added to a stirred solution of 3-buten-2-one (14.0 mL, 173 mmol) and compound **15** (19.3 g, 68.8 mmol) in CH_2Cl_2, (500 mL) and the green mixture was heated to reflux for 4 h. Then the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the dark residue by flash chromatography (hexane/EtOAc = 3:2 → 1:1) yielded the product as a pale yellow oil (22.2 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.74 (m, 1H), 6.58 (s, 2H), 6.10 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.05 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.62 – 2.53 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 172.2, 153.5, 145.5, 138.3, 132.0, 131.3, 105.8, 67.0, 61.0, 56.3, 32.6, 27.5, 27.2. IR (neat): 2998, 2942, 2840, 1732, 1697, 1673, 1628, 1592,

1507, 1460, 1422, 1360, 1332, 1237, 1154, 1125,1044, 1006, 976, 828, 781, 693, 610, 585, 528 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{22}O_6Na$ $[M+Na^+]$: 345.13086, found: 345.13094.

3,4,5-Trimethoxybenzyl (*E*)-6-((triethylsilyl)oxy)hepta-4,6-dienoate (17): Triethylsilyl trifluoromethanesulfonate (11.5 mL, 51.1 mmol) was added dropwise to a stirred solution of compound **16** (14.0 g, 43.4 mmol) and triethylamine (12.0 mL, 86.1 mmol) in Et_2O (150 mL) at 0 °C. The slightly turbid mixture was stirred at 0 °C for 1.5 h and was then poured onto saturated aqueous $NaHCO_3$ solution (150 mL). The layers were separated, the aqueous layer was extracted with *tert*-butyl methyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 5:1 + 0.5% triethylamine) yielded the product as a pale yellow oil (16.9 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 6.10 – 5.83 (m, 2H), 5.04 (s, 2H), 4.24 (d, J = 0.7 Hz, 1H), 4.20 (d, J = 0.8 Hz, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 2.52 – 2.40 (m, 4H), 1.02 – 0.94 (m, 9H), 0.71 (td, J = 8.0, 0.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 154.8, 153.5, 138.1, 131.7, 129.1, 129.0, 105.6, 94.5, 66.7, 61.0, 56.3, 34.0, 27.4, 6.9, 5.1. IR (neat): 2955, 2913, 2877, 2839, 1734, 1655, 1591, 15081459, 1421, 1378, 1330, 1236, 1151, 1126, 1005, 962, 921, 822, 781, 730, 585, 527, 463 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{36}O_6SiNa$ $[M+Na^+]$: 459.21734, found 459.21754.

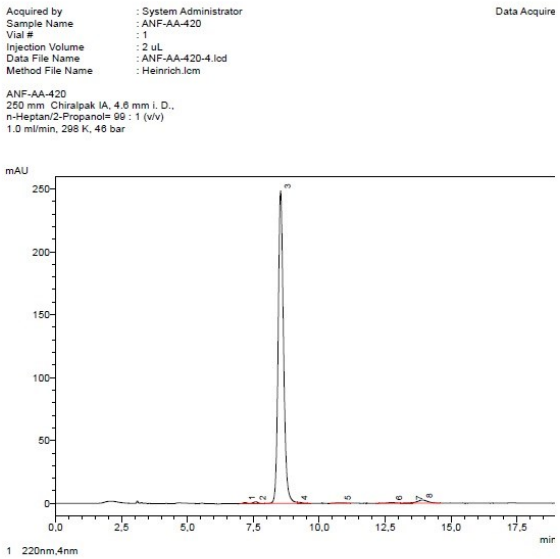


3,4,5-Trimethoxybenzyl 3-((2*S*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-((triethylsilyl)oxy)-5,6-dihydro-2*H*-pyran-2-yl)propanoate (19): Aldehyde **13** (1.96 g, 10.1 mmol) and diene **17** (2.32 g, 5.32 mmol) were added to a mixture of Jacobsen's $Cr^{(III)}$-catalyst **10** [33] (262 mg, 0.5 mmol, 9 mol%) and powdered 4 Å molecular sieves (1.08 g) and the resulting thick brown mixture was stirred at room temperature. After 72 h a second portion of aldehyde **13** (1.86 g, 9.58 mmol) was added to the reaction mixture. After being stirred for 144 h in total the mixture was diluted with hexane:EtOAc 4:1 (10 mL), filtered through a pad of silica, the silica was rinsed with hexane:EtOAc 4:1 (90 mL in total) and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 6:1 + 1% triethylamine)



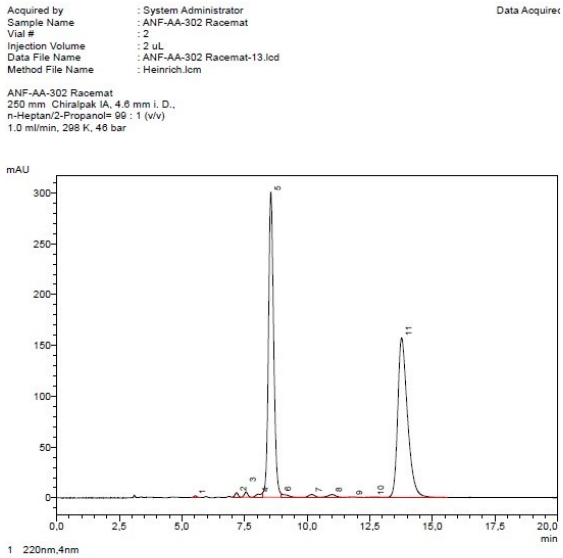
yielded the product as a yellow oil (2.51 g, 76% yield). $[\alpha]_D^{20} = -32.6$ (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 6.52 (s, 2H), 5.06 (s, 2H), 4.76 (t, *J* = 1.6 Hz, 1H), 4.31 – 4.10 (m, 1H), 3.82 (s, 3H), 3.77 (ddt, *J* = 10.0, 8.3, 4.4 Hz, 2H), 3.64 (dt, *J* = 10.3, 5.4 Hz, 1H), 3.39 (s, 6H), 2.71 – 2.52 (m, 2H), 2.19 – 1.99 (m, 2H), 1.98 – 1.87 (m, 2H), 1.79 – 1.59 (m, 2H), 0.99 (t, *J* = 8.1 Hz, 9H), 0.97 (s, 9H), 0.68 – 0.61 (t, *J* = 8.1 Hz 6H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 173.2, 154.2, 150.1, 139.5, 132.1, 106.6, 105.5, 73.3, 71.1, 66.6, 60.5, 59.5, 55.8, 39.4, 36.9, 32.1, 30.3, 26.2, 18.5, 7.0, 5.5, −5.17, −5.23. IR (neat): 2954, 2934, 2878, 2856, 1736, 1668, 1592, 1508, 1461, 1421, 1382, 1360, 1332, 1238, 1198, 1156, 1127, 1094, 1006, 960, 903, 834, 775, 744, 729, 665, 581, 527 cm^{-1}. HRMS (ESI): m/z calculated for $C_{32}H_{56}O_8Si_2Na$ [M+Na^+]: 647.34060, found 647.34120.

The enantiomeric excess of the product was determined by chiral HPLC to be 96%. Conditions: 250 mm Chiralpak IA, 4.6 mm i. d., *n*-heptane/2-propanol= 99 : 1 (v/v),1.0 ml/min, 298 K, 46 bar, 96% ee, (t_R(major) = 8.5 min, t_R(minor) = 13.9 min)]



PDA Ch1 220nm

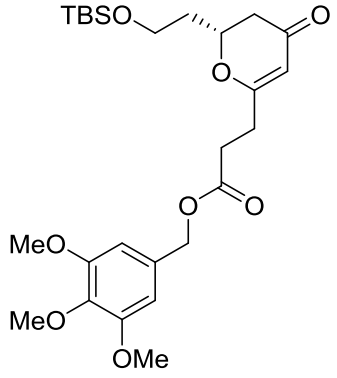
Peak #	Ret. Time	Area %	Name
1	7,18	0,20	
2	7,59	0,44	
3	8,53	96,31	1. Enantiomer 96.3 % ee
4	9,16	0,33	
5	10,82	0,31	
6	12,76	0,38	
7	13,53	0,20	
8	13,92	1,82	2. Enantiomer
Total		100,00	



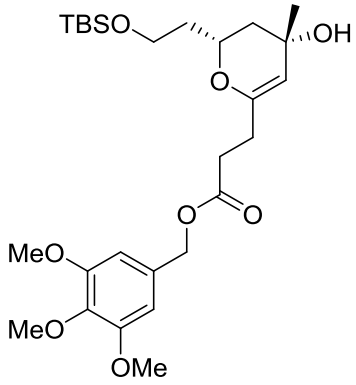
PDA Ch1 220nm

Peak #	Ret. Time	Area %	Name
1	5,53	0,15	
2	7,18	0,42	
3	7,56	0,55	
4	8,05	0,58	
5	8,55	48,61	1. Enantiomer
6	8,96	0,63	
7	10,19	0,52	
8	10,99	0,66	
9	11,81	0,08	
10	12,67	0,15	
11	13,77	47,66	2. Enantiomer
Total		100,00	

3,4,5-Trimethoxybenzyl (*R*)-3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-oxo-3,4-dihydro-2*H*-pyran-6-yl)propanoate (20): Palladium(II) acetate (174 mg, 0.775 mmol, 10 mol%) was added to a stirred solution of compound **19** (4.75 g, 7.6 mmol) in DMSO (8 mL) and the resulting orange mixture was stirred vigorously under O_2 atmosphere for 48 h. Then the mixture was diluted with Et_2O (50 mL) and poured onto water (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (7 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 3:1 → 1:1 + 1% triethylamine) yielded the product as a pale yellow oil (3.02 g, 78%). $[\alpha]_D^{20}$ = +58.1 (c = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 6.51 (s, 2H), 5.32 (d, *J* = 0.8 Hz, 1H), 4.98 (s, 2H), 4.29 – 4.20 (m, 1H), 3.82 (s, 3H), 3.55 – 3.40 (m, 2H), 3.43 (s, 6H), 2.25 (s, 4H), 2.21 – 2.03 (m, 2H), 1.63 (ddt, *J* = 14.1, 8.0, 5.2 Hz, 1H), 1.43 (dddd, *J* = 14.0, 8.0, 5.9, 4.8 Hz, 1H), 0.92 (s, 9H), 0.004 (s, 3H), −0.002 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 190.7, 173.4, 171.4, 154.3, 139.8, 131.5, 106.9, 104.8, 76.6, 67.1, 60.5, 58.8, 56.0, 41.5, 37.5, 30.9, 29.8, 26.1, 18.4, −5.29, −5.34. IR (neat): 2953, 2930, 2886, 2856, 1735, 1666, 1607, 1593, 1508, 1462, 1422, 1398, 1386, 1332, 1292, 1237, 1154, 1126, 1089, 1045, 1005, 963, 887, 864, 834, 809, 776, 733, 693, 684, 665, 606, 583, 548, 527, 504, 470, 455, 439, 432 527 cm^{-1}. HRMS (ESI): m/z calculated for $C_{26}H_{40}O_8SiNa$ $[M+Na^+]$: 531.23847, found: 531.23863.

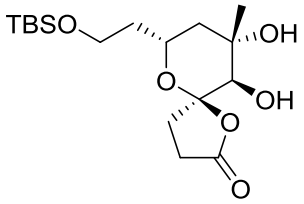


3,4,5-Trimethoxybenzyl 3-((2*R*,4*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-4-methyl-3,4-dihydro-2*H*-pyran-6-yl)propanoate (21): Methylmagnesium chloride (6.4 mL, 3 M in THF, 19.2 mmol) was added to a solution of compound **20** (1.64 g, 3.22 mmol) in THF (32 mL) at – 65 °C. After being stirred at this temperature for 6 h, the reaction was quenched carefully with aqueous phosphate buffer (10 mL, pH 7, 0.1 M) and the resulting mixture was diluted with *tert*-butyl methyl ether (50 mL). The resulting slurry was allowed to reach room temperature, and the supernatant solution was decanted from a precipitate. The grey residue was extracted with *tert*-butyl methyl ether (3 x 50 mL), and the combined organic layers were washed with brine (50 mL). The brine layer was back extracted with *tert*-butyl methyl ether



(50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 3:2 + 1% triethylamine) yielded the product as a colorless oil (1.30 g, 77%). $[\alpha]_D^{20}$ = +3.5 (c = 1.07, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6) δ 6.53 (s, 2H), 5.04 (d, *J* = 0.7 Hz, 2H), 4.49 – 4.47 (m, 1H), 4.03 (dddd, *J* = 11.2, 8.0, 4.7, 2.3 Hz, 1H), 3.82 (s, 3H), 3.70 (ddd, *J* = 10.1, 8.0, 5.2 Hz, 1H), 3.63 (dt, *J* = 10.1, 5.7 Hz, 1H), 3.41 (s, 6H), 2.53 – 2.43 (m, 2H), 2.40 (ddt, *J* = 7.4, 6.7, 0.7 Hz, 2H), 1.82 (ddt, *J* = 13.5, 8.1, 5.3 Hz, 1H), 1.70 (ddd, *J* = 13.2, 2.3, 1.7 Hz, 1H), 1.65 (dddd, *J* = 12.6, 8.0, 5.9, 4.7 Hz, 1H), 1.59 – 1.54 (m, 1H), 1.25 (s, Hz, 3H), 0.96 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (151 MHz, C_6D_6) δ 172.3, 154.3, 152.8, 139.6, 131.9, 106.8, 105.8, 72.4, 66.8, 66.7, 60.5, 59.5, 55.9, 44.1, 38.5, 32.2, 30.7, 29.7, 26.1, 18.5, −5.2, −5.3. IR (neat): 3501, 3478, 3444, 2953, 2929, 2884, 2856, 1735, 1671, 1592, 1508, 1461, 1422, 1379, 1360, 1332, 1289, 1237, 1152, 1126, 1098, 1005, 947, 891, 834, 775, 734, 664, 581, 527, 432 cm^{-1}. HRMS (ESI): m/z calculated for $C_{27}H_{44}O_8SiNa$ $[M+Na^+]$: 547.26977, found: 547.27013.

(5*R*,7*R*,9*S*,10*R*)-7-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-9,10-dihydroxy-9-methyl-1,6-dioxaspiro[4.5]decan-2-one (22a): A solution of potassium hexacyanoferrate(III) (2.9 g, 8.8 mmol), potassium carbonate (1.22 g, 8.83 mmol), methanesulfonamide (0.56 g, 5.9 mmol), potassium osmate (VI) dihydrate (33 mg, 0.088 mmol, 3mol%) and $(DHQD)_2PHAL$ (172 mg, 0.221 mmol, 7.5mol%) in water (15 mL) and *tert*-butanol (2 mL) was added to a solution of compound **21** (1.75 g, 2.93 mmol) in *tert*-butanol (15 mL) at room temperature. After being stirred for 3 h, the mixture was diluted with EtOAc (10 mL) and the reaction was quenched carefully with $NaHSO_3$ (3.7 g, 36 mmol) in small portions. When the frothing had subsided, the layers were separated and the deep blue aqueous layer was extracted with EtOAc (10x20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/*tert*-butyl methyl ether = 1:9 → pure *tert*-butyl methyl ether) yielded the product as a colorless oil (0.86 g, 81%). $[\alpha]_D^{20}$ = +50.5 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 4.06 (dddd, *J* = 12.1, 7.9, 4.6, 2.2 Hz, 1H), 3.64 – 3.52 (m, 2H), 3.32 (s, 1H), 2.26 – 2.01 (m, 4H), 1.80 (brs, 1H), 1.70 – 1.47 (m, 5H), 1.28 (d, *J* = 0.8 Hz, 3H), 0.99 (s, 9H), 0.66 (brs, 1H) (this signal corresponds to ½ eq. water), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 175.7, 108.2, 78.4, 71.4, 68.1, 59.2, 45.2, 38.8, 31.7, 27.9, 26.1, 21.6, 18.5, −5.2, −5.3. IR (neat): 3428, 2952, 2929, 2857, 1765,



1472, 1388, 1360, 1335, 1252, 1204, 1126, 1088, 1021, 994, 964, 906, 874, 834, 809, 774, 733, 649, 604, 563, 526,497, 439 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{32}O_6SiNa$ $[M+Na^+]$: 383.18604, found: 383.18573.

(5*R*,7*R*,9*S*,10*R*)-9,10-Dihydroxy-7-(2-hydroxyethyl)-9-methyl-1,6-dioxaspiro[4.5]decan-2-one (24): Tetrabutylammonium fluoride solution (1 M in THF, 3.0 mL, 3.0 mmol) was added to a stirred solution of **22a** (470 mg, 1.2 mmol) in THF (16 mL) at ambient temperature. After 18 h, flash (2 g) was added to the reaction mixture and the resulting suspension was evaporated to dryness. Purification of the residue by flash chromatography (EtOAc:EtOH = 93:7 → 90:10) yielded the product as colorless oil (278 mg, 94%). $[\alpha]_D^{20}$ = +85.5 (c = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3CN) δ 3.94 (dddd, J = 12.3, 7.4, 5.3, 2.1 Hz, 1H), 3.56 (t, J = 6.3 Hz, 2H), 3.46 (s, 1H), 2.67 (bs, 1H), 2.62 – 2.43 (m, 3H), 2.06 – 1.98 (m, 1H), 1.78 (dd, J = 13.2, 2.0 Hz, 1H), 1.69 – 1.50 (m, 3H), 1.28 (d, J = 0.8 Hz, 3H). ^{13}C NMR (75 MHz, CD_3CN) δ 177.4, 109.7, 78.5, 71.6, 69.5, 59.0, 45.8, 39.1, 32.5, 28.6, 21.7. IR (neat): 3389, 2945, 1763, 1666, 1449, 1387, 1340, 1280, 1211, 1096, 1071, 1055, 1024, 954, 911, 864, 804, 726, 649, 568, 527 cm^{-1}. HRMS (ESI): m/z calculated for $C_{11}H_{17}O_6$ $[M-H^+]$: 245.10307, found 245.10320.

(5*R*,7*S*,9*S*,10*R*)-9,10-Dihydroxy-9-methyl-7-alkenyl-1,6-dioxaspiro[4.5]decan-2-one (25): Tributylphosphine (0.26 mL, 1.04 mmol) was added to a stirred solution of **24** (125 mg, 0.508 mmol) and 2-nitrophenyl selenocyanate (208 mg, 0.916 mmol) in THF (12 mL) at 0 °C. After being stirred for 1h, the reaction mixture was cooled to – 78 °C. A solution of 3-chloroperbenzoic acid (520 mg, 2.11 mmol) in CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred further at – 78 °C. After 45 min 2-methyl-2-butene (1.1 mL, 10 mmol) and Et_3N (0.75 mL, 5.4 mmol) were added. After being stirred for 1.5 h at – 78 °C, the reaction mixture was warmed to ambient temperature. Flash (5 g) was added and the resulting suspension was evaporated to dryness. Purification of the residue by flash chromatography (EtOAc:toluene = 2:1 → 3:1) yielded the product as a pale brown solid. This material was triturated with toluene (3x2 mL) to yield the product as off white solid (95 mg, 82%). Crystals suitable for X-ray diffraction were grown from the product by vapor diffusion of pentane into a CH_2Cl_2 solution of **25**. Melting range: 135 – 136 °C. $[\alpha]_D^{20}$ = +64.0 (c = 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 5.60 (ddd, J = 17.4, 10.6, 5.6

Hz, 1H), 5.06 (dt, J = 17.3, 1.5 Hz, 1H), 4.92 (dt, J = 10.6, 1.4 Hz, 1H), 4.20 (dddt, J = 10.3, 5.9, 4.7, 1.4 Hz, 1H), 3.20 (d, J = 5.9 Hz, 1H), 2.22 – 1.88 (m, 3H), 1.65 – 1.49 (m, 3H), 1.16 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 176.2, 137.4, 115.7, 108.5, 78.0, 71.9, 71.4, 45.0, 31.6, 27.8, 21.5. IR (neat): 3469, 3451, 3429, 3416, 3397, 3358, 3304, 3235, 2978, 2924, 2854, 1764, 1648, 1449, 1416, 1383, 1359, 1275, 1209, 1084, 1024, 998, 978, 956, 909, 862, 824, 805, 787, 751, 736, 682, 648, 617, 593, 573, 553, 534, 518, 507, 488, 480, 466, 453, 441, 425, 416 cm^{-1}. HRMS (ESI): m/z calculated for $C_{11}H_{16}O_5Na$ [M+Na$^+$]: 251.08899, found 251.08903.

(5*R*,7*S*,9*S*,10*R*)-9-Methyl-9,10-bis((triethylsilyl)oxy)-7-alkenyl-1,6-dioxaspiro[4.5]decan-2-one (27): Chlorotriethylsilane (1.1 mL, 6.6 mmol) was added to a stirred solution of **25** (150 mg, 0.657 mmol), 4-(dimethylamino)pyridine (162 mg, 1.32 mmol) and silver nitrate (560 mg, 3.3 mmol) in DMF (2.5 mL) and pyridine (2.5 mL). The reaction mixture became turbid immediately due to precipitated silver chloride. After 4 h the reaction mixture was diluted with *tert*-butyl methyl ether (50 mL) and was filtered through a pad of flash (3x3 cm). The flash was rinsed with *tert*-butyl methyl ether (5x10 mL). The filtrate was washed with saturated aqueous sodium chloride solution (25 mL) and the aqueous layer was extracted with *tert*-butyl methyl ether (2x25 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 19:1) yielded the product as a colorless oil (258 mg, 86%). $[\alpha]_D^{20}$ = +42.7 (c = 0.65, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 5.72 (ddd, J = 17.3, 10.6, 5.6 Hz, 1H), 5.19 (dt, J = 17.3, 1.5 Hz, 1H), 4.99 (dt, J = 10.5, 1.4 Hz, 1H), 4.45 – 4.29 (m, 1H), 3.62 (s, 1H), 2.29 – 2.07 (m, 3H), 1.88 – 1.71 (m, 3H), 1.51 (d, J = 0.7 Hz, 3H), 0.97 (ap. dt, J = 15.6, 7.9 Hz, 18H), 0.67 (ap. qd, J = 8.3, 7.9, 3.8 Hz, 6H), 0.57 (q, J = 8.1 Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 174.8, 137.6, 115.7, 108.3, 80.3, 75.7, 71.4, 46.5, 3.18, 27.7, 22.6, 7.4, 7.3, 7.2, 5.5. IR (neat): 2955, 2912, 2877, 1790, 1459, 1417, 1384, 1359, 1265, 1237, 1206, 1175, 1146, 1117, 1098, 1043, 1004, 944, 916, 882, 843, 800, 741, 726, 675 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{44}O_5Si_2Na$ [M+Na$^+$]: 479.26195, found 479.26275.

(5*R*,7*R*,9*S*,10*R*)-7-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-9-methyl-9,10-bis((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-2-one (100): Chlorotriethylsilane (0.8 mL, 4.8 mmol) was added to a solution of compound **22a** (362 mg, 1.0 mmol), 4-(dimethylamino)pyridine (248 mg, 2.0 mmol) and silver nitrate (692 mg, 4.1 mmol) in DMF (5 mL) and pyridine (5 mL) at room temperature. Immediately after the addition a colorless solid precipitated. After being stirred for 3.5 h the mixture was diluted with *tert*-butyl methyl ether (10 mL), filtered through a pad of silica and the silica was rinsed with further *tert*-butyl methyl ether (5x10 mL). The slightly turbid filtrate was washed with brine (60 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (3x40 mL) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 25:1) yielded the product as a colorless solid (450 mg, 76%). Melting range: 50 – 52 °C. $[\alpha]_D^{20}$ = +50.3 (c = 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 4.17 (dddd, *J* = 12.0, 7.7, 4.5, 1.9 Hz, 1H), 3.73 – 3.64 (m, 2H), 3.63 (s, 1H), 2.35 – 2.10 (m, 3H), 1.90 – 1.64 (m, 5H), 1.53 (s, Hz, 3H), 1.01 (s, 9H), 1.01 – 0.96 (m, 18H), 0.73 – 0.65 (m, 6H), 0.61 (q, *J* = 7.7 Hz, 6H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 174.5, 108.3, 80.7, 75.9, 67.7, 59.5, 46.9, 39.0, 32.4, 27.9, 26.1, 22.7, 18.6, 7.4, 7.3, 7.2, 5.6, −5.2, −5.3. IR (neat): 2954, 2936, 2877, 1791, 1461, 1417, 1384, 1361, 1337, 1240, 1203, 1142, 1127, 1099, 1005, 970, 915, 884, 839, 777, 741, 672 cm^{-1}. HRMS (ESI): m/z calculated for $C_{29}H_{60}O_6Si_3Na$ [M+Na$^+$]: 611.35810, found: 611.35935.

(5R,7S,9S,10R)-7-(2-Bromoethyl)-9-methyl-9,10-bis((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-2-one (98a): Bromine (100 µl, 1.95 mmol) was added to a solution of triphenylphosphine (568 mg, 2.16 mmol) in CH_2Cl_2 (22 mL) at 0 °C. After being stirred for 10 min at 0 °C, the mixture was warmed to room temperature. After being stirred for a further 15 min, the resulting solution was added to a solution of compound **100** (1.02 g, 1.73 mmol) in CH_2Cl_2 (11 mL) at 0 °C over the course of 5 min. After being stirred at 0 °C for 6 h, the resulting mixture was added slowly to a well stirred mixture of CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) at 0 °C. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (4x20 mL) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash

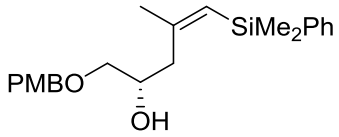
chromatography (hexane/EtOAc = 100:5 → 100:6) yielded the product as a colorless oil (828 mg, 89%). $[\alpha]_D^{20}$ = + 54.0 (c = 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 3.76 (dddd, *J* = 11.0, 8.9, 3.6, 2.1 Hz, 1H), 3.53 (s, 1H), 3.12 (ddd, *J* = 9.9, 8.7, 5.1 Hz, 1H), 3.00 (ddd, *J* = 9.9, 8.2, 7.4 Hz, 1H), 2.26 – 2.04 (m, 3H), 1.77 – 1.49 (m, 5H), 1.46 (s, 3H), 0.98 (m, Hz, 18H), 0.67 (qd, *J* = 7.9, 3.8 Hz, 6H), 0.62 – 0.55 (m, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 174.0, 107.5, 79.9, 75.3, 68.6, 45.8, 38.4, 31.7, 28.2, 27.3, 22.3, 7.0, 6.9, 6.8, 5.2. IR (neat): 2954, 2912, 2877, 1789, 1459, 1417, 1384, 1340, 1266, 1236, 1203, 1139, 1114, 1019, 1005, 977, 918, 880, 841, 741, 727, 674 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{45}O_5Br_1Si_2Na$ [M+Na^+]: 559.18813, found: 559.18807.

(*S*)-2-(((4-Methoxybenzyl)oxy)methyl)oxirane (68): 4-Methoxybenzyl chloride (5.0 mL, 37 mmol) was added slowly to a suspension of sodium hydride (1.15 g, 47.9 mmol) in DMF (60 mL) at 0 °C. After 10 min (*R*)-glycidol (2.3 mL, 35 mmol) was added dropwise and the mixture was allowed to reach room temperature. After being stirred for 18 h the mixture was poured carefully onto saturated aqueous NH_4Cl solution (60 mL) and the aqueous layer was extracted with *tert*-butyl methyl ether (4x60 mL). The organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/*tert*-butyl methyl ether = 7:3) yielded the product as a colorless oil (5.84 g, 87%). $[\alpha]_D^{20}$ = −5.2 (c = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, CDCl3): δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.42 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.20 – 3.15 (m, 1H), 2.79 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.61 (dd, *J* = 5.0, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 130.1, 129.6, 114.0, 73.1, 70.7, 55.4, 51.0, 44.5. IR (neat): 3051, 2998, 2934, 2912, 2860, 2837, 1613, 1586, 1513, 1464, 1302, 1248, 1175, 1091, 1034, 901, 822, 766, 583, 522 cm^{-1}. HRMS (ESI): m/z calculated for $C_{11}H_{14}O_3Na$ [M+Na^+]: 217.08351, found: 217.08334.

