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DISSERTATION

Titel der Dissertation

„Decarboxylative Grob-type Fragmentations in the Synthesis of Trisubstituted (*Z*)-Olefins; Application to Epothilone B, Discodermolide and Peloruside A“

Verfasserin

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für meine Eltern Mathi und Erhard

und die zwei wichtigsten Menschen in meinem Leben Kami und Christiane

I was gratified to be able to answer promptly, and I did.

I said I didn't know.

(Mark Twain, boy's life)

Acknowledgement

I would like to thank many people, friends and colleagues, without whom this work would not have been possible. First of all, I'm very grateful to my Ph.D. supervisor, Prof. Johann Mulzer, for the possibility to work in his group on this interesting project, his constant interest in my progress and his motivation for total synthesis, which challenged me to learn and accomplish more and more.

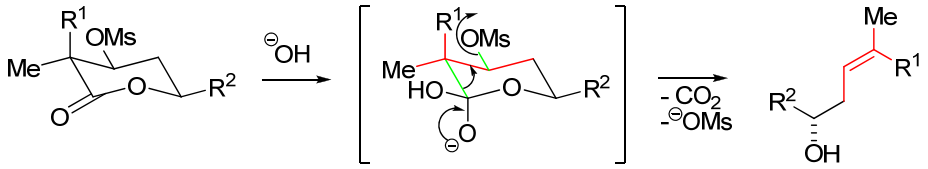
I especially want to thank my long term colleagues and friends, Wolfgang Felzmann, Tanja Gaich and Neil Sheddan, for numerous discussions, advice and their personal and chemical support. I want to acknowledge my lab mates in the Oesi lab, Thomas Magauer, Eliane Schweizer and Lutz Kleemann, for the nice working atmosphere and putting up with my moods. Furthermore, I want to thank all the past and present members of the Mulzer group, Roland Barth, Valentin Enev, Andreas Gollner, Alexey Gromov, Martin Himmelbauer, Anna Innitzer, Katja Jantos, Dagmar Kapeller, Marion Kögl (I won't forget), Stefan Marchart, Harry Martin, Jürgen Ramharter, Peter Siengalewicz, Konrad Tiefenbacher, Harald Weinstabl and the Rinner group, Christian Aichinger, Rita Fürst, Christoph Lentsch, Christina Nowikow, Uwe Rinner, who made every day a pleasure to come to work. Without the NMR team, Lothar Brecker, Susanne Felsinger, Hanspeter Kählig, Cati Tyl, a lot of unexpected reactions would have remained in the dark. Equally, Sabine Schneider, Peter Unteregger, Michael Zinke, are thanked for their service jobs with HPLC and MS. Finally, I want to thank our technicians Martina Drescher, Martin Lux-Amon, Jale Özgür, for providing dry solvent and lab materials and Walter Dietrich for ordering chemicals.

I would also like to express my gratitude to my friends: Christiane, the best friend one can have, Ela, for her constant encouragement, and Kami, for his strength, support and belief in me in these not always easy times.

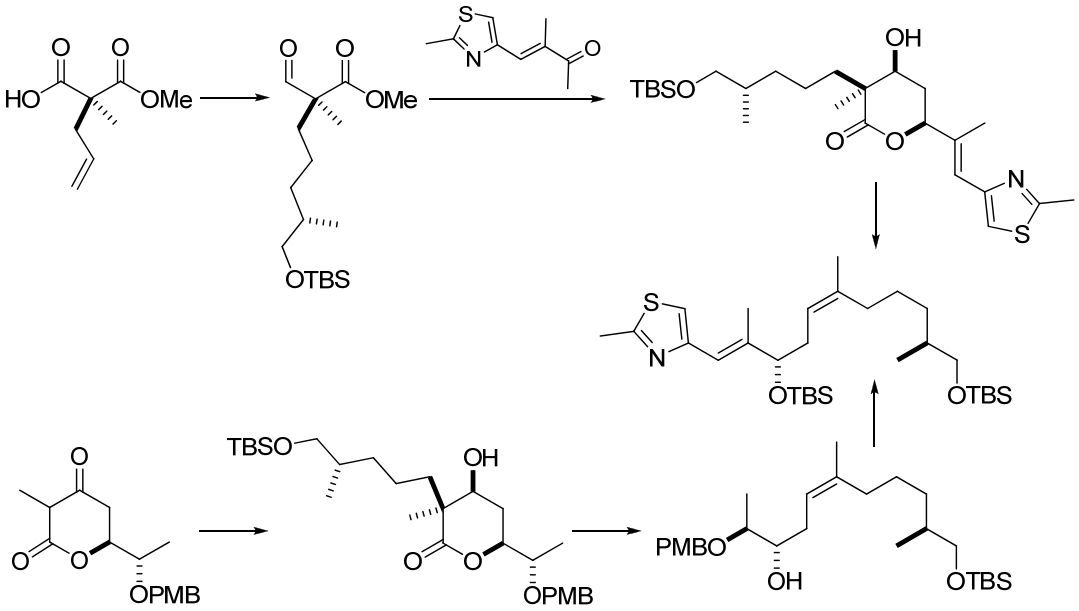
Finally, I heartily want to thank my family: my parents, Mathi and Erhard, who have always supported me financially and morally throughout my whole studies, and my brother and sister, Basti and Jojo, for teaching me to live my dreams.

Graphical Abstract

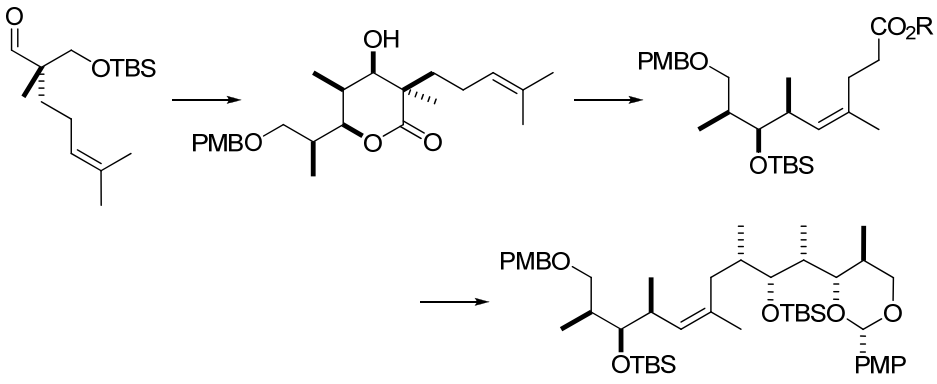
The Hydroxide Induced Decarboxylative Grob-type Fragmentation



Northern Fragment of Epothilone B



Discodermolide



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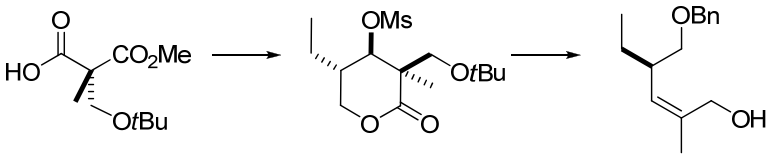
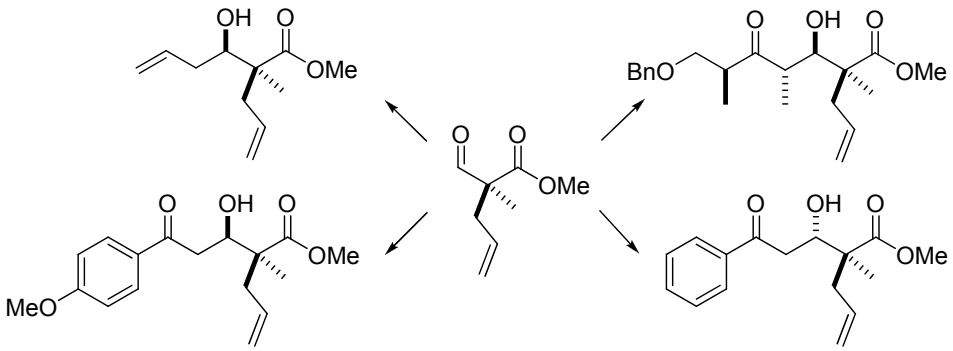


Nucleophile Additions



Abstract

Methyl branched trisubstituted (*Z*)-double bonds are a common motif in many polyketides with interesting biological activity such as epothilone B, discodermolide and peloruside A. These natural products are potent antitumor agents which, like paxlitaxel have a stabilizing effect on microtubules and thus interrupt the mitotic cycle and lead to apoptosis. Due to their pharmacological importance their synthesis has been investigated intensively. Regardless the numerous different strategies which have been employed, like carbonyl olefination, olefin metathesis, alkyne functionalization, allylic rearrangements and cross coupling chemistry, the stereoselective construction of the trisubstituted double bond has been the weak point in these efforts concerning yields and selectivity. As many of these protocols employ toxic and/or expensive reagents, the question arises why simple E2 elimination and in particular the well-known Grob fragmentation has not been used before. We envisaged a new hydroxide induced decarboxylative Grob-type fragmentation as olefination reaction to solve this problem. The strategy was centered on *β*-mesyloxy-*δ*-lactones. Axial addition of the hydroxide leads to a tetrahedral intermediate, which undergoes fragmentation *via* a chair transition state to form the olefin stereounambiguously. On preparing the fragmentation precursor, three stereogenic centers, one of which is quaternary, have to be generated. In analogy to the Grob fragmentation the stereochemical requirements are the antiperiplanar arrangement of the bonds to be broken during the course of the reaction. The synthesis of the fragmentation precursors started from aldehydes featuring quaternary *α*-centers, which were prepared in enantioselective way by enzymatic desymmetrization of *meso* malonates in case of epothilone B and peloruside A or by organoaluminium-promoted epoxide rearrangement in case of discodermolide. This stereoinformation was used to prepare the missing stereocenters on the chain by aldol strategy. All *δ*-lactones fragmented to the desired olefins in excellent selectivity and yield and the formal synthesis goals were reached easily. The scope of the fragmentation reaction was probed by employing different diastereomeric cyclic and acyclic precursors. Diastereoisomers which fulfill all stereochemical requirements to react *via* the chair transition state gave smoothly the olefins. On the other hand, diastereoisomers with the leaving group in axial position, thus making the fragmentation *via* the chair transition state impossible, gave, presumably *via* the open chain carboxylate, both the olefin and the *β*-lactone. *En route* to the fragmentation precursors unexpected behavior of the aldehydes with the quaternary centers was observed. This induced further investigations of nucleophile additions to this kind of aldehydes which turned out to give preferentially the product by substrate control of the electrophile.

Zusammenfassung

Methylverzweigte, trisubstituierte (*Z*)-Doppelbindungen sind ein häufig vorkommendes Strukturmotiv in vielen Polyketiden, wie Epothilon B, Discodermolid und Pelorusid A, die sich durch ihre interessanten biologischen Eigenschaften auszeichnen. Diese Naturstoffe sind hochaktive Antitumorwirkstoffe und ähnlich wie Paxlitaxel stabilisieren sie Mikrotubuli, wodurch der Mitosezyklus gestört wird und die Apoptose eintritt. Auf Grund dieser wichtigen pharmakologischen Eigenschaften wurde ihre Synthese gründlich untersucht. Obwohl die verschiedensten olefinbildenden Strategien wie Carbonylolefinierungen, Olefinmetathese, Funktionalisierung von Alkinen, Allylumlagerungen und Kreuzkupplungen angewandt wurden, war dieser Schritt oft der Schwachpunkt bezüglich Selektivität und Ausbeute. Außerdem wurden häufig toxische und/oder teure Reagenzien verwendet, sodass sich die Frage stellte, warum simple E2 Eliminierungen und im speziellen die bekannte Grob-Fragmentierung bislang nicht angewandt wurden. Diese Arbeit beschreibt eine neue, durch Hydroxidionen induzierte, Grob-Fragmentierung als Olefinierungsreaktion. Unsere Strategie konzentrierte sich auf *β*-Mesyloxy-*δ*-lactone. Der axiale Angriff eines Hydroxidions führt zu einer tetraedrischen Zwischenstufe, die über eine Sesselkonformation fragmentiert und so stereochemisch eindeutig Olefine bildet. Bei der Herstellung der Fragmentierungsvorstufen müssen drei Stereozentren, von denen eines quarternär ist, aufgebaut werden. Stereochemische Voraussetzungen sind in Analogie zur Grob-Fragmentierung eine antiperiplanare Anordung der zu brechenden Bindungen. Die Synthese der Fragmentierungsvorstufen begann ausgehend von Aldehyden mit quaternären *α*-Zentren, die einerseits bei Epothilon B und Pelorusid A durch enzymatische Hydrolyse von *meso* Malonaten und andererseits bei Discodermolid durch Epoxidumlagerung enantioselektiv hergestellt wurden. Ihre Stereoinformation wurde genutzt, um mittels Aldolstrategie die verbleibenden Stereozentren der Kette aufzubauen. Alle *δ*-Lactone konnten in hervorragender Selektivität und Ausbeute in die gewünschten Olefine fragmentiert werden, um die Formalsyntheseziele zu erreichen. Um die Bandbreite der Reaktion zu testen, wurden verschiedene diastereomere zyklische und azyklische Fragmentierungsvorstufen untersucht. Diastereomere, die alle stereochemischen Vorraussetzungen erfüllten, um über einen Sessel-Übergangszustand zu fragmentieren, ergaben die gewünschten Olefine. Diastereomere mit der Abgangsgruppe in axialer Anordnung, die nicht über einen Sessel-Übergangszustand fragmentieren können, lieferten vermutlich über das offene Carboxylat Olefin and *β*-Lacton. Die unerwartete Stereokontrolle der Aldoladdition in der Epothilonsynthese des Aldehydes mit quaternärem *α*-Zentrum führte zur weiteren Untersuchung von Nucleophiladditionen an ähnliche Verbindungen. Die Stereochemie der Produkte wurde vorrangig durch Substratkontrolle des Elektrophils induziert.

Publications, Posters and Oral Presentations Resulting from this Thesis

Publications

"Synthesis of (*Z*)-Trisubstituted Olefins by Decarboxylative Grob-type Fragmentations: Epothilone D, Discodermolide and Peloruside A", K. Prantz, J. Mulzer; *Chemistry - A European Journal*, **2009**, submitted.

"Decarboxylative Grob-type Fragmentations in the Synthesis of (*Z*)-Trisubstituted Olefins. Application to Peloruside A, Discodermolide and Epothilone D", K. Prantz, J. Mulzer; *Angewandte Chemie International Edition*, **2009**, *48*, 5030-5033; „Decarboxylierende Grob-Fragmentierung zur Synthese trisubstituierter Z-Olefine: Anwendung auf Pelorusid A, Discodermolid und Epothilon D", K. Prantz, J. Mulzer; *Angewandte Chemie,* **2009**, *121*, 5130-5133.

"Epothilones - A Fascinating Family of Microtubule Stabilizing Antitumor Agents", J. Mulzer, K.-H. Altmann, G. Höfle, R. Müller, K. Prantz; *Comptes rendus Chimie*, **2008**, *11*(11-12), 1336-1368.

"The Epothilones: An Outstanding Family of Anti-Tumour Agents - From Soil to the Clinic", J. Mulzer, K.-H. Altmann, G. Höfle, R. Müller, K. Prantz; in *Progress in the Chemistry of Organic Natural Products*, Vol 90, SpringerWienNewYork, **2009**. (ISBN: 978-3-211-78206-4).

Posters

Poster presentation at the "Synthese Fest" of the Ludwig-Maximilian University entitled "Decarboxylative Grob-type Fragmentations in the Synthesis of (*Z*)-Trisubstituted Olefins. Application to Epothilone D, Discodermolide and Peloruside" in Munich, Germany (March 2009).

Poster presentation at the "Ischia Advanced School of Organic Chemistry (IASOC 2008)" entitled "Decarboxylative Grob-type Fragmentation as an Olefin Synthesis, applied to Epothilone B, Discodermolide and Peloruside" in Ischia, Italy (September 2008).

Poster presentation at the "11th Belgium Organic Synthetic Symposium (BOSS11)" entitled "Decarboxylative Grob-type Fragmentation as Olefin Synthesis, applied to Epothilone B and Discodermolide" in Ghent, Belgium (July 2008).

Poster presentation at the "Fellows Meeting 2007" of the Ernst Schering foundation entitled "Studies toward the Synthesis of the C-12,13-(*Z*)-Double Bond of Epothilone B" in Berlin, Germany (June 2007).

Poster presentation at the "18. Irseer Naturstofftage der DECHEMA e.V." entitled "Stereocontrolled Synthesis of the 12,13-(*Z*)-Double Bond of Epothilone B" in Irsee, Germany (February 2006).

Oral Presentations

Invited lecture at the "Symposium of Organic Chemistry" at ESPCI entitled "Decarboxylative Grob-type Fragmentations in the Synthesis of (*Z*)-trisubstituted Olefins; Application to Epothilone D, Discodermolide and Peloruside" in Paris, France (February 2009).

Selected short talk at the "Ischia Advanced School of Organic Chemistry (IASOC 2008)" entitled "Decarboxylative Grob-type Fragmentation as an Olefin Synthesis, applied to Epothilone B, Discodermolide and Peloruside" in Ischia, Italy (September 2008).

Invited lecture at the "Doktorandenworkshop – Naturstoffchemie" entitled "Decarboxylative Fragmentierung als Olefinsynthese, angewandt auf Epothilon B und Discodermolid" in Jena, Germany (April 2008).