Dimethyl(phenyl)silyllithium: Chloro(dimethyl)phenylsilane (5.1 mL, 30 mmol) was added dropwise to a well stirred suspension of lithium sand (0.47 g, 68 mmol, containing 2% sodium) in THF (30 mL) at 0 °C. The mixture slowly turned red and finally brown. After being stirred at 0 °C for 14 h, the brown mixture was filtered into a flame dried Schlenk flask and the filtrate was used directly in the next step.

Propyne Stock Solution: Propyne (1.0 mL, 0.66 g, 17 mmol) was condensed into a graduated Schlenk flask at −78 °C from a cylinder (ABCR, Karlsruhe) and pre-cooled THF was added to give a total volume of 17 mL. The resulting 1 M stock solution was thoroughly mixed by moving a stir bar up and down with a magnet, taking care to keep it cold. Afterwards the solution was stored at dry ice temperature.

(*S*,*Z*)-5-(Dimethyl(phenyl)silyl)-1-((4-methoxybenzyl)oxy)-4-methylpent-4-en-2-ol (103):

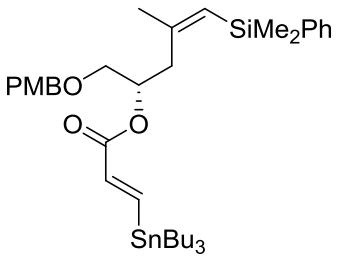


Dimethyl(phenyl)silyllithium (28 mL, 1 M in THF, 28 mmol) was added to a well stirred suspension of copper(I) cyanide (1.25 g, 14 mmol) in THF (15 mL) at 0 °C. The intense reddish-brown mixture was stirred at 0 °C for 30 min before being cooled to −78 °C. A cold (−78 °C) solution of propyne (14 mL, 1 M in THF, 14 mmol) was added quickly via cannula to the above mixture, and the resulting mixture was stirred at −78 °C for 4 h. Epoxide **68** (1.75 g, 9.0 mmol) dissolved in THF (10 mL + 2x10 mL to rinse) and immediately afterwards boron trifluoride diehtyl etherate (2.2 mL, 18 mmol) were added to the reaction mixture. After 1 h triethylamine (4.0 mL, 30 mmol) and EtOH (5 ml) were added and the resulting dark mixture was allowed to reach room temperature. The mixture was concentrated under reduced pressure to a tar-like consistency, re-dissolved in *tert*-butyl methyl ether (50 mL) and adsorbed on silica (10 g). After evaporation of the solvent under reduced pressure the crude material was purified by flash chromatography (CH_2Cl_2:*tert*-butyl methyl ether = 99:1 → 98.5:1.5) to yield the product a pale yellow oil (1.76 g, 51%). $[\alpha]_D^{20}$ = −3.9 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, CDCl3): δ 7.58 – 7.50 (m, 2H), 7.34 – 7.31 (m, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.52 (t, *J* = 1.4 Hz, 1H), 4.39 (s, 2H), 3.89 (dddt, *J* = 8.6, 7.2, 4.9, 3.5 Hz, 1H), 3.81 (s, 3H), 3.25 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.09 (dd, *J* = 9.6, 7.3 Hz, 1H), 2.28 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.13 (dd, *J* = 13.6, 4.9 Hz, 1H), 1.98 (d, *J* = 3.7 Hz, 1H), 1.92 (d, *J* = 1.4 Hz, 3H), 0.38 (s, 3H), 0.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 153.5, 140.2, 134.0, 130.2, 129.5, 129.0, 128.0, 126.3, 114.0, 74.2, 73.1, 69.0, 55.4, 41.1, 27.1, −0.5, −0.7. IR (neat): 3568, 3453, 3067, 3046, 2998, 2952, 2907, 2860, 1613, 1513, 1427, 1370, 1302, 1247, 1174, 1110, 1036, 828, 731, 701, 646, 571, 474 cm^{-1}. HRMS (ESI): m/z calculated for $C_{22}H_{30}O_3SiNa$ [M+Na$^+$]: 393.18564, found: 393.18585.

Ethyl (*E*)-3-(tributylstannyl)acrylate (*E*-44): Tributyltin hydride (7.3 mL, 27 mmol) was added to a stirred solution of ethyl propiolate (2.6 mL, 26 mmol) and 2,2′-azobis(2-methylpropionitrile) (255 mg, 1.55 mmol) in toluene (100 mL). After being stirred at 70 °C for 16 h, the mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 99:1 → 96:4) yielded the product as a colorless oil (4.4 g, 44%).). ^{1}H NMR (400 MHz, CDCl3): δ 7.74 (d, *J* = 19.4 Hz, 1H), 6.30 (d, *J* = 19.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.59 – 1.39 (m, 6H), 1.36 – 1.24 (m, 9H), 1.06 – 0.93 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 152.6, 136.5, 60.5, 29.1, 27.4, 14.4, 13.8, 9.8. IR (neat): 2956, 2922, 2872, 2853, 1724, 1590, 1464, 1366, 1307, 1261, 1204, 1152, 1073, 1035, 997, 961, 865, 841, 825, 747, 691, 666, 600, 507, 461 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{34}O_2SnNa$ [M+Na^+]: 413.14723, found: 413.14686.

(*E*)-3-(Tributylstannyl)acrylic acid (64): Ester ***E*-44** (4.4 g, 11 mmol) dissolved in THF (40 mL) was added to a stirred solution of lithium hydroxide (1.35 g, 56.5 mmol) in water (50 mL) and methanol (40 mL) at room temperature. After being stirred for 48 h the mixture was transferred to a separatory funnel and was washed with hexane (2x100 mL). The aqueous layer was adjusted to pH 1 with aqueous HCl (2 M, 40 mL) and extracted with EtOAc (4x100 mL). The organic layers were dried over sodium sulfate and concentrated under reduced pressure. The product was obtained as colorless oil (3.2 g, 78%) and was used in the next step without further purification. ^{1}H NMR (400 MHz, CDCl3): δ 7.91 (dd, *J* = 19.4, 0.7 Hz, 1H), 6.32 (d, *J* = 19.4 Hz, 1H), 1.61 – 1.39 (m, 6H), 1.36 – 1.26 (m, 6H), 1.07 – 0.93 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 156.7, 135.6, 29.1, 27.4, 13.8, 9.9. IR (neat): 2955, 2922, 2871, 2854, 1702, 1638, 1592, 1530, 1463, 1405, 1377, 1359, 1293, 1246, 1181, 1076, 1044, 996, 961, 866, 842, 827, 754, 670, 601, 553, 512, 457 cm^{-1}. HRMS (ESI): m/z calculated for $C_{15}H_{31}O_2Sn$ [M+H^+]: 363.13399, found: 363.13363.

(*S,Z*)-5-(Dimethyl(phenyl)silyl)-1-((4-methoxybenzyl)oxy)-4-methylpent-4-en-2-yl (*E*)-3-(tributylstannyl)acrylate (105): 2,4,6-Trichlorobenzoyl chloride (1.35 mL, 8.6 mmol) was added to a solution of compound **64** (3.23 g, 8.9 mmol) and triethylamine (4.9 mL, 35 mmol) in toluene (23 mL) at 0 °C. After being stirred for 5 min the mixture was allowed to reach room temperature and stirred for further 2 h before it was cooled again to 0 °C. Compound **103** (2.6 g, 7.0 mmol) dissolved in toluene (5 mL + 2x5 mL to rinse) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) were added, the resulting mixture was allowed to reach room temperature and was stirred for 2 h. The mixture was diluted with *tert*-butyl methyl ether (200 mL) and was washed with aqueous HCl (100 mL, 1 M), water (100 mL) and aqueous saturated $NaHCO_3$ solution (100 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 19:1 → 14:1) yielded the product as a colorless oil (3.24 g, 63%).). $[\alpha]_D^{20}$ = +23.8 (c = 1.28, $CHCl_3$) ^{1}H NMR (400 MHz, CDCl3): δ7.75 (d, *J* = 19.4 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.32 (dd, *J* = 4.4, 2.0 Hz, 3H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 19.4 Hz, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 5.31 – 5.24 (m, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.35 (dd, *J* = 5.0, 1.4 Hz, 2H), 2.50 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.29 (dd, *J* = 14.0, 4.6 Hz, 1H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.56 – 1.42 (m, 6H), 1.31 (h, *J* = 7.3 Hz, 6H), 1.06 – 0.92 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 9H), 0.39 (s, 3H), 0.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 159.3, 153.0, 152.6, 140.1, 136.5, 134.0, 130.3, 129.3, 128.9, 127.9, 126.3, 113.9, 72.8, 71.2 (two signals overlap), 55.4, 39.1, 29.1, 27.4, 27.0, 13.8, 9.8, −0.3, −0.6. IR (neat): 3068, 2955, 2926, 2852, 1718, 1614, 1587, 1513, 1463, 1442, 1427, 1375, 1302, 1246, 1153, 1111, 1038, 996, 961, 821, 729, 699, 647, 598, 512, 473 cm^{-1}. HRMS (ESI): m/z calculated for $C_{37}H_{58}O_4SnNa$ $[M+Na^+]$: 737.30179, found: 737.30241.

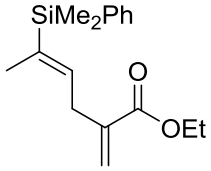


Dimethyl(phenyl)silyllithium: Chloro(dimethyl)phenylsilane (11 mL, 64 mmol) was added dropwise to a well stirred suspension of lithium sand (0.99 g, 143 mmol, contains 2% sodium) in THF (65 mL) at 0 °C. The mixture slowly turned red and finally brown. After being stirred at 0 °C for 14 h, the brown mixture was filtered into a flame dried Schlenk flask and the filtrate was stored ≤ 0 °C and was used directly in the next step.

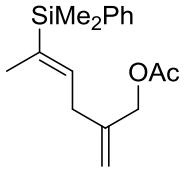
(*E*)-3-(Dimethyl(phenyl)silyl)but-2-en-1-ol (29): Dimethyl(phenyl)silyllithium (60 mL, 1 M in THF, 60 mmol) was added slowly via cannula to a well stirred solution of triethylaluminum (35 mL, 25% in toluene, 64 mmol) at 0 °C. The resulting brown mixture was stirred at 0 °C for 30 min. Copper(I) cyanide (107 mg, 1.2 mmol, 4mol%) and but-2-yn-1-ol (2.2 mL, 30 mmol) dissolved in THF (20 mL + 2x5 mL to rinse) were added sequentially and the mixture was stirred at 0 °C for 1 h. The mixture was carefully poured onto aqueous saturated NH_4Cl solution (150 mL) at 0 °C. The thick reddish-brown suspension was filtered through a pad of silica and the residue and silica were further extracted with *tert*-butyl methyl ether (4x100 mL). The layers of the biphasic filtrate were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2x50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/ *tert*-butyl methyl ether = 8:2 → 7:3) yielded the product as pale yellow oil (5.42 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.38 – 7.32 (m, 3H), 5.96 (tq, *J* = 5.9, 1.7 Hz, 1H), 4.29 (t, *J* = 4.9 Hz, 2H), 1.70 (dt, *J* = 1.8, 0.9 Hz, 3H), 0.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.0, 137.6, 134.1, 129.2, 127,9, 59.9, 15.2, −3.5. IR (neat): 3321, 3068, 3009, 2956, 2905, 1427, 1360, 1247, 1109, 1065, 1008, 944, 815, 773, 730, 699, 641, 473, 425 cm^{-1}. HRMS (ESI): m/z calculated for $C_{12}H_{18}OSiNa$ [M+Na$^+$]: 229.10191, found: 229.10195.

(*E*)-(4-Bromobut-2-en-2-yl)dimethyl(phenyl)silane (30): A solution of triphenylphosphine (6.0 g, 23 mmol) in CH_2Cl_2 (40 mL) was added over the course of 1 h to a well stirred solution of compound **29** (4.3 g, 21 mmol) and carbon tetrabromide (7.3 g, 22 mmol) in CH_2Cl_2 (40 mL) at room temperature. After the addition, the mixture was stirred for another 30 min. Silica (35 g) was added and the solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography (hexane/ *tert*-butyl methyl ether = 199:1) yielded the product as colorless oil (5.63 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.39 – 7.34 (m, 3H), 6.09 (tq, *J* = 7.9, 1.8 Hz, 1H), 4.03 (d, *J* = 7.6 Hz, 2H), 1.77 (d, *J* = 1.8 Hz, 3H), 0.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 137.5, 135.1, 134.1, 129.3, 128.0, 27.4, 14.6, −3.6. IR (neat): 3068, 3049, 3020, 2957, 1427, 1248, 1202, 1110, 1058, 941, 830, 809, 773, 729, 698, 579, 481, 466 cm^{-1}. HRMS (EI): m/z calculated for $C_{12}H_{17}SiBr$ [M$^+$]: 268.02830, found: 268.02838.

Ethyl (*E*)-5-(dimethyl(phenyl)silyl)-2-methylenehex-4-enoate (31): Ethyl benzoylacetate (4.1 mL, 22 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.5 mL, 23 mmol) were added sequentially to a stirred solution of compound **30** (5.6 g, 21 mmol) in toluene (40 mL) at room temperature. A colorless precipitate formed and the orange mixture warmed up slightly. After being stirred for 1 h the mixture was diluted with *tert*-butyl methyl ether (100 mL) and was washed with water (2x50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The remaining orange oil was dissolved in THF (40 mL). Paraformaldehyde (1.26 g, 42 mmol) and potassium carbonate (5.77 g, 42 mmol) were added and the orange mixture was heated under reflux for 19 h. The mixture was cooled to room temperature, filtered through a pad of Celite and the Celite was further rinsed with *tert*-butyl methyl ether (2x50 mL). The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/ *tert*-butyl methyl ether = 29:1 → 24:1) yielded the product as pale colorless oil (4.62 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.37 – 7.31 (m, 3H), 6.17 (d, *J* = 1.3 Hz, 1H), 5.83 (tq, *J* = 6.9, 1.8 Hz, 1H), 5.51 (q, *J* = 1.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.14 (dt, *J* = 6.9, 0.9 Hz, 2H), 1.69 (dt, *J* = 1.7, 0.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 139.4, 138.6, 137.2, 137.1, 134.1, 129.1, 127.8, 124.8, 60.8, 30.9, 14.9, 14.4, −3.3. IR (neat): 3069, 3050, 2957, 2907, 1717, 1632, 1616, 1427, 1368, 1323, 1301, 1247, 1206, 1135, 1111, 1027, 943, 831, 812, 773, 731, 700, 644, 473, 455 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{24}O_2SiNa$ [M+Na$^+$]: 311.14378, found: 311.14350.

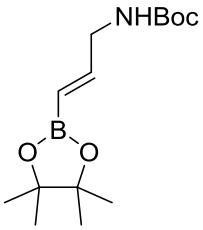


(*E*)-5-(Dimethyl(phenyl)silyl)-2-methylenehex-4-en-1-yl acetate (33): A solution of compound **31** (4.6 g, 16 mmol) in Et_2O (40 mL) was slowly added to a solution of diisobytylaluminum hydride (35 mL, 1 M in CH_2Cl_2, 35 mmol) at 0 °C. The mixture was allowed to reach room temperature over the course of 4 h. After being stirred for another 10 h, aqueous HCl (65 mL, 2 M) was added carefully. When the frothing had subsided, the layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over potassium carbonate and sodium sulfate and were concentrated under reduced pressure to a volume of ~ 50 mL. Triethylamine (4.5 mL, 32 mmol), acetic anhydride (1.8 mL, 19 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) were added to the solution of the intermediate alcohol at 0 °C. The mixture was allowed to reach room temperature and was stirred for 4 h. The



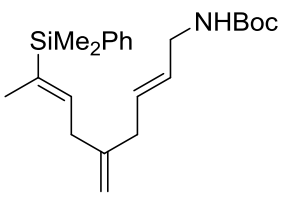
mixture was poured onto water (50 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/*tert*-butyl methyl ether = 24:1 → 19:1) yielded the product as colorless oil (4.31 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H), 7.39 – 7.31 (m, 3H), 5.83 (tq, *J* = 7.1, 1.8 Hz, 1H), 5.05 (d, *J* = 1.3 Hz, 1H), 4.96 (dt, *J* = 1.5, 0.8 Hz, 1H), 4.52 (dd, *J* = 1.4, 0.8 Hz, 2H), 2.91 (d, *J* = 7.0 Hz, 2H), 2.08 (s, 3H), 1.68 (d, *J* = 1.7 Hz, 3H), 0.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 142.6, 138.5, 137.2, 137.1, 134.1, 129.0, 127.9, 113.1, 67.1, 32.6, 21.1, 14.9, −3.3. IR (neat) 3086, 3008, 2956, 1741, 1655, 1615, 1428, 1372, 1224, 1110, 1027, 957, 907, 813, 772, 730, 696, 635, 605, 475, 459 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{24}O_2SiNa$ [M+Na$^+$]: 311.14378, found: 311.14365.

***tert*-Butyl (*E*)-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)carbamate (36):** Pinacol



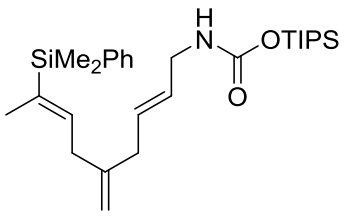
borane (4.5 mL, 31 mmol) and a suspension of dicyclohexylborane (0.36 g, 2 mmol) in THF (2 mL) were added to a solution *N*-Boc-propargylamine (3.53 g, 20.7 mmol) in THF (20 mL) and the resulting mixture was stirred at 40 – 50 °C for 3 h. The mixture was cooled to room temperature and air was bubbled through the mixture for 2 h. The solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 85:15 → 80:20) yielded the product as colorless solid (5.82 g, 99%). Melting range: 69 – 70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (dt, *J* = 18.1, 4.7 Hz, 1H), 5.58 (dt, *J* = 18.0, 1.9 Hz, 1H), 4.62 (s, 1H), 3.90 – 3.76 (m, 2H), 1.44 (s, 9H), 1.26 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 149.5, 119.3 (barely detectable [151]), 83.5, 79.6, 44.1, 28.6, 24.9. IR (neat): 3361, 2977, 2930, 1698, 1643, 1520, 1455, 1365, 1322, 1271, 1248, 1167, 1144, 1051, 996, 971, 890, 850, 780, 623, 579 cm^{-1}. HRMS (ESI): m/z calculated for $C_{14}H_{26}NO_4BNa$ [M+Na$^+$]: 306.18471, found: 306.18441.

***tert*-Butyl ((2*E*,7*E*)-8-(dimethyl(phenyl)silyl)-5-methylenenona-2,7-dien-1-yl)carbamate**



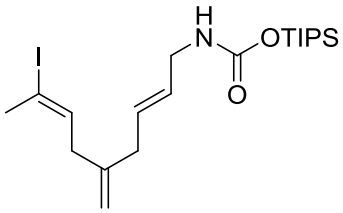
(37): Dichlorobis(tri(2-furyl)phosphine)palladium(II)[152] (255 mg, 0.40 mmol, 2.7mol%) was added to a stirred solution of compound **33** (4.23 g, 14.6 mmol), compound **36** (5.73 g, 20.2 mmol) and potassium fluoride (2.4 g, 41 mmol) in MeOH (75 mL) at room temperature. After being stirred for 4 h the mixture was diluted with brine (150 mL) and extracted with EtOAc (4x150 mL). The combined organic layers were dried over sodium sulfate and concentrated under

reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 11:1 → 10:1) yielded the product as colorless oil (5.1 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.37 – 7.32 (m, 3H), 5.83 (ddt, *J* = 7.0, 5.3, 1.8 Hz, 1H), 5.61 (dtt, *J* = 14.8, 6.6, 1.3 Hz, 1H), 5.52 – 5.43 (m, 1H), 4.76 (dd, *J* = 6.6, 0.9 Hz, 2H), 4.51 (s, 1H), 3.70 (d, *J* = 6.1 Hz, 2H), 2.83 (d, *J* = 6.4 Hz, 2H), 2.73 (d, *J* = 6.4 Hz, 2H), 1.66 (d, *J* = 1.8 Hz, 3H), 1.45 (s, 9H), 0.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 146.8, 138.7, 138.3, 136.3, 134.1, 130.3, 129.0, 128.5, 127.9, 110.8, 79.4, 42.6, 39.4, 35.3, 28.6, 14.9, −3.3. IR (neat): 3350, 3069, 2976, 2928, 1704, 1645, 1614, 1503, 1428, 1391, 1366, 1247, 1170, 1111, 971, 894, 831, 814, 773, 732, 701, 636, 474 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{35}NO_2SiNa$ [M+Na$^+$]: 408.23293, found: 408.23276.

Triisopropylsilyl ((2*E*,7*E*)-8-(dimethyl(phenyl)silyl)-5-methylenenona-2,7-dien-1-yl)carbamate (82): 

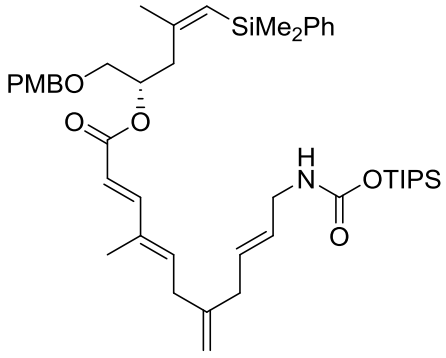
Triisopropylsilyl triflate (2.2 mL, 7.9 mmol) was added dropwise to a stirred solution of compound **37** (2.7 g, 7.0 mmol) and lutidine (2.1 mL, 18 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was allowed to reach room temperature. After being stirred for 6 h, the mixture was poured onto saturated aqueous $NaHCO_3$ solution (50 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3x25 ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 100:0 → 14:1) yielded the product as colorless oil (3.0 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.36 – 7.32 (m, 3H), 5.83 (td, *J* = 7.0, 1.7 Hz, 1H), 5.67 – 5.58 (m, 1H), 5.53 – 5.45 (m, 1H), 4.79 – 4.69 (m, 3H), 3.77 – 3.71 (m, 2H), 2.83 (d, *J* = 7.0 Hz, 2H), 2.73 (d, *J* = 6.8 Hz, 2H), 1.66 (d, *J* = 1.8 Hz, 3H), 1.36 – 1.23 (m, 3H), 1.08 (d, *J* = 7.4 Hz, 18H), 0.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 146.8, 138.7, 138.3, 136.3, 134.1, 130.5, 129.0, 128.3, 127.9, 110.8, 43.1, 39.4, 35.3, 18.0, 14.9, 12.3, −3.3. IR (neat):3462, 3342, 3069, 2945, 2867, 1695, 1614, 1504, 1464, 1428, 1389, 1247, 1139, 1111, 1017, 999, 971, 920, 884, 831, 813, 773, 731, 700, 672, 459 cm^{-1}. HRMS (ESI): m/z calculated for $C_{28}H_{47}NO_2Si_2Na$ [M+Na$^+$]: 508.30376, found: 508.30359.

Triisopropylsilyl ((2E,7E)-8-iodo-5-methylenenona-2,7-dien-1-yl)carbamate (83): N-



Iodosuccinimide (2.6 g, 11 mmol) was added to a stirred solution of compound **82** (3.4 g, 7.0 mmol) and lutidine (1.4 mL, 12 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (22 mL) at 0 °C. After being stirred at 0 °C for 1 h, the dark red mixture was poured onto saturated aqueous $Na_2S_2O_3$ solution (50 mL). The resulting almost colorless mixture was extracted with CH_2Cl_2 (5x50 ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc = 14:1) yielded the product as orange oil (2.1 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (td, J = 7.7, 1.5 Hz, 1H), 5.64 – 5.47 (m, 2H), 4.79 4.82 – 4.68 (m, 3H), 3.75 (dt, J = 6.0, 3.1 Hz, 2H), 2.72 (d, J = 6.3 Hz, 2H), 2.69 (d, J = 8.0 Hz, 2H), 2.36 (d, J = 1.4 Hz, 3H), 1.35 – 1.24 (m, 3H), 1.08 (d, J = 7.4 Hz, 18H). 13C NMR (101 MHz, CDCl3) δ 154.9, 145.1, 138.4, 130.0, 128.6, 111.8, 95.2, 43.1, 39.1, 37.1, 27.6, 18.00, 12.2. IR (neat): 3342, 2944, 2893, 2866, 1690, 1504, 1463, 1428, 1388, 1344, 1256, 1140, 1079, 1050, 1016, 999, 971, 883, 784, 669, 514, 459, 416 cm−1. HRMS (ESI): m/z calculated for C20H36NO2ISiNa [M+Na+]: 500.14522, found: 500.14509.

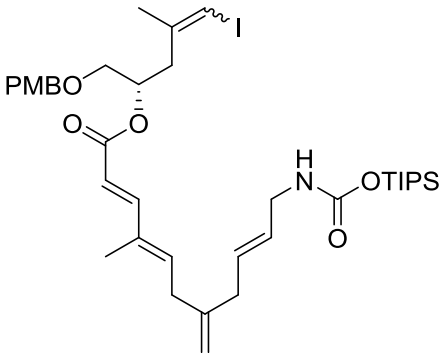
(*S,Z*)-5-(Dimethyl(phenyl)silyl)-1-((4-methoxybenzyl)oxy)-4-methylpent-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (106): Tetrakis(triphenylarsine)palladium(0) [80] (0.36 g, 0.27mmol, 6mol%) was added



to a mixture of compound **105** (3.18 g, 4.45 mmol) and compound **83** (2.15 g, 4.5 mmol), all components were dissolved in DMF (20 mL) and stirred vigorously at room temperature for 16 h. The mixture was diluted with brine (100 mL) and was extracted with *tert*-butyl methyl ether (5x100 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 9:1 → 5:1) yielded the product as pale yellow oil (2.82 g, 82%). $[\alpha]_D^{20}$ = +25.3 (c = 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.35 – 7.30 (m, 4H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.90 (t, *J* = 7.7 Hz, 1H), 5.78 (d, *J* = 15.7 Hz, 1H), 5.66 – 5.58 (m, 1H), 5.56 – 5.48 (m, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 5.30 (ddt, *J* = 9.1, 5.7, 4.5 Hz, 1H), 4.84 – 4.71 (m, 3H), 4.43 (d,

J = 11.7 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.75 (dt, *J* = 5.8, 2.9 Hz, 2H), 3.38 – 3.30 (m, 2H), 2.89 (d, *J* = 7.6 Hz, 2H), 2.74 (d, *J* = 6.5 Hz, 2H), 2.51 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.29 (dd, *J* = 14.0, 4.7 Hz, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.35 – 1.24 (m, 3H), 1.08 (d, *J* = 7.4 Hz, 18H), 0.39 (s, 3H), 0.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 159.3, 154.9, 152.6, 149.6, 145.7, 140.1, 138.7, 134.4, 133.9, 130.3, 129.9, 129.3, 128.9, 128.7, 127.9, 126.2, 116.3, 113.9, 111.7, 72.8, 71.8, 70.9, 55.4, 43.1, 39.5, 39.1, 35.3, 27.0, 18.0, 12.3, 12.2, −0.3, −0.7. IR(neat): 3361, 3067, 2945, 2866, 1701, 1619, 1512, 1464, 1427, 1390, 1365, 1301, 1245, 1167, 1111, 1036, 1018, 981, 883, 856, 821, 805, 782, 729, 699, 670, 647, 573, 513, 474 cm^{-1}. HRMS (ESI): m/z calculated for $C_{45}H_{67}NO_6Si_2Na$ [M+Na$^+$]: 796.43992, found 796.44058.