Invited lecture at the "Vienna Symposium of Organic Chemistry" entitled "Studies toward the Synthesis of the C-12,13-(*Z*)-Double Bond of Epothilone B – A new Fragmentation Reaction" in Vienna, Austria (September 2007).

Invited lecture at the "Fellows Meeting 2007" of the Ernst Schering foundation entitled "Studies toward the Synthesis of the C-12,13-(*Z*)-Double Bond of Epothilone B" in Berlin, Germany (June 2007).

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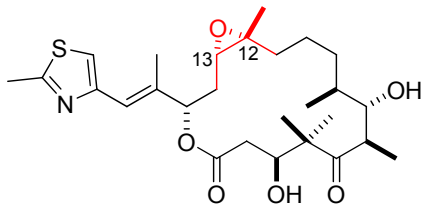
1. Introduction

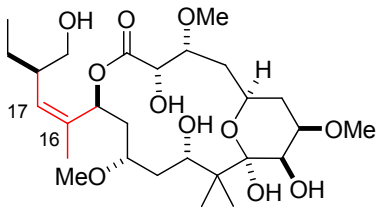
1.1. Background

One of the major challenges for a synthetic organic chemist is the stereoselective formation of both single and double carbon-carbon bonds. While there are numerous olefination methods known, to date a variety of natural occurring structures remain which lack a successful synthesis concerning selectivity and/or yield; methyl branched (*Z*)-olefins especially have proven to be a major challenge.

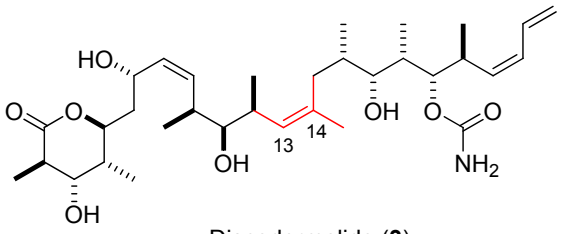
There are a huge number of natural products from different sources with interesting biological activities which feature a trisubstituted (*Z*)-double bond; three highly active compounds with moderate complexity are shown below, which are all microtubule stabilizing anticancer agents (MSAA).



Epothilone B (**1**)



Peloruside A (**2**)



Discodermolide (**3**)

Figure 1: The MSAA epothilone B (**1**), discodermolide (**3**) and peloruside A (**2**).

1.2. Antitumor Agents

1.2.1. Introduction

Cancer is a group of diseases characterized by anormal and uncontrolled cell division, unfortunately in most cases neither its cause nor its mode of action to cause death is known. There are four major forms of treatment: *surgery* (wide surgical excision of the tumor and the surrounding tissue), *radiotherapy* (some tumors are radiosensitive; often used to reduce the size of a tumor before surgery or to destroy remaining cancer cells after surgery), *hormones* (some tumors require hormones for their growth and therefore regress when deprived of these) and *anticancer drugs* (chemotherapy); which method is applied depends on the nature of the individual tumor and often combinations are used.[1]

1.2.2. Chemotherapy

The main difference between cancer cells and normal cells is the rapid and uncontrolled cell division in these anormal cells, like normal cells they synthesize deoxyribonucleic acid (DNA). The difference is therefore a quantitative, meaning that agents which react with anormal cells will very likely also react with the normal ones. Thus, chemotherapy relies on the rapid cell division as distinguishing feature and the fact that cancer cell mitoses can be halted fast enough to leave the normal cells sufficient time for self repair mechanisms to work. Anticancer drugs arrest the growth and division of cells by inhibiting the synthesis of DNA or RNA, altering the structure of DNA, inhibiting protein synthesis or disrupting the mitotic spindle. So there are two major modes of action of cytotoxic drugs: damaging the DNA by intercalation, alkylation, oxidation, double strand cross linking, rupture, antimetabolites and related, and by interrupting the mitotic cycle by stabilization or destabilization of microtubules.[2, 3]

1.2.3. Microtubule Stabilizing Anticancer Agents[4]

The so-called microtubules are a fundamental part of the cytoskeleton and are vital for mitosis, motility, secretion and proliferation.[5] One of their most important functions is building the mitotic spindle, which controls the movement of the daughter chromosomes throughout

the cell division. Microtubules are dynamic structures made of many individual protein subunits (Figure 2). First the *α*- and *ß*-tubule dimerize to form *α*/*ß*-heterodimers which polymerize further to protofilaments. Subsequent aggregation of this protofilaments leads to microtubules which are in a mobile equilibrium with the smaller fragments. De- and polymerization of microtubules is crucial for the correct segregation of the chromatides. Any disruption of the equilibrium interrupts the mitotic cycle and leads to apoptosis, the "programmed" cell death. Microtubule binding agents act in the metaphase of mitosis, when the mitotic spindle is fully developed.[6]

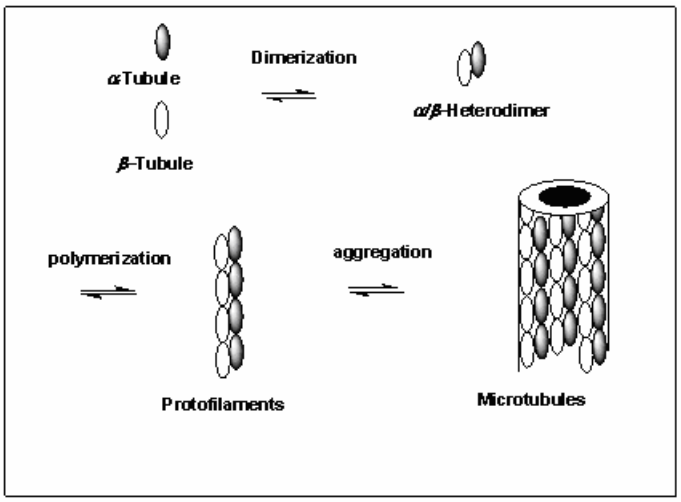
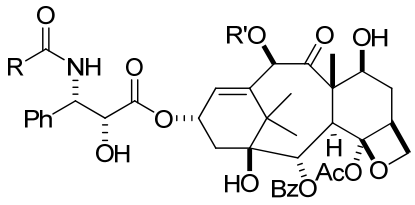
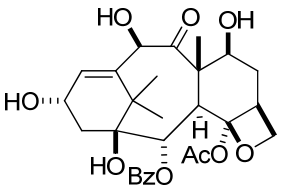


Figure 2: Formation of the microtubules in the cell.

This mode of action was first found in paclitaxel (**4**), a diterpene, isolated in 1971 from the pacific yew tree *taxus brevifolia*, by Wall and Wani who named it taxol® (**4**) (Scheme 1).[7] To today, it is one of the most widely used anticancer drugs with annual sales of about 1 billion USD. Even though it is far from being an ideal drug for several reasons – poor bioavailability, solubility problems, several serious side effects and multi drug resistance (MDR). Lately it was found that paclitaxel (**4**) induced the over expression of P-glycoprotein PgP, an energy-dependent drug transport protein, which generally results in broad-spectrum resistance to many anticancer agents. The supply problem, due to the poor yielding isolation from the tree, was circumvent by the development of a semisynthetic route from 10-deacetylbaccatin III (**5**), isolated from the European yew *taxus baccata*, which also serves to provide the more potent synthetic congener taxotere (**6**).



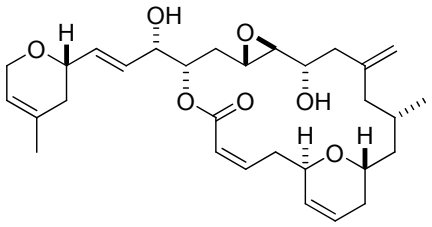
Taxol® (**4**) R = Ph, R' = Ac
Taxotere® (**6**) R = *t*Bu, R' = H



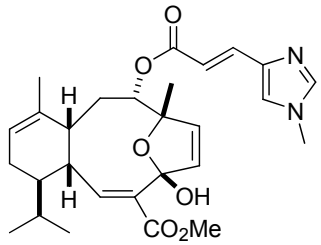
10-deacetylbaccatin (**5**)

Scheme 1: Taxenes.

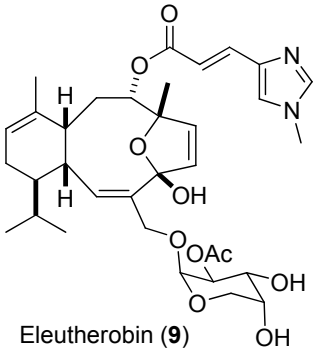
Other natural products like laulimalide (**7**)**,** sarcodyctin (**8**), eleutherobin (**9**) and dictyostatin (**10**) (Scheme 2), have been found, similar to epothilone and taxol, to have stabilizing capability.[5] Ojima has proposed a common pharmacophore uniting these structure diverse molecules.[8]



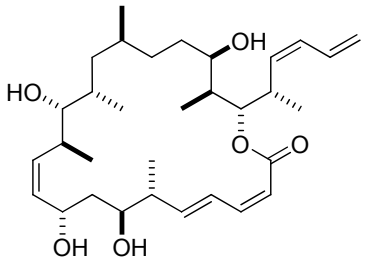
Laulimalide (**7**)



Sarcodyctin A (**8**)



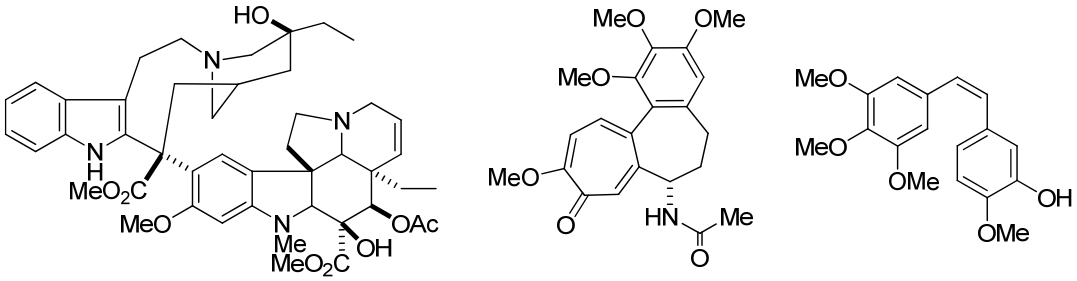
Eleutherobin (**9**)



Dictyostatin (**10**)

Scheme 2: Microtubule stabilizing natural products.

On the other hand, vinblastine (**11**), colchicine (**12**) and combretastatin A-7 (**13**) (Scheme 3) cause apoptosis by depolymerization of microtubules.[5]



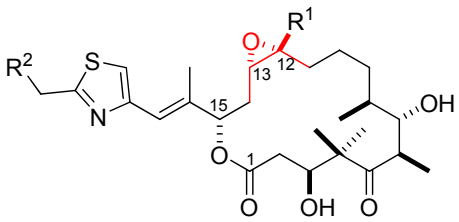
Vinblastine (**11**) Colchicine (**12**) Combretastatin A-7 (**13**)

Scheme 3: Inhibitors of microtubule polymerization.

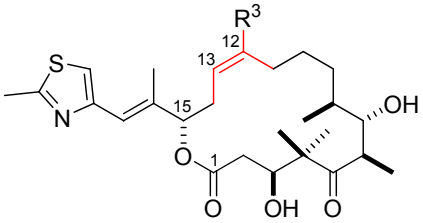
1.3. Isolation, Structural Elucidation and Biological Activity

1.3.1. Epothilones[9, 10]

In 1987 two metabolites, later named epothilone A (**14**) and B (**1**), were isolated by Höfle and Reichenbach at GFB (Gesellschaft für Biologisch-chemische Forschung) in Braunschweig from the mycobacterium *sorangium cellulosum* strain Soce90, which was harvested off the shores of the Zambesi River in the Republic of South Africa. The family of epothilones meanwhile comprises many members from which epothilone A to F (**1**, **14**-**18**) are the most common (Scheme 4).



Epothilone A (**14**) R^1 = H, R^2 = H
Epothilone B (**1**) R^1 = Me, R^2 = H
Epothilone E (**17**) R^1 = H, R^2 = OH
Epothilone F (**18**) R^1 = Me, R^2 = OH



Epothilone C (**15**) R^3 = H
Epothilone D (**16**) R^3 = Me

Scheme 4: Family of epothilones.

The epothilones are 16-membered macrolides, named after their fundamental structural features (**epo**xide, **thi**azol**e** and ket**one**). The absolute configuration of epothilone B (**1**) is known from spectroscopic and crystal data (Figure 3). Its structural features are the 16-membered macrolactone, seven stereogenic centres and a thiazolalkylidene moiety.

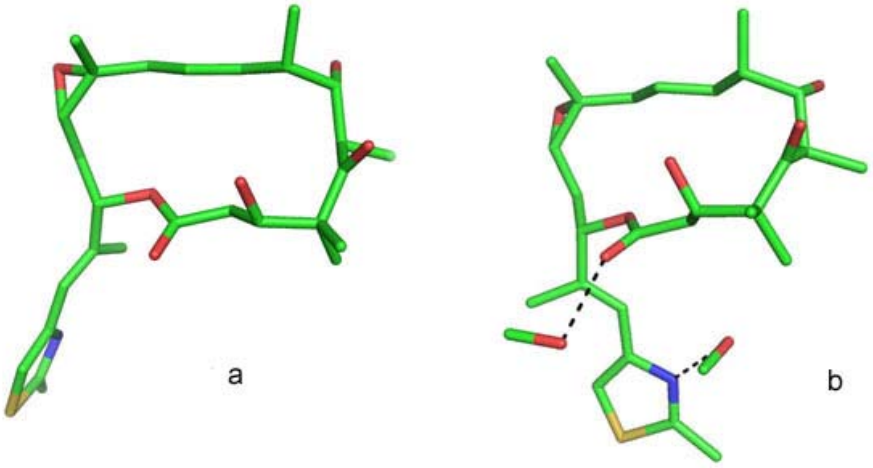
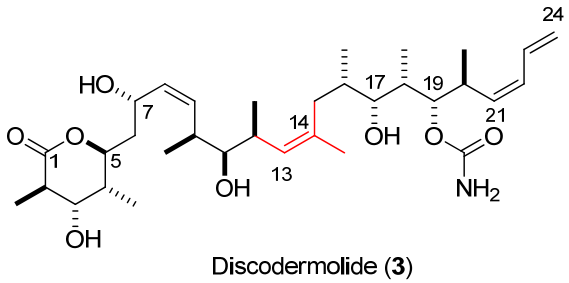


Figure 3: (a) X-ray crystal structures of epothilone B (**1**) from dichloromethane/petroleum ether and (b) methanol/water (modelling by W.-D. Schubert).[11]

In early tests, epothilone A (**14**) and B (**1**) both exhibited antifungal activity but also significant toxicity in cell culture assays thus interest in this family of natural products ceased. Until 1993, when they scored a hit in parallel tests by Merck, Sharp and Dohme, which were screening for natural products with taxane-like antitumor activity. In the tubulin polymerization assay, epothilone A (**14**) turned out to be as active as paclitaxel (**4**) and epothilone B (**1**) even fifty times more active. Epothilone B (**1**) showed further advantages over paclitaxel (**4**): it is more soluble in water, acts more rapidly, is also available in kg quantities by fermentation and is still active against cell lines showing multi-drug-resistance (MDR). Apparently epothilone B (**1**) and paclitaxel (**4**) either bind to the same or to a similar allosteric site as they show a classical competitive inhibitor pattern.

1.3.2. Discodermolide[12]

Discodermolide (**3**) was isolated in 1990 by Gunasekera and co-workers at the Harbor Branch Oceanographic Institute from the Caribbean deep-sea sponge *Discodermia dissolute*, which was initially collected off the Bahamas at a depth over 33 m.[13, 14] After exhaustive extractions and purification crystalline discodermolide (**3**) was isolated in 0.002% wet weight from the frozen sponge. Structure determination by extensive NMR studies revealed a linear C_{24} backbone featuring 13 stereogenic centers, a tetrasubstituted *δ*-lactone, one di- and one trisubstituted (*Z*)-alkene, a carbamate moiety and a terminal (*Z*)-diene (Scheme 5). The relative configuration was determined by single-crystal X-ray diffraction, whereas the absolute configuration was only proven by the first total synthesis of the unnatural antipode by Schreiber and co-workers in 1993.[15] Discodermolide (**3**) reveals in solution as well as in crystalline form a U-shaped conformation due to the two internal (*Z*)-alkenes to minimize the allylic strain, thus it shares a close stereochemical homology with dictyostatin (**10**).[16]



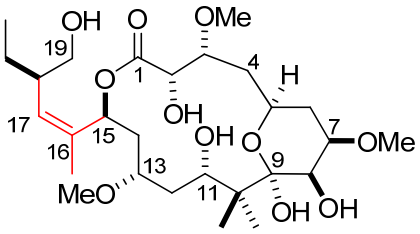
Discodermolide (**3**)

Scheme 5: Discodermolide (**3**).

Initially, discodermolide (**3**) was found to be a potent immunosuppressive agent and to exhibit antifungal activity.[17, 18] Further biological screening revealed striking cytotoxicity through a similar mechanism like paclitaxel (**4**) by stabilizing microtubule, but far more potent then taxol® (**4**). Additionally the anti-proliferation activity remains in cell lines already resistant to taxol® (**4**). Competition studies to probe the binding site showed the ability of discodermolide (**3**) to replace taxol® (**4**) which indicates the same or overlapping binding sites on *β*-tubule. However, the presence of taxol® (**4**) increased the cytotoxicity of discodermolide (**3**) significantly, which suggests overlapping binding sites and demonstrates a useful synergetic potential, when used in a combination therapy. This remarkable bioprofile attracted the attention of Novartis Pharma AG, but unfortunately, after an enormous synthetic effort, trials had to be halted in clinical Phase I due to severe toxicity.

1.3.3. Peloruside A[19]

Peloruside A (**2**) was isolated in 2000 from the marine sponge *Mycale hentscheli* by Northcote an co-workers collected from the Pelorus Sound on the north coast of the South Island of New Zealand.[20] 170 g wet weight sponge yielded 3 mg of peloruside A (**2**). It is a highly oxygenated, stereochemically rich polyketide featuring a 16-membered macrolide containing a pyranose ring, ten stereogenic centers and a branched unsaturated side chain (Scheme 6). The relative configuration was determined by extensive NMR studies, but only the total synthesis of *ent*-peloruside A (***ent*-2**) by De Brabander in 2003 established the absolute configuration.[21]



Peloruside A (**2**)

Scheme 6: Peloruside A (**2**).

Soon after the isolation its paclitaxel-like microtubule stabilizing activity was reported.[22, 23] Peloruside A (**2**) exhibits cytotoxicity against a range of cancer cells and retains potency against MDR cells. Laulimalide (**7**) was able to displace peloruside A (**2**), which suggests that these compounds have related binding sites different from the taxol® binding site on the *β*-tubule. Synergistic effects have been observed with taxoid site drugs like taxol® (**4**), epothilone B (**1**), discodermolide (**3**) and others.

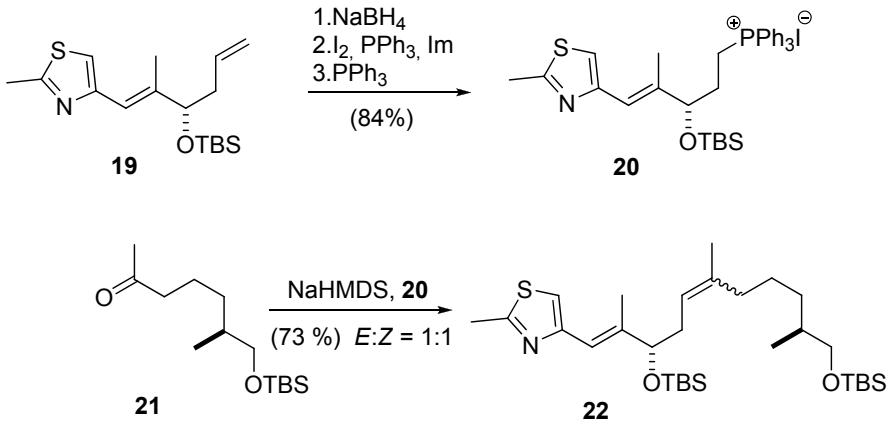
2. Literature Syntheses

This chapter will provide an overview of the literature syntheses regarding the introduction of the trisubstituted (*Z*)-double bond and thus is divided in different olefination strategies.

2.1. Carbonyl Olefination Reactions

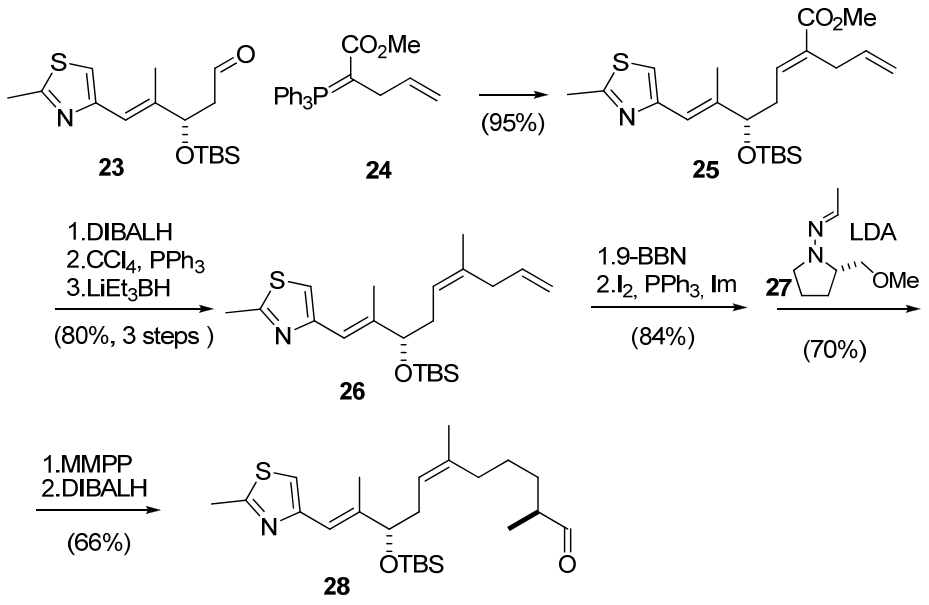
2.1.1. Wittig Reaction

Nicolaou used a classic Wittig reaction in his epothilone B (**1**) synthesis, employing phosphonium iodide **20** and methyl ketone **21** to generate the trisubstituted double bond in 73% yield as 1:1 mixture of *E:Z* diastereoisomers (Scheme 7).[24]



Scheme 7: Nicolaou's Wittig reaction.

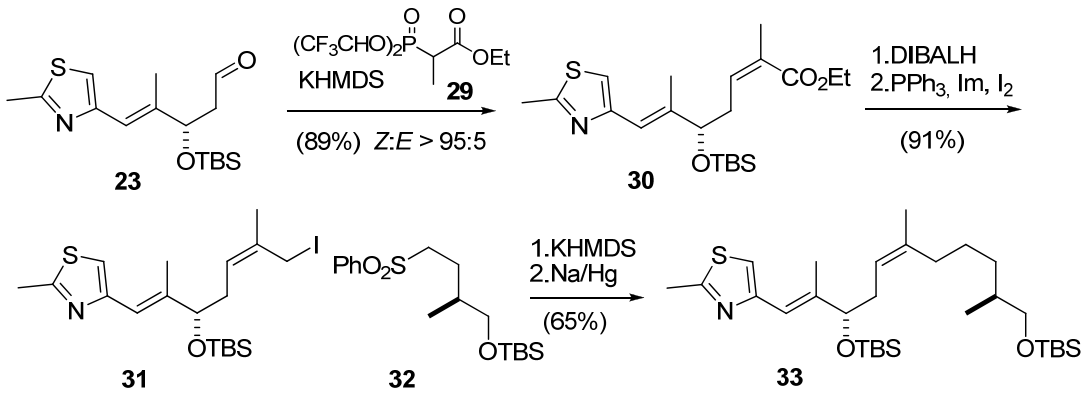
Nicolaou was able to improve the selectivity by employing stabilized Wittig ylide **24** with aldehyde **23**, to get to (*E*)-olefin **25** as single diastereoisomer in excellent yield (Scheme 8). A drawback was the ester functionality, which had to be reduced to the methyl group of the desired trisubstituted (*Z*)-olefin **26** in three additional steps by reduction to the allylic alcohol and deoxygenation by reduction of the corresponding chloride formed under Apple conditions. Five additional steps led to northern fragment **28**.



Scheme 8: Nicolaou's Wittig reaction using a stabilized ylide.

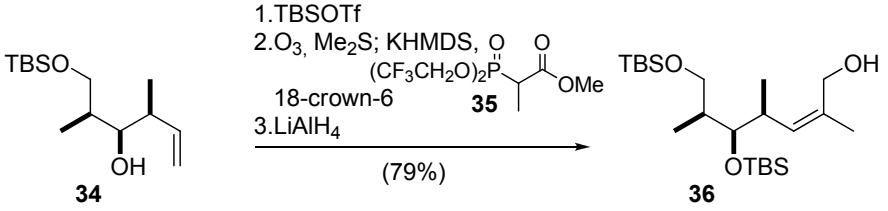
2.1.2. Still-Gennari Reaction

Mulzer employed a Still-Gennari reaction in his epothilone B (**1**) synthesis, which provided in 89% yield (*Z*)-olefin **30** in an excellent *E:Z* ratio (Scheme 9). The ester moiety of **30** was reduced to the allylic alcohol, converted into unstable iodide **31**, and immediately coupled with monodeprotonated sulfone **32**. Reductive removal of the sulfone group with sodium amalgam led to northern fragment **33**.[25]



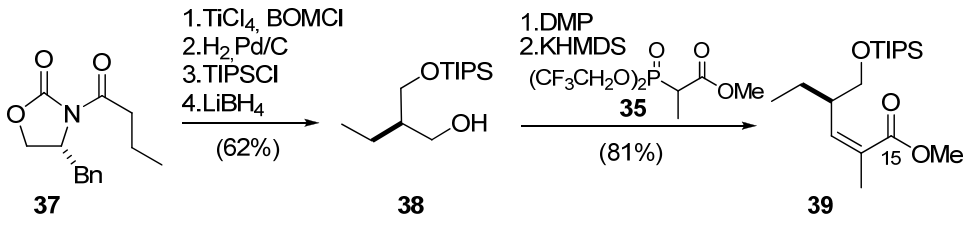
Scheme 9: Mulzer's Still-Gennari olefination.

Schreiber and co-workers achieved the first total synthesis of the unnatural antipode of discodermolide (**2**) in 1993,[15] followed by a fully detailed report of the natural enantiomer in 1996,[26] always relying on the Still-Gennari olefination to install the desired (*Z*)-olefin. For the synthesis of stereo-triad **34** the Roush crotylation was used. Protection of the homoallylic alcohol as its silyl ether was followed by oxidative cleavage to provide the required aldehyde for the olefination (Scheme 10). The trisubstituted (*Z*)-olefin in **36** was installed in excellent yield and selectivity and the allylic alcohol could be further converted, *via* the mesylate, into the corresponding bromide for coupling with a C16-C24 ketone.



Scheme 10: Schreiber's Still-Gennari olefination for discodermolide (**F**).

Taylor used a Still-Gennari olefination to stereoselectively generate the trisubstituted (*Z*)-alkene in the peloruside A side chain **39**.[27] The stereogenic center came from a stereoselective Evans alkylation. After change of protecting groups, the auxiliary was reductively removed and the newly generated free primary alcohol **38** was oxidized to the corresponding aldehyde (Scheme 11). Olefination gave exclusively desired (*Z*)-olefin **39** and for this molecule the substitution pattern is appropriate as peloruside A (**2**) contains a hydroxyl group at C15, so no redundant functionality had to be removed like in the epothilone B (**1**) synthesis.



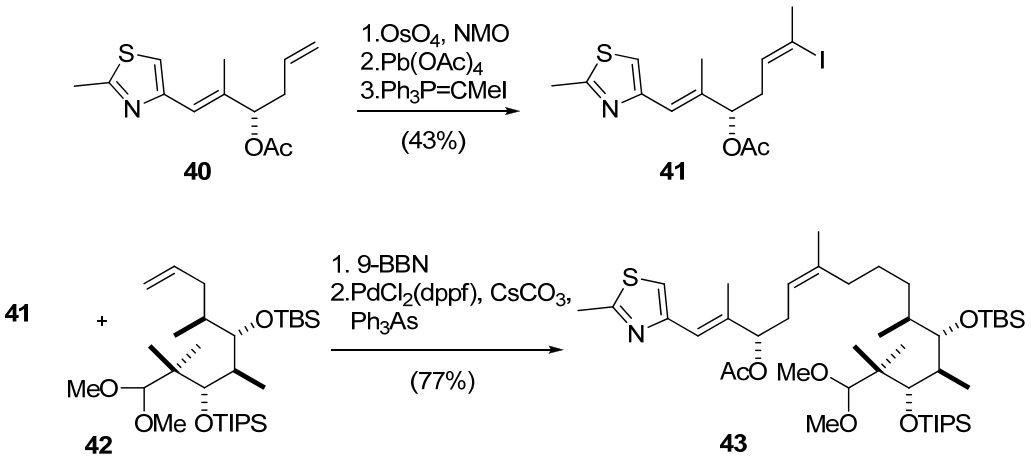
Scheme 11: Taylor's synthesis of the branched side chain of peloruside A (**2**).

There is of course a number of olefination methods left like Peterson, Julia or Corey-Winter olefination, which have not been investigated in any of the syntheses for one of these three natural products.

2.2. Cross Coupling reactions

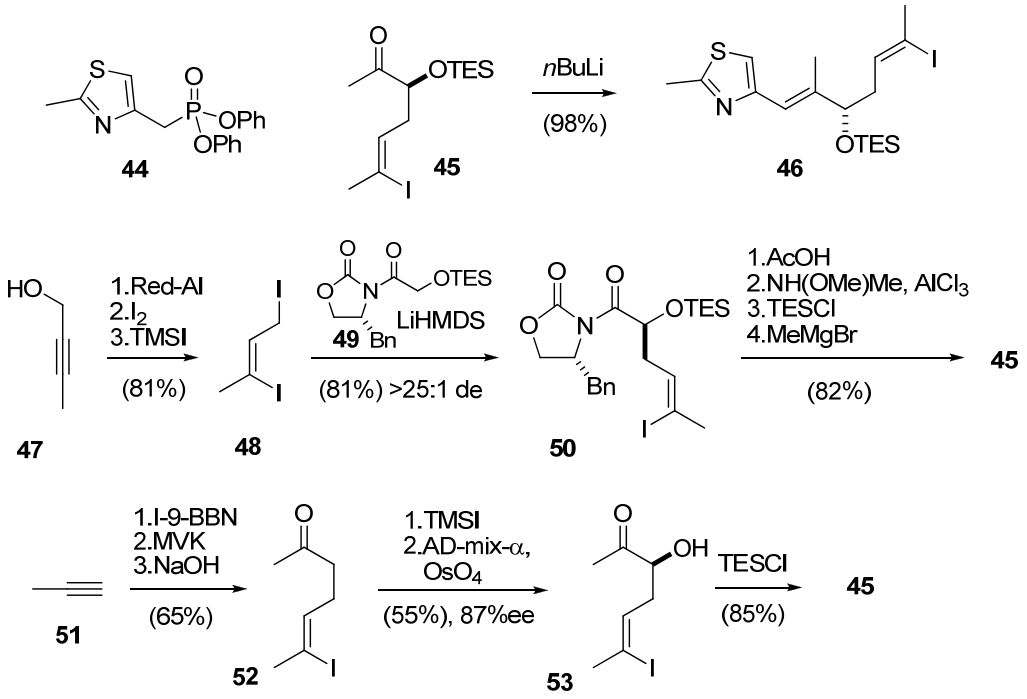
2.2.1. Suzuki Coupling

State of the art for the synthesis of the epothilone B (**1**) double bond, remains Danishefsky's Suzuki coupling which he employed in the first total synthesis in 1997 (Scheme 12). Starting from homoallylic alcohol **40**, which was cleaved by ozonolysis to the corresponding aldehyde and condensed with the appropriate Wittig reagent, (*Z*)-vinyl iodide **41** was reached as only product, albeit in only 43% yield.[28] Now the key Suzuki coupling could be probed, therefore olefin **42** underwent hydroboration with 9-BBN and the resulting borane was directly coupled with (*Z*)-vinyl iodide **41** under palladium mediation, which resulted in 77% yield of highly advanced intermediate **43** featuring the trisubstituted (*Z*)-double bond.



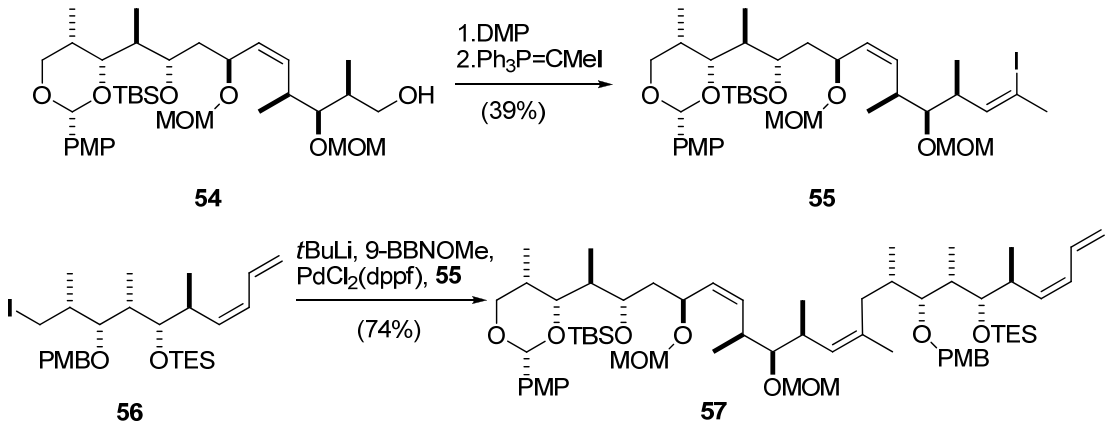
Scheme 12: Danishefsky's Suzuki coupling.

Later Danishefsky developed alternative ways to synthesize the crucial (*Z*)-vinyl iodide on big scale *via* a Horner-like condensation between ketone **45** and phosphonate **44** (Scheme 13).[29] Thus, a simple, straightforward synthesis of ketone **45** featuring the (*Z*)-vinyl iodide had to be developed. The first approach depended on a highly diastereoselective Evans alkylation of **49** with diiodide **48**, generated from 2-butynol (**47**) in two steps. Three more steps afforded ketone **45** *via* the Weinreb amide. The second, faster but less selective route starts with the known reaction of propyne (**51**) with *B*-iodo-9-BBN and methyl vinyl ketone to produce **52**. The hydroxyl group was introduced in 87% ee by Sharpless asymmetric dihydroxylation of the silyl enol ether of **52**. Silyl ether formation gave ketone **45**.