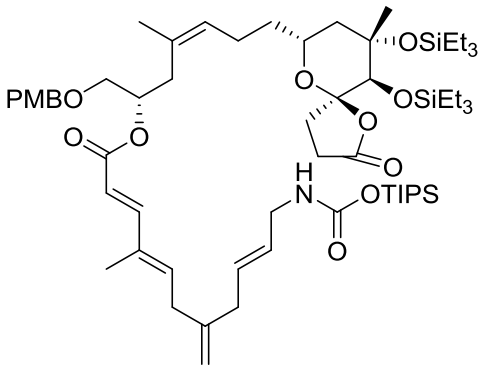
(*S*,*Z*)-5-Iodo-1-((4-methoxybenzyl)oxy)-4-methylpent-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (85): A



solution of bis(pyridine)iodonium tetrafluoroborate (400 mg, 1.08 mmol) in MeCN (10 mL +2x5 mL to rinse) was added to a stirred solution of compound **106** (743 mg, 0.96 mmol) in MeCN (20 mL) at −20 °C. After 2 h, aqueous saturated $Na_2S_2O_3$ solution (20 mL) was added and the resulting mixture was warmed to ambient temperature and extracted with CH_2Cl_2 (1x100 and 3x20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 88:12 → 85:15) yielded the product as colorless oil (453 mg, 62%). The product consists of an inseparable mixture of the *Z*- and *E*-isomer at the newly formed C-I bond with an *Z*:*E* ratio of 3:1. $[\alpha]_D^{20}$ = +11.3 (c = 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6, major (=*Z*)-isomer) δ 7.66 (d, *J* = 15.6 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.72 – 5.59 (m, 3H), 5.39 – 5.31 (m, 1H), 5.22 (dt, *J* = 15.3, 5.8 Hz, 1H), 4.75 (s, 1H), 4.68 (s, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.20 (s, 1H), 3.57 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.54 – 3.48 (m, 2H), 3.40 (d, *J* = 4.8 Hz, 1H) 3.30 (s, 3H), 2.81 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.57 (d, *J* = 7.6 Hz, 2H), 2.50 – 2.40 (m, 3H), 1.65 (d, *J* = 1.4 Hz, 3H), 1.48 (s, 3H), 1.42 – 1.32 (m, 3H), 1.18 (d, *J* = 7.4 Hz, 18H). ^{13}C NMR (101 MHz, C_6D_6, major (=*Z*)-isomer) δ 166.6, 159.8, 154.7, 149.8, 145.72, 144.0, 138.6, 134.5, 130.7, 130.6, 129.6, 129.5, 129.2, 116.9, 114.1, 111.6, 77.7, 73.1, 71.4, 70.6 54.8,

43.1, 40.9, 39.5, 35.30, 23.5, 18.2, 12.6, 12.0. IR (neat): 3375, 2944, 2866, 1700, 1620, 1512, 1463, 1390, 1364, 1301, 1246, 1166, 1092, 1036, 1018, 980, 884, 807, 674, 572, 517, 480 cm^{-1}. HRMS (ESI): m/z calculated for $C_{37}H_{57}NO_6I_1Si$ $[M+H^+]$: 766.29944, found 766.30002.

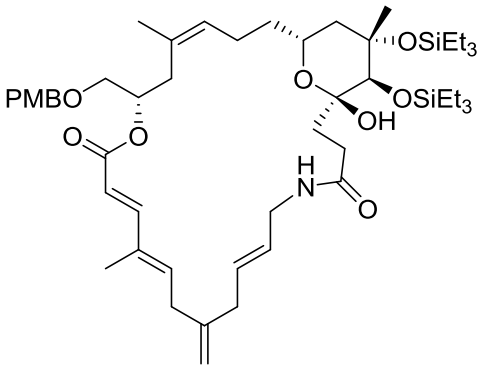
(*S*,*Z*)-1-((4-Methoxybenzyl)oxy)-4-methyl-7-((5*R*,7*R*,9*S*,10*R*)-9-methyl-2-oxo-9,10-bis((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-7-yl)hept-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (89): Rieke zinc [95] 111 mg, 1.7 mmol) and DMF (4.2 mL) were added to compound **98a** (460 mg, 0.855 mmol) and the resulting suspension was stirred vigorously at room temperature for 6 h to yield an approximately 0.2 M solution of the required organozinc reagent **99a**. Excess zinc was allowed to settle and the supernatant solution (4.1 mL) was used in the cross coupling step.



In a separate Schlenk flask manganese dust (55 mg, 1.0 mmol) was added to a stirred solution of $[Pd(dppf)Cl_2•CH_2Cl_2]$ (84 mg, 0.10 mmol) and triphenylarsine (71 mg, 0.23 mmol) in DMF (5 mL). After being stirred at room temperature for 15 min the manganese was allowed to settle and 3.5 mL of the intense purple supernatant solution was added to a stirred solution of compound **85** (493 mg, 0.64 mmol, Z:E = 3:1) in THF (4 mL). After 5 min, the above organozinc solution was added slowly to the stirred red – purple mixture. The color of the mixture first turned reddish brown and after 15 min greenish yellow. After being stirred for 2.5 h the mixture was diluted with water (50 mL) and was extracted with tert-butyl methyl ether (6x50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:*tert*-butyl methyl ether = 4:1) yielded the product as pale yellow oil (370 mg, 52%, 70% with respect to the *Z*-isomer). $[\alpha]_D^{20}$ = +17.9 (c = 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 7.67 (d, *J* = 15.7 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.05 (d, *J* = 15.6 Hz, 1H), 5.69 (t, *J* = 7.6 Hz, 1H), 5.67 – 5.61 (m, 1H), 5.40 – 5.19 (m, 3H), 4.76 (s, 1H), 4.70 (s, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.27 – 4.18 (m, 1H), 3.89 (dddd, *J* = 11.9, 10.0, 5.2, 1.8 Hz, 1H), 3.64 (s, 1H), 3.60 (d, *J* = 4.6 Hz, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.33 (s, 3H), 2.68 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.63 – 2.52 (m, 3H), 2.47 (d, *J* = 6.9 Hz, 2H), 2.44 – 2.11 (m, 5H), 1.90 – 1.78 (m, 5H), 1.68 (t, *J* = 12.2 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.45 - 129 (m, 4H), 1.18

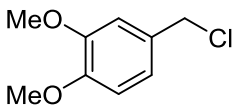
(d, *J* = 7.4 Hz, 18H), 1.05 – 0.97 (m, 18H), 0.76 – 0.57 (m, 12H). ^{13}C NMR (101 MHz, C_6D_6) δ 174.9, 166.7, 159.8, 154.7, 149.6, 145.8, 138.6, 134.5, 132.2, 130.8, 129.6, 129.5, 129.2, 117.1, 114.2, 111.6, 108.4, 80.7, 75. 9, 73.2, 71.6, 71.3, 70.1, 54.8, 46.8, 43.1, 39.5, 36.1, 35.3, 34.0, 32.4, 28.0, 24.44, 24.39, 22.8, 18.2, 12.6, 12.1, 7.5, 7.4, 7.3, 5.6. IR (neat): 3369, 2952, 2874, 1786, 1704, 1622, 1514, 1462, 1384, 1301, 1247, 1163, 1139, 1115, 1018, 917, 884, 847, 742, 675, 547, 488 cm^{-1}. HRMS (ESI): m/z calculated for $C_{60}H_{101}NO_{11}Si_3Na$ [M+Na$^+$]: 1118.65747, found: 1118.65688.

(1*S*,7*E*,12*E*,14*E*,18*S*,20*Z*,24*R*,26*S*,27*R*)-1-Hydroxy-18-(((4-methoxybenzyl)oxy)methyl)-13,20,26-trimethyl-10-methylene-26,27-bis((triethylsilyl)oxy)-17,28-dioxa-5-azabicyclo[22.3.1]octacosa-7,12,14,20-tetraene-4,16-dione (93): Hydrogen fluoride pyridine (70% HF, 0.72 mL, 5.6 mmol) was added to a stirred solution of compound **89** (205 mg, 187 µmol) in THF (15 mL) at 0 °C. After being stirred for 10 min at 0 °C, the reaction was quenched with aqueous sodium hydroxide solution (2 M, 25 mL) and the resulting mixture was extracted with CH_2Cl_2 (7x30 mL). The combined organic layers were dried over $MgSO_4$, diluted with toluene (100 mL) and concentrated under reduced pressure to a volume of ~ 100 mL. This procedure was repeated twice, taking care to keep the volume ≥ 100 mL. The remaining solution was diluted with toluene to a total volume of 190 mL. 2-Hydroxypyridine (355 mg, 3.74 mmol) was added and the resulting solution was stirred at 90 °C for 64 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAC = 3:1 → 2:1) yielded the product as colorless oil (75 mg, 45%). $[\alpha]_D^{20}$ = +27.6 (c = 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 7.54 (dd, *J* = 15.7, 0.8 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.72 – 5.56 (m, 2H), 5.42 – 5.37 (m, 1H), 5.19 – 5.06 (m, 2H), 5.05 – 5.01 (m, 1H), 4.71 – 4.69 (m, 2H), 4.64 (s, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.07 (ddt, *J* = 10.7, 8.0, 2.7 Hz, 1H), 3.70 – 3.61 (m, 2H), 3.59 (d, *J* = 4.6 Hz, 2H), 3.40 – 3.27 (m, 4H), 2.95 – 2.80 (m, 2H), 2.72 – 2.56 (m, 3H), 2.46 (d, *J* = 5.5 Hz, 2H), 2.38 (dd, *J* = 14.4, 7.4 Hz, 2H), 2.31 – 2.22 (m, 2H), 1.91 – 1.73 (m, 6H), 1.68 – 1.62 (m, 1H), 1.59 (s, 3H), 1.54 – 1.45 (m, 1H), 1.50 (d, *J* = 1.2 Hz, 3H), 1.16 – 1.10 (m, 9H), 1.04 (t, *J* = 7.9 Hz, 9H), 0.91 – 0.83 (m, 6H), 0.69 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (101 MHz,

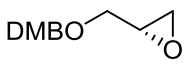


C_6D_6) δ 173.5, 166.8, 159.9, 149.7, 146.0, 140.1, 133.3, 131.3, 130.8, 130.7, 129.6, 128.7, 128.5, 116.9, 114.2, 113.1, 97.9, 82.0, 76.5, 73.1, 71.4, 71.2, 66.7, 54.8, 47.3, 41.4, 40.1, 36.6, 35.6, 34.0, 29.5, 24.4, 24.1, 23.3, 12.2, 7.53, 7.50, 7.48, 5.8. IR (neat): 3309, 3074, 2952, 2912, 2876, 1710, 1625, 1514, 1458, 1380, 1361, 1302, 1247, 1168, 1107, 1020, 982, 849, 740 cm^{-1}. HRMS (ESI): m/z calculated for $C_{50}H_{81}NO_9Si_2Na$ [M+Na^+]: 918.53421, found: 918.53471.

4-(Chloromethyl)-1,2-dimethoxybenzene (S1): Thionyl chloride (11.0 mL, 152 mmol) was added slowly to a stirred solution of 3,4-dimethoxybenzyl alcohol (14.6 mL, 100 mmol) and pyridine (10.0 mL, 124 mmol) in CH_2Cl_2 (500 mL) at 0 °C. After 2.5 h, a second amount of thionyl chloride (3.0 mL, 41 mmol) was added to the reaction mixture. After 3.5 h water (300 mL) was added carefully and the resulting mixture was warmed to ambient temperature. The layers were separated and the organic layer was washed with saturated aqueous ammonium chloride solution (3x100 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness under reduced pressure to yield the product as colorless solid (17.0 g, 91%). The properties of the product were in good accordance with those reported previously.[153]

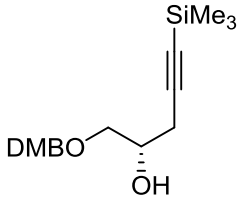


(*S*)-2-(((3,4-Dimethoxybenzyl)oxy)methyl)oxirane (S2): (*R*)-Glycidol (2.0 mL, 30 mmol) was added carefully to a suspension/solution of sodium hydride (800 mg, 33.3 mmol) and 4-(chloromethyl)-1,2-dimethoxybenzene **S1** (5.96 g, 31.9 mmol) in DMF (50 mL) at 0 °C. After the addition, the reaction mixture was allowed to reach ambient temperature. After 22 h, saturated aqueous sodium chloride solution (60 mL) was added carefully to the reaction mixture. The resulting mixture was extracted with *tert*-butyl methyl ether (1x100 and 3x50 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 4:1 → 3:2) yielded the product as pale yellow oil (6.76 g, 85%). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}} = -2.2$ (c = 3.1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 1.8 Hz, 1H), 6.87 – 6.83 (m, 1H), 6.80 (dd, J = 8.1, 0.9 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.72 (ddd, J = 11.5, 3.0, 0.9 Hz, 1H), 3.38 (ddd, J = 11.5, 5.9, 1.1 Hz, 1H), 3.15 (tdd, J = 5.2, 4.3, 2.9 Hz, 1H), 2.76 (tt, J = 4.9, 0.9 Hz, 1H), 2.58 (ddd, J = 5.1, 2.7, 1.0 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 148.7, 130.4, 120.4, 111.1, 110.9, 73.2, 70.6, 55.92, 55.85, 50.9 44.3.IR (neat): 3054, 3000, 2937, 2908, 2862, 2836, 2254, 1608, 1593, 1515, 1464, 1454, 1442, 1419, 1386, 1366, 1333, 1262, 1235, 1195, 1157, 1137, 1088,1026, 982, 911, 855, 808, 764, 725, 669, 647,

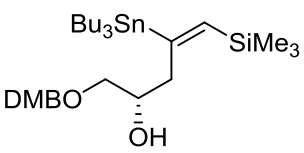


593, 555, 514, 461, 444 cm^{-1}. HRMS (ESI): m/z calculated for $C_{12}H_{16}O_4Na$ [M+Na^+]: 247.09408, found 247.09420.

(*S*)-1-((3,4-Dimethoxybenzyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-ol (S3): *n*-Butyllithium solution (1.6 M in hexane, 30 mL, 48 mmol) was slowly added to a solution of trimethylsilylacetylene (7.0 mL, 4.9 g, 50 mmol) in THF (30 mL) at –78 °C. After the addition, the reaction mixture was stirred for 20 min at –78 °C before it was warmed to 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was cooled to – 78 °C. Thereafter the cold solution was added to a cold (–78 °C) solution of the epoxide **S2** (5.75 g, 25.6 mmol) in THF (30 mL) followed by boron trifluoride diethyl etherate (4.0 mL, 4.6 g, 32 mmol). The resulting mixture was stirred for 5 h at –78 °C. Thereafter saturated sodium bicarbonate solution (50 mL) was added and the resulting mixture was warmed to ambient temperature. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (4x50 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 2:1) yielded the product as pale yellow oil (8.32 g, 93%). $[\alpha]_D^{20}$ = + 14.5 (c = 0.71, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.79 (m, 3H), 4.50 (s, 2H), 3.93 (ddt, J = 8.4, 6.4, 3.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.58 (dd, J = 9.6, 3.9 Hz, 1H), 3.47 (dd, J = 9.6, 6.6 Hz, 1H), 2.57 – 2.39 (m, 3H), 0.13 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 149.2, 148.9, 130.5, 120.5, 111.2, 111.0, 102.6, 87.4, 73.5, 72.7, 69.0, 56.0, 56.0, 28.5, 25.2, 0.1. IR (neat): 3002, 2956, 2905, 2865, 2837, 2175, 1608, 1593, 1515, 1464, 1419, 1364, 1331, 1249, 1261, 1237, 1195, 1157, 1138, 1098, 1081, 1028, 940, 839, 808, 760, 698, 724, 668, 648, 592, 558, 526, 499, 468, 453, 437 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{26}O_4SiNa$ [M+Na^+]: 345.14926, found 345.14951.

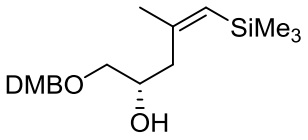


(*S,E*)-1-((3,4-Dimethoxybenzyl)oxy)-4-(tributylstannyl)-5-(trimethylsilyl)pent-4-en-2-ol (S4): Tributyltinhydride (6.8 mL, 25 mmol) was added over the course of 20 min to a solution of **S3** (7.82 g, 22.5 mmol) and molybdenum catalyst **59** [73] (610 mg, 1.7 mmol) in THF (22 mL). The resulting mixture was stirred for 30 min after the addition before it was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 7:1 + 1% Et_3N → 6:1 + 1% Et_3N) yielded the product as pale yellow oil (10.1 g, 73%). $[\alpha]_D^{20}$ = − 1.7 (c = 3.8, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.80 (m, 3H), 5.97 (d, J = 1.2 Hz, 1H), 4.51 (d,



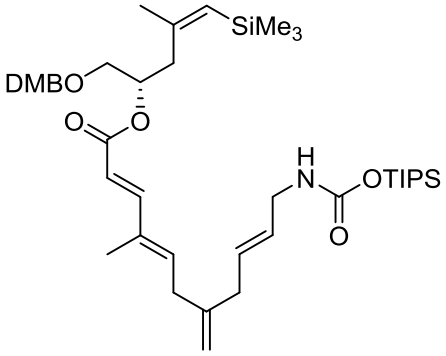
J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 – 3.80 (m, 1H), 3.46 (dd, J = 9.6, 3.4 Hz, 1H), 3.35 (dd, J = 9.6, 7.6 Hz, 1H), 2.67 – 2.43 (m, 2H), 2.20 (d, J = 1.9 Hz, 1H), 1.54 – 1.41 (m, 6H), 1.36 – 1.24 (m, 6H), 0.96 – 0.81 (m, 15H), 0.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 149.2, 148.8, 147.2, 130.7, 120.5, 111.2, 111.0, 74.2, 73.5, 70.3, 56.0, 55.9, 44.2, 29.3, 27.5, 13.8, 10.4, 0.9. IR (neat): 3502, 2953, 2920, 2870, 2853, 1730, 1594, 1551, 1516, 1464, 1419, 1376, 1337, 1263, 1244, 1193, 1157, 1139, 1080, 1030, 959, 853, 836, 807, 766, 746, 689, 669, 593, 505, 451, 404 cm^{-1}. HRMS (ESI): m/z calculated for $C_{29}H_{54}O_4SiSnNa$ [$M+Na^+$]: 637.27049, found 637.27136.

(*S,Z*)-1-((3,4-Dimethoxybenzyl)oxy)-4-methyl-5-(trimethylsilyl)pent-4-en-2-ol (S5): A



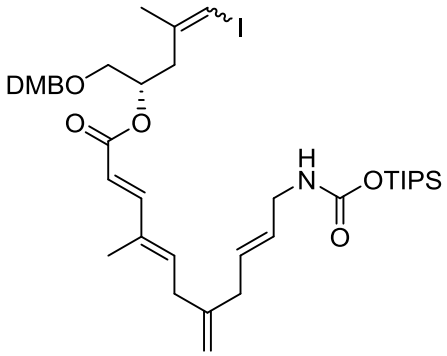
solution of iodine (0.5 M in THF, 32 mL, 16 mmol) was added to a solution of **S4** (9.47 g, 15.4 mmol) in THF (40 mL) at 0 °C. After 5 min a solution of methylzinc iodide (~ 1 M in DMF, 60 mL, 60 mmol) was slowly added to the reaction mixture. [$(SPhos)_2PdCl_2$] [154] was added and the resulting mixture was warmed to ambient temperature. After 4 h, water (200 mL) was added and the resulting mixture was extracted with *tert*-butyl methyl ether (5x100 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 75:25 → 65:35) yielded the product as colorless oil (4.61 g, 88%). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = − 1.0 (c = 1.54, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ ‘ 6.92 – 6.80 (m, 3H), 5.38 (d, J = 1.4 Hz, 1H), 4.52 (d, J = 11.6 Hz), 4.48 (d, J = 11.2 Hz), 4.01 (dddd, J = 12.0, 7.9, 5.9, 3.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.49 (dd, J = 9.5, 3.3 Hz, 1H), 3.36 (dd, J = 9.6, 7.4 Hz, 1H), 2.38 (dd, J = 13.5, 8.9 Hz, 1H), 2.25 – 2.17 (m, 1H), 1.88 (d, J = 1.3 Hz, 3H), 0.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 149.2, 148.8, 130.6, 128.8, 120.5, 111.2, 111.0, 7.31, 73.5, 68.8, 56.1, 56.0, 41.0, 26.9, 0.6. . IR (neat): 3507, 2997, 2951, 2903, 2857, 2836, 1613, 1593, 1515, 1452, 1144, 1442, 1419, 1370, 1330, 1260, 1245, 1197, 1157, 1138, 1095, 1028, 946, 869, 834, 807, 767, 746, 689, 643, 619, 583, 556, 449, 432 cm^{-1}. HRMS (ESI): m/z calculated for $C_{18}H_{30}O_4SiNa$ [$M+Na^+$]:361.18056, found 361.18079.

(*S,Z*)-1-((3,4-Dimethoxybenzyl)oxy)-4-methyl-5-(trimethylsilyl)pent-4-en-2-yl (*E*)-3-(tributylstannyl)acrylate (S6): 2,4,6-Trichlorobenzoyl chloride (2.3 mL, 15 mmol) was added slowly to a solution of **64** (5.22 g, 14.5 mmol) and Et_3N (9.4 mL, 67 mmol) in toluene (40 mL) at 0 °C. The resulting turbid mixture was warmed to ambient temperature. After being stirred for 2.25 h, the reaction mixture was cooled to 0 °C. A solution of **S5** (4.41 g, 13.0 mmol) in toluene (30 mL) was added and the reaction mixture was again warmed to ambient temperature. After being stirred for 2 h, the reaction mixture was diluted with *tert*-butyl methyl ether (400 mL). The resulting solution was washed with aqueous hydrochloric acid (1 M, 150 mL), water (150 mL) and saturated aqueous sodium bicarbonate solution (150 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 17:1 → 10:1) yielded the product as colorless oil (6.31 g, 71%). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 13.1 (c = 3.31, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 19.4 Hz, 1H), 6.90 – 6.77 (m, 3H), 6.30 (d, J = 19.4 Hz, 1H), 5.37 (ddt, J = 9.1, 5.8, 4.5 Hz, 1H), 5.30 (d, J = 1.5 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.57 (dd, J = 10.7, 5.9 Hz, 1H), 3.52 (dd, J = 10.6, 4.5 Hz, 1H), 2.57 (dd, J = 13.9, 9.2 Hz, 1H), 2.37 (dd, J = 13.9, 4.6 Hz, 1H), 1.86 (d, J = 1.4 Hz, 3H), 1.60 – 1.42 (m, 6H), 1.37 – 1.25 (m, 6H), 1.00 – 0.94 (m, 6H), 0.88 (t, J = 7.3 Hz, 9H), 0.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 153.1, 150.4, 149.1, 148.7, 136.4, 130.8, 128.6, 120.3, 111.0, 111.0, 73.1, 71.5, 70.9, 56.0, 55.9, 39.0, 29.1, 27.4, 26.8, 13.8, 9.8, 0.6. . IR (neat): 295249272853, 2871, 1719, 1618, 1592, 1516, 1464, 1442, 1419, 1375, 1359, 1307, 1260, 1246, 1203, 1155, 1139, 1092, 1068, 1031, 996, 960, 870, 836, 806, 767, 746, 690, 663, 598, 617, 554, 510, 451, 430, 408 cm^{-1}. HRMS (ESI): m/z calculated for $C_{33}H_{58}O_5SiSnNa$ $[M+Na^+]$:705.29670, found 705.29759.

(*S*,*Z*)-1-((3,4-Dimethoxybenzyl)oxy)-4-methyl-5-(trimethylsilyl)pent-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (S7): 

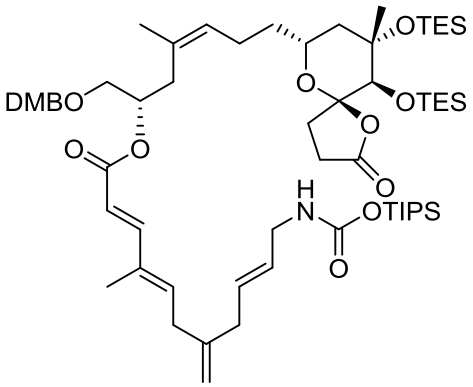
A suspension of tetrakis(triphenylarsine)palladium(0) [80] (0.87 g, 0.65 mmol) in DMF (25 mL) was added to a solution of stannane **S6** (6.22 g, 9.13 mmol) and alkenyl iodide **83** (4.68 g, 9.81 mmol) in DMF (20 mL). The resulting mixture was stirred at ambient temperature. After being stirred for 21 h, the reaction mixture was poured onto saturated aqueous sodium chloride solution (200 mL). The resulting mixture was extracted with *tert*-butyl methyl ether (5x150 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (toluene:EtOAc = 93:7 → 90:10) yielded the product as colorless oil (5.23 g, 77%). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 11.3 (c = 1.84, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 15.7, 0.8 Hz, 1H), 6.93 – 6.77 (m, 3H), 5.90 (t, J = 7.6 Hz, 1H), 5.82 (d, J = 15.7 Hz, 1H), 5.66 – 5.57 (m, 1H), 5.55 – 5.48 (m, 1H), 5.40 (ddt, J = 9.2, 5.8, 4.6 Hz, 1H), 5.30 (d, J = 1.5 Hz, 1H), 4.82 – 4.72 (m, 3H), 4.52 (d, J = 11.7 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.75 (dt, J = 6.0, 3.1 Hz, 2H), 3.60 – 3.47 (m, 2H), 2.88 (d, J = 7.6 Hz, 2H), 2.73 (d, J = 6.5 Hz, 2H), 2.57 (dd, J = 13.8, 9.1 Hz, 1H), 2.37 (dd, J = 13.9, 4.8 Hz, 1H), 1.86 (d, J = 1.4 Hz, 3H), 1.76 (d, J = 1.2 Hz, 3H), 1.36 – 1.23 (m, 3H), 1.08 (d, J = 7.4 Hz, 18H), 0.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 154.9, 150.5, 149.6, 149.1, 148.7, 145.6, 138.7, 134.3, 130. 8, 129.9, 128.7, 128.6, 120.3, 116.3, 111.6, 111.0, 110.9, 73.1, 71.5, 70.7, 56.0, 55.9, 43.0, 39.4, 38.9, 35.3, 30. 5, 26.8, 17.98, 17.95, 12.3, 12.2, 0.6. IR (neat): 3371, 2945, 2894, 2866, 1699, 1646, 1621, 1594, 1515, 1464, 1442, 1420, 1390, 1364, 1300, 1259, 1245, 1158, 1139, 1092, 1064, 1030, 1019, 981, 921, 882, 870, 836, 803, 767, 748, 689, 670, 649, 618, 593, 565, 557, 540, 516, 497, 481, 460,454, 441, 422, 331 cm^{-1}. HRMS (ESI): m/z calculated for $C_{41}H_{67}NO7Si_2Na$ [M+Na^+]: 764.43483, found 764.43514.