Scheme 13: Danishefsky's alterative way for the (*Z*)-vinyl iodide.

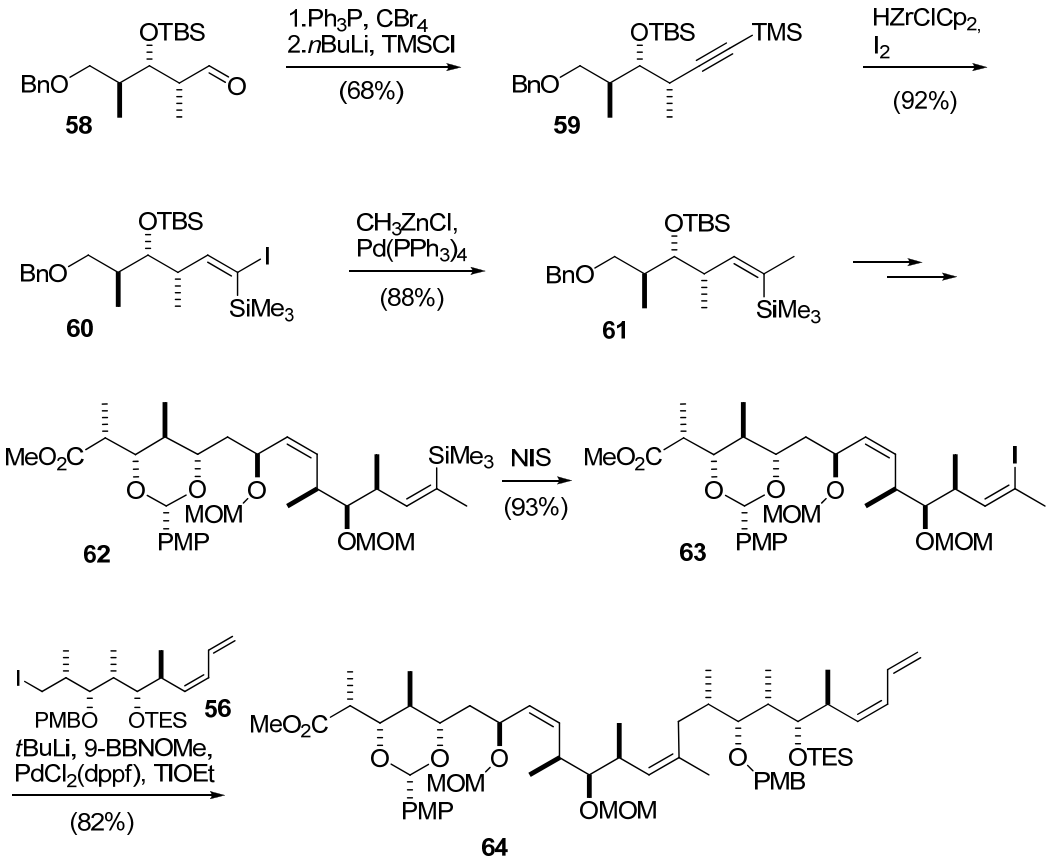
Marshall employed a Suzuki coupling to build up the whole carbon skeleton of discodermolide (**3**) at a late stage. The most challenging reaction of the entire sequence was the conversion of the aldehyde, derived from alcohol **54** by Dess-Martin oxidation, into (*Z*)-vinyl iodide **55** (Scheme 14). Yields for the olefination were in the range of 40% of an 85:15 inseparable mixture of (*Z*)- to (*E*)-isomers; and an unsaturated aldehyde as main by-product through elimination of the *β*-OMOM group. The following Suzuki coupling proceeded in good yield and selectivity to generate the desired trisubstituted (*Z*)-olefin in **57**.



Scheme 14: Marshall's discodermolide (**3**) synthesis.

Panek's strategy relied on a hydrozirkonation-cross-coupling approach to allow a convergent assembling of the trisubstituted (*Z*)-olefin by installation of the crucial vinyl iodide early but

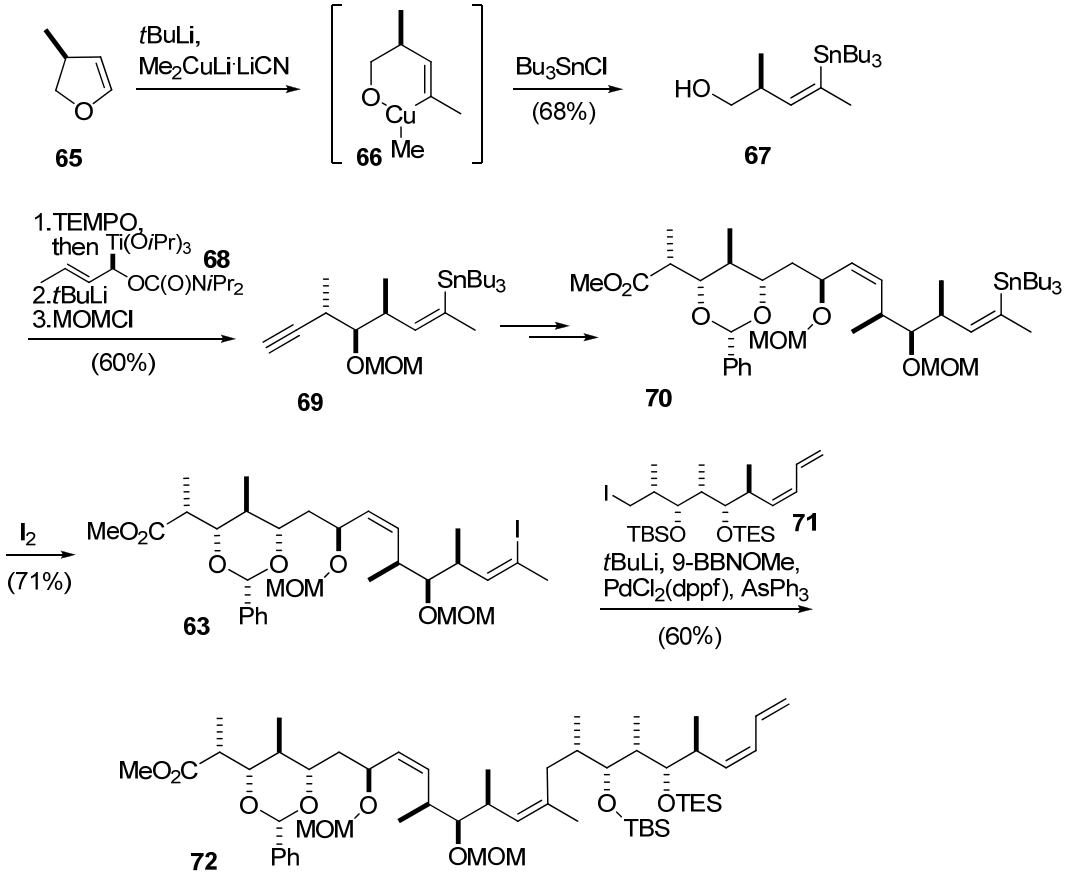
keeping it masked as vinyl silane throughout the synthesis (Scheme 15).[30] Thus, aldehyde **58** was prepared by double stereodifferentiating crotylation reactions using chiral crotylsilanes and was homologated by Corey-Fuchs olefination. The generated vinyl dibromide was treated with base and the resulting lithium acetylene was trapped to yield alkine **59**. Hydrozirconation with Schwartz's reagent and quenching with iodine was carried out and provided in 92% yield and excellent selectivity the geminal iodovinylsilane **60**. Negishi coupling of **60** with methylzinc chloride catalyzed with palladium gave methyl branched vinyl silane **61**. The masked vinyl iodide was carried through a number of transformations to **62** and Kishi's iododesilylation conditions were used to generate **63**. Now Suzuki coupling with trialkyl boronate generated from alkyl iodide **56** gave in good yields and selectivity the desired trisubstituted (*Z*)-double bond in **64**.



Scheme 15: Panek's discodermolide (**3**) synthesis.

Another example to circumvent the installation of the (*Z*)-vinyl iodide for the Suzuki coupling by Zhao-Wittig reaction was the synthesis by Betzer, Ardisson and co-workers who employed a dyotropic rearrangement of a lithiodihydrofuran to generate a vinyl stannane (Scheme 16).[31] Thus, starting from dihydrofurane **65** deprotonation to the corresponding lithio derivative was followed by a 1,2-cuprate transfer with a cyano-Gilman dimethyl cuprate

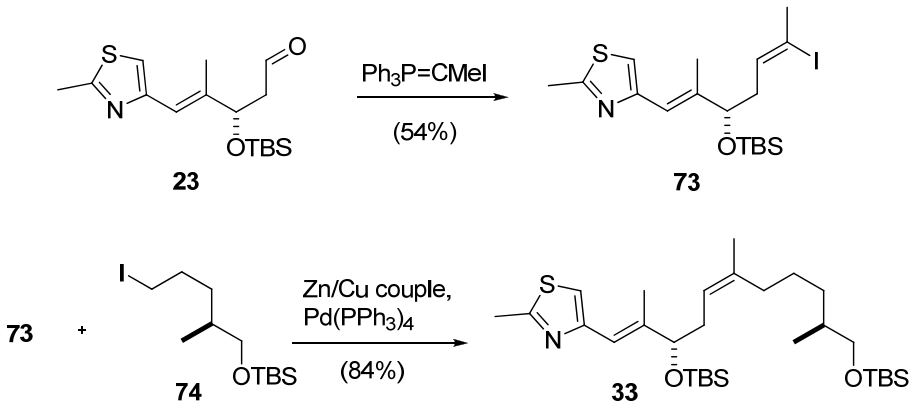
to accomplish the installation of the methyl branched olefin which was trapped as (*Z*)-vinyltin derivative **67**. After oxidation to the aldehyde, diastereoselective allylation with (*R*)-crotyltitanium **68** generated an *O*-enecarbamate which was converted to terminal alkyne **69** by Fritsch-Buttenberg-Wiechell rearrangement. Further conversions featured **70** which was iododestannated with iodine to generate (*Z*)-vinyl iodide **63** and coupling with the trialkyl boronate generated from alkyl iodide **71** assembled the whole carbon skeleton of discodermolide (**3**) in acceptable yield and excellent selectivity.



Scheme 16: Discodermolide (**3**) synthesis by Betzer and Ardisson.

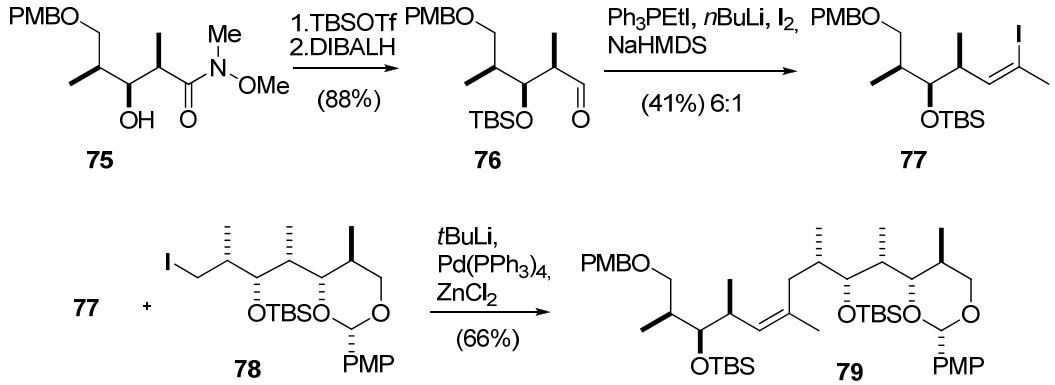
2.2.2. Negishi Coupling

Schinzer used in his approach to epothilone B (**1**) a Negishi coupling, therefore a (*Z*)-vinyl iodide was also needed, which was generated by Zhao-Wittig reaction from aldehyde **23** (Scheme 17).[32, 33] Thus, (*Z*)-vinyl iodide **73** was obtained in very good selectivity but in only very moderate yield, palladium catalyzed coupling with **74** yielded in stereochemically homogenous form the northern fragment **33** of epothilone B containing the desired trisubstituted (*Z*)-double bond.



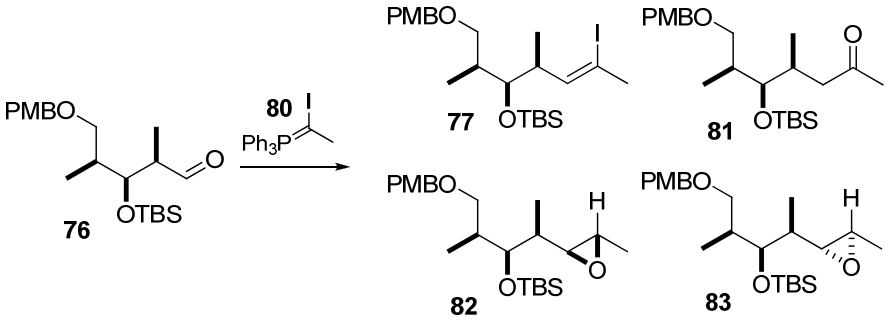
Scheme 17: Schinzer's Negishi coupling.

Smith III and co-workers were the second to finish a total synthesis of the unnatural discodermolide enantiomer in 1995, followed by a synthesis on gram scale of the natural compound.[34, 35] A Negishi coupling was employed to install the crucial trisubstituted double bond in **79**, which worked in acceptable yield and good selectivity (Scheme 18). Unfortunately the generation of the (*Z*)-vinyl iodide again proved troublesome apparent in both the low yield and moderate selectivity to synthesis **77**.



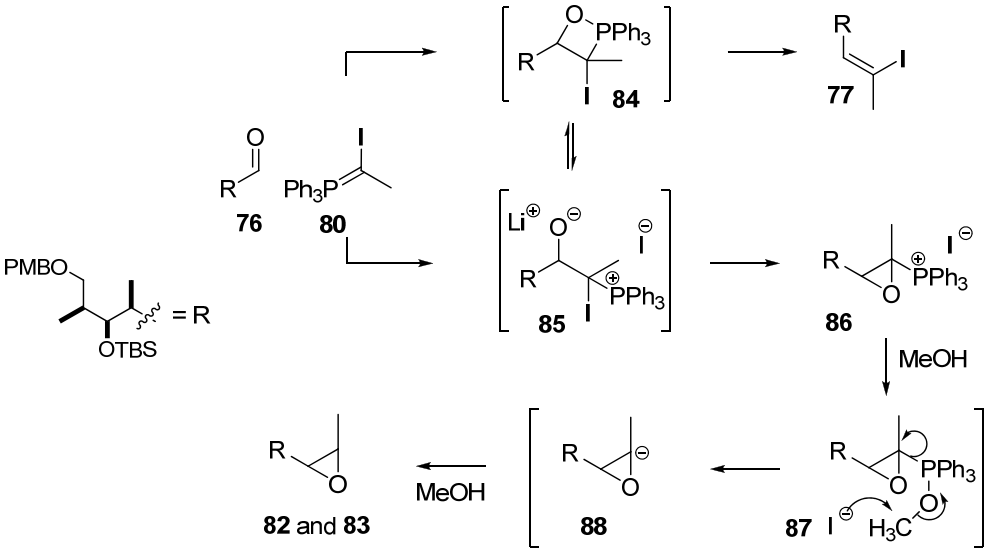
Scheme 18: Smith's first generation approach to discodermolide (**3**).

In an additional study, Smith III investigated the mechanism of the Zhao-Wittig reaction and found, apart from desired (*Z*)-vinyl iodide **77**, three different by-products: methyl ketone **81** and two diastereomeric *cis* epoxides **82** and **83**.[36] Variation of the reaction temperature hardly had any effect on the yield of the iodoalkene but changed markedly the contribution of the by-products, i.e.: at lower temperatures no ketone formation was observed whereas at higher temperatures it was the only by-product observed.



Scheme 19: Unexpected by-products in the Zhao-Wittig reaction.

The formation of the epoxides can be rationalized *via* the betaine intermediate **85** (Scheme 20), which is formed in the presence of lithium salts, and can then be transformed to the epoxy phosphonium salt **86** by a Darzen-like addition-cyclization pathway competitive to the expected formation of vinyl iodide **77**. Methanolysis converts the epoxy phosphonium salt **86** into epoxide **82** and **83** presumably *via* oxiranyl anion **88**. The conversion of epoxy phosphonium salt **86** into the methyl ketone is not well understood but might be due to the instability of oxiranyl anion **88** at elevated temperatures.

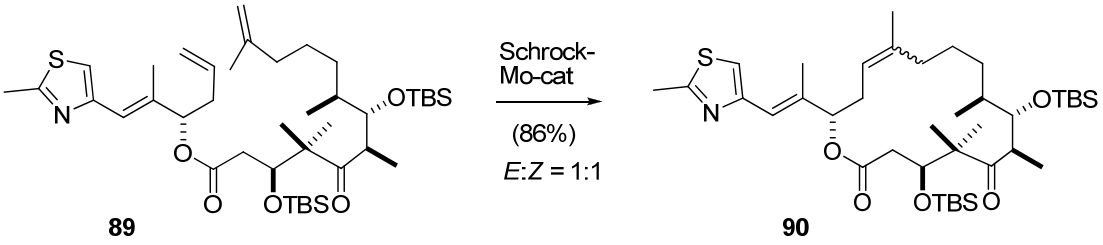


Scheme 20: Rationalization for by-product formation in the Zhao-Wittig reaction.

2.3. Ring Closing Metathesis (RCM)

2.3.1. RCM as Macrocyclization

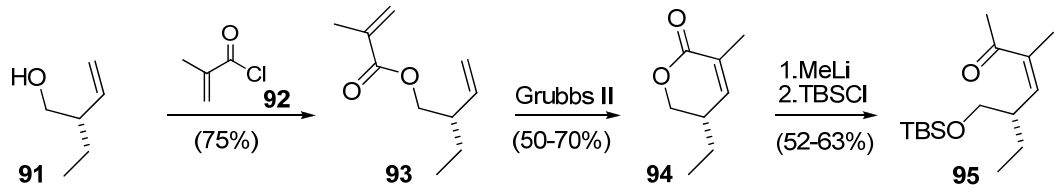
RCM as a strategy for the macrocyclization was also investigated by Danishefsky (Scheme 21).[28] Alas, despite variation of the catalyst and the substrate, the best conditions resulted in a 1:1 *E*:*Z* mixture of diastereoisomers in quite good yield.



Scheme 21: Danishefsky's RCM approach.

2.3.2. RCM of Medium-Sized Rings

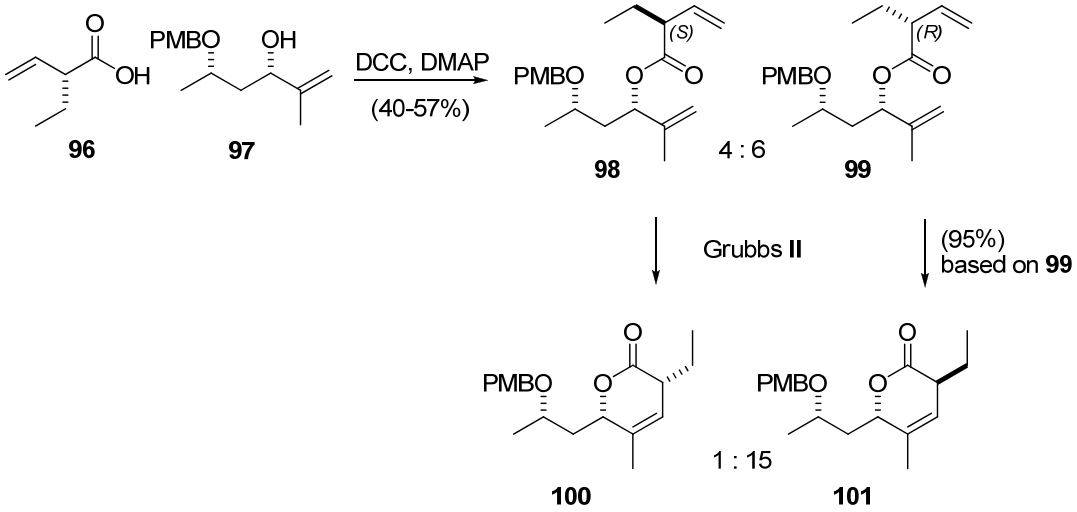
In the first total synthesis of *ent*-peloruside A (***ent*-2**) by De Brabander in 2003 the trisubstituted (*Z*)-olefin was generated by RCM of a six-membered ring (Scheme 22).[21] The RCM precursor was generated by acylation of homoallylic alcohol **91** with methacryloyl chloride (**92**). Treatment with Grubbs' second generation catalyst provided lactone **94** in 50% to 70% yield with 20% of the dimer. The required trisubstituted enone **95** was then generated by the addition of methyl lithium and silyl protection of the primary alcohol.



Scheme 22: De Brabander's RCM for the peloruside A side chain **95**.

A very interesting observation was made by Ermolenko, who also used a RCM to generate the trisubstituted (*Z*)-olefin of peloruside A (**2**) (Scheme 23).[37] Upon preparation of the RCM precursor esterification under standard Steglich conditions with DCC and DMAP led to

severe racemization of the acid, thus giving an inseparable mixture of esters **98** and **99**. When this mixture was subjected to the RCM reaction employing Grubbs' second generation catalyst, after three days, a resolution of the diastereoisomers had taken place. Unreacted ester **98** was recovered almost completely, while the desired lactone **101** was formed out of the correct ester **99**, additionally yields based on **99** were very good.

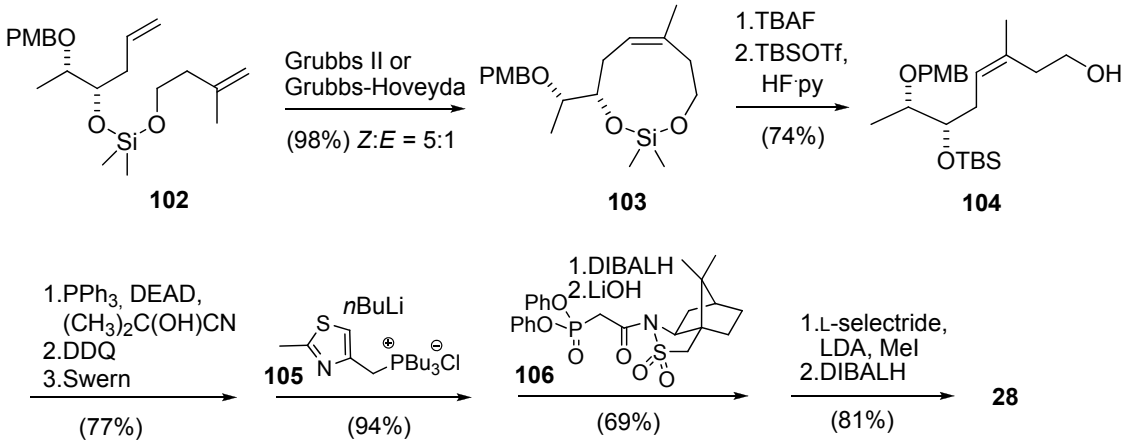


96 **97** **98** **99** **100** **101**

Scheme 23: Highly diastereomer-discriminating RCM.

Kalesse describe a successful RCM strategy to close a ten-membered lactone for the disubstituted (*Z*)-double bond of epothilone A (**14**).[38]

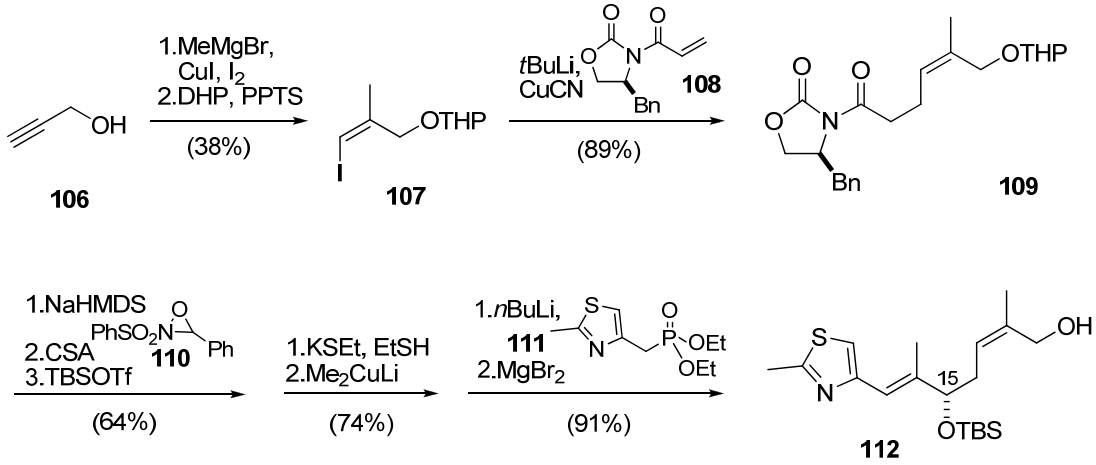
Mulzer later employed a RCM to form a nine-membered silicon-tethered ring containing the crucial trisubstituted double bond of epothilone B (**1**) (Scheme 24).[39] Compound **102** was used as substrate and thus delivered the nine-membered ring in a diastereomeric ratio of 5:1 in favor of (*Z*)-olefin **103**. After opening of the nine-membered ring the diastereoisomers were separated. The quite simple triol had to be converted into northern fragment **28** by step wise elongation *via* introduction of one carbon by a Mitsunobu reaction and two more by a Horner-Wadsworth-Emmons reaction with Oppolzer's sultam **106**, which also enabled the generation of the chiral methyl group at C8. The thiazolalkylidene moiety was installed by Wittig reaction.



Scheme 24: Mulzer's RCM approach to a medium sized ring.

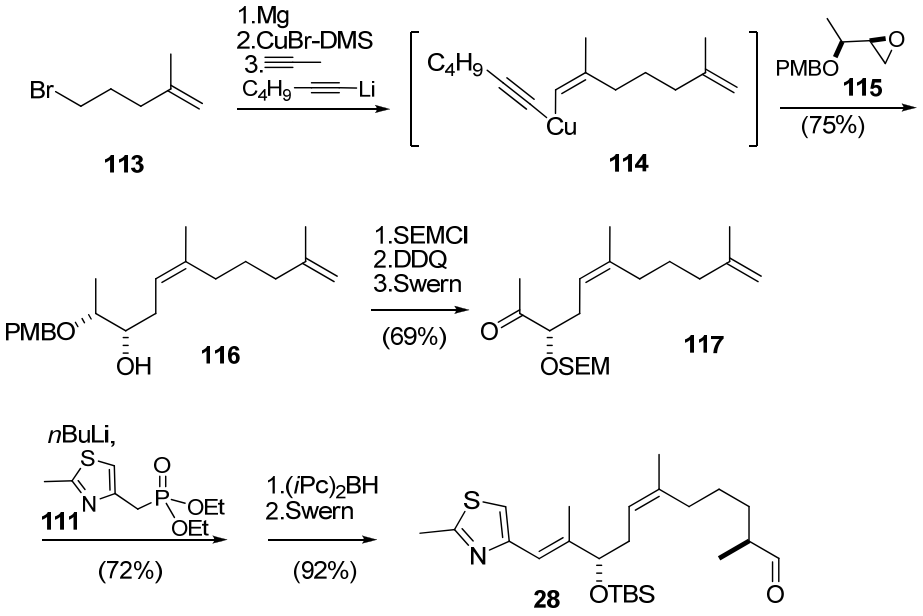
2.4. Cupration

The epothilone B (**1**) synthesis of White took advantage of the clean regio- and stereoselectivity of carbocupration of propargylic alcohol (**106**) to establish the (*Z*)-double bond in low yields in iodo alcohol **107** at the very beginning (Scheme 25).[40] Halogen-metal exchange was followed by transmetallation with copper cyanide for conjugated addition to oxazolidinone **108**. Then the C15 hydroxyl group was introduced using Davis' oxaziridine **110**. After protection and removal of the chiral auxiliary, the thiazolalkylidene moiety was introduced by Horner reaction of the corresponding methyl ketone to generate **112**.



Scheme 25: White's carbocupration.

Avery established the desired (*Z*)-configuration of the epothilone B northern fragment **28** by classic Normant alkyne cupration and electrophilie trapping, which additionally also set the stereochemistry at C15 (Scheme 26).[41, 42] Therefore, the Grignard reagent prepared from bromide **113** was transmetallated to provide the cuprate and step wise elongated by the addition of propyne and lithiohexyne. Intermediate **114** was used to open epoxide **115** which provided desired (*Z*)-olefin **116** in good yield. Protecting group manipulations and oxidation generated methyl ketone **117**, which after HWE reaction, was regio- and stereoselectively hydroborated, followed by oxidation to give **28**.

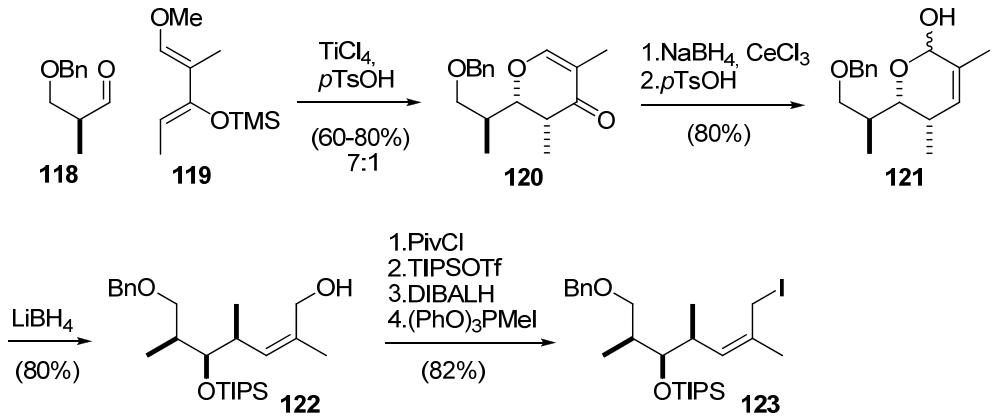


Scheme 26: Avery's Normant alkyne cupration and electrophile trapping.

2.5. Pericyclic Reactions

2.5.1. Cycloadditions: Hetero-Diels-Alder Reaction

Cycloadditions have also been used to generate trisubstituted (*Z*)-double bonds incorporated in a ring system, as was shown by Myles in his synthesis of discodermolide (**3**) (Scheme 27).[43, 44] He took advantage of a titanium promoted hetero-Diels-Alder reaction between aldehyde **118** and Danishefsky diene **119** to generate pyrone **120** in a 7:1 diastereomeric ratio, whose cyclic framework enforced complete control of the alkene geometry. After Luche reduction, acid mediated Ferrier rearrangement led to lactol **121**. Reductive opening gave primary alcohol **122**. The corresponding allyl iodide **123** was accessible by protecting group manipulations and conversion into the iodide, which could be used in an alkylation reaction with the C16-C21 ketone.

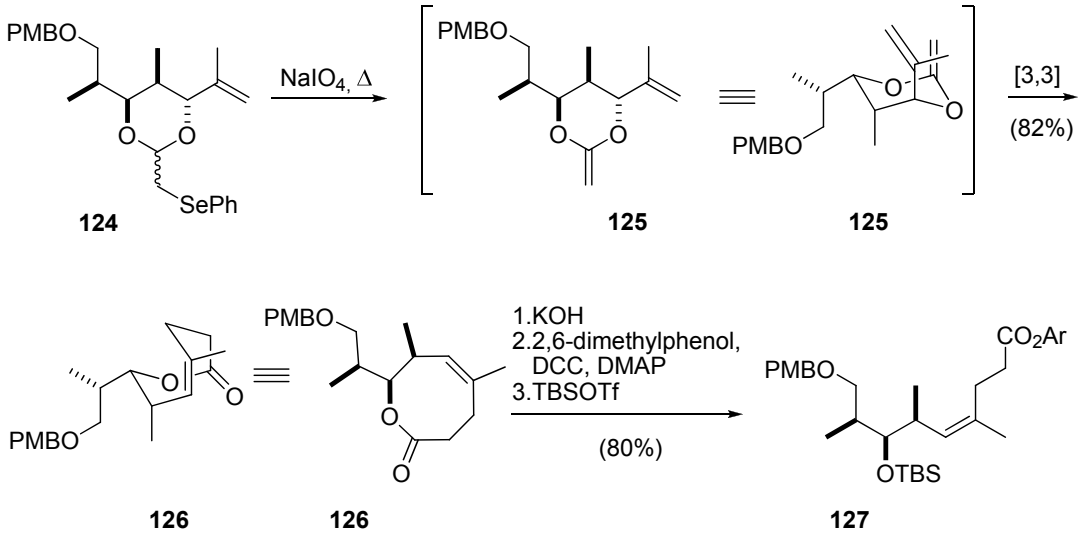


Scheme 27: Myles' hetero-Diels-Alder for the discodermolide (**3**) synthesis.

2.5.2. Claisen-type [3,3]-Rearrangement

In his first generation synthesis of discodermolide (**3**) Paterson generated the trisubstituted double bond by a Claisen-type [3,3]-rearrangement (Scheme 28).[45, 46] As precursor a 2:1 diastereomeric mixture of acetal **124** was used, whose stereocenters were generated by his well established boron mediated *anti*-aldol addition. After oxidation of the selenide to the selenoxide, ketene acetal **125** formed, which rearranged *via* the preferred bicyclic-chair conformation to give eight-membered lactone **128** with complete stereocontrol. Ring opening

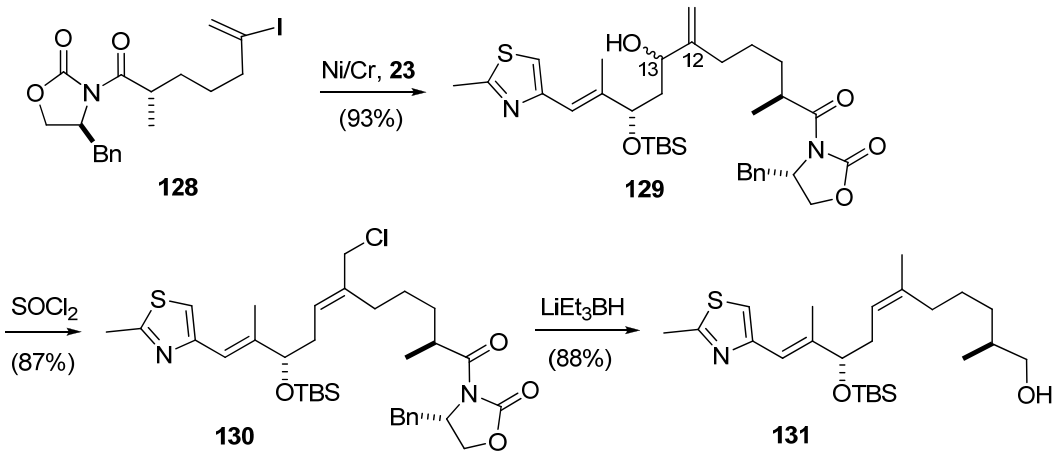
of the lactone to the hydroxy acid was followed by esterification under Steglich conditions and silyl protection of the secondary alcohol to generate aryl ester **127**.