(*S*)-1-((3,4-Dimethoxybenzyl)oxy)-5-iodo-4-methylpent-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (S8): N-



Iodosuccinimide (233 mg, 1.04 mmol) was added to a solution of lutidine (0.24 mL, 2.1 mmol) and **S7** (381 mg, 0.513 mmol) in acetonitrile (10 mL) at 0 °C. After 44 h saturated aqueous sodium thiosulfate solution (15 mL) was added to the reaction mixture. The resulting mixture was warmed to ambient temperature and was extracted with CH_2Cl_2 (4x30 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 4:1 → 3:1) yielded the product as colorless oil (*Z*:*E* ~ 5.5:1) (267 mg, 65%). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 10.0 (c = 3.0, $CHCl_3$) ^{1}H NMR (major isomer, 400 MHz, $CDCl_3$) δ 7.36 (dd, J = 15.7, 0.8 Hz, 1H), 6.91 – 6.79 (m, 3H), 5.98 (d, J = 1.5 Hz, 1H), 5.92 (t, J = 7.7 Hz, 1H), 5.82 (d, J = 15.7 Hz, 1H), 5.65 – 5.57 (m, 1H), 5.51 (dt, J = 15.2, 5.7 Hz, 1H), 5.37 (dq, J = 8.7, 5.0 Hz, 1H), 4.87 – 4.71 (m, 3H), 4.53 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.75 (dt, J = 6.0, 2.9 Hz, 2H), 3.62 – 3.54 (m, 2H), 2.88 (d, J = 7.6 Hz, 2H), 2.76 – 2.63 (m, 3H), 2.52 (dd, J = 13.8, 5.0 Hz, 1H), 1.93 (d, J = 1.4 Hz, 3H), 1.76 (d, J = 1.2 Hz, 3H), 1.34 – 1.22 (m, 3H), 1.07 (d, J = 7.4 Hz, 18H). ^{13}C NMR (major isomer, 101 MHz, $CDCl_3$) δ 166.9, 154.9, 149.9, 149.1, 148.7, 145.6, 143.8, 138.9, 134.3, 130.7, 129.8, 128.7, 120.4, 116.1, 111.7, 111.1, 110.9, 77.5, 73.2, 71.0, 70.5, 56.0, 55.9, 43.0, 40.5, 39.4, 35.3, 24.1, 17.9, 12.2. IR (neat): 3372, 3071, 2943, 2865, 1698, 1621, 1594, 1514, 1463, 1421, 1390, 1364, 1300, 1260, 1236, 1158, 1139, 1092, 1061, 1029, 980, 921, 884, 855, 803, 782, 767, 673, 594, 563, 510, 481, 460, 428 cm^{-1}. HRMS (ESI): m/z calculated for $C_{38}H_{58}INO_7SiNa$ [M+Na$^+$]: 818.29195, found 818.29246.

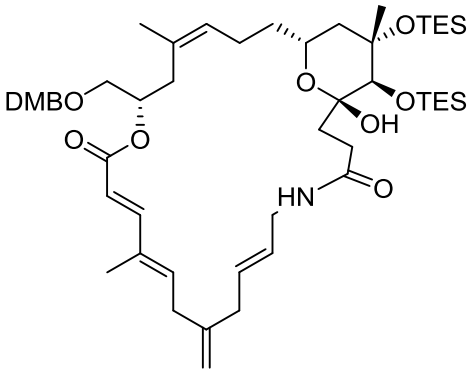
(*S*,*Z*)-1-((3,4-Dimethoxybenzyl)oxy)-4-methyl-7-((5*R*,7*R*,9*S*,10*R*)-9-methyl-2-oxo-9,10-bis((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-7-yl)hept-4-en-2-yl (2*E*,4*E*,9*E*)-4-methyl-7-methylene-11-((((triisopropylsilyl)oxy)carbonyl)amino)undeca-2,4,9-trienoate (S9): Rieke zinc [95] (53 mg, 0.81 mmol) and DMF (2.1 mL) were added to compound **98a** (228 mg, 0.423 mmol) and the resulting suspension was stirred vigorously at room temperature for 2.5 h to yield an approximately 0.2 M solution of the required organozinc reagent **99a**. The zinc was allowed to settle and the supernatant solution (2.0 mL) was used in the cross coupling step.



In a separate Schlenk flask manganese dust (55 mg, 1.0 mmol) was added to a stirred solution of [Pd(dppf)Cl_2•CH_2Cl_2] (34 mg, 0.042 mmol) and triphenylarsine (26 mg, 0.085 mmol) in DMF (2 mL). After being stirred at room temperature for 15 min, the manganese was allowed to settle and 1.7 mL of the intense purple supernatant solution was added to a stirred solution of compound **S8** (210 mg, 0.264 mmol, *Z*:*E* ~ 5:1) in THF (1 mL). After 5 min, the above organozinc solution was added slowly to the stirred red – purple mixture. The color of the mixture first turned reddish brown and after 15 min greenish yellow. After being stirred for 2.5 h the mixture was diluted with water (20 mL) and was extracted with *tert*-butyl methyl ether (6x20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 80:20 → 78:22) yielded the product as colorless oil (165 mg, 55%, 67% based on the *Z*-isomer). $[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 29.60 (c = 0.25, $CHCl_3$) ^{1}H NMR (400 MHz, C_6D_6) δ 7.65 (d, J = 15.7 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.65 (d, J = 8.0 Hz, 1H), 6.04 (d, J = 15.7 Hz, 1H), 5.68 (q, J = 6.7, 6.1 Hz, 2H), 5.41 – 5.17 (m, 3H), 4.75 (d, J = 1.7 Hz, 1H), 4.71 – 4.63 (m, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.26 (bs, 1H), 3.95 – 3.84 (m, 1H), 3.67 – 3.61 (m, 3H), 3.54 – 3.51 (m, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 2.69 (dd, J = 13.6, 7.9 Hz, 1H), 2.60 (d, J = 8.1 Hz, 2H), 2.59 – 2.53 (m, 1H), 2.52 – 2.37 (m, 3H), 2.36 – 2.12 (m, 4H), 1.89 – 1.78 (m, 5H), 1.68 (t, J = 12.2 Hz, 1H), 1.62 – 1.55 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H), 1.44 – 1.32 (m, 5H), 1.18 (d, J = 7.4 Hz, 18H), 1.00 (td, J = 7.9, 1.8 Hz, 18H), 0.73 – 0.59 (m, 12H). ^{13}C NMR (101 MHz, C_6D_6) δ 174.9, 166.7, 154.7, 150.4, 149.9, 149.6, 145.7, 138.7, 134.5, 132.2, 131.3, 129.4, 129.2, 120.6, 117.1, 112.3, 112.2, 111.6, 108.4, 80.6, 75.9, 73.4, 71.6, 71.3,

70.1, 55.7, 55.6, 46.9, 43.1, 39.5, 36.1, 35.3, 34.0, 32.4, 27.9, 24.5, 24.4, 22.8, 18.2, 12.6, 12.1, 7.5, 7.3, 7.3, 5.6. IR (neat): 3379, 2951, 2873, 1786, 1703, 1624, 1516, 1463, 1419, 1384, 1263, 1238, 1159, 1139, 1020, 917, 884, 850, 804, 741, 480, 462 cm^{-1}. HRMS (ESI): m/z calculated for $C_{61}H_{103}NO_{12}Si_3Na$ [M+Na^+]: 1148.66803, found 1148.66925.

(1*S*,7*E*,12*E*,14*E*,18*S*,20*Z*,24*R*,26*S*,27*R*)-18-(((3,4-Dimethoxybenzyl)oxy)methyl)-1-hydroxy-13,20,26-trimethyl-10-methylene-26,27-bis((triethylsilyl)oxy)-17,28-dioxa-5-azabicyclo[22.3.1]octacosa-7,12,14,20-tetraene-4,16-dione (111): Hydrogen fluoride pyridine (70% HF, 0.25 mL, 1.9 mmol) was added to a stirred solution of compound **S9** (73 mg, 65 µmol) in THF (7.5 mL) at 0 °C. After being stirred for 15 min at 0 °C, the mixture was quenched with aqueous sodium hydroxide solution (2 M, 12 mL) and the resulting mixture was extracted with CH_2Cl_2 (7x20 mL). The combined organic layers were dried over magnesium sulfate, diluted with toluene (80 mL) and concentrated under reduced pressure to a volume of ~ 80 mL. This procedure was repeated three times, taking care to keep the volume ≥ 50 mL. The remaining solution was diluted with toluene to a total volume of 65 mL. 2-Hydroxypyridine (128 mg, 1.35 mmol) was added and the resulting solution was stirred at 90 °C for 40 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc = 70:30 → 65:35) yielded the product as colorless oil (25.5 mg, 43%). $[\alpha]_D^{20}$ = + 30.6 (c = 0.33, $CHCl_3$) ^{1}H NMR (400 MHz, C_6D_6) δ 7.54 (d, J = 15.7 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 8.1, 2.0 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.03 (d, J = 15.7 Hz, 1H), 5.65 (dd, J = 8.9, 5.9 Hz, 2H), 5.45 – 5.37 (m, 1H), 5.19 – 5.08 (m, 2H), 5.08 – 5.01 (m, 1H), 4.74 (s, 1H), 4.72 – 4.61 (m, 2H), 4.48 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.08 (ddd, J = 11.8, 7.9, 3.6 Hz, 1H), 3.73 – 3.59 (m, 4H), 3.49 (s, 3H), 3.41 (s, 3H), 3.33 (dt, J = 14.5, 5.5 Hz, 1H), 2.96 – 2.81 (m, 2H), 2.74 – 2.52 (m, 3H), 2.50 – 2.32 (m, 4H), 2.31 – 2.20 (m, 2H), 1.89 – 1.71 (m, 3H), 1.78 (s, 3H), 1.69 – 1.45 (m, 3H), 1.60 (s, 3H), 1.50 (s, 3H), 1.13 (t, J = 7.9 Hz, 9H), 1.04 (t, J = 7.9 Hz, 9H), 0.92 – 0.79 (m, 6H), 0.69 (q, J = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 173.5, 166.8, 150.4, 149.9, 149.7, 146.0, 140.1, 133.3, 131.3, 130.8, 128.7, 120.6, 116.9, 113.2, 112.4, 112.1, 97.9, 82.0, 76.5, 73.4, 71., 71.2, 66.7, 55.7, 47.4, 41.4, 40.1, 36.6, 35.6, 34.1, 29.5, 24.4, 24.1,



23.3, 12.2, 7.52, 7.50, 7.47, 5.8. IR (neat): 3311, 3072, 2952, 2912, 2875, 1709, 1625, 1644, 1594, 1516, 1462, 1419, 1380, 1361, 1328, 1303, 1265, 1238, 1160, 1137, 1108, 1024, 982, 855, 808, 739, 676, 642, 611, 595, 560, 527, 516, 499, 484, 460, 443, 431 cm^{-1}. HRMS (ESI): m/z calculated for $C_{51}H_{83}NO_{10}Si_2Na$ [M+Na^+]: 948.54478, found 948.54511.

(1*S*, 7*E*, 12*E*, 14*E*, 18*S*, 20*Z*, 24*R*, 26*S*, 27*R*)-1-Hydroxy-18-(hydroxymethyl)-13,20,26-trimethyl-10-methylene-26,27-bis((triethylsilyl)oxy)-17,28-dioxa-5-azabicyclo[22.3.1]octacosa-7,12,14,20-tetraene-4,16-dione (110): A cold (0 °C) solution of trityl tetrafluoroborate (0.95 mL, 0.05 M, 47.5 µmol) in CH_2Cl_2 was added to a stirred solution of compound **93** (42 mg, 47 µmol) in CH_2Cl_2 (10 mL) at 0 °C. The progress of the reaction was monitored by TLC (hexane:EtOAc = 2:1, UV and anisaldehyde). After 1h, another portion of a cold solution of trityl tetrafluoroborate (0.6 mL, 0.05 M, 30 µmol) in CH_2Cl_2 was added. After 2 h, 2,6-di-*tert*-butylpyridine (30.0 µL, 25.6 mg, 134 µmol) was added and the mixture was concentrated *in vacuo*. Purification by flash chromatography (hexane:EtOAC = 2:1 → 3:2) yielded the product as colorless oil (16 mg, 44%). $[\alpha]_D^{20}$ = +15.5 (c = 0.20, $CHCl_3$). ^{1}H NMR (600 MHz, C_6D_6) δ 7.55 (dd, *J* = 15.7, 0.7 Hz, 1H), 5.98 (dd, *J* = 15.7, 0.6 Hz, 1H), 5.71 (t, *J* = 8.0 Hz, 1H), 5.36 – 5.30 (m, 2H), 5.20 – 5.07 (m, 3H), 4.72 – 4.70 (m, 2H), 4.47 (s, 1H), 4.04 – 3.97 (m, 1H), 3.73 (d, *J* = 11.9 Hz, 1H), 3.63 (s, 1H), 3.63 – 3.57 (m, 1H), 3.52 – 3.46 (m, 2H), 2.87 – 2.79 (m, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.55 (ddd, *J* = 13.7, 7.9, 6.9 Hz, 1H), 2.48 (d, *J* = 6.6 Hz, 2H), 2.44 – 2.38 (m, 2H), 2.38 – 2.33 (m, 1H), 2.17 (dd, *J* = 13.4, 6.8 Hz, 1H), 1.89 (dt, *J* = 13.4, 6.5 Hz, 1H), 1.80 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.75 – 1.70 (m, 4H), 1.60 (dt, *J* = 15.9, 6.9 Hz, 1H), 1.55 (s, 3H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.50 – 1.44 (m, 1H), 1.10 (t, *J* = 7.9 Hz, 9H), 1.04 (t, *J* = 7.9 Hz, 9H), 0.87 – 0.82 (m, 6H), 0.68 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (151 MHz, C_6D_6) δ 173.7, 167.1, 149.9, 146.0, 140.2, 133.2, 131.3, 130.8, 128.7, 128.4, 116.8, 113.3, 98.1, 81.8, 76.4, 73.8, 66.8, 64.5, 47.4, 41.4, 40.3, 36.9, 36.6, 36.0, 33.6, 29.8, 24.5, 24.3, 23.3, 12.2, 7.51, 7.48, 7.4, 5.8. IR (neat): 3364, 3075, 2952, 2916, 2876, 1708, 1646, 1625, 1541, 1458, 1379, 1261, 1241, 1167, 1134, 1106, 1068, 1019, 982, 856, 807, 739, 681 cm^{-1}. HRMS (ESI): m/z calculated for $C_{42}H_{73}NO_8Si_2Na$ [M+Na^+]: 798.47670, found: 798.47684.

Methyl 2-((2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-Tris((*tert*-butyldimethylsilyl)oxy)-6-((2*S*,3*R*,4*R*)-4-((2*S*,4*S*,5*R*)-5-((*E*)-3-((1*S*,7*E*,12*E*,14*E*,18*S*,20*Z*,24*R*,26*S*,27*R*)-1-hydroxy-13,20,26-trimethyl-10-methylene-4,16-dioxo-26,27-bis((triethylsilyl)oxy)-17,28-dioxa-5-azabicyclo[22.3.1]octacosa-7,12,14,20-tetraen-18-yl)allyl)-4-methyltetrahydrofuran-2-yl)-2,3,4-tris((triethylsilyl)oxy)butyl)tetrahydro-*2H*-pyran-2-yl)acetate (120): Sulfur trioxide pyridine complex (23.0 mg, 145 µmol) was added to a stirred solution of compound **110** (9.0 mg, 12 µmol), *N,N*-diisopropylethylamine (37 µL, 27 mg, 0.21 mmol) and dimethyl sulfoxide (90 µL, 99 mg, 1.3 mmol) in CH_2Cl_2 (1 mL) at – 20 °C. After 1 h, aqueous saturated NH_4Cl solution (2 mL) was added and the mixture was allowed to reach ambient temperature. The resulting mixture was extracted with *tert*-butyl methyl ether (80 mL). The organic layer was washed with aqueous saturated NH_4Cl solution (4x10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The aldehyde was used in the next step without further purification.

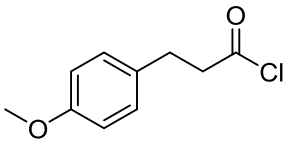
A solution of lithium bis(trimethylsilyl)amide (78 µL, 0.46 M, 36 µmol) in THF was added to a solution of compound **119** (47.6 mg, 36 µmol) in DMF:DMPU (3:1 v/v, 0.6 mL) at – 40 °C. After stirring at this temperature for 2 min, a solution of $ZnCl_2$ (72 µL, 0.5 M, 36 µmol) in THF was added. After being stirred for 3 min, the solution was added via canula to a solution of compound **112** (crude from the previous step, ≤ 12 µmol) in DMF:DMPU (3:1 v/v, 0.3 mL) at –40 °C and the flask and canula were rinsed with DMF:DMPU (3:1 v/v, 2x0.3 mL). The resulting mixture was stirred at the same temperature for 5 min and was then warmed to 20 °C. After being stirred for 72 h the mixture was diluted with aqueous saturated NaCl solution (20 mL) and the resulting mixture was extracted with *tert*-butyl methyl ether (4x25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexane:EtOAC = 19:1 → 5:1) yielded the product as colorless oil (6.1 mg, 28%).$[\alpha]_D^{20}$ = +24.5 (c = 0.22, $CHCl_3$). ^{1}H NMR (500 MHz, , C_6D_6) δ 7.55 (d, J = 15.6 Hz, 1H), 6.13 (dt, J = 14.7, 7.1 Hz, 1H), 6.07 (d, J = 15.7 Hz, 1H), 5.91 (dd, J = , 8.8, 7.2, Hz, 1H), 5.76 (dd, J = 15.5, 6.9 Hz, 1H), 5.62 (t, J = 7.7 Hz, 1H), 5.46 (t, J = 7.5 Hz, 1H), 5.17 – 5.02 (m, 2H), 4.95 (s, 1H), 4.89 (s,

1H), 4.69 (d, J = 2.3 Hz, 2H), 4.60 – 4.53 (m, 2H), 4.38 (td, J = 9.1, 5.7 Hz, 1H), 4.19 (d, J = 10.5 Hz, 1H), 4.17 – 4.11 (m, 1H), 4.07 – 3.96 (m, 3H), 3.93 (m, 1H), 3.68 (s, 1H), 3.67 – 3.43 (m, 5H), 3.39 (s, 3H), 3.03 (dd, J = 13.3, 8.8 Hz, 1H), 2.91 (ddd, J = 15.1, 8.5, 5.8 Hz, 1H), 2.81 (dd, J = 15.6, 3.7 Hz, 1H), 2.74 – 2.64 (m, 2H), 2.62 – 2.54 (m, 2H), 2.52 – 2.22 (m, 9H), 1.99 – 1.81 (m, 7H), 1.78 (t, J = 12.1 Hz, 1H), 1.73 – 1.47 (m, 9H), 1.41 – 0.77 (m, 99H), 0.71 (q, J = 7.9 Hz, 6H). 0.272 (s, 3H), 0.269 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 173.5, 171.9, 166.4, 149.4, 146.0, 139.9, 133.28, 131.19, 131.16, 131.1, 130.7, 128.6, 128.5, 117.1, 113.1, 97.9, 84.2, 82.0, 80.7, 77.7, 76.5, 76.0, 74.8, 74.5, 73.5, 73.0, 71.6, 70.8, 66.9, 65.5, 51.2, 47.3, 41.3, 40.14, 40.10, 38.7, 37. 9, 37.8, 36.9, 36.8, 36.7, 36.3, 35.6, 29.6, 26.6, 26.5, 26.0, 24.5, 24.3, 23.3, 18.7, 18.6, 18.1, 16.9, 12.3, 7.8, 7.6, 7.54, 7.51, 7.47, 6.3, 6.1, 6.0, 5.8, -3.1, -3.4, -4.3, -4.52, -4.53, -4.54. IR (neat): 3363, 2953, 2929, 2877, 2858, 1716, 1741, 1627, 1649, 1549, 1512, 1461, 1415, 1379, 1361, 1334, 1252, 1164, 1092, 1006, 972, 938, 920, 900, 875, 835, 814, 776, 741, 678, 560, 437, 459, 424, 408 cm^{-1}. HRMS (ESI): m/z calculated for $C_{97}H_{187}NO_{17}Si_8Na$ [M+Na^+]: 1885.18455, found: 1885.18397.

Methyl 2-((2*R*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Trihydroxy-6-((2*S*,3*R*,4*S*)-2,3,4-trihydroxy-4-((2*S*,4*S*,5*R*)-4-methyl-5-((*E*)-3-((1*S*,7*E*,12*E*,14*E*,18*S*,20*Z*,24*R*,26*S*,27*R*)-1,26,27-trihydroxy-13,20,26-trimethyl-10-methylene-4,16-dioxo-17,28-dioxa-5-azabicyclo[22.3.1]octacosa-7,12,14,20-tetraen-18-yl)allyl)tetrahydrofuran-2-yl)butyl)tetrahydro-*2H*-pyran-2-yl)acetate (121): Aqueous Hydrogen fluoride (0.28 mL, 51%, 8.2 mmol) was added to a stirred solution of compound **120** (12 mg, 6.4 µmol) in MeCN (2.7 mL). After 6 h, trimethylsilanol (1.6 mL, 17 mmol) was added to the mixture. After being stirred for further 30 min, the resulting mixture was concentrated *in vacuo*. Purification by preparative LC (YMC Triart C18 5 µm 10150 00550, gradient MeOH/water: 70:30 → 100:0, 4.0 mL/min, 7.5 MPa) yielded the product as colorless oil that solidified in the freezer (2.2 mg, 36%). $[\alpha]_D^{25}$ = +8.3 (c = 0.02, MeOH). ^{1}H NMR (500 MHz, MeOD) δ 7.27 (d, J = 15.6 Hz, 1H), 5.93 (dd, J = 6.7, 8.5 Hz, 1H), 5.86 – 5.74 (m, 1H), 5.79 (d, J = 15.9 Hz, 1H), 5.59 (ddt, J = 15.1, 6.8, 1.1 Hz, 1H), 5.57 – 5.49 (m, 1H), 5.48 – 5.46 (m, 1H), 5.45 (ddd, J = 9.5, 6.9, 5.1 Hz, 1H), 5.28 (t, J = 7.4 Hz, 1H), 4.85 (m, 2H, overlapped by H_2O signal), 4.12 (ddd, J = 10.2, 5.9, 4.5 Hz, 1H), 4.05 (dt, J = 9.8, 4.6 Hz, 1H), 3.99 (td, J = 6.6, 2.8 Hz, 1H), 3.92 (ddd, J = 9.6, 8.4, 2.9 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.75 (dd, J = 15.4, 5.1 Hz, 1H), 3.67 (s, 3H), 3.69 – 3.61 (m, 1H), 3.61 – 3.47 (m, 5H), 3.28 (s, 1H), 3.10 (t, J = 8.4 Hz, 1H), 3.04 (dd, J = 15.7, 8.5 Hz, 1H), 2.92 (dd, J = 16.1, 6.7 Hz, 1H), 2.87 (dd, J = 15.9, 2.9 Hz, 1H), 2.80 – 2.,73 (m, J = 2H), 2.69 (dd, J = 13.5, 9.5 Hz, 1H), 2.52 (ddd, J = 15.5, 9.1, 6.7 Hz, 1H), 2.42 (dd, J = 16.0, 9.6 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.25 – 2.00 (m, 7H), 1.97 – 1.86 (m, 3H), 1.79 (s, 3H), 1.76 – 1.72 (m, 1H) 1.72 (s, 3H), 1.63 – 1.42 (m, 4H), 1.39 (s, 3H), 1.03 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 176.2, 173.9, 168.3, 150.7, 147.3, 140.9, 135.1, 132.1, 131.9, 131.3, 131.1, 129.4, 129.2, 117.2, 113.1, 98.5, 86.2, 80.2, 79.4, 75.8, 75.3, 74.8, 74.7, 73.7, 73.6, 73.0, 72.8, 71.5, 71.4, 68.0, 52.3, 46.5, 41.9, 40.6, 40.5, 38.4 (two signals overlap), 38.3, 37.9, 37.0, 36.6, 36.2, 31.0, 30.4, 24.8, 23.9, 21.8, 16.7, 12.8. IR (neat): 3358, 2924, 2856, 1707, 1624, 1555, 1437, 1360, 1380, 1305, 1268, 1170, 1065, 1080, 1016, 979, 894, 844, 735, 702, 613, 628, 581, 566, 543, 525, 489, 415, 432 cm^{-1}. HRMS (ESI): m/z calculated for $C_{49}H_{75}NO_{17}Na$ [M+Na$^+$]: 972.49272, found: 972.49351.

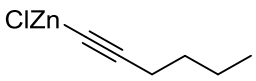
6.3 An Enantiodivergent Approach to Chiral Allenes:

3-(4-Methoxyphenyl)propanoyl chloride (S10): Oxalyl chloride (4.8 mL, 56 mmol) was added



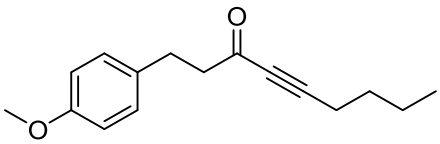
to a stirred suspension of 3-(4-methoxyphenyl)propionic acid (8.1 g, 45 mmol) and DMF (0.1 mL, 1.3 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After the addition the resulting mixture was warmed to ambient temperature. After being stirred for 12 h, the reaction mixture was transferred into a distillation apparatus. The solvent was removed at ambient temperature (~ 10 mbar). The residue was distilled at 1 mbar. The product was collected at 130 – 132 °C / 1 mbar as pale yellow liquid. This material was used directly.

Hex-1-yn-1-ylzinc(II) chloride (S11): A solution of *n*-butyllithium (1.5 M in hexane, 65 mL, 98



mmol) was added slowly to a stirred solution of 1-hexyne (13 mL, 113 mmol) in THF (30 mL) at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was warmed to 0 °C. After 30 min a solution of dry, freshly fused zinc chloride (15.9 g, 117 mmol) in THF (100 mL) was added via cannula to the reaction mixture. The resulting mixture was allowed to reach ambient temperature and was used directly.

1-(4-Methoxyphenyl)non-4-yn-3-one (S12): A solution of hex-1-yn-1-ylzinc(II) chloride (~ 0.5

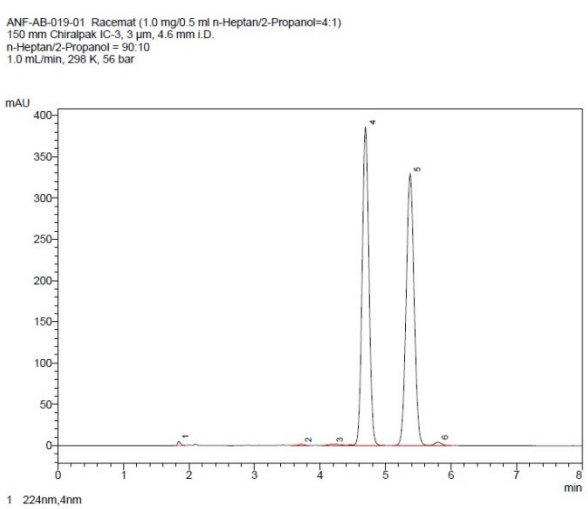


M in THF/hexane, 100 mL, ~ 50 mmol) was added to a stirred solution of acid chloride **S10** (7.4 g, 37 mmol) and tetrakis(triphenylphosphine)palladium(0) (215 mg, 0.186 mmol) in THF (20 mL) at 0 °C. The resulting mixture was allowed to reach ambient temperature. After 2 h saturated aqueous ammonium chloride solution (50 mL) was added, the layers were separated and the aqueous layer was extracted with *tert* butyl methyl ether (3x50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc 19:1 → 17:1) yielded the product as pale yellow oil (7.48 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 2.95 – 2.88 (m, 2H), 2.87 – 2.74 (m, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.63 – 1.49 (m, 2H), 1.49 – 1.35 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.3, 158.1, 132.4, 129.3, 114.0, 94.9, 80.9, 55.3, 47.3, 29.8, 29.2, 22.0, 18.7, 13.5. IR (neat): 3000, 2958, 2934, 2873, 2836, 2250, 2214, 1669, 1612, 1584, 1512, 1465, 1442, 1422, 1405, 1380, 1361, 1324, 1300, 1245, 1177, 1160, 1106, 1035, 995, 978, 907, 824, 728, 648, 575, 539,

518, 486 cm^{-1}. HRMS (ESI): m/z calculated for $C_{16}H_{20}O_2Na$ [M+Na^+]: 267.13555, found 267.13590.