Scheme 28: Paterson's discodermolide (**3**) synthesis.

2.5.3. Allylic Rearrangement

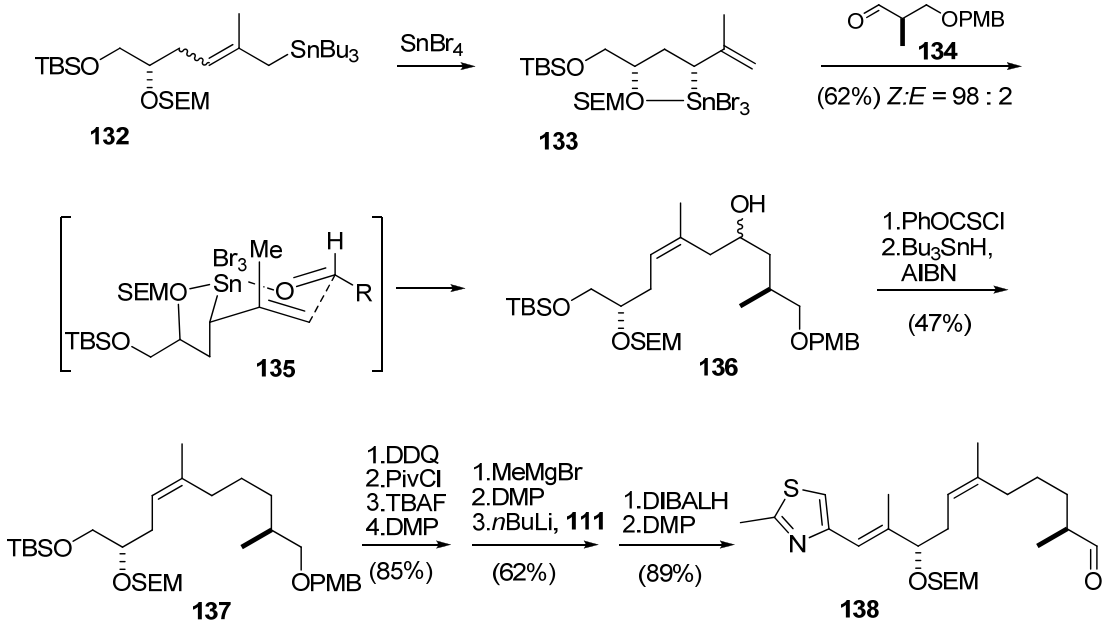
Taylor used a different synthetic strategy in his epothilone B (**1**) synthesis in form of a tandem sequence (Scheme 29). A Nozaki-Hiyama-Kishi coupling to form the C12-C13 bond in **129** was followed by a stereoselective thionyl chloride induced allylic rearrangement to generate the trisubstituted double bond in **130**.[47] Super hydride very efficiently removed both the auxiliary and the allylic chloride to generate **131**.



Scheme 29: Taylor's approach to the epothilone B trisubstituted double bond.

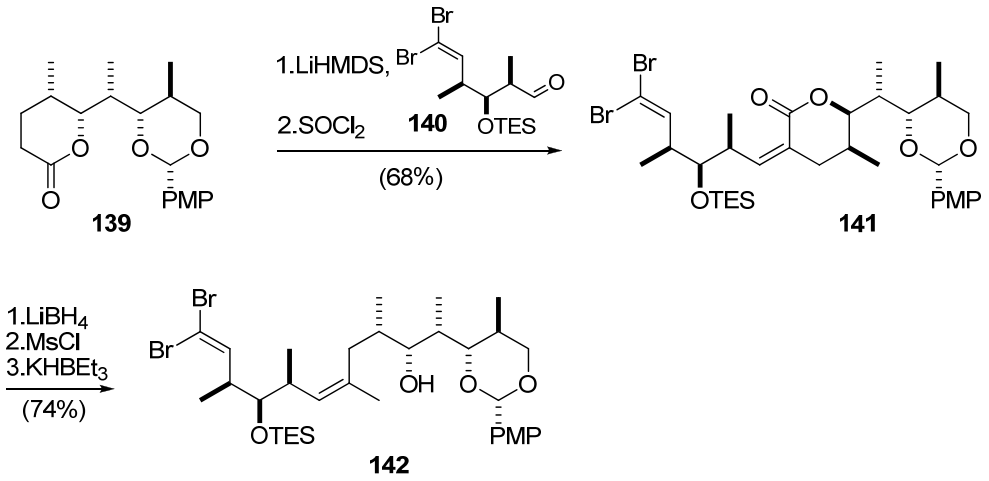
2.6. Miscellaneous

Thomas applied his tin(IV) bromide promoted reaction between allylstannane **132** and aldehyde **134** to introduce the trisubstituted double bond of the epothilone B northern fragment **238** (Scheme 30).[48, 49] Bis-protected dihydroxyalkenylstannane **132** was transmetallated to allytin tribromide which reacted in a stereoselective manner with aldehyde **134** to give alcohol **136** in 62% yield as a 1:1 epimeric mixture, containing less than 2% of the (*E*)-isomer. The (*Z*)-stereogeometry of the double bond was fixed due to the axial position of the *α*-substituent situated next to tin in the six membered transition state **135**. The hydroxyl group was removed by Barton-McCombie deoxygenation. After further protecting group manipulations and introduction of the methyl ketone *via* Grignard addition and oxidation, the thiazole ring was attached by HWE olefination to give northern fragment **138**.



Scheme 30: Thomas' synthesis of epothilone B (**1**).

Evans relied on his established aldol methodology to build up the required stereogenic centers in the advanced fragments **139** and **140** of his discodermolide synthesis (Scheme 31).[12] The trisubstituted (*Z*)-olefin came from a two-step formal aldol condensation between aldehyde **140** and lactone **139**. A three step sequence of reductive lactone opening followed by deoxygenation established the desired trisubstituted (*Z*)-olefin moiety in **142**.



Scheme 31: Evans' synthesis of discodermolide (**3**).

3. Grob Fragmentation

3.1. Introduction

Fragmentation reactions have been known for quite a long time as powerful tools to build up double or even triple bonds.[50] According to the definition by Grob, these are processes where the reacting molecule breaks in three fragments (Figure 4). The electrofugal group a=b forms stable cations or neutral molecules, the middle group c=d gives an unsaturated fragment and the nucleofugal group X^- leaves with the binding electron pair.[51, 52] Substrates contain a certain carbon and heteroatom combination and are typically 1,3-dihetero-functionalized compounds featuring a nucelophilic atom with a negative charge or lone electron pair and a leaving group in a 1,3 relationship.

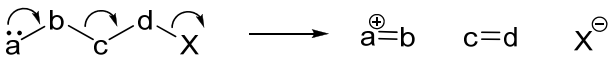


Figure 4: Schematic Grob Fragmentation.

Fragmentation substrates can also react *via* different pathways like substitution of the leaving group, elimination or ring-closing reaction (Figure 5), but in general careful selection of the conditions minimizes these intermolecular processes.

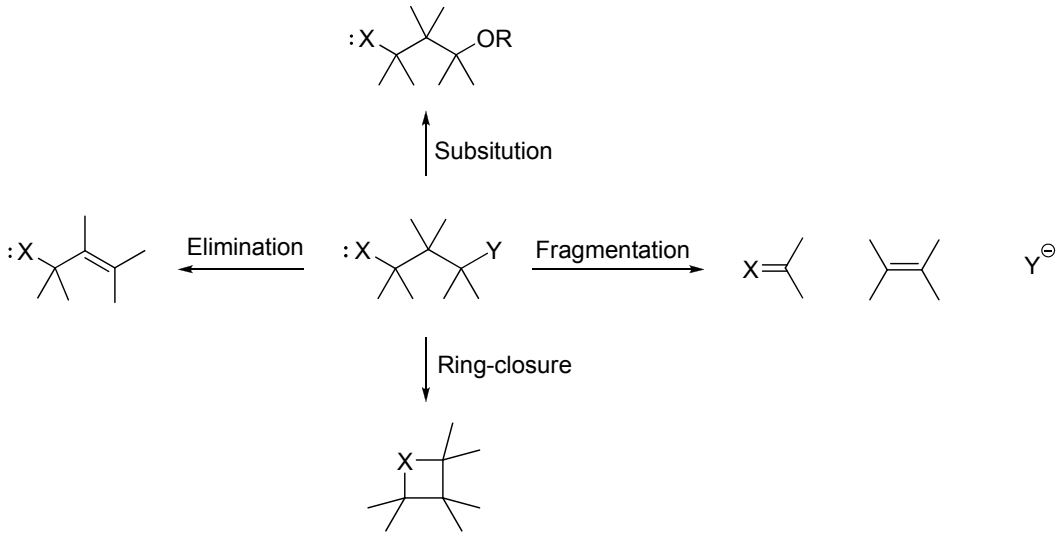


Figure 5: Possible reaction pathways of 1,3-diheterosubstituted compounds.

Stereoelectronic and stereochemical factors influence the outcome of the reaction, which can proceed *via* a concerted or a stepwise mechanism (Figure 6).[53] In the two step process,

either similar to an E1 or S_N1 reaction, the leaving group is first cleaved to form a carbocation, which can then further react *via* fragmentation, elimination, substitution or ring-closure or the elecrofugal group leaves first to form a carbanion, which can eliminate the leaving group Y^- in the second step. In the concerted process each of the five centers contributes to the transition state which results in strict structural and stereoelectronic requirements.

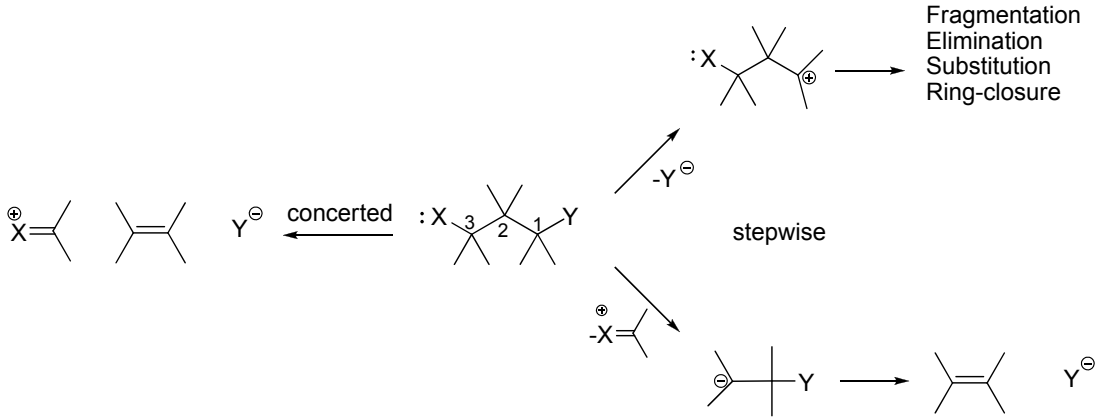
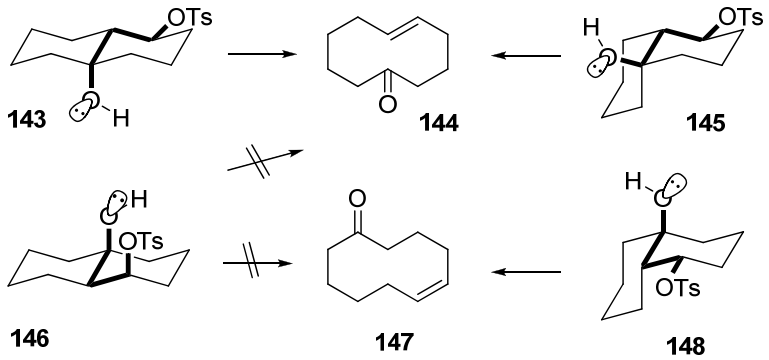


Figure 6: Concerted vs. stepwise mechanism.

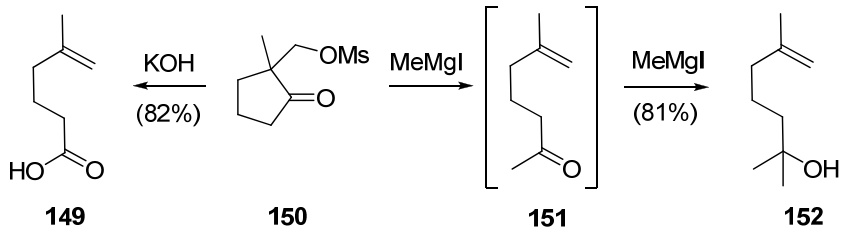
For a typical fragmentation reaction, stereoelectronically two polarized bonds are needed, which will be broken during the course of the reaction, a substituent with an electron donating lone pair and an electron withdrawing leaving group. Stereochemical requirements of the Grob fragmentation are the antiperiplanar arrangement of the leaving group and the electron pair of the electrofugal group to the C2-C3 bond or with other words: that the two breaking bonds are antiperiplanar to each other (Scheme 32). This can be illustrated impressively by the base induced fragmentation of cyclic 1,3-diol monosulfonates **143**, **145**, **146** and **148**.[54] The fragmentation of 1,3-diols is also known as Wharton fragmentation.



Scheme 32: Wharton fragmentation for medium-sized rings.

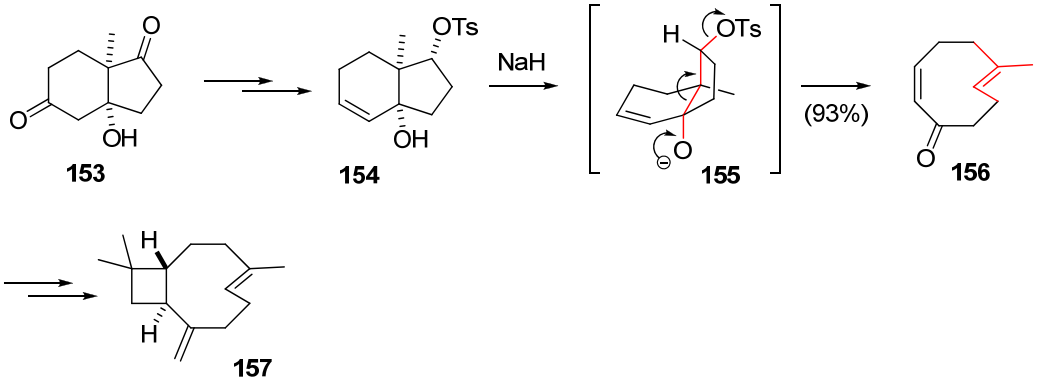
3.2. Some Examples in Literature

The first fragmentation was published by Eschenmoser in 1952 (Scheme 33), who used *β*-mesyloxy ketone **150** which was treated with potassium hydroxide or methyl magnesium iodide to generate fragmentation product **149** and **152**, respectively.[55]



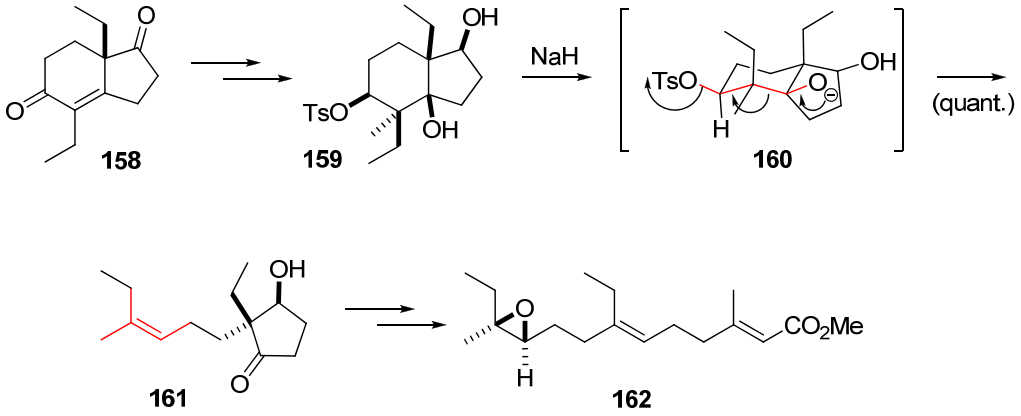
Scheme 33: First fragmentation described by Eschenmoser.

Corey used a fragmentation reaction in his synthesis of *β*-caryophyllene (**157**) where he very efficiently elaborated a fused bicyclic ring system to a nine-membered ring (Scheme 34).[56] Bicycle **153** was thus generated by the Hajos-Parrish procedure and elaborated into fragmentation precursor **154**, which upon treatment with sodium hydride underwent fragmentation in excellent yield and selectivity. Further elaboration led to *β*-caryophyllene (**157**).



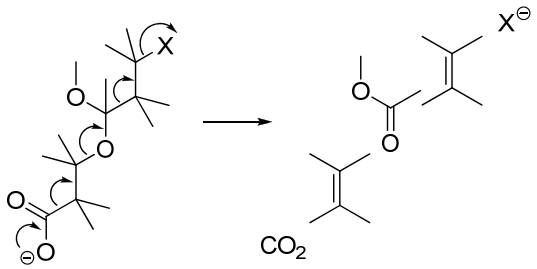
Scheme 34: Corey's *β*-caryophyllene synthesis.

Open chain olefins have also been synthesised like the (*Z*)-olefin of juvenile insect hormones by Edwards.[57] Robinson annulation of simple starting material generated bicycle **158**, which was converted to fragmentation precursor **159** by a series of reduction, selective alkylation and finally installation of the leaving group. Fragmentation worked smoothly in the presence of sodium hydride to generate desired trisubstituted (*Z*)-olefin **161**.

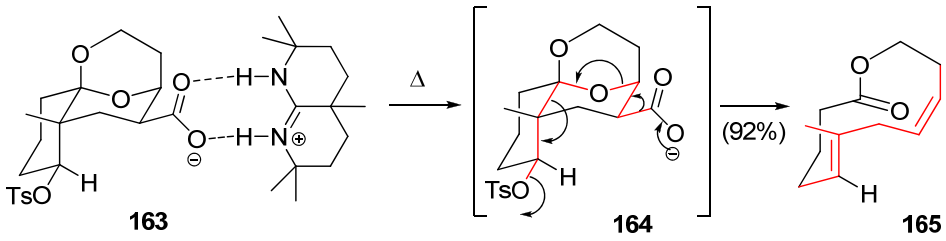


Scheme 35: Fragmentation to build a linear trisubstituted olefin.

Eschenmoser described a decarboxylative double fragmentation as macrolide synthesis, generating two double bonds in one step (Scheme 36).[58] As elaborated fragmentation precursor crystalline amidinium salt **163** was used which upon heating was converted to **165**, presumably by a two step mechanism *via* the dioxoniumion to give two double bonds - a disubstituted (*Z*)- and a trisubstituted (*E*)-olefin (Scheme 37).



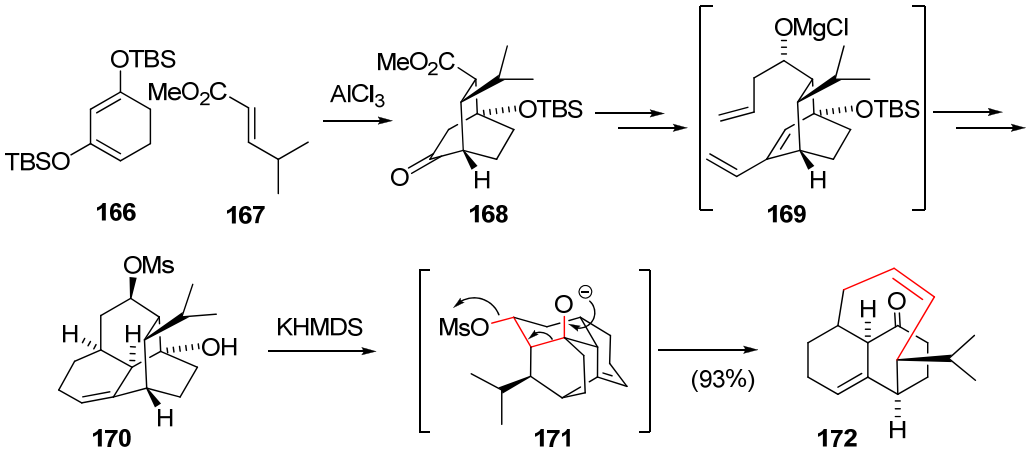
Scheme 36: Schematic decarboxylative double fragmentation.



Scheme 37: Eschenmoser's decarboxylative double fragmentation.

In his synthesis of vinigrol Baran accessed the tricyclic carbon skeleton by Grob fragmentation of a tetracyclic ring system at a late stage of the synthesis (Scheme 38).[59] The complex tetracyclic precursor **170** was constructed very elegantly and efficiently by two

Diels-Alder reactions and upon treatment with KHMDS the core structure of vinigrol **172** was reached in very good yield.



Scheme 38: Baran's vinigrol synthesis.

4. Results and Discussion – The Concept

4.1. The Hydroxide Induced Decarboxylative Grob-type Fragmentation

Our attention was first caught by the challenge to develop a new route for the stereoselective introduction of the trisubstituted C12,13-(*Z*)-double bond of epothilone D (**16**). The northern fragment of epothilone D (**16**) seemed to be an ideal example due to the huge number of different olefination strategies already applied in many total and formal syntheses as mentioned above, which still have not provided completely convincing results.

For this purpose a new hydroxide induced decarboxylative Grob-type fragmentation should be used (Figure 7), whose applicability was already proven by model studies and a short racemic synthesis.[60]

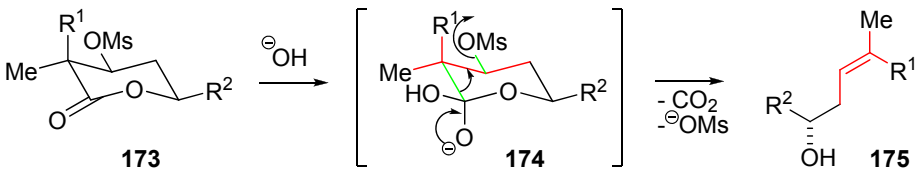
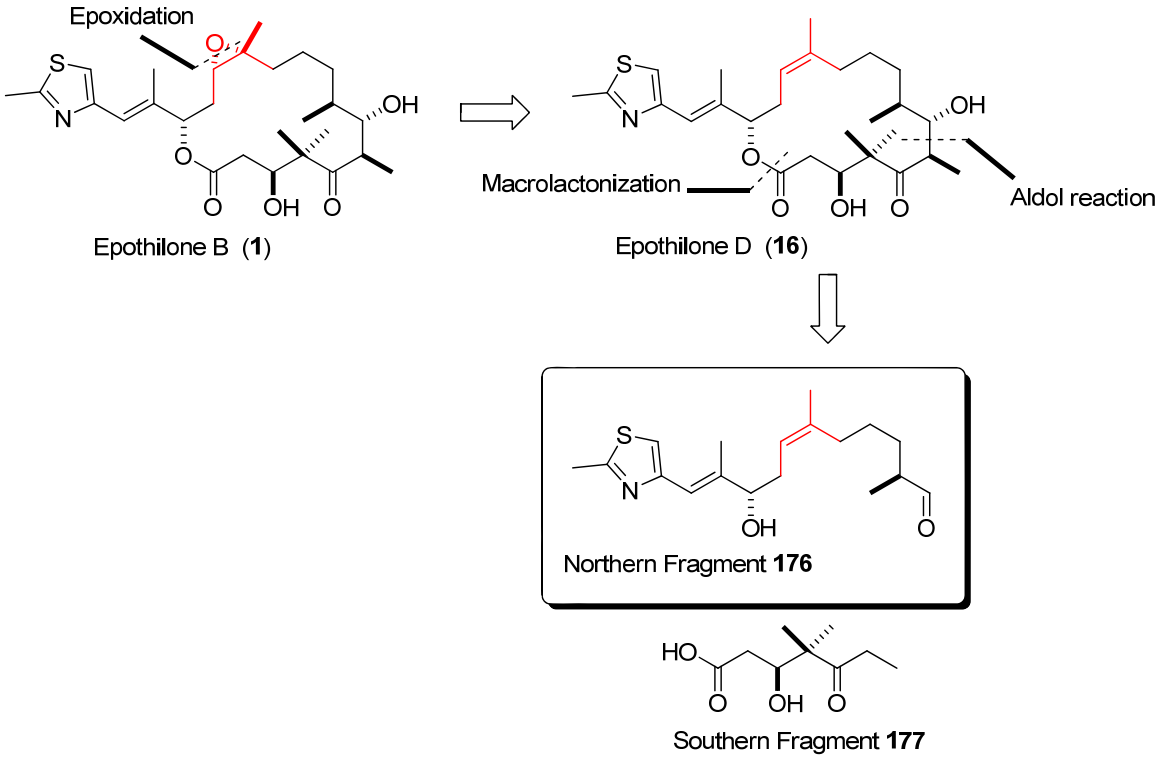


Figure 7: Hydroxide induced decarboxylative Grob-type fragmentation.

As fragmentation precursor *ß*-mesyloxy-*δ*-lactone **173** was chosen. Upon addition of hydroxide the tetrahedral intermediate **174** will be formed, which undergoes fragmentation to form olefin **175** stereounambiguously by elimination of carbon dioxide and the leaving group. On preparing lactone **173**, three stereogenic centers, one of them quaternary,[61-63] have to be generated with the relative configuration indicated. For stereoelectronic reasons, clean fragmentation can be expected if the lactone adopts a chair conformation with the OMs-substituent in an equatorial position. This may be facilitated by introducing a bulky residue R^2 *cis* to the OMs which anchors the desired conformer. The fragmentation generates a homoallylic carbinol center, which is stereogenic in both epothilone B (**1**) (C15) and discodermolide (**3**) (C11). Thus, these centers have to be homochiral requiring the fragmentation precursor **173** to be prepared in a diastereo- *and* enantioselective manner.

5. Results and Discussion - Epothilone B

5.1. General Retrosynthesis



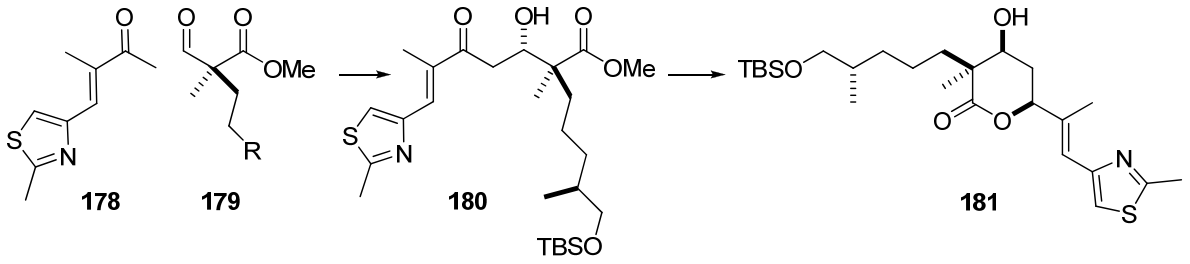
Scheme 39: General retrosynthesis of epothilone B (**1**).

In most syntheses the C12,13-epoxide is introduced in the last step through stereoselective epoxidation of the C12,13-olefin in epothilone D (**16**). Further disconnection by opening the macrolactone to the *seco*-acid and dissection between C6 and C7 leads to the northern fragment (**176**) containing the trisubstituted (*Z*)-double bond and the smaller southern fragment (**177**) (Scheme 39).

For the synthesis of the northern fragment **176** of epothilone B two independent strategies were pursued: on the one hand, preparation of the whole carbon skeleton and lactonization of a highly advanced *ß*,*δ*-dihydroxy ester with the fragmentation reaction in the last step, the PLE route; and on the other hand, an early lactone formation and introduction of the quaternary center on a *ß*-keto lactone with the fragmentation reaction halfway thru the synthesis, the lactate route.

5.2. First Approach: Pig Liver Esterase (PLE) Route

This approach starts with the enantioselective generation of the quaternary center, which should then serve to control the formation of the remaining centers by means of a stereochemical relay (Scheme 40). The key steps are the enantioselectively generation of the quaternary center of **179** by enzymatic desymmetrization of a *meso* compound and the substrate controlled aldol addition with methyl ketone **178** to assemble the whole carbon skeleton. Reduction followed by cyclization gives fragmentation precursor **181**.

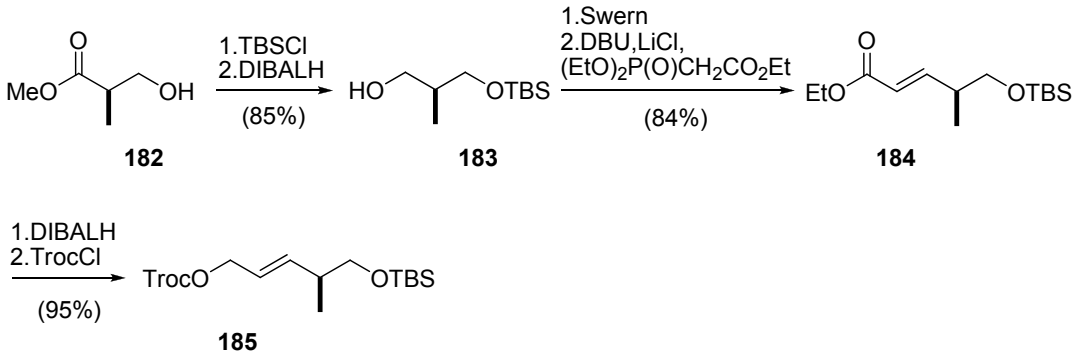


Scheme 40: Synthetic strategy for the PLE route.

5.2.1. Quaternary Center by Desymmetrization

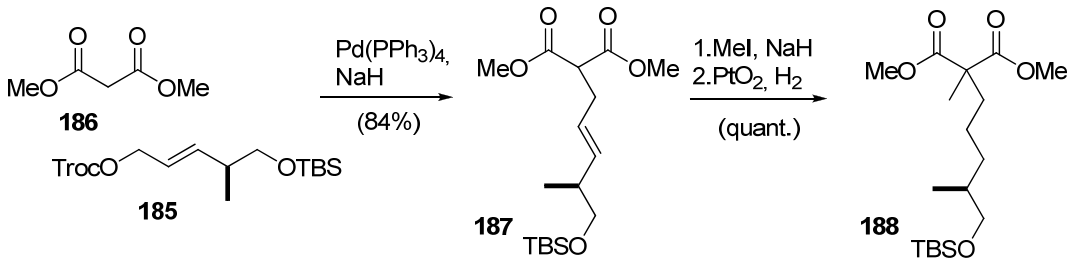
Synthesis of the *meso* substrate

The synthesis of side chain **185** was accomplished in a straight forward manner starting from (*R*)-Roche ester (**182**). Protection as its silyl ether under standard conditions and reduction to alcohol **183** was followed by Swern oxidation (Scheme 41). The resulting *α*-chiral aldehyde was C2 elongated by means of a Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions, giving exclusively *α*,*ß*-unsaturated (*E*)-ester **184**.[64] DIBALH reduction to the corresponding allylic alcohol was followed by protection, to give elongated allylic carbonate **185**.



Scheme 41: Synthesis of allylic carbonate **185**.

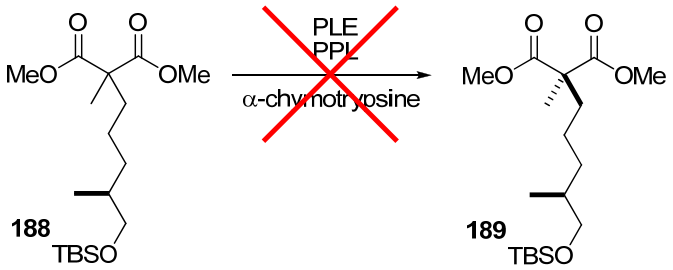
The allylic side chain **185** was attached to dimethyl malonate (**186**) in a Tsuji-Trost reaction. Subsequent methylation created the quaternary center (Scheme 42).[65, 66] For the hydrogenation various standard methods such as palladium on charcoal or $Pd(OH)_2$ were tested and led either to decomposition or TBS cleavage. Finally, using Adam's catalyst turned out to be the method of choice.[67]



Scheme 42: Preparation of *meso* malonate **188**.

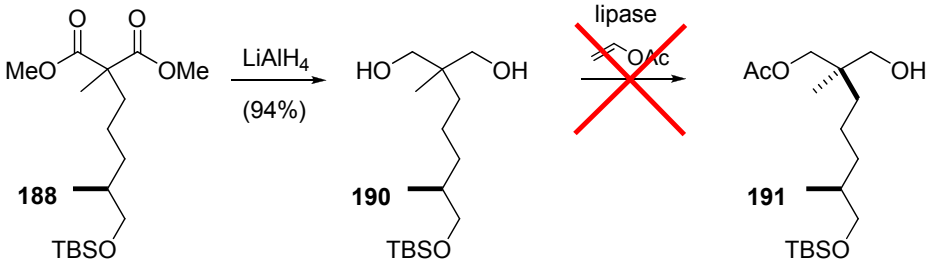
Enzymatic Hydrolysis of 188

With *meso* malonate **188** in hand, enzymatic desymmetrization was attempted testing different enzymes for example pig liver esterase (PLE), porcupine pancreas lipase (PPL) and *α*-chymotrypsine in biphasic or aqueous buffer systems using a pH-stat-controlled burette (Scheme 43). Even though these enzymes are reported to have a broad substrate scope, none of the mentioned resulted in any conversion.[68, 69]



Scheme 43: Enzymatic desymmetrisation by hydrolysis.

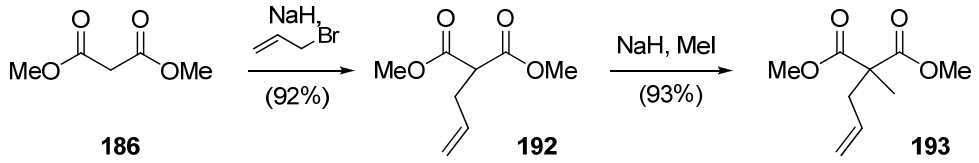
Beside the enzymatic hydrolysis it was tested whether enantioselective esterification of *meso* diol **190** might prove more successful (Scheme 44). Therefore, malonate **188** was reduced to diol **190** and subjected to desymmetrization investigating different lipases like PPL, *Pseudomonas sp.* lipase (PSL), lipase AK and chirazyme with vinyl acetate as acetate donor. Only with chirazyme traces of product could be observed, however the best result after intensive optimization was 15% conversion after one week reaction time at 40 °C in pure vinyl acetate, making this not a practicable strategy.