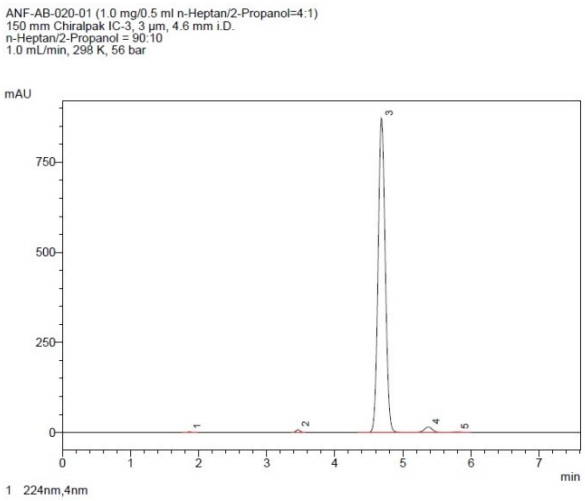
(*S*)-1-(4-Methoxyphenyl)non-4-yn-3-ol (S13): RuCl[(*S,S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) [155] (42 mg, 0.07 mmol) was added to a stirred solution of ketone **S12** (1.12 g, 4.6 mmol) in isopropanol (40 mL). After 1.5 h, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc 9:1 → 7:1) yielded the product as pale yellow oil (0.98 g, 87%). $[\alpha]_D^{20}$ = +32.1 (c = 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.35 (td, J = 6.5, 4.6 Hz, 1H), 3.79 (s, 3H), 2.73 (t, J = 7.8 Hz, 2H), 2.23 (td, J = 7.0, 2.0 Hz, 2H), 2.07 – 1.85 (m, 2H), 1.71 (d, J = 5.3 Hz, 1H), 1.56 – 1.36 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 133.7, 129.5, 114.0, 86.1, 81.1, 62.2, 55.4, 40.1, 30.9, 30.7, 22.1, 18.5, 13.7. IR (neat): 3383, 2955, 2931, 2861, 2835, 1611, 1584, 1511, 1465, 1379, 1327, 1300, 1243, 1176, 1106, 1035, 905, 822, 807, 746, 704, 566, 522 cm^{-1}. HRMS (ESI): m/z calculated for $C_{16}H_{22}O_2Na$ [M+Na^+]: 269.15120, found 269.15149.

The enantiomeric excess of the product was determined by chiral HPLC to be 95.9%. Conditions: 150 mm Chiralpak IC-3, 3 µm, 4.6 mm i.D., n-Heptan/2-Propanol = 90:10, 1.0 mL/min, 298 K, 56 bar.



PDA Ch1 224nm

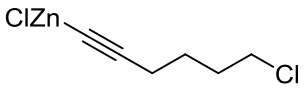
Peak #	Ret. Time	Area %	Name
1	1,84	0,27	
2	3,71	0,16	
3	4,19	0,44	
4	4,69	49,24	1. Enantiomer
5	5,37	49,35	2. Enantiomer
6	5,80	0,54	
Total		100,00	



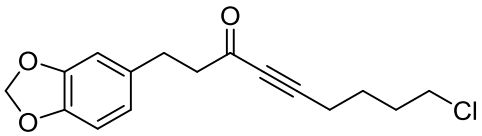
PDA Ch1 224nm

Peak #	Ret. Time	Area %	Name
1	1,86	0,10	
2	3,45	0,49	
3	4,68	97,19	1. Enantiomer 95.9 % ee
4	5,37	2,01	2. Enantiomer
5	5,79	0,21	
Total		100,00	

(6-Chlorohex-1-yn-1-yl)zinc(II) chloride (S14): A solution of *n*-butyllithium (1.6 M in hexane, 22 mL, 35 mmol) was added slowly to a stirred solution of 6-chloro-1-hexyne (4.5 mL, 37 mmol) in THF (30 mL) at −78 °C. After being 1 h solution of dry zinc chloride (1 M in THF, 39 mL, 39 mmol) was added via cannula to the reaction mixture. After 30 min resulting mixture was warmed to 0 °C and was used directly.

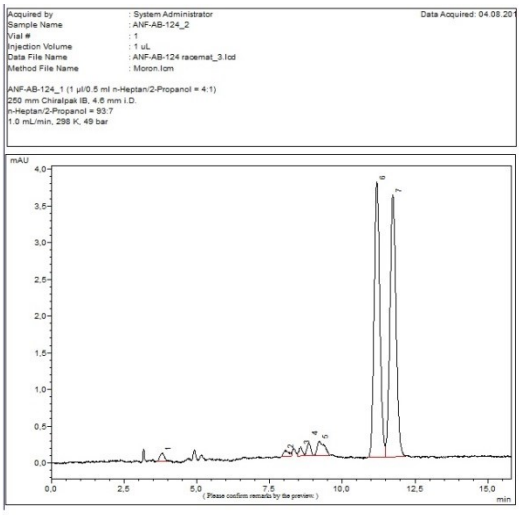


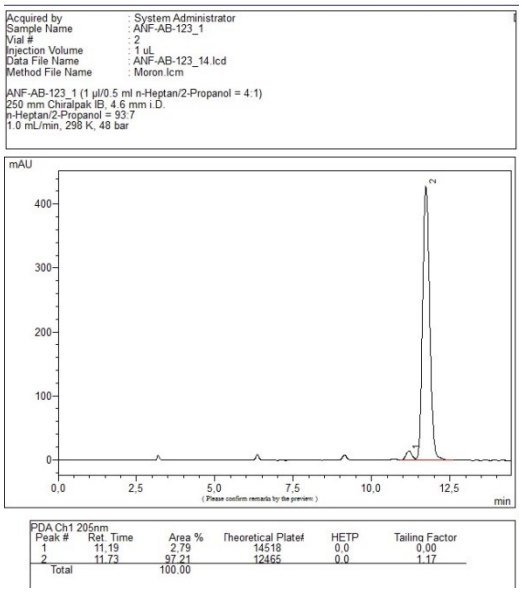
3-(Benzo[d][1,3]dioxol-5-yl)propanoic acid (S15): Thionyl chloride (5.5 mL, 76 mmol) was added to a stirred solution of 3-(3,4-methylenedioxyphenyl)propionic acid (6.4 g, 33 mmol) in benzene (65 mL). The reaction mixture was heated under reflux for 2 h. The reaction mixture was cooled to ambient temperature and was concentrated under reduced pressure. The residue was dissolved in THF (20 mL) and cooled to 0 °C. This solution and tetrakis(triphenylphosphine)palladium(0) (199 mg, 0.172 mmol) were successively added to the solution of (6-chlorohex-1-yn-1-yl)zinc(II) chloride (~35 mmol) at 0 °C and the resulting reaction mixture was stirred at ambient temperature. After 1.5 h saturated aqueous ammonium chloride solution (50 mL) was added, the layers were separated and the aqueous layer was extracted with *tert* butyl methyl ether (3x40 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc 9:1) yielded the product as pale yellow oil (7.25 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 3.56 (t, J = 6.4 Hz, 2H), 2.89 (ddd, J = 7.8, 6.6, 1.7 Hz, 2H), 2.85 – 2.76 (m, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.83 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.0, 147.8, 146.1, 134.2, 121.3, 109.0, 108.4, 101.0, 93.6, 81.4, 47.4, 44.3, 31.5, 29.8, 25.0, 18.4. IR (neat): 2953, 2899, 2779, 2212, 1669, 1608, 1503, 1488, 1443, 1403, 1364, 1334, 1292, 1243, 1189, 1161, 1121, 1098, 1038, 991, 934, 861, 810, 771, 738, 725, 713, 650, 603, 586, 505 cm^{-1}. HRMS (GC-EI): m/z calculated for $C_{16}H_{17}O_3Cl$ [M^+]: 292.08607, found 292.08608.



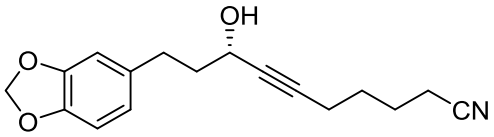
(*S*)-1-(Benzo[d][1,3]dioxol-5-yl)-9-chlorononon-4-yn-3-ol (S16): A solution of RuCl[(*S,S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) [155] (201 mg, 0.337 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of ketone **S15** (6.1 g, 21 mmol) in degassed isopropanol (200 mL). After 1.5 h, a second batch of RuCl[(*S,S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) (100 mg, 0.167 mmol) dissolved in CH_2Cl_2 (2 mL) was added to the reaction mixture. After 3 h in total, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 85:15 → 5:1) yielded the product as pale yellow oil (5.1 g, 83%). $[\alpha]_{D}^{20}$ = +31.2 (c = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 7.8, 1.7 Hz, 1H), 5.92 (s, 2H), 4.41 – 4.24 (m, 1H), 3.57 (t, J = 6.5 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.28 (td, J = 6.9, 2.0 Hz, 2H), 2.00 – 1.84 (m, 4H), 1.81 (d, J = 5.1 Hz, 1H), 1.74 – 1.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.8, 135.3, 121.3, 109.1, 108.3, 100.9, 85.1, 81.8, 62.0, 44.6, 4.95, 3.7, 31.3, 25.9, 18.2. IR (neat): 3372, 2944, 2866, 2777, 1608, 1502, 1488, 1441, 1333, 1301, 1243, 1187, 1124, 1097, 1036, 926, 905, 862, 810, 772, 724, 648, 604, 505, 422 cm^{-1}. HRMS (ESI): m/z calculated for $C_{16}H_{19}O_3ClNa$ [M+Na^+]: 317.09149, found 317.09140.

The enantiomeric excess of the product was determined by chiral HPLC to be 94.4%. Conditions: 250 mm Chiralpak IB, 4.6 mm i.D., n-Heptan/2-Propanol = 93:7, 1.0 mL/min, 298 K, 48 bar.

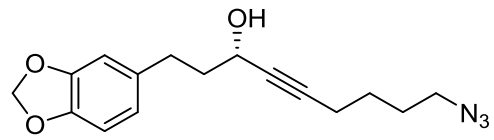




(*S*)-10-(Benzo[d][1,3]dioxol-5-yl)-8-hydroxydec-6-ynenitrile (S17): Compound **S16** (830 mg, 2.82 mmol) was added to a suspension of sodium iodide (48 mg, 0.32 mmol) and sodium cyanide (302 mg, 6.16 mmol) in DMF (3 mL). The resulting mixture was stirred at 60 °C for 18 h. The reaction mixture was cooled to ambient temperature and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (4x20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2x20 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 65:35 → 50:50) yielded the product as colorless oil (650 mg, 81%). $[\alpha]_{D}^{20}$ = +27.8 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 4.38 – 4.29 (m, 1H), 2.69 (t, J = 7.7 Hz, 2H), 2.39 (t, J = 6.9 Hz, 2H), 2.30 (td, J = 6.7, 2.0 Hz, 2H), 2.02 – 1.86 (m, 2H), 1.84 – 1.74 (m, 3H), 1.73 – 1.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.9, 135.2, 121.3, 119.6, 109.1, 108.3, 100.93, 84.4, 82.2, 61.9, 39.9, 31.3, 27.5, 24.6, 18.1, 17.0. IR (neat): 3411, 2936, 2865, 2779, 2247, 1608, 1503, 1489, 1442, 1351, 1332, 1245, 1188, 1098, 1122, 1037, 926, 905, 862, 811, 774, 748, 725, 714, 685, 639, 606, 553, 552 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{19}NO_3Na$ [M+Na^+]: 308.12571, found 308.12572.

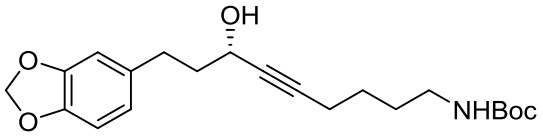


(*S*)-9-Azido-1-(benzo[d][1,3]dioxol-5-yl)non-4-yn-3-ol (S18): Compound **S16** (1.48 g, 5.0 mmol) was added to a suspension of sodium iodide (158 mg, 1.05 mmol) and sodium azide (652 mg, 10.0 mmol) in DMF (5 mL). The resulting mixture was stirred at 60 °C for 28 h. The reaction mixture was cooled to ambient temperature, diluted with water (50 mL) and extracted with *tert*-butyl methyl ether (4 x 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 30 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 4:1 → 3:1) yielded the product as colorless oil (1.02 g, 68%). $[\alpha]_{D}^{20}$ = +28.8 (c = 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 1.7 Hz, 1H), 6.65 (dd, J = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 4.34 (dtd, J = 8.2, 6.5, 2.0 Hz, 1H), 3.31 (t, J = 6.7 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.28 (td, J = 6.9, 2.0 Hz, 2H), 1.94 (tt, J = 7.8, 6.5 Hz, 2H), 1.78 – 1.67 (m, 3H), 1.65 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.9, 135.3, 121.3, 109.1, 108.3, 100.9, 85.1, 81.9, 62.0, 51.1, 40.0, 31.4, 28.1, 25.9, 18.4. IR (neat):

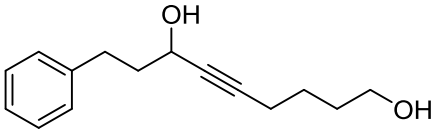


3392, 2931, 2865, 2776, 2197, 2093, 1608, 1502, 1488, 1441, 1352, 1333, 1242, 1187, 1120, 1097, 1035, 925, 905, 861, 809, 772, 749, 724, 713, 637, 604, 556, 503, 467, 421 cm^{-1}. HRMS (ESI): m/z calculated for $C_{16}H_{19}N_3O_3Na$ [M+Na^+]: 324.13186, found 324.13185.

***tert*-Butyl (*S*)-(9-(benzo[d][1,3]dioxol-5-yl)-7-hydroxynon-5-yn-1-yl)carbamate (S19):** A solution of **S18** (440 mg, 146 mmol) in THF (5 mL) and water (0.2 mL, 11 mmol) was added to a stirred solution of triphenylphosphine (480 mg, 1.83 mmol) in THF (5 mL). After 2.5 h, a solution of di-*tert*-butyl dicarbonate (365 mg, 1.67 mmol) in CH_2Cl_2 (2 mL) was added. After 4 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 7:3) yielded the product as colorless oil, which solidified in the freezer (354 mg, 65%). Melting range: 72 - 74 °C. $[\alpha]_D^{20}$ = +24.7 (c = 0.99, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 7.9, 1.7 Hz, 1H), 5.91 (s, 2H), 4.56 (bs, 1H), 4.33 (dtd, J = 8.5, 6.6, 2.0 Hz, 1H), 3.15 (q, J = 6.6 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.25 (td, J = 6.8, 2.0 Hz, 2H), 2.15 (bs, 1H), 2.02 – 1.86 (m, 2H), 1.63 – 1.50 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.14, 147.7, 145.8, 135.4, 121.3, 109.1, 108.3, 100.9, 85.4, 81.8, 79.4, 61.9, 39.9, 31.4, 29.4, 28.6, 25.7, 18.5. IR (neat): 3352, 2975, 2929, 2865, 1686, 1608, 1503, 1488, 1441, 1392, 1366, 1332, 1272, 1243, 1165, 1097, 1037, 927, 905, 863, 810, 781, 734, 713, 670, 639, 607, 508, 467, 436, 421, 408 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{29}NO_5Na$ [M+Na^+]: 398.19379, found 398.19414.

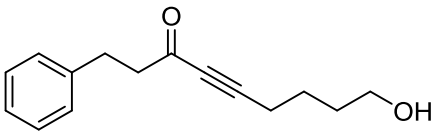


9-Phenylnon-5-yne-1,7-diol (S20): A solution of *n*-butyllithium (1.6 M in hexane, 12 mL, 19.2 mmol) was added to a stirred solution of 5-hexyn-1-ol (1.0 mL, 9.1 mmol) in THF (30 mL) at – 78 °C. After 1 h, the reaction mixture was warmed to 0 °C. After 30 min at 0 °C, the reaction mixture was cooled to – 78 °C. 3-Phenylpropionaldehyde (1.2 mL, 9.1 mmol) was added. After 1 h the reaction mixture was warmed to 0 °C. After 30 min, saturated aqueous ammonium chloride solution (40 mL) was added, and the resulting mixture was warmed to ambient temperature and the layers were separated. The aqueous layer was extracted with *tert*-butyl methyl ether (3x30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane:EtOAc 1:1 → 2:3) yielded the product as colorless oil (1.43 g, 68%). ^{1}H NMR (400

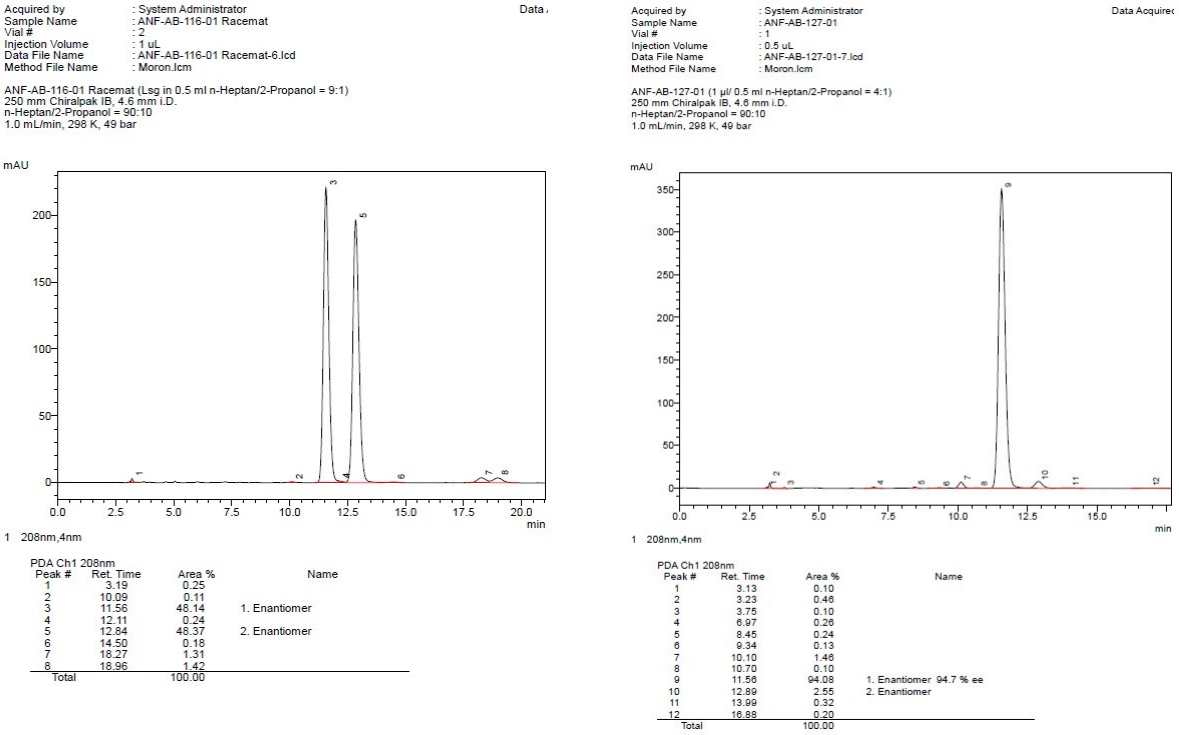


MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 4.43 – 4.30 (m, 1H), 3.68 (dt, J = 10.2, 5.0 Hz, 1H), 2.78 (t, J = 7.9 Hz, 2H), 2.28 (td, J = 6.8, 2.0 Hz, 2H), 2.07 – 1.91 (m, 2H), 1.74 – 1.57 (m, 3H), 1.44 (bs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 128.62, 128.55, 126.1, 85.6, 81.6, 62.5, 62.1, 39.8, 31.9, 31.6, 25.1, 18.6. IR (neat): 3329, 3085, 3063, 3026, 2936, 2863, 2233, 1603, 1496, 1454, 1431, 1331, 1155, 1133, 1056, 1030, 914, 780, 749, 699, 666, 587, 535, 495, 444, 431, 319 cm^{-1}. HRMS (ESI): m/z calculated for $C_{15}H_{20}O_2Na$ [M+Na^+]: 255.13555, found.

9-Hydroxy-1-phenylnon-4-yn-3-one (S21): Manganese dioxide [156] (3.2 g, ~ 85%, 33 mmol) was added to a stirred solution of **S20** (1.29 g, 5.55 mmol) in CH_2Cl_2 (10 mL). After 48 h a second batch of manganese dioxide (5.4 g, ~ 85%, 53 mmol) was added. After 24 h the reaction mixture was filtered through a plug of celite. The residue was rinsed with EtOAc (5x30 mL) and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 1:1 → 2:3) yielded the product as colorless oil (0.78 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.21 – 7.16 (m, 3H), 3.65 (bs, 2H), 3.00 – 2.92 (m, 2H), 2.85 (ddd, J = 8.3, 6.9, 1.1 Hz, 2H), 2.47 – 2.30 (m, 2H), 1.79 (bs, 1H), 1.73 – 1.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.3, 140.4, 128.6, 128.4, 126.3, 94.6, 81.1, 62.1, 47.0, 31.7, 30.0, 24.2, 18.8. IR (neat): 3412, 3086, 3063, 3027, 2935, 2868, 2210, 1666, 1604, 1497, 1454, 1422, 1403, 1362, 1327, 1287, 1245, 1205, 1159, 1058, 1030, 983, 937, 880, 845, 814, 770, 749, 698, 665, 588, 561, 487, 426, 443, 175 cm^{-1}. HRMS (ESI): m/z calculated for $C_{15}H_{18}O_2Na$ [M+Na^+]: 253.11909, found 253.11977.



(*S*)-9-Phenylnon-5-yne-1,7-diol (S22): A solution of RuCl[(*S,S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) [155] (43 mg, 0.072 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of ketone **S21** (0.767 g, 3.33 mmol) in degassed isopropanol (50 mL). After 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 1:1 → 2:3) yielded the product as pale yellow oil (0.66 g, 86%). $[\alpha]_{D}^{20}$ = +24.1 (c = 0.88, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 94.7%. Condition: 250 mm Chiralpak IB, 4.6 mm i.d., n-heptan/2-propanol = 90:10, 1.0 mL/min, 298 K, 49 bar

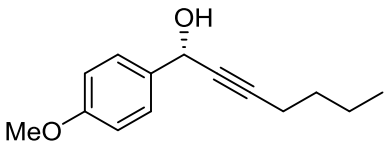


The remaining physical properties were identical as those of the corresponding racemate **S20**.

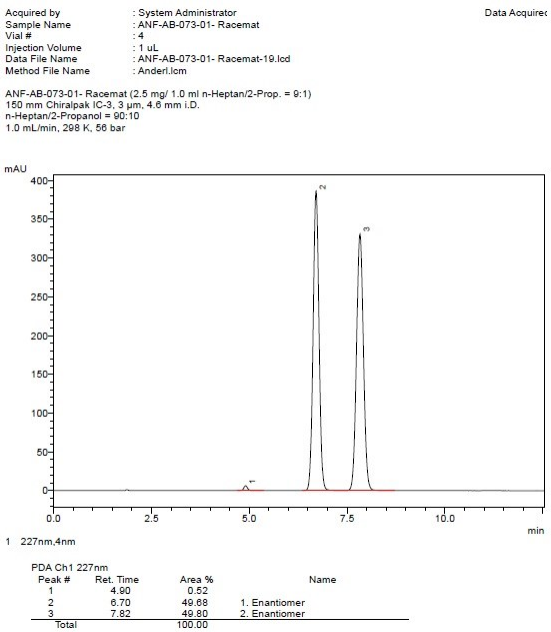
1-(4-Methoxyphenyl)hept-2-yn-1-one (S23): A solution of hex-1-yn-1-ylzinc(II) chloride (~ 0.5 M in THF/hexane, 50 mL, ~ 25 mmol) was added to a stirred solution of 4-methoxybenzoyl chloride (2.7 mL, 20 mmol) and tetrakis(triphenylphosphine)palladium(0) (127 mg, 0.11 mmol) in THF (20 mL) at 0 °C and the resulting mixture was allowed to reach ambient temperature. After 3 h, saturated aqueous ammonium chloride solution (30 mL) was added to the

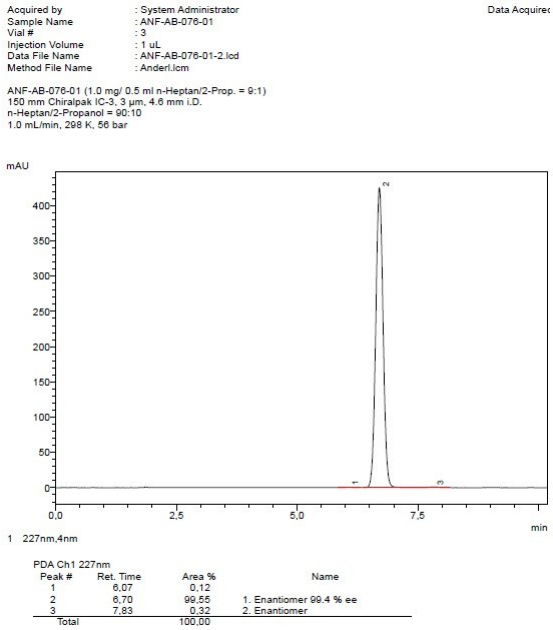
reaction mixture. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (3x30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 14:1 → 13:1) yielded the product as colorless oil (3.99 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H), 2.49 (t, J = 7.1 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.55 – 1.44 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 164.4, 132.1, 130.5, 113.9, 96.1, 79.8, 55.7, 30.1, 22.2, 19.1, 13.7. IR (neat): 3009, 2958, 2934, 2872, 2841, 2239, 2199, 1635, 1593, 1574, 1508, 1459, 1442, 1421, 1380, 1316, 1302, 1251, 1182, 1164, 1113, 1027, 962, 985, 910, 845, 813, 795, 758, 744, 687, 659, 629, 598, 509 cm^{-1}. HRMS (GC-EI): m/z calculated for $C_{14}H_{16}O_2$ [M^+]: 216.11448, found 216.11483.

(*S*)-1-(4-Methoxyphenyl)hept-2-yn-1-ol (S24): Borane dimethyl sulfide complex (1.6 mL, 18 mmol) was added to a stirred solution of ketone **S23** (1.3 g, 6.0 mmol) and (*S*)-(−)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 1.4 mL, 1.4 mmol) in THF (60 mL) at – 60 °C. After 96 h, methanol (8 mL) was added. After 3.5 h, the reaction mixture was warmed to ambient temperature and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 6:1 → 4:1) yielded the product as colorless oil (0.972 g, 74%). $[\alpha]_D^{20}$ = −24.2 (c = 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.01 – 6.80 (m, 2H), 5.40 (s, 1H), 3.81 (s, 3H), 2.28 (td, J = 7.0, 2.0 Hz, 2H), 2.06 (s, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.36 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 133.8, 128.2, 114.0, 87.6, 80.2, 64.6, 55.5, 30.8, 22.1, 18.7, 13.7. IR (neat): 3393, 2957, 2932, 2871, 2837, 1610, 1587, 1510, 1463, 1379, 1328, 1303, 1245, 1172, 1133, 1108, 1032, 992, 935, 887, 833, 765, 739, 695, 634, 596, 566 cm^{-1}. HRMS (GC-EI): m/z calculated for $C_{14}H_{18}O_2$ [M^+]: 218.13013, found 218.13005.

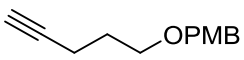


The enantiomeric excess of the product was determined by chiral HPLC to be 99.4%. Conditions: 150 mm Chiralpak IC-3, 3 µm, 4.6 mm i.D. n-heptan/2-propanol = 90:10, 1.0 mL/min, 298 K, 56 bar

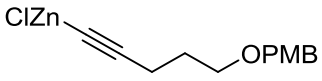




1-Methoxy-4-((pent-4-yn-1-yloxy)methyl)benzene (S25): 4-Pentyne-1-ol (2.8 mL, 30 mmol) was added slowly to a stirred suspension of sodium hydride (1.07 g, 44.6 mmol) in THF (60 mL). After 45 min, tetrabutylammonium iodide (1.1 g, 3 mmol) and 4-methoxybenzyl chloride (4.1 mL, 30 mmol) were added to the reaction mixture. After 120 h saturated aqueous ammonium chloride solution (50 mL) was added carefully, and the layers were separated and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane:EtOAc 14:1) yielded the product as colorless liquid (5.47 g, 89%). The physical properties of the product were in full accordance with the literature: [157]



(5-((4-Methoxybenzyl)oxy)pent-1-yn-1-yl)zinc(II) chloride (S26): A solution of n-butyllithium (1.6 M in hexane, 16 mL, 25.6 mmol) was added to a stirred solution of alkyne **S25** (5.4 g, 26 mmol) in THF (30 mL) at – 78 °C. After 30



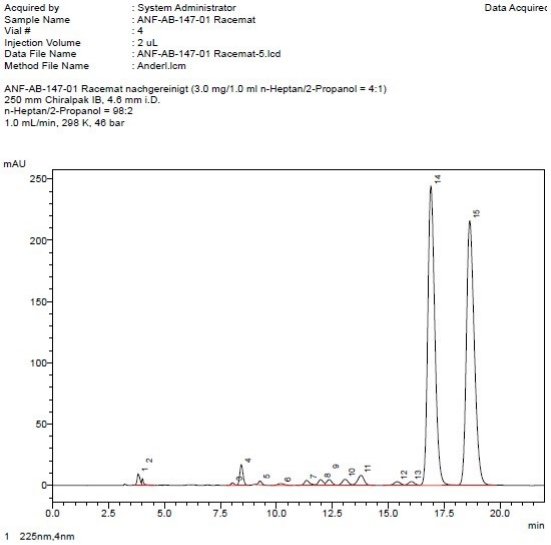
min, the reaction mixture was warmed to 0 °C. After 45 min a solution of zinc chloride (1 M in THF, 27 mL, 27 mmol) was added via cannula to the reaction mixture. After 45 min this mixture was used directly as ~ 0.35 M solution of the organozinc reagent.

1-Cyclohexyl-6-((4-methoxybenzyl)oxy)hex-2-yn-1-one (S27): Tetrakis(triphenylphosphine) palladium(0) (51 mg, 0.044 mmol) and cyclohexanecarboxylic acid chloride (1.1 mL, 8.2 mmol) were added to a solution of (5-((4-methoxybenzyl)oxy)pent-1-yn-1-yl)zinc(II) chloride (~ 0.35 M in THF/hexane, 25 mL, 8.8 mmol) at 0 °C and the resulting mixture was warmed to ambient temperature. After 2.5 h, saturated aqueous ammonium chloride solution (25 mL) was added, the layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (3x25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane:EtOAc 9:1) yielded the product as colorless oil (2.33 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.53 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 7.1 Hz, 2H), 2.33 (tt, J = 11.0, 3.6 Hz, 1H), 1.98 – 1.91 (m, 2H), 1.86 (tt, J = 7.1, 6.1 Hz, 2H), 1.80 – 1.73 (m, 2H), 1.69 – 1.60 (m, 1H), 1.44 – 1.15 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 159.3, 130.4, 129.4, 113.9, 94.3, 80.4, 72.9, 68.2, 55.4, 52.4, 28.4, 28.2, 25.9, 25.5, 16.1. IR (neat): 3000, 2930, 2854, 2795, 2210, 1664, 1612, 1586, 1512, 1463, 1450, 1423, 1391, 1364, 1348, 1302, 1244, 1215, 1191, 1171, 1164, 1126, 1100, 1078, 1034, 966, 956, 920, 894, 877, 844, 818, 782, 760, 708, 670, 637, 586, 572, 553, 516, 483, 476, 445 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{26}O_3Na$ [M+Na^+]: 337.17741, found 337.17750.

(*S*)-1-Cyclohexyl-6-((4-methoxybenzyl)oxy)hex-2-yn-1-ol (S28): A solution of RuCl[(*S,S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2](η^6-cymene) [155] (86 mg, 0.144mmol) in CH_2Cl_2 (1 mL) was added to a stirred solution of ketone **S27** (2.25 g, 7.16 mmol) in degassed isopropanol (71 mL). After 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc 4:1 → 3:1) yielded the product as pale yellow oil (1.66 g, 73%). $[\alpha]_{D}^{20}$ = +3.1 (c = 1.17, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 4.15 – 4.06 (m, 1H), 3.80 (s, 3H), 3.53 (t, J = 6.2 Hz, 2H), 2.33 (td, J = 7.0, 2.0 Hz, 2H), 1.86 – 1.72 (m, 6H), 1.67 (dtd, J = 12.4, 3.0, 1.5 Hz, 1H),

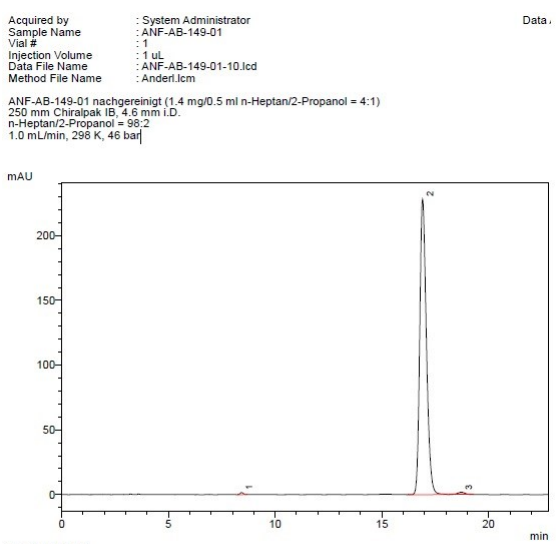
1.62 (dd, J = 5.7, 1.0 Hz, 1H), 1.54 – 1.41 (m, 1H), 1.30 – 0.97 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 130.7, 129.4, 113.9, 85.7, 80.6, 72.8, 68.6, 67.6, 55.4, 44.5, 29.0, 28.7, 28.3, 26.6, 26.1, 26.0, 15.8. IR (neat): 3416, 2924, 2851, 1612, 1586, 1513, 1464, 1450, 1364, 1347, 1326, 1302, 1247, 1209, 1173, 1100, 1080, 1034, 1011, 983, 893, 844, 820, 758, 598, 578, 546, 540, 517, 505, 486 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{28}O_3Na$ [M+Na$^+$]: 339.19306, found 339.19271.

The enantiomeric excess of the product was determined by chiral HPLC to be 98.1%. Conditions: 250 mm Chiralpak IB, 4.6 mm i.D. n-heptan/2-propanol = 98:2, 1.0 mL/min, 298 K, 46 bar.



PDA Ch1 225nm

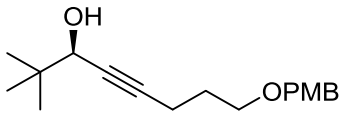
Peak #	Ret. Time	Area %	Name
1	3.81	0.67	
2	4.01	0.29	
3	8.04	0.19	
4	8.43	1.49	
5	9.27	0.27	
6	10.21	0.26	
7	11.35	0.60	
8	11.98	0.83	
9	12.36	0.68	
10	13.07	0.82	
11	13.78	1.43	
12	15.40	0.54	
13	16.03	0.51	
14	16.91	45.92	1. Enantiomer
15	18.64	45.69	2. Enantiomer
Total		100.00	



PDA Ch1 225nm

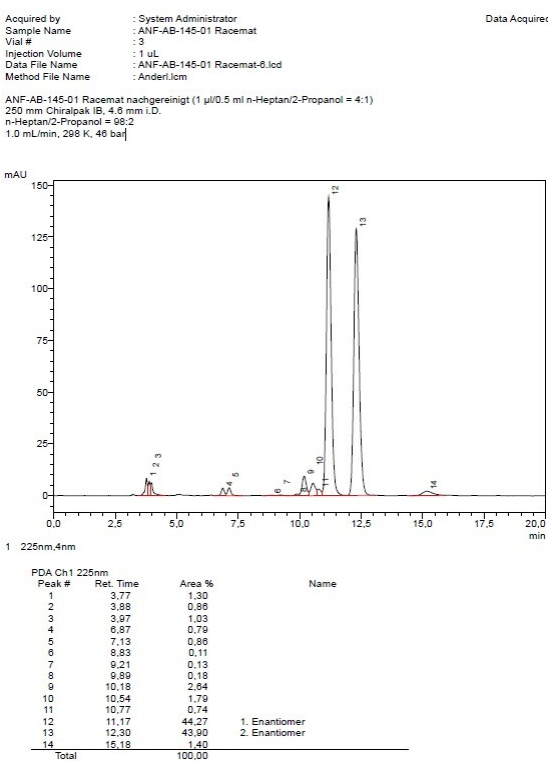
Peak #	Ret. Time	Area %	Name
1	8.42	0.31	
2	16.90	98.75	1. Enantiomer 98.1 % ee
3	18.71	0.94	2. Enantiomer
Total		100.00	

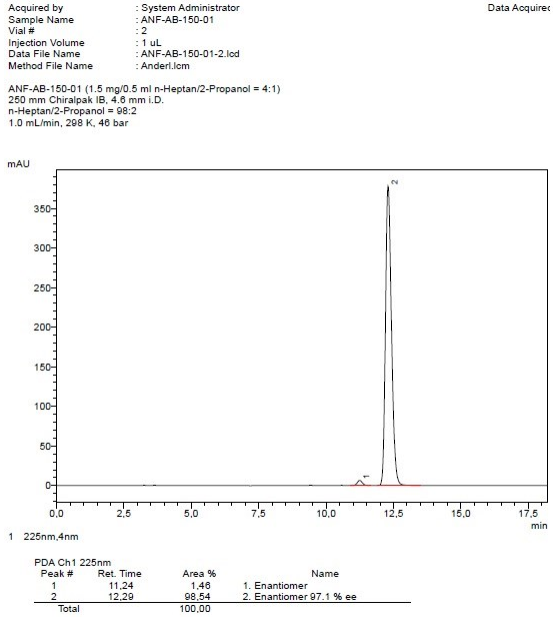
(*R*)-8-((4-Methoxybenzyl)oxy)-2,2-dimethyloct-4-yn-3-ol (S29): Triethylamine (0.54 mL, 3.9 mmol) was added to a stirred solution/suspension of (1*S*,2*R*)-(+)-N-methylephedrine (683 mg, 3.81 mmol) and dried zinc trifluoromethanesulfonate (1.27 g, 3.49 mmol) in toluene (7 mL). After 40 min a solution of alkyne **S25** (612 mg, 3.0 mmol) in toluene (2 mL) was added. After 30 min trimethylacetaldehyde (0.36 mL, 3.3 mmol) was added to the reaction mixture. After 26 h saturated aqueous ammonium chloride solution (20 mL), the layers were separated and the



aqueous layer was extracted with *tert*-butyl methyl ether (3x30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL), dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane:EtOAc 5:1 → 4:1) yielded the product as colorless oil (0.55 g, 63%).$[\alpha]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.6 (c = 1.16, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.44 (s, 2H), 3.96 (dt, J = 6.1, 2.0 Hz, 1H), 3.80 (s, 3H), 3.53 (t, J = 6.2 Hz, 2H), 2.33 (td, J = 7.0, 2.0 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.67 (dd, J = 6.1, 0.8 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 130.7, 129.4, 113.9, 85.6, 80.2, 72.8, 71.7, 68.6, 55.4, 36.0, 29.1, 25.4, 15.7. IR (neat): 3439, 2953, 2905, 2866, 1612, 1586, 1512, 1479, 1463, 1443, 1392, 1362, 1323, 1302, 1245, 1210, 1173, 1134, 1099, 1076, 1035, 1005, 935, 904, 891, 846, 820, 760, 708, 637, 582, 540, 516 cm^{-1}. HRMS (ESI): m/z calculated for $C_{18}H_{26}O_3Na$ [M+Na^+]: 313.17741, found 313.17713.

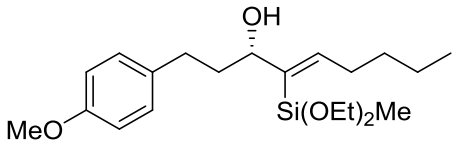
The enantiomeric excess of the product was determined by chiral HPLC to be 97.1%. Conditions: 250 mm Chiralpak IB, 4.6 mm i.D., n-heptan/2-propanol = 98:2, 1.0 mL/min, 298 K, 46 bar.



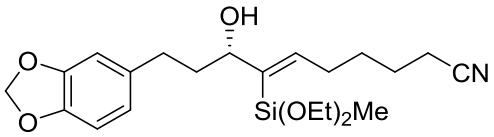


General Procedure A: Ruthenium-catalyzed *trans*-hydrosilylation: Methyldiethoxysilane (1.05 – 1.1 equiv.) was added to a stirred solution of the propargylic alcohol and $[Cp^*RuCl]_4$ (2.5 – 5mol% [Ru]) in CH_2Cl_2 (0.2 M). When the starting material was completely consumed as judged by TLC, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography yielded the corresponding *Z*-alkenylsilane.

(*S,Z*)-4-(Diethoxy(methyl)silyl)-1-(4-methoxyphenyl)non-4-en-3-ol (*Z*-142): Via general procedure A from **S13**. Flash chromatography: hexane:EtOAc = 10:1. Yield: 340 mg, 53%. $[\alpha]_D^{20} = -4.3$ (c = 0.88, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.11 (t, J = 7.6 Hz, 1H), 3.93 (q, J = 7.8 Hz, 1H), 3.85 – 3.72 (m, 7H), 3.46 (d, J = 10.2 Hz, 1H), 2.66 (ddd, J = 13.9, 10.3, 5.6 Hz, 1H), 2.54 (ddd, J = 13.9, 10.2, 6.1 Hz, 1H), 2.29 – 2.13 (m, 2H), 1.97 (dddd, J = 13.4, 10.2, 7.8, 5.7 Hz, 1H), 1.77 (ddt, J = 13.0, 10.3, 6.2 Hz, 1H), 1.42 – 1.29 (m, 4H), 1.28 – 1.19 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H), 0.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 146.9, 138.4, 134.7, 129.5, 113.9, 79.7, 58.4, 55.4, 40.8, 32.01, 31.97, 31.4, 22.7, 18.4, 18.3, 14.2, −1.9. IR (neat): 3502, 2956, 2925, 2873, 2835, 1612, 1584, 1511, 1455, 1412, 1390, 1364, 1299, 1244, 1175, 1165, 1070, 1101, 1038, 946, 873, 819, 802, 760, 730, 702, 690, 638, 566, 546, 513, 444, 429, 213 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{36}O_4SiNa$ $[M+Na^+]$: 403.22751 , found 403.22766.

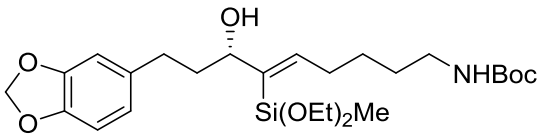


(*S,Z*)-10-(Benzo[d][1,3]dioxol-5-yl)-7-(diethoxy(methyl)silyl)-8-hydroxydec-6-enenitrile (*Z*-144): Via general procedure A from **S17**. Flash chromatography: hexane:EtOAc = 5:1. Yield = 115 mg, 48%. $[\alpha]_D^{20} = -4.3$ (c = 0.62, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 6.07 (td, J = 7.5, 0.9 Hz, 1H), 5.92 (s, 2H), 3.99 – 3.88 (m, 1H), 3.86 – 3.72 (m, 4H), 3.33 (d, J = 10.0 Hz, 1H), 2.65 (ddd, J = 13.8, 10.1, 5.5 Hz, 1H), 2.53 (ddd, J = 13.9, 9.9, 6.4 Hz, 1H), 2.36 (t, J = 7.0 Hz, 2H), 2.27 (qd, J = 7.3, 5.8 Hz, 2H), 1.93 (dddd, J = 13.6, 9.9, 8.2, 5.5 Hz, 1H), 1.82 – 1.69 (m, 1H), 1.73 – 1.63 (m, 2H), 1.62 – 1.49 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.7, 144.7, 140.1, 136.3, 121.3, 119.6, 109.1, 108.3, 100.9, 79.2, 58.52, 58.49, 40.7, 32.6, 30.7, 28.8, 25.2, 18.4, 18.3, 17.28, -1.9. IR(neat): 3495, 2972, 2926, 2244, 1612, 1503, 1488, 1441, 1390, 1364, 1243, 1187, 1164, 1099,

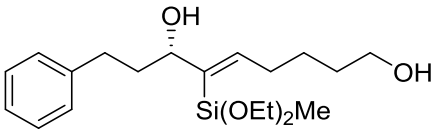


1069, 1037, 936, 857, 804, 760, 688, 640, 559, 504, 423 cm^{-1}. HRMS (ESI): m/z calculated for $C_{22}H_{33}NO_5SiNa$ [M+Na^+]: 442.20202, found 442.20244.

***tert*-Butyl (*S,Z*)-(9-(benzo[d][1,3]dioxol-5-yl)-6-(diethoxy(methyl)silyl)-7-hydroxynon-5-en-1-yl)carbamate (*Z*-146):** Via general procedure A from **S19**. Flash chromatography: hexane:EtOAc = 3:1. Yield = 191 mg, 70%. $[\alpha]_D^{20}$ = − 2.4 (c = 0.9, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.8, 1.7 Hz, 1H), 6.08 (td, J = 7.6, 0.9 Hz, 1H), 5.91 (s, 2H), 4.51 (bs, 1H), 3.97 – 3.88 (m, 1H), 3.78 (qd, J = 7.0, 5.0 Hz, 4H), 3.40 (d, J = 10.1 Hz, 1H), 3.11 (q, J = 6.6 Hz, 2H), 2.64 (ddd, J = 13.7, 10.2, 5.5 Hz, 1H), 2.52 (ddd, J = 13.8, 10.0, 6.3 Hz, 1H), 2.22 (qd, J = 7.4, 6.0 Hz, 2H), 1.93 (dddd, J = 13.6, 10.0, 8.1, 5.6 Hz, 1H), 1.75 (ddt, J = 13.5, 10.2, 6.2 Hz, 1H), 1.49 (q, J = 6.9 Hz, 2H), 1.43 (s, 9H), 1.41 – 1.36 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 147.7, 146.0, 145.6, 139.1, 136.4, 121.3, 109.1, 108.3, 100.9, 79.3, 58.5, 40.8, 32.6, 31.26, 30.1, 28.6, 27.0, 18.4, 18.3, -1.9. IR (neat): 3358, 3344, 3013, 2973, 2928, 2885, 1694, 1611, 1504, 1488, 1441, 1391, 1365, 1244, 1165, 1100, 1070, 1039, 1001, 937, 857, 804, 761, 731, 675, 666, 646, 600, 557, 514, 507, 492, 485, 463, 454, 438, 431 cm^{-1}. HRMS (ESI): m/z calculated for $C_{26}H_{43}NO_7SiNa$ [M+Na^+]: 532.27010, found 532.27034.

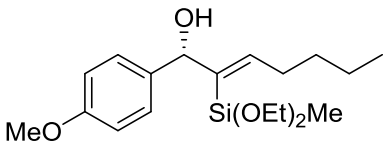


(*S,Z*)-6-(Diethoxy(methyl)silyl)-9-phenylnon-5-ene-1,7-diol (*Z*-148): Via general procedure A from **S22**. Flash chromatography: hexane:*tert*-butyl methyl ether (3:1 → 2:1). Yield = 101 mg, 50%. $[\alpha]_D^{20}$ = − 9.3 (c = 0.5, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 6.12 (td, J = 7.6, 0.9 Hz, 1H), 4.02 – 3.89 (m, 1H), 3.85 – 3.73 (m, 4H), 3.65 (td, J = 6.4, 5.2 Hz, 2H), 3.44 (dd, J = 10.2, 0.8 Hz, 1H), 2.73 (ddd, J = 13.7, 10.5, 5.5 Hz, 1H), 2.60 (ddd, J = 13.8, 10.3, 6.1 Hz, 1H), 2.26 (qd, J = 7.3, 4.8 Hz, 2H), 2.00 (dddd, J = 13.5, 10.3, 7.9, 5.5 Hz, 1H), 1.81 (ddt, J = 13.5, 10.5, 6.1 Hz, 1H), 1.65 – 1.56 (m, 2H), 1.52 – 1.41 (m, 2H), 1.30 (q, J = 4.9 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 142.6, 139.0, 128.6, 128.5, 125.8, 79.6, 62.9, 58.5, 40.6, 32.9, 32.5, 31.3, 26.0, 18.4, 18.3, -1.9. IR (neat): 3408, 3064, 3026, 2972, 2926, 1614, 1496, 1454, 1390, 1364, 1294, 1258, 1164, 1101, 1067, 944, 817, 791, 760, 699,

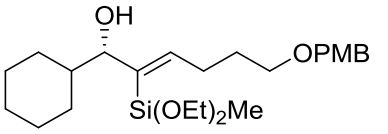


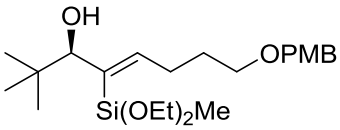
554, 491 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{34}O_4SiNa$ [M+Na^+]: 389.21186, found 389.21172.

(*S,Z*)-2-(Diethoxy(methyl)silyl)-1-(4-methoxyphenyl)hept-2-en-1-ol (*Z*-150): Via general procedure A from **S24**. Flash chromatography: hexane:EtOAc 10:1 + 1% Et_3N. Yield = 605 mg, 71%. $[\alpha]_D^{20}$ = − 51.0 (c = 0.66, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.25 (td, J = 7.6, 0.9 Hz, 1H), 5.10 (d, J = 9.3 Hz, 1H), 4.07 (d, J = 9.7 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.68 (m, 2H), 3.63 – 3.46 (m, 2H), 2.28 (qd, J = 7.4, 1.0 Hz, 2H), 1.49 – 1.32 (m, 4H), 1.20 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 147.6, 138.3, 136.8, 127.3, 113.3, 80.3, 58.4, 55.4, 32.0, 31.4, 22.7, 18.2, 18.2, 14.2, -2.3. IR (neat): 3478, 2959, 2925, 2874, 2836, 1611, 1584, 1509, 1465, 1442, 1390, 1364, 1301, 1245, 1170, 1101, 1071, 1037, 1007, 947, 885, 821, 802, 760, 676, 632, 582, 529, 508, cm^{-1}. HRMS (ESI): m/z calculated for $C_{19}H_{32}O_4SiNa$ [M+Na^+]: 375.19621, found: 375.19641.



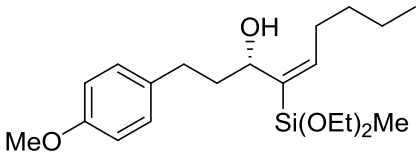
(*S,Z*)-1-Cyclohexyl-2-(diethoxy(methyl)silyl)-6-((4-methoxybenzyl)oxy)hex-2-en-1-ol (*Z*-152): Via general procedure A from **S28**. Flash chromatography: hexane:EtOAc = 6:1. Yield = 129 mg, 58% $[\alpha]_D^{20}$ = + 16.3 (c = 0.7, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.02 (td, J = 7.6, 0.8 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.83 – 3.71 (m, 4H), 3.53 – 3.39 (m, 3H), 3.24 (d, J = 10.7 Hz, 1H), 2.36 – 2.26 (m, 2H), 2.12 (d, J = 12.9 Hz, 1H), 1.81 – 1.60 (m, 5H), 1.50 (d, J = 12.8 Hz, 1H), 1.45 – 1.33 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.19 – 1.06 (m, 3H), 0.97 – 0.86 (m, 1H), 0.75 (qd, J = 12.2, 3.7 Hz, 1H), 0.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 146.7, 138.0, 130.7, 129.4, 113.9, 85.6, 72.7, 69.6, 58.37, 58.35, 55.4, 44.0, 30.7, 30.0, 29.8, 28.2, 26.7, 26.4, 26.3, 18.3, 18.3, -2.1. IR (neat): 3498, 2971, 2922, 2850, 1612, 1586, 1513, 1449, 1390, 1363, 1302, 1247, 1206, 1171, 1099, 1074, 1036, 949, 891, 820, 763, 691, 668, 637, 584, 514 cm^{-1}. HRMS (ESI): m/z calculated for $C_{25}H_{42}O_5SiNa$ [M+Na^+]: 473.26937, found: 473.26962.



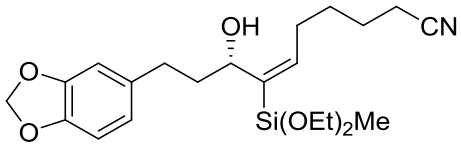
(*R,Z*)-4-(Diethoxy(methyl)silyl)-8-((4-methoxybenzyl)oxy)-2,2-dimethyloct-4-en-3-ol (*Z*-154): 

Via general procedure A from **S29**. Flash chromatography: hexane:EtOAc = 7:1. Yield = 40 mg, 16% $[\alpha]_{D}^{20}$ = + 13.3 (c = 0.62, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.09 (td, J = 7.7, 1.0 Hz, 1H), 4.42 (s, 2H), 4.02 (d, J = 10.5 Hz, 1H), 3.80 (s, 3H), 3.87 – 3.64 (m, 5H), 3.45 (t, J = 6.6 Hz, 2H), 2.37 – 2.28 (m, 2H), 1.78 – 1.65 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 148.9, 136.0, 130.7, 129.4, 113.9, 88.6, 72.7, 69.5, 58.5, 58.38, 55.4, 36.6, 30.0, 28.4, 27.2, 18.22, 18.19, -2.2. IR (neat): 3493, 2970, 2867, 1612, 1587, 1513, 1478, 1463, 1442, 1390, 1362, 1302, 1246, 1171, 1099, 1070, 1036, 1009, 945, 819, 758, 698, 666, 560, 514, 439 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{40}O_5SiNa$ [M+Na$^+$]: 447.25372, found: 447.25355.

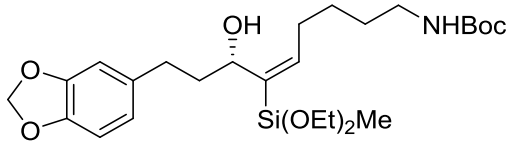
General procedure B: Platinum-catalyzed *cis*-hydrosilylation of propargylic alcohols: Methyldiethoxysilane (1.05 – 1.1 equiv.) was added to a stirred solution of the propargylic alcohol and $Pt(dba)_3$ (1mol%) in toluene (0.2 M). When the starting material was completely consumed, as judged by TLC, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography yielded the corresponding *E*-alkenylsilane. The desired major proximal isomer was in all examined cases the less polar one and eluted first.

(*S,E*)-4-(Diethoxy(methyl)silyl)-1-(4-methoxyphenyl)non-4-en-3-ol (*E*-142): 

Via general procedure B from **S13**. Flash chromatography: hexane:EtOAc = 9:1. Yield = 859 mg, 55%. $[\alpha]_{D}^{20}$ = − 41.3 (c = 1.16, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.88 (ddd, J = 7.7, 6.5, 1.3 Hz, 1H), 4.46 (td, J = 8.9, 5.1 Hz, 1H), 3.87 – 3.67 (m, 7H), 3.31 (d, J = 8.9 Hz, 1H), 2.73 (ddd, J = 14.2, 10.0, 5.0 Hz, 1H), 2.58 (ddd, J = 14.2, 10.0, 6.9 Hz, 1H), 2.16 – 1.99 (m, 1H), 1.99 – 1.82 (m, 2H), 1.76-1.61 (dddd, J = 13.7, 10.0, 6.9, 5.0 Hz, 1H), 1.43 – 1.15 (m, 10H), 0.87 (t, J = 7.1 Hz, 3H), 0.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 144.0, 140.4, 134.5, 129.5, 113.9, 71.1, 58.6, 55.4, 40.8, 31.5, 28.6, 22.6, 18.41, 18.38, 14.1, -2.9. IR (neat): 3499, 2957, 2926, 2862, 1612, 1584, 1512, 1456, 1390, 1299, 1246, 1165, 1073, 948, 762 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{36}O_4SiNa$ [M+Na$^+$]:403.22751, found: 403.22782.

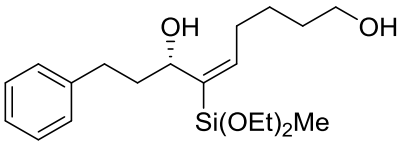
(*S,E*)-10-(Benzo[d][1,3]dioxol-5-yl)-7-(diethoxy(methyl)silyl)-8-hydroxydec-6-enenitrile (*E*-144): 

Via general procedure B from **S17**. Flash chromatography: hexane:EtOAc = 4:1. Yield = 132 mg, 44%. $[\alpha]_{D}^{20}$ = − 41.3 (c = 1.05, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.65 (dd, J = 7.9, 1.7 Hz, 1H), 5.924 (d, J = 1.4 Hz, 1H), 5.916 (d, J = 1.4 Hz, 1H), 5.83 (ddd, J = 7.6, 6.4, 1.1 Hz, 1H), 4.40 (dd, J = 9.1, 4.7 Hz, 1H), 3.80 (q, J = 7.0 Hz, 2H), 3.78 (q, J = 7.0 Hz, 2H), 3.26 (bs, 1H), 2.70 (ddd, J = 14.0, 9.2, 5.1 Hz, 1H), 2.58 (ddd, J = 14.0, 9.2, 7.6 Hz, 1H), 2.31 (t, J = 7.0 Hz, 2H), 2.12 (dq, J = 15.0, 7.6 Hz, 1H), 2.01 – 1.86 (m, 2H), 1.75 – 1.59 (m, 3H), 1.58-1.50 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H) 0.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.7, 141.9, 141.8, 136.0, 121.4, 119.6, 109.1, 108.2, 100.9, 70.6, 58.7, 40.6, 32.0, 28.2, 27.9, 25.1, 18.4, 17.1, -3.0. IR(neat): 3486, 2972, 2928, 2884, 2250, 1609, 1489, 1441, 1390, 1364, 1245, 1164, 1101, 1072, 1038, 937 cm^{-1}. HRMS (ESI): m/z calculated for $C_{22}H_{33}NO_5SiNa$ [M+Na$^+$]: 442.20202, found: 442.20204.

***tert*-Butyl (*S,E*)-(9-(benzo[d][1,3]dioxol-5-yl)-6-(diethoxy(methyl)silyl)-7-hydroxynon-5-en-1-yl)carbamate (*E*-146):** 

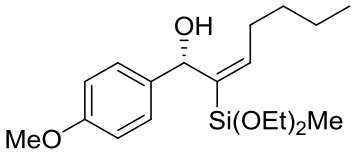
Via general procedure B from **S19**. Flash chromatography: hexane:EtOAc = 4:1. Yield = 128 mg, 63%. $[\alpha]_{D}^{20}$ = − 33.4 (c = 1.04, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.5Hz, 1H), 6.65 (dd, J = 7.9, 1.5 Hz, 1H), 5.91 (s, 2H), 5.85 (ddd, J = 7.6, 6.4, 1.1 Hz, 1H), 4.55 – 4.37 (m, 2H, H10), 3.80 (q, J = 7.0 Hz, 2H), 3.79 (q, J = 7.0 Hz, 2H), 3.31 (bs, 1H), 3.15 – 3.00 (m, 2H), 2.70 (ddd, J = 14.1, 9.6, 5.0 Hz, 1H), 2.56 (ddd, J = 14.1, 9.6, 7.1 Hz, 1H), 2.08 (dq, J = 14.9, 7.6 Hz, 1H), 2.00 – 1.82 (m, 2H), 1.72 – 1.55 (m, 1H), 1.50 – 1.28 (m, 13H), 1.23 (t, J = 7.0, 6H), 0.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 147.6, 145.6, 143.1, 141.1, 136.2, 121.3, 109.1, 108.3, 100.8, 79.2, 70.8, 58.6, 40.7, 40.5, 32.1, 29.9, 28.6, 28.4, 26.5, 18.4, -2.9. IR(neat): 3430, 3360, 2974, 2930, 1693, 1609, 1504, 1489, 1422, 1366, 1246, 1168, 1039, 938, 809 cm^{-1}. HRMS (ESI): m/z calculated for $C_{26}H_{43}NO_7SiNa$ [M+Na$^+$]: 532.27010, found: 532.27073.

(*S,E*)-6-(Diethoxy(methyl)silyl)-9-phenylnon-5-ene-1,7-diol (*E*-148): Via general procedure B



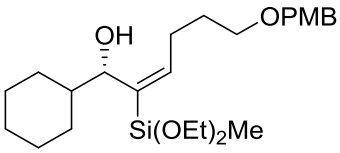
from **S22**. Flash chromatography: hexane:EtOAc = 7:3. Yield = 104 mg, 53%. $[\alpha]_D^{20}$ = − 40.2 (c = 1.03, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 5.96 – 5.80 (ddd, J = 7.6, 6.5, 1.1, 1H), 4.46 (ddd, J = 8.7, 4.9, 1.0 Hz, 1H), 3.80 (q, J = 7.0 Hz, 2H), 3.79 (q, J = 7.0 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H), 2.79 (ddd, J = 14.2, 9.9, 5.0 Hz, 1H), 2.65 (ddd, J = 14.2, 9.9, 7.0 Hz, 1H), 2.14 – 2.03 (m, 1H), 2.03 – 1.88 (m, 2H), 1.71 (dddd, J = 13.8, 9.9, 7.0, 5.0 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.46 – 1.37 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 142.4, 141.0, 128.7, 128.5, 125.9, 71.0, 62.8, 58.6, 40.5, 32.4, 28.5, 25.5, 18.6, 18.4, -2.9. IR(neat): 3420, 2971, 2926, 1605, 1496, 1454, 1390, 1257, 1102, 947, 761 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{34}O_4SiNa$ [M+Na^+]: 389.21186, found: 389.21196.

(*S,E*)-2-(Diethoxy(methyl)silyl)-1-(4-methoxyphenyl)hept-2-en-1-ol (*E*-150): Via general



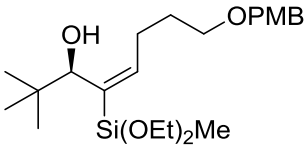
procedure B from **S24**. Flash chromatography: hexane:*tert*-butyl methyl ether = (95:5 → 85:15). Yield = 296 mg, 61%. $[\alpha]_D^{20}$ = − 57.9 (c = 1.13, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 3H), 4.67 (td, J = 9.0, 4.6 Hz, 1H), 3.94 – 3.76 (m, 7H), 3.11 (d, J = 9.0 Hz, 1H), 1.75 (dtd, J = 13.6, 9.4, 4.6 Hz, 1H), 1.67 – 1.52 (m, 1H), 1.52 – 1.41 (m, 1H), 1.41 – 1.19 (m, 9H), 0.89 (t, J = 7.2 Hz, 3H), 0.34 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 141.9, 140.0, 130.4, 129.9, 113.7, 71.5, 58.7, 55.4, 38.2, 28.4, 22.8, 18.4, 14.2, -2.7. IR(neat): 3498, 2957, 2929, 1607, 1508, 1465, 1442, 1390, 1293, 1250, 1176, 1075, 1035, 793, 766 cm^{-1}. HRMS (ESI): m/z calculated for $C_{19}H_{32}O_4SiNa$ [M+Na^+]: 375.19621, found: 375.19637.

(*S,E*)-1-Cyclohexyl-2-(diethoxy(methyl)silyl)-6-((4-methoxybenzyl)oxy)hex-2-en-1-ol (*E*-



152): Via general procedure B from **S28**. Flash chromatography: hexane:EtOAc = 9:1. Yield = 252 mg, 59%. $[\alpha]_D^{20}$ = + 73.1 (c = 1.10, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H, 6.87 (d, J = 8.7 Hz, 2H), 6.05 – 5.77 (m, 1H), 4.43 (s, 2H), 4.08 (d, J = 9.0 Hz, 1H), 3.85 – 3.67 (m, 7H), 3.58 – 3.35 (m, 2H), 3.37 (s, 1H), 2.30 (td, J = 15.1, 8.0 Hz, 1H), 2.23 – 1.94 (m, 2H), 1.94 – 1.45 (m, 6H), 1.45 – 1.30 (m, 1H), 1.30 – 1.04 (m, 9H), 1.04 – 0.89 (m, 1H), 0.88

– 0.74 (m, 1H) 0.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 144.0, 139.9, 130.8, 129.4, 113.9, 76.0, 72.7, 69.5, 58.5, 55.4, 44.8, 29.8, 29.7, 29.5, 26.7, 26.4, 26.3, 25.9, 18.4, -3.0. IR(neat): 3502, 1970, 2922, 2851, 1612, 1513, 1449, 1339, 1247, 1171, 1099, 1074, 952, 919, 762 cm^{-1}. HRMS (ESI): m/z calculated for $C_{26}H_{42}O_4SiNa$ [M+Na$^+$]: 473.26960, found: 473.26950.

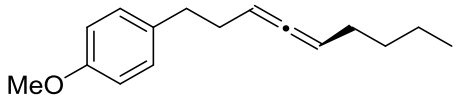
(*R,E*)-4-(Diethoxy(methyl)silyl)-8-((4-methoxybenzyl)oxy)-2,2-dimethyloct-4-en-3-ol (*E*-154): 

Via general procedure B from **S29**. Flash chromatography: hexane:EtOAc = 9:1. Yield = 152 mg, 54%. $[\alpha]_D^{20}$ = − 13.1 (c = 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.97 (ddd, J = 8.7, 5.2, 1.2 Hz, 1H), 4.42 (s, 2H), 4.21 (s, 1H), 3.91 (bs, 1H), 3.83-3.73 (m, 7H), 3.51 – 3.38 (m, 2H), 2.40 (td, J = 15.5, 8.5 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.81 – 1.57 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H) 0.90 (s, 9H), 0.25 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 145.7, 138.5, 130.6, 129.3, 113.8, 79.7, 72.6, 69.3, 58.5, 58.2, 55.3, 37.1, 29.3, 26.6, 18.1, -3.2. IR(neat): 3494, 2971, 2906, 2868, 1613, 1513, 1465, 1390, 1362, 1248, 1170, 1100, 1073, 948, 821 cm^{-1}. HRMS (ESI): m/z calculated for $C_{23}H_{41}O_5Si$ [M+H$^+$]: 425.27178, found: 425.27212.

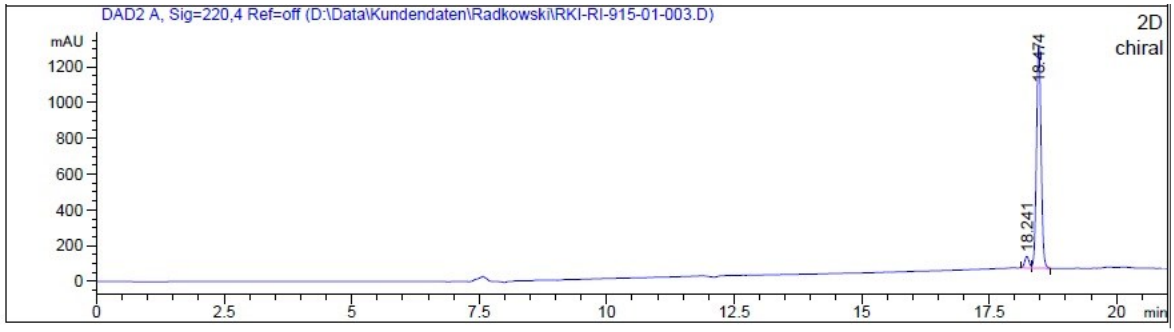
General procedure C: Conversion of *Z*-alkenylsilanes to allenes: The respective *Z*-alkenylsilane (1 equiv.) was added to a stirred solution of mesitylcopper (1.5 equiv.) in THF (0.2 M with respect to the alkenylsilane). The resulting mixture was stirred at ambient temperature for 15 min, before a solution of dry magnesium chloride (0.5 M in THF, 1 equiv.) was added to it. The resulting mixture was stirred at ambient temperature, until the starting material was completely consumed as judged by TLC. At this point the reaction mixture was diluted with *tert*-butyl methyl ether and washed with aqueous ammonia/saturated aqueous ammonium chloride solution (9:1). The aqueous layer was extracted with *tert*-butyl methyl ether and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography yielded the corresponding enantioenriched allene.

General procedure D: Conversion of *E*-alkenylsilanes to allenes: A solution of the respective *E*-alkenylsilane (1 equiv.) in THF (1 M) was added to a stirred solution of mesitylcopper (3.3 equiv.) and triethyl phosphite (6.5 equiv.) in THF (same volume as the solution of the alkenylsilane) at 0 °C. The resulting mixture was stirred at 0 °C, until the starting material was completely consumed as judged by TLC. At this point the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography yielded the corresponding enantioenriched allene.

(*R*)-1-Methoxy-4-(nona-3,4-dien-1-yl)benzene (*R*-143): Via general procedure C from ***Z*-142**.



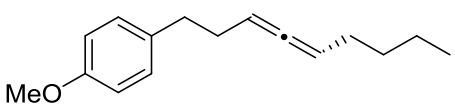
Flash chromatography: hexane:EtOAc 50:1. Yield = 11 mg, 78%. $[\alpha]_D^{20}$ = − 67.4 (c = 0.81, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.79 (s, 3H), 2.66 (t, J = 7.8 Hz, 2H), 2.32 – 2.18 (m, 2H), 1.95 (m, 2H), 1.38 – 1.30 (m, 4H), 0.93 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1, 157.9, 134.2, 129.5, 113.8, 91.6, 90.4, 55.4, 34.8, 31.5, 31.2, 28.8, 22.3, 14.1. IR(neat) 2955, 2927, 2855, 1962, 1612, 1584, 1512, 1455, 1300, 1244, 1176, 1106, 1039, 821 cm^{-1}. HRMS (ESI): m/z calculated for $C_{16}H_{22}ONa$ [M+Na$^+$]: 253.15628, found: 253.15625. The enantiomeric excess was determined by chiral HPLC to be 91%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol/water-gradient: 60% - 10' - 90% B 1.0 ml/min, 37.6 MPa, 298 K, 220 nm



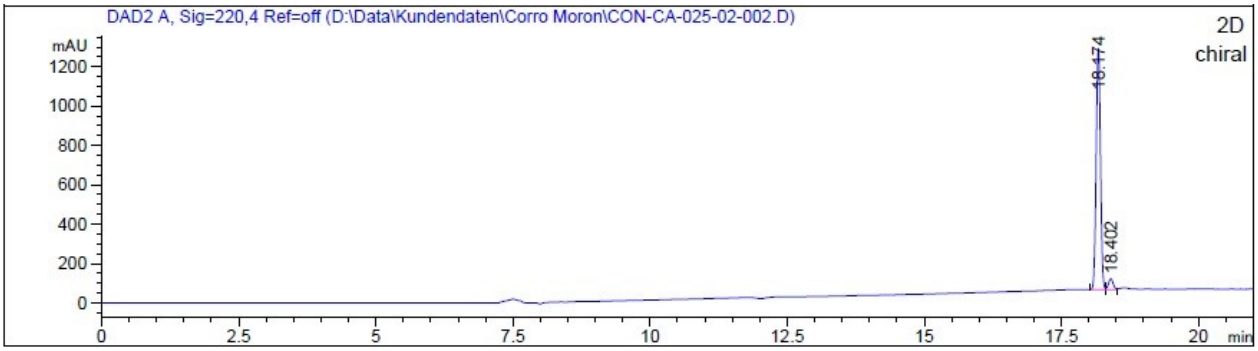
Signal 2: DAD2 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	18.241	BV	0.0930	390.09351	64.79618	4.6996	1. Enantiomer	ee = 90.6%
2	18.474	VB	0.0987	7910.42773	1248.81384	95.3004	2. Enantiomer	
Totals :				8300.52124	1313.61002			

(*S*)-1-Methoxy-4-(nona-3,4-dien-1-yl)benzene (*S*-143): Via general procedure D from ***E*-142**.

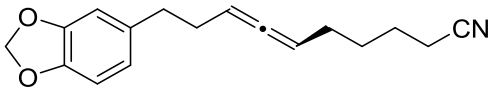


Flash chromatography: hexane:*tert*-butyl methyl ether = 99:1. Yield = 11 mg, 91%. $[\alpha]_{D}^{20}$ = + 50.3 (c = 1.39, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 91%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol/water-gradient, 60% - 10' - 90% B 1.0 ml/min, 37.9 MPa, 298 K, 220 nm.

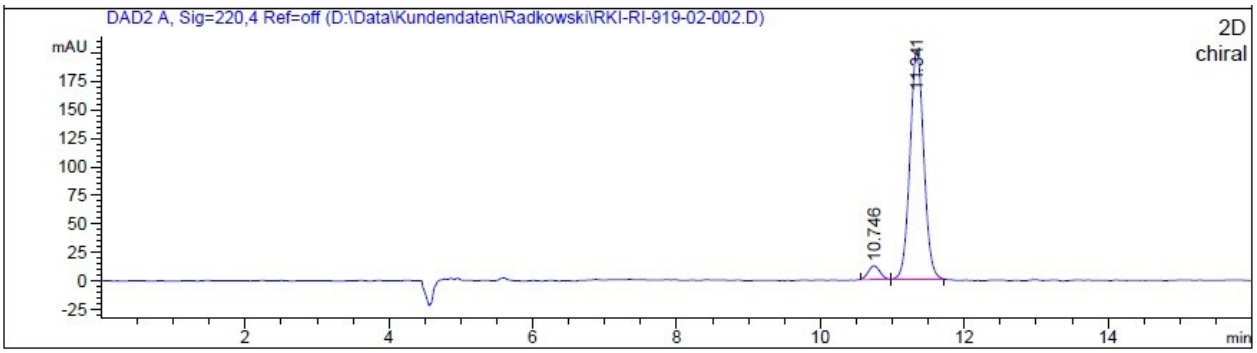


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	18.174	BV	0.0847	6663.56348	1224.57214	95.3868	1. Enantiomer	ee = 90.8%
2	18.402	VV	0.0918	322.27380	54.64944	4.6132	2. Enantiomer	
Totals :				6985.83728	1279.22158			

(*R*)-10-(Benzo[d][1,3]dioxol-5-yl)deca-6,7-dienenitrile (*R*-145): Via general procedure C from



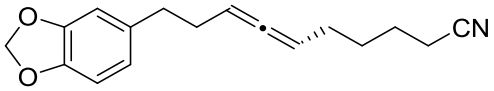
***Z*-144**. Flash chromatography: hexane:EtOAc: (10:1 → 6:1). Yield = 15 mg, 78%. $[\alpha]_{D}^{20}$ = − 49.8 (c = 0.8, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 1.5 Hz, 1H), 6.61 (dd, J = 7.9, 1.5 Hz, 1H), 5.89 (s, 2H), 5.26 – 4.82 (m, 2H), 2.66 – 2.56 (m, 2H), 2.30 (t, J = 7.1 Hz, 2H), 2.27 – 2.17 (m, 2H), 2.01 – 1.90 (m, 2H), 1.71 – 1.59 (m, 2H), 1.57 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 147.6, 145.7, 135.7, 121.4, 119.8, 109.1, 108.2, 100.9, 90.9, 90.4, 35.3, 31.0, 28.0, 24.9, 17.1. IR(neat): 2929, 2247, 1963, 1608, 1502, 1488, 1441, 1361, 1242, 1187, 1097, 1037, 934, 808 cm^{-1}. HRMS (ESI): m/z calculated for $C_{17}H_{19}NO_2Na$ [M+Na^+]: 292.13080, found: 292.13075. The enantiomeric excess of the product was determined by chiral HPLC to be 90%. 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol/water = 85:15, 1.0 ml/min, 25.3 MPa, 298 K, 220 nm.



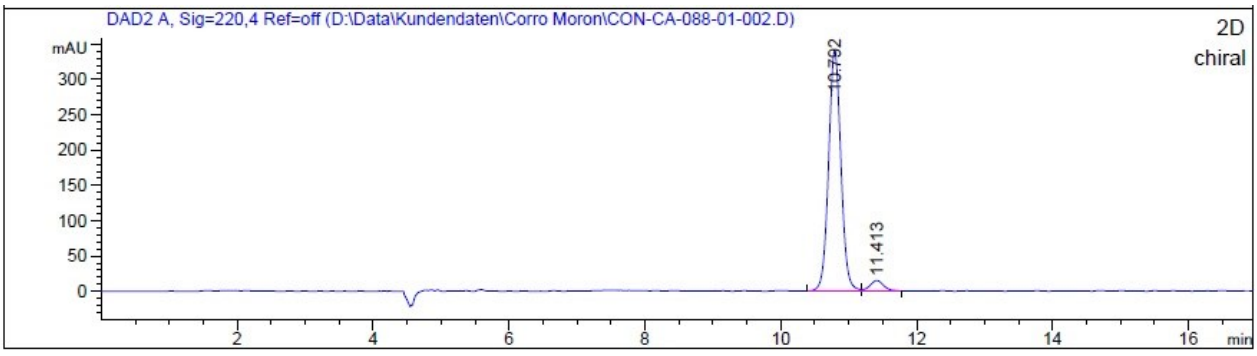
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	10.746	BV	0.1334	136.28426	12.02950	4.8271	1. Enantiomer
2	11.341	VB	0.2041	2687.04468	200.76625	95.1729	2. Enantiomer
Totals :				2823.32893	212.79575		

ee = 90.3%

(*S*)-10-(Benzo[d][1,3]dioxol-5-yl)deca-6,7-dienenitrile (*S*-145): Via general procedure D from



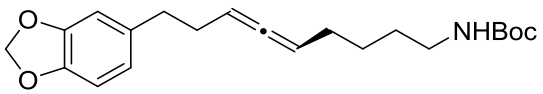
***E*-144**. Flash chromatography: hexane:*tert*-butyl methyl ether. Yield = 11 mg, 72%. $[\alpha]_{D}^{20}$ = + 49.2 (c = 0.60, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 91%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol/water = 85:15, 1.0 ml/min, 25.1 MPa, 298 K, 220 nm.



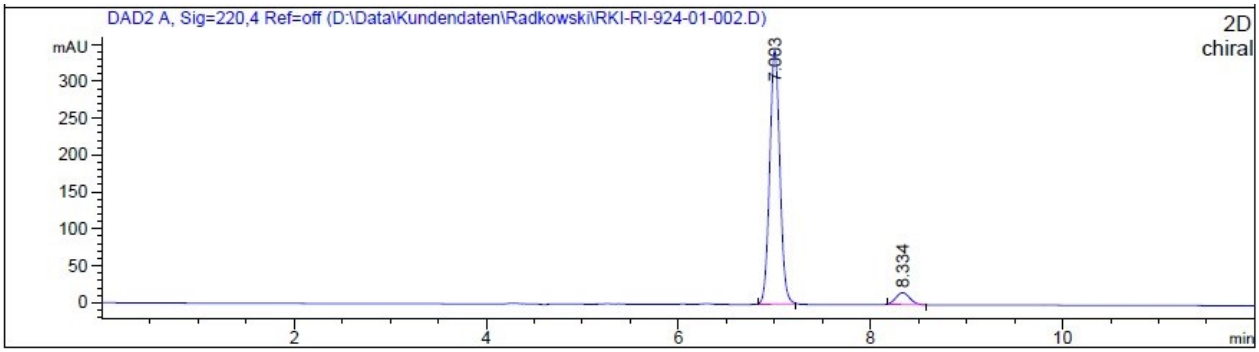
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	10.792	BB	0.1916	4286.77832	339.46994	95.3648	1. Enantiomer
2	11.413	BV	0.1667	208.35805	14.80598	4.6352	2. Enantiomer
Totals :				4495.13637	354.27592		

ee = 90.7%

***tert*-Butyl (*R*)-(9-(benzo[d][1,3]dioxol-5-yl)nona-5,6-dien-1-yl)carbamate (*R*-147):** Via



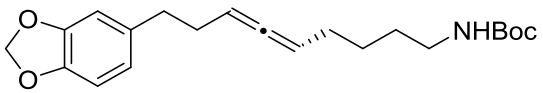
general procedure C from ***Z*-146**. Flash chromatography: hexane:EtOAc 9:1 Yield = 30 mg, 80%. $[\alpha]_D^{20}$ = − 45.9 (c = 0.64, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 1.6 Hz, 1H), 6.61 (dd, J = 7.9, 1.76Hz, 1H), 5.89 (s, 2H), 5.13 – 4.99 (m, 2H), 4.48 (bs, 1H), 3.08 (m, 1H), 2.60 (t, J= 7.6 Hz, 2H), 2.26 – 2.17 (m, 2H), 1.93 (tdd, J = 7.0, 3.2, 0.7 Hz, 2H), 1.50 – 1.30 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 155.8, 147.6, 145.7, 135.9, 121.4, 109.1, 108.2, 100.9, 91.2, 90.5, 79.4, 40.6, 35.3, 31.1, 29.6, 28.6, 26.4. IR(neat): 3352, 2975, 2931, 2857, 1961, 1702, 1503, 1490, 1443, 1365, 1245, 1170, 1040, 937, 810 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{29}NO_4Na$ [M+Na^+]: 382.19888, found: 382.19882. The enantiomeric excess of the product was determined by chiral HPLC to be 88%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitrile/water = 70:30, 1.0 ml/min, 16.8 MPa, 298 K, 220 nm.



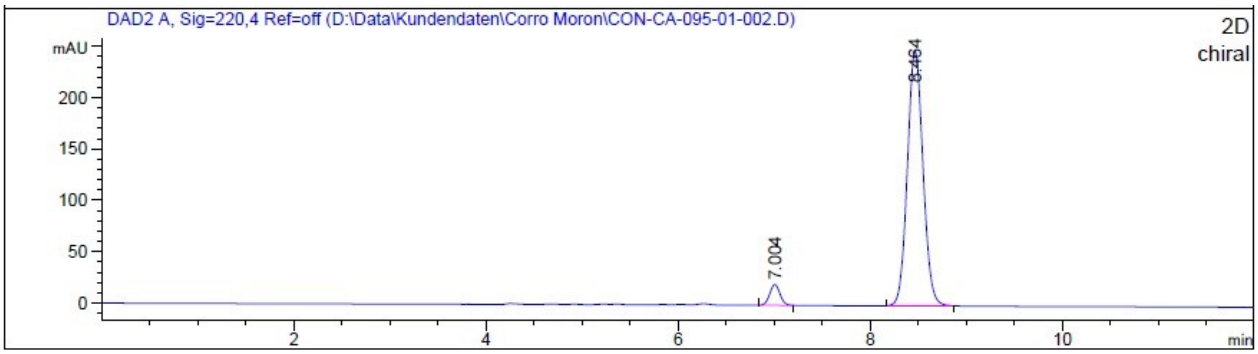
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	7.003	BB	0.1140	2528.55518	344.06818	93.9881	1. Enantiomer
2	8.334	BB	0.1278	161.73912	16.05108	6.0119	2. Enantiomer
Totals :				2690.29430	360.11925		

ee = 88.0%

***tert*-Butyl (*S*)-(9-(benzo[d][1,3]dioxol-5-yl)nona-5,6-dien-1-yl)carbamate (*S*-147):** Via general



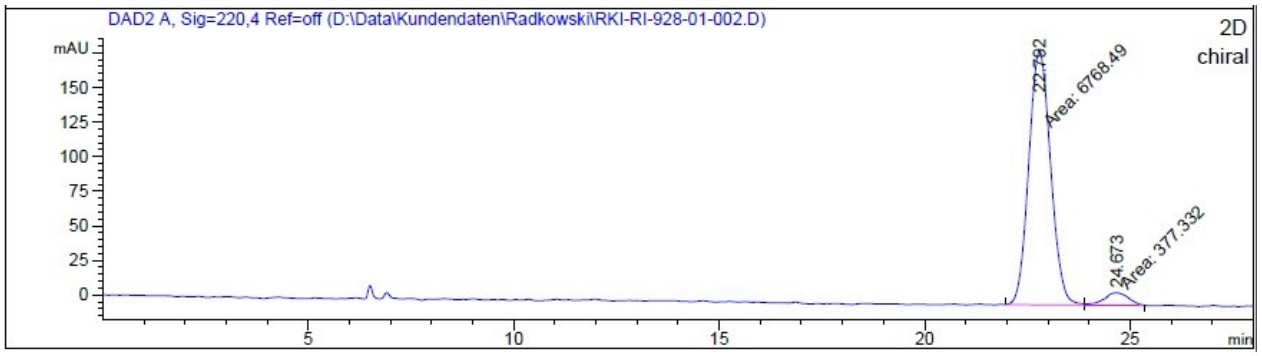
procedure D from ***E*-146**. Flash chromatography: hexane:EtOAc = 4:1. Yield = 6 mg, 44%. $[\alpha]_D^{20}$ = + 40.0 (c = 1.09, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 89%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitrile/water = 70:30, 1.0 ml/min, 16.4 MPa, 298 K, 220 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	7.004	BB	0.1134	150.07182	20.15515	5.0876	1. enantiomer
2	8.464	BB	0.1741	2799.69165	247.80788	94.9124	2. enantiomer
Totals :				2949.76347	267.96302		

ee = 89.8%

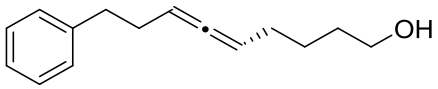
(*R*)-9-Phenylnona-5,6-dien-1-ol (*R*-149): Via general procedure C from ***Z*-148**. Flash chromatography: hexane:EtOAc 5:1. Yield = 13 mg, 41%. $[\alpha]_{D}^{20}$ = − 62.5 (c = 0.67, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.18 – 7.11 (m, 3H), 5.20 – 5.05 (m, 2H), 3.64 (t, J = 6.6 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.39 – 2.24 (m, 2H), 2.01 – 1.93 (m, 2H), 1.63 – 1.52 (m, 2H), 1.48 – 1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 142.0, 128.7, 128.4, 125.9, 91.3, 90.6, 63.0, 35.6, 32.3, 30.8, 28.7, 25.3. IR(neat): 3336, 3063, 2927, 2855, 1963, 1604, 1496, 1453, 1264, 1066, 871, 744, 698 cm^{-1}. HRMS (ESI): m/z calculated for $C_{15}H_{20}ONa$ [M+Na^+]: 239.14063, found: 239.14060. The enantiomeric excess of the product was determined by chiral HPLC to be 89%. Conditions: 150 mm Amycoat RP, 4.6 mm i.D., methanol/water = 75:25, 0.5 ml/min, 13.5 MPa, 298 K, 220 nm.

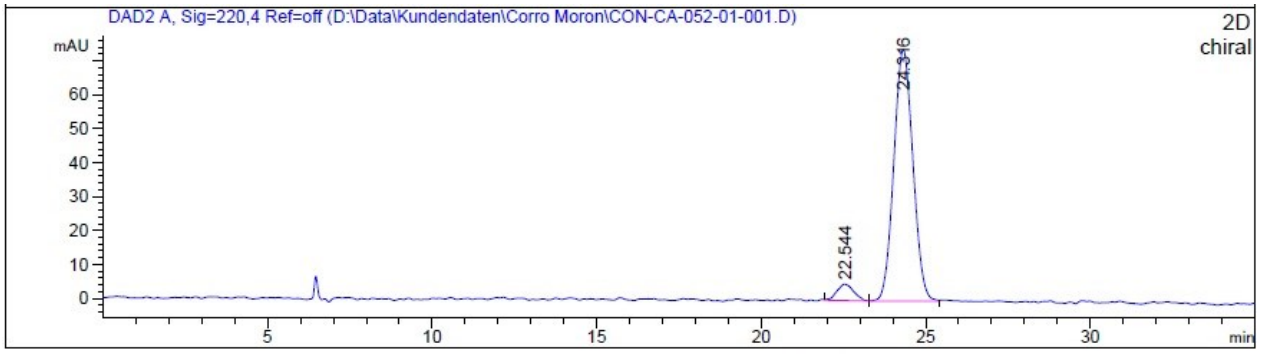


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	22.792	MF	0.6159	6768.48877	183.15793	94.7195	1. Enantiomer
2	24.673	FM	0.6883	377.33218	9.13656	5.2805	2. Enantiomer
Totals :				7145.82095	192.29449		

ee = 89.4%

(*S*)-9-Phenylnona-5,6-dien-1-ol (*S*-149): Via general procedure D from ***E*-148**. Flash chromatography: hexane:EtOAc = 9:1. Yield = 6 mg, 29%. The enantiomeric excess of the product was determined by chiral HPLC to be 89%. Conditions: 150 mm 3-AmyCoat RP, 4.6 mm i.D., methanol/water = 75:25, 0.5 ml/min, 12.6 MPa, 298 K, 220 nm.

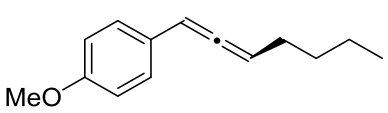




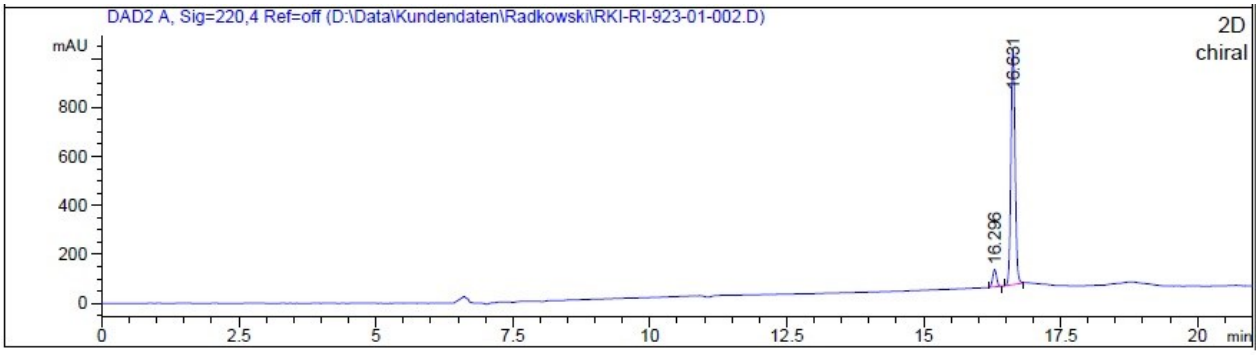
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	22.544	BV	0.5684	171.43858	4.80342	5.4253	1. enantiomer
2	24.316	VB	0.6303	2988.51880	74.12851	94.5747	2. enantiomer
Totals :				3159.95738	78.93193		

ee = 89.1%

(*R*)-1-(Hepta-1,2-dien-1-yl)-4-methoxybenzene (*R*-151): Via general procedure C from ***Z*-150**.



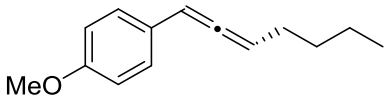
Flash chromatography: pure hexane. Yield = 34 mg, 51%. $[\alpha]_D^{20}$ = − 89.9 (c = 0.63, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 6.850 (d, J = 8.7 Hz, 2H), 6.08 (dt, J = 6.7, 3.0 Hz, 1H), 5.54 (q, J = 6.7 Hz, 1H), 3.80 (s, 3H), 2.12 (ddd, J = 14.3, 6.7, 3.0 Hz, 2H), 1.54 – 1.35 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6, 158.7, 127.7, 114.5, 114.2, 95.2, 94.1, 55.6, 31.5, 28.8, 22.4, 14.0. IR(neat): 2956, 2929, 2857, 1950, 1579, 1510, 1464, 1441, 1302, 1171, 1034, 832 cm^{-1}. HRMS (EI): m/z calculated for $C_{14}H_{18}O$ [M^+]: 202.13522, found: 202.13495. The enantiomeric excess of the product was determined by chiral HPLC to be 87%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol / water-Gradient: 60% - 10' - 90% B 1.0 ml/min, 38.2 MPa, 298 K 220 nm.



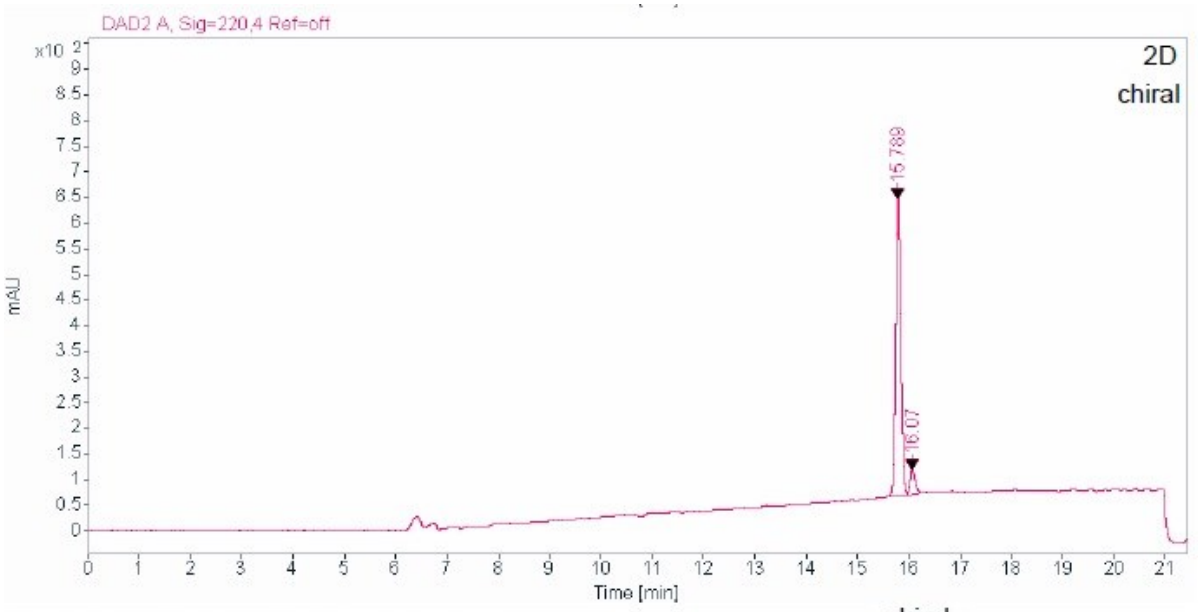
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	16.296	BB	0.0778	357.56464	70.96156	6.5504	1. Enantiomer
2	16.631	BB	0.0824	5101.12744	960.70984	93.4496	2. Enantiomer
Totals :				5458.69208	1031.67139		

ee = 86.9%

(*S*)-1-(Hepta-1,2-dien-1-yl)-4-methoxybenzene (*S*-151): Via general procedure D from ***E*-150**.



Flash chromatography: Column chromatography: hexane:*tert*-butyl methyl ether (100:0 → 99:1). Yield = 26 mg, 51%. $[\alpha]_D^{20}$ = + 40.0 (c = 0.05, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 85%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., methanol/water-gradient: 60% - 10' - 90% B, 1.0 ml/min, 37.4 MPa, 298 K, 220 nm.

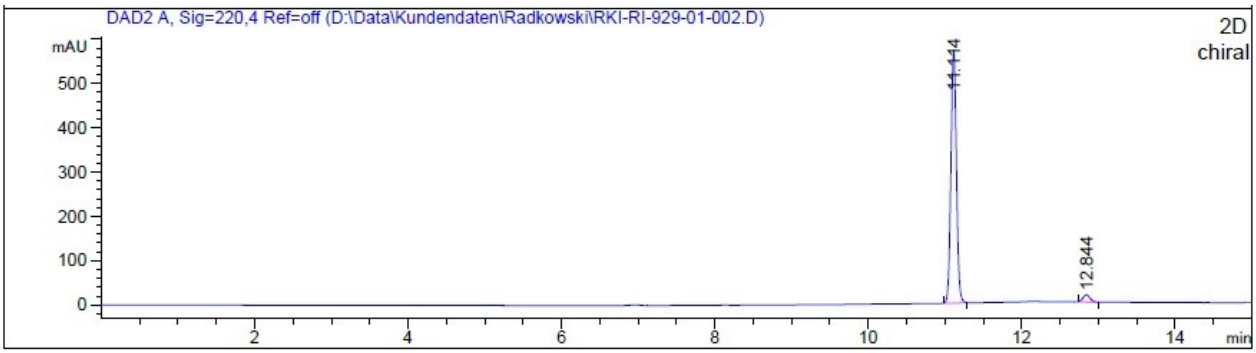


Signal: DAD2 A, Sig=220,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
15.789	BB	0.1029	3885.1641	577.8719	92.4747	1. Enantiomer
16.070	BB	0.1032	316.1644	46.2968	7.5253	2. Enantiomer
		Sum	4201.3285			

ee = 85.0%

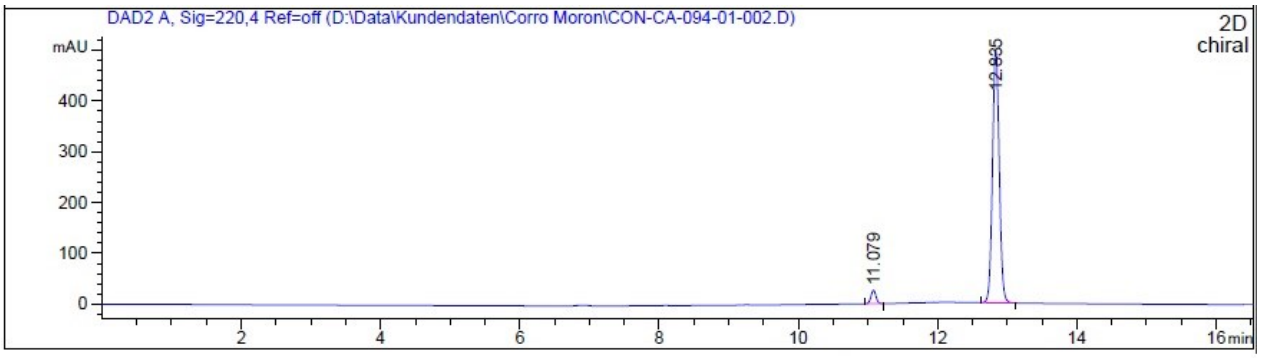
(*R*)-1-(((6-Cyclohexylhexa-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (*R*-153): Via general procedure C from ***Z*-152**. Flash chromatography: hexane:EtOAc = 8:1. Yield = 24 mg, 66%. $[\alpha]_{D}^{20}$ = − 54.3 (c = 0.74, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.51 – 4.91 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.48 (t, J = 6.6, 2H), 2.15 – 2.00 (m, 2H), 2.00 – 1.83 (m, 1H), 1.82 – 1.55 (m, 6H), 1.36 – 0.97 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 159.3, 130.9, 129.4, 113.9, 97.7, 91.4, 72.7, 69.7, 55.4, 37.4, 33.3, 33.2, 29.3, 26.3, 26.2, 25.8. IR(neat): 2922, 2849, 1956, 1613, 1568, 1512, 1448, 1363, 1302, 1246, 1172, 1100, 1037, 819 cm^{-1}. HRMS (ESI): m/z calculated for $C_{20}H_{28}O_2Na$ $[M+Na^+]$: 323.19815, found: 323.19815. The enantiomeric excess of the product was determined by chiral HPLC to be 93%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitrile/water-gradient: 70% - 5' - 90% B 1.0 ml/min, 17.0 MPa, 298 K, 220 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	11.114	BB	0.0772	2834.57764	570.71167	96.5094	1. Enantiomer
2	12.844	BB	0.0955	102.52317	16.11491	3.4906	2. Enantiomer
Totals :				2937.10081	586.82658		

ee = 93.0%

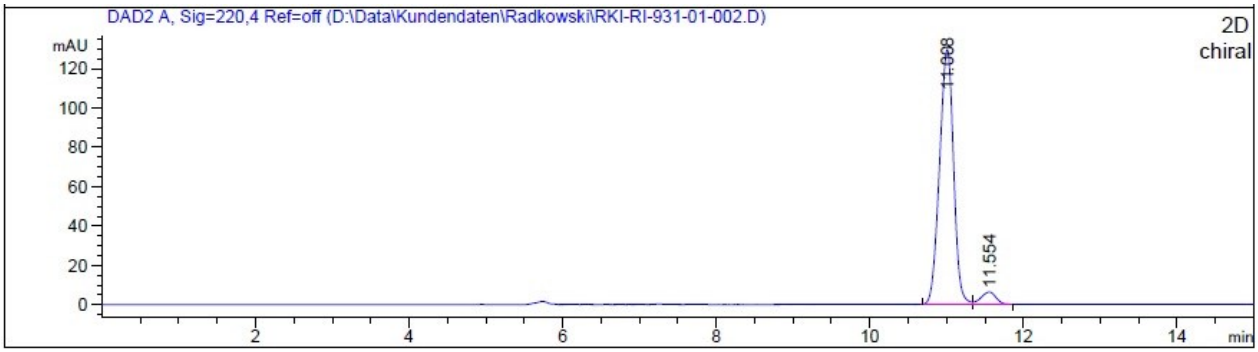
(*S*)-1-(((6-Cyclohexylhexa-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (*S*-153): Via general procedure D from ***E*-152**. Flash chromatography: hexane:*tert*-buutyl methyl ether = 24:1. Yield = 28 mg, 82%. $[\alpha]_{D}^{20}$ = + 39.6 (c = 1.07, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 93%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitrile/water-gradient: 70% - 5' - 90% B, 1.0 ml/min, 16.4 MPa, 298 K, 220 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	11.079	BB	0.0770	131.37808	26.44735	3.7503	1. enantiomer
2	12.835	BB	0.1056	3371.77026	497.28555	96.2497	2. enantiomer
Totals :				3503.14835	523.73290		

ee = 92.5%

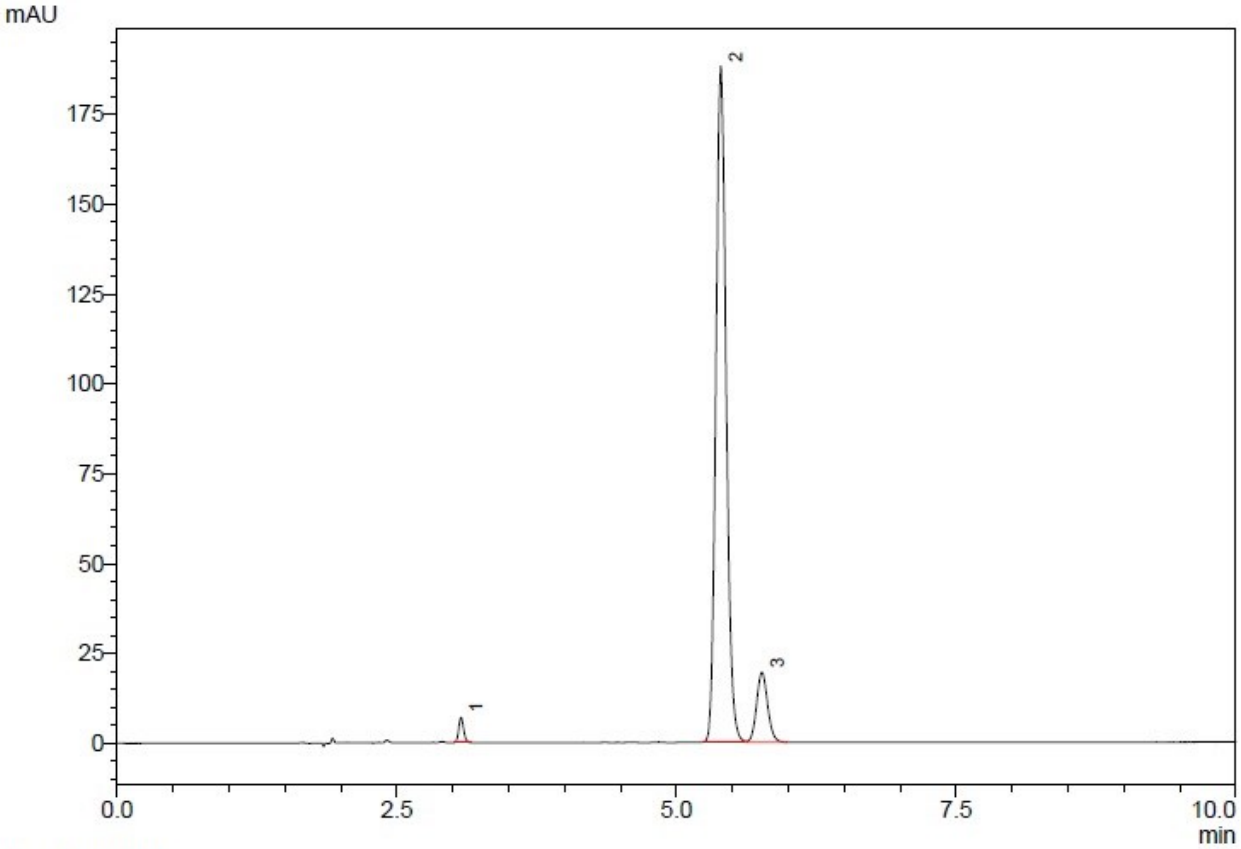
(*S*)-1-(((7,7-Dimethylocta-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (*S*-155): Via general procedure C from ***Z*-154**. Flash chromatography: hexane:EtOAc = 10:1. Yield = 7 mg, 27%. $[\alpha]_D^{20}$ = + 41.5 (c = 0.65, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.16 (q, J = 6.4 Hz, 1H), 5.09 (dt, J = 6.4, 3.1 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.48 (t, J = 6.8, 1.0 Hz, 2H), 2.12 – 1.97 (m, 2H), 1.72 (p, J = 6.8 Hz, 2H), 1.02 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 159.3, 131.1, 130.9, 129.4, 113.9, 103.6, 92.4, 72.7, 69.7, 55.4, 31.8, 30.4, 29.4, 25.9. IR (film, CHCl3) 2958, 2901, 2861, 1959, 1613, 1586, 1512, 1462, 1362, 1302, 1246, 1172, 1099, 1037, 819 cm^{-1}. HRMS (ESI): m/z calculated for $C_{18}H_{26}O_2Na$ [M+Na$^+$]: 297.18250, found: 297.18243. The enantiomeric excess of the product was determined by chiral HPLC to be 90%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitrile/water = 65:35, 1.0 ml/min, 18.2 MPa, 298 K, 220 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral
1	11.008	BB	0.1901	1642.70837	129.61588	95.0380	1. Enantiomer
2	11.554	BB	0.1596	85.76683	6.31787	4.9620	2. Enantiomer
Totals :				1728.47520	135.93374		

ee = 90.1%

(*R*)-1-(((7,7-Dimethylocta-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (*R*-155): Via general procedure D from ***E*-154**. Flash chromatography: hexane:EtOAc = 9:1. Yield = 6 mg, 42%. $[\alpha]_D^{20}$ = − 60.5 (c = 0.20, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC to be 80%. Conditions: 150 mm Chiralpak AS-3R, 4.6 mm i.D., acetonitril/water = 70:30, 1.0 mL/min, 16.7 MPa, 298 K, 220 nm.



1 220nm,4nm

PDA Ch1 220nm

Peak #	Ret. Time	Area %	Name	
1	3.07	1.58		
2	5.40	88.56	1. Enantiomer	= 80.0 % ee
3	5.76	9.86	2. Enantiomer	
Total		100.00		

6.4 List of Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BBN	9-Borabicyclo(3.3.1)nonane
Bn	benzyl
Br	broad
Bu	butyl
Bz	benzoyl
calcd	calculated
cm	centimeter
cod	cyclooctadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane

DCM	dichloromethane (methylene chloride)
d	doublet
DIBAl-H	diisobutylalumnium hydride
DMA	dimethylacetamide
DMAP	N,N-dimethyl 4-aminopyridine
DMF	dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ent	enantiomeric
epi	epimeric
Et	ethyl
g	gram
h	hour
hep	heptet
HDA	hetero-Diels-Alder
HFIP	hexafluoroisopropanol

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	iso (branched)
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
L	liter
l.l.s.	longest linear sequence
LC	liquid chromatography
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar (mol/L)
m	multiplet
Me	methyl
Mes	mesityl
mg	miligram
min	minute
mL	mililiter
MOM	methoxy methyl
mp.	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MTBE	*tert*-butyl methyl ether

n	normal (linear)
μg	microgram
μL	microliter
NaHMDS	sodium hexamethyldisilazide
n.d.	not determined
NHC	N-heterocyclic carbene
NMI	N-Methylimidazole
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
PCC	pyridinium chlorochromate
Ph	phenyl
Pin	pinacol
PG	Protecting group
PMB	*para*-methoxybenzyl
Pr	propyl
q	quartet
quant	quantitative
rac	racemic
RCAM	ring closing alkyne metathesis
RCM	ring closing (olefin) metathesis
ROESY	rotating frame nuclear overhauser effect spectroscopy

RT	room temperature
s	singlet
s.m.	starting material
sat.	saturated
t	triplet
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-n-butylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
TBS	dimethyltert-butylsilyl
TC	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)-ethyl
Ts	toluenesulfonyl
Tsoc	triisopropyloxy carbonyl

7 Literature

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