Scheme 44: Enzymatic desymmetrization by esterification.

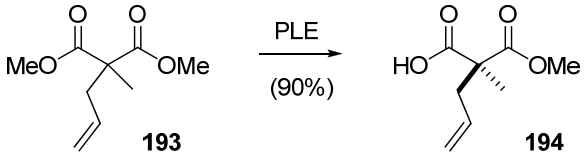
Simpler substrate for the enzymatic hydrolysis

Extensive literature search suggested that the long apolar side chain with the polar end seemed to be the problem, as most of the tested enzymes are reported to either tolerate small to very bulky apolar groups or short polar groups. Thus, a simplified substrate **193** was prepared starting again from dimethyl malonate (**186**) by allylation with allyl bromide and subsequent methylation to install the quaternary center of *meso* malonate **193** (Scheme 45).



Scheme 45: Preparation of simplified *meso* malonate **193**.

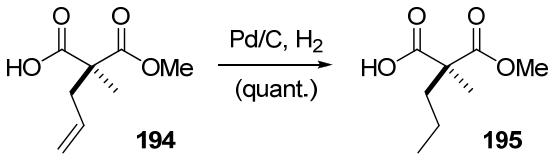
This time treatment with PLE smoothly provided mono acid **194** in good yield and high enantioselectivity (Scheme 46). Conversion worked quickest in an aqueous buffer at ambient temperature. The reaction can also be carried out in biphasic mixtures; however such conditions result in prolonged reaction times.



Scheme 46: Enzymatic desymmetrization by hydrolysis of **193**.

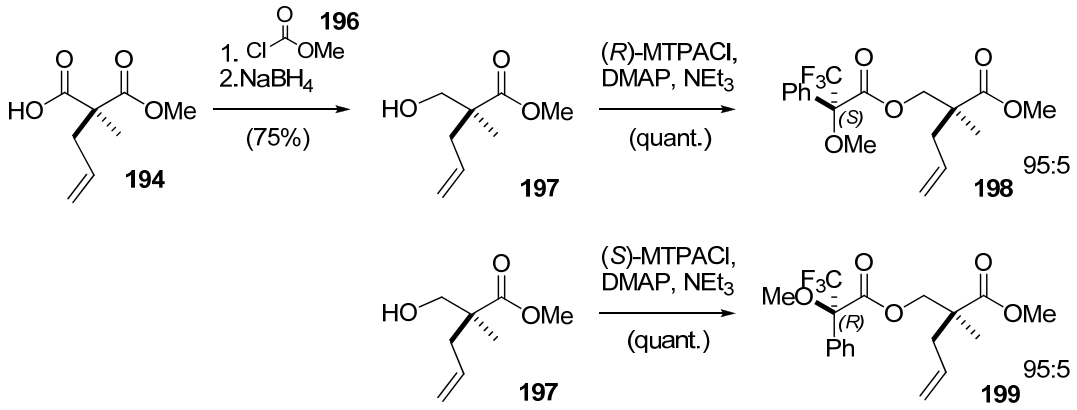
Determination of the absolute configuration and enantiomeric ratio

The absolute configuration was assigned by comparison with literature data of the hydrogenated mono acid **195** (Scheme 47).[70, 71]



Scheme 47: Conversion of **194** into known mono acid **195**.

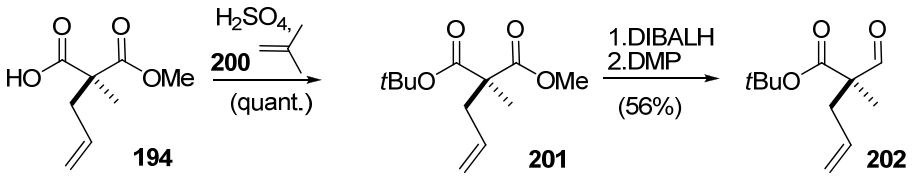
For the determination of the enantiomeric excess the carboxylic group of mono acid **194** was first selectively reduced to alcohol **197** *via* the mixed anhydride and then further converted with Mosher's chloride into the corresponding ester **198** and **199** (Scheme 48).[72] ^{1}H-NMR, ^{19}F-NMR and HPLC analysis of Mosher's ester **198** and **199** confirmed a 95:5 ratio of major to minor MTPA diastereoisomer which equates to 90% ee.



Scheme 48: Determination of the diasteromeric ratio of Mosher's ester **198** and **199**.

Selective manipulation of the methyl ester group

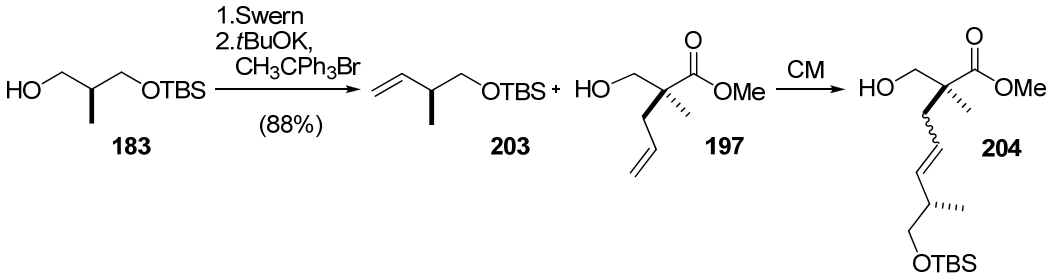
The greate advantage of mono acid **194** is the possibility to versatilely and independently manipulate three of the substituents of the quaternary center. On one hand, the allylic moiety can be elaborated in many ways; and on the other hand, both carbonyl groups can be further transformed selectively and independently. Thus, conversion into the *tert*-butyl ester by treatment with isobutene (**200**) under acidic conditions worked excellent and now the less sterically hindered ester was reduced to the corresponding alcohol in 74% yield and further oxidized to aldehyde **202** (Scheme 49).



Scheme 49: Selective conversion of the methyl ester of malonate **201**.

5.2.2. Chain Elongation

The first idea was to directly elongate the allylic moiety of **197** by cross metathesis (CM) with olefin **203** derived from alcohol **183** (Scheme 50).[73, 74] Swern oxidation of alcohol **183** was followed by Wittig reaction to generate the rather volatile terminal olefin **203**.



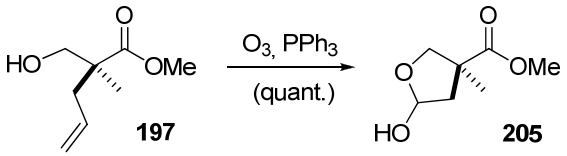
Scheme 50: Chain elongation of **197** by cross metathesis.

Despite extensive optimization, a selection is shown below (Table 1), yields unfortunately never exceeded 38%, which might be due to deactivation of the catalyst by the bishomoallylic alcohol of mono ester **197**. An intramolecular stabilization between the hydroxyl group of **197** and the metal of the ruthenium carbenoid, in the reaction of olefin **197** with the catalyst *via* the metalacyclobutane, to form a five membered cyclic intermediate is possible.

catalyst	solvent	rxn time	197 (eq.)	203 (eq.)	yield
Grubbs II (5 mol%)	DCM	24 h	1	1	24%
Grubbs II (5 mol%)	DCM	24 h	1	2	26%
Grubbs-Hoveyda II (5 mol%)	DCM	48 h	1	2	28%
Grubbs-Hoveyda II (10 mol%)	DCM	48 h	1	2	38%
Grubbs-Hoveyda II (10 mol%)	toluene	1 h	1	2	15%

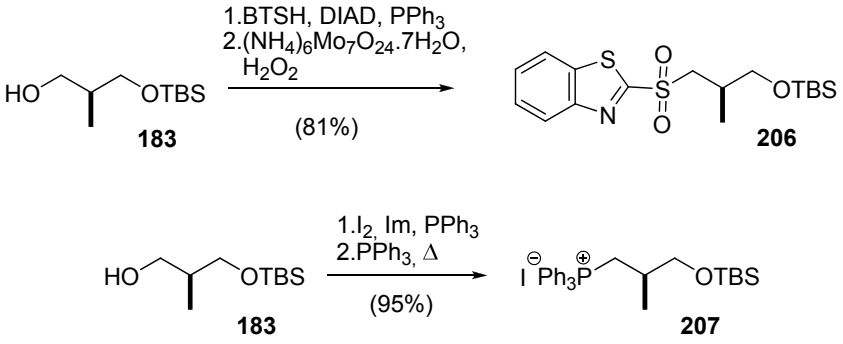
Table 1: Cross metathesis conditions.

At the same time, classical olefination methods such as Wittig reaction and Julia-Lythgoe-Kocienski reaction were also probed.[75] The allylic moiety of **197** was therefore cleaved by ozonolysis to the aldehyde functionality which was immediately attacked by the bishomoallylic hydroxyl group to give five-membered lactol **205** (Scheme 51).



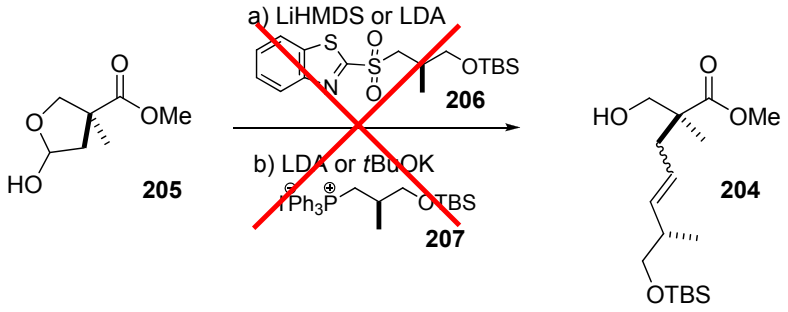
Scheme 51: Ozonolysis of the allylic moiety.

Sulfone **206** was derived from alcohol **183** by conversion to the sulfide under Mitsunobu conditions and subsequent oxidation. To be able to use higher temperatures and longer reaction times also the corresponding Wittig salt **207** was prepared (Scheme 52).[76] Thus, alcohol **183** was transformed by Appel reaction into the corresponding iodide. Treatment with PPh_3 generated upon heating the desired Wittig salt **207**.



Scheme 52: Preparation of Julia sulfone **206** and Wittig salt **207**.

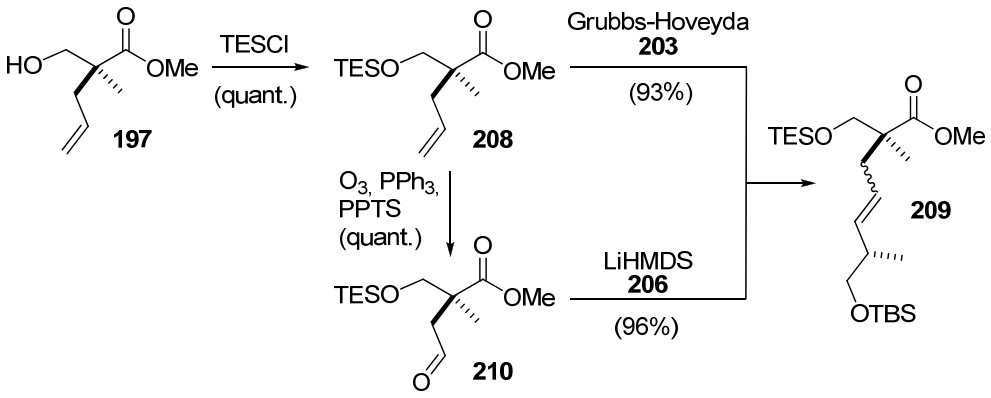
However, lactol **205** proved to be nonreactive in the attempted carbonyl olefination reactions (Scheme 53), possibly due to the steric hindrance exhibited by the quaternary center and the high stability of the five-membered ring the amount of the aldehyde in the equilibrium was too small to enable the olefination reaction.



Scheme 53: Chain elongation by carbonyl olefination.

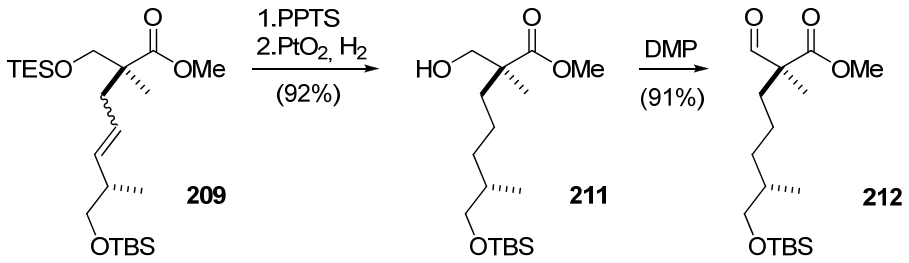
As the free alcohol functionality seemed to be responsible for the difficulties by deactivation of the catalyst in case of the cross metathesis and by lactol formation to inhibit carbonyl

olefination, it was transformed into its triethyl silyl ether (Scheme 54). CM, with the Grubbs-Hoveyda catalyst in DCM, proceeded smoothly to give almost quantitatively the desired elongated olefin **209** in an inconsequential *E*:*Z* mixture. Oxidative cleavage of **208** gave aldehyde **210** along with varying amounts of lactol **205**, whose formation could fortunately be suppressed by the addition of 10 mol% of PPTS. With aldehyde **210** in hand, Julia-Lythgoe-Kocienski olefination reaction gave in nearly quantitative yield desired elongated olefin **209** in an inconsequential 1:1 *E*:*Z* mixture.



Scheme 54: Successful chain elongation of silyl ether **208**.

The TES group was easily cleaved with substoichiometric amounts of PPTS and the double bond was hydrogenated using Adam's catalyst. Subsequent oxidation with Dess-Martin periodinane (DMP) yielded aldehyde **212** for the following aldol addition (Scheme 55).

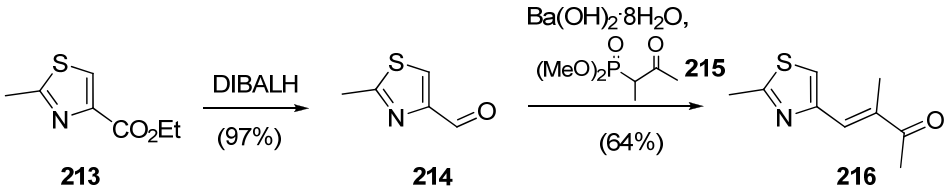


Scheme 55: Synthesis of aldehyde **212**.

5.2.3. Fragmentation Precursor

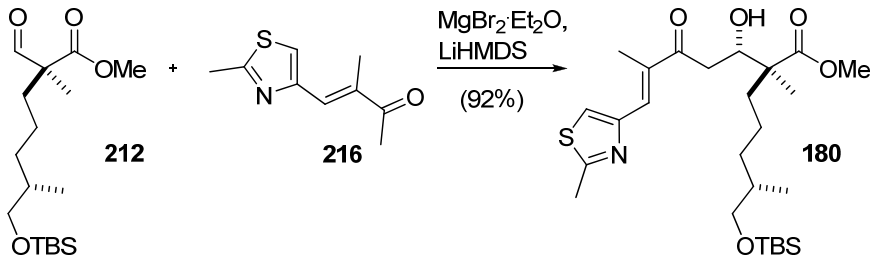
Aldol addition with the lithium enolate of ketone 216

With aldehyde **212** in hand, an aldol addition to build up the complete carbon skeleton of the fragmentation precursor was possible. As enolizable partner for aldehyde **212** thiazole methyl ketone **216** was prepared in two steps (Scheme 56). Thus, known ester **213** was generated by condensation of thioacetamide and ethyl bromopyruvate,[77] and reduced to aldehyde **214**, which was used in a Horner-Wadsworth-Emmons reaction with phosphonate **215**, prepared by *α*-methylation of the product from an Arbuzov reaction between chloroacetone and trimethyl phosphate,[78] to gain enone **216**.



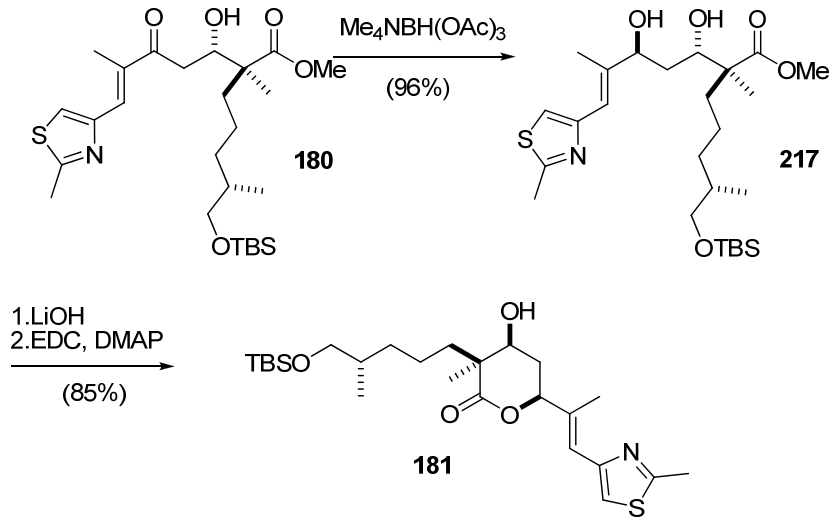
Scheme 56: Synthesis of methyl ketone **216**.

Aldehyde **212** was then incubated with magnesium bromide etherate and added to the lithium enolate of methyl ketone **216** and the aldol product was formed as a single diastereoisomer in excellent yield (Scheme 57).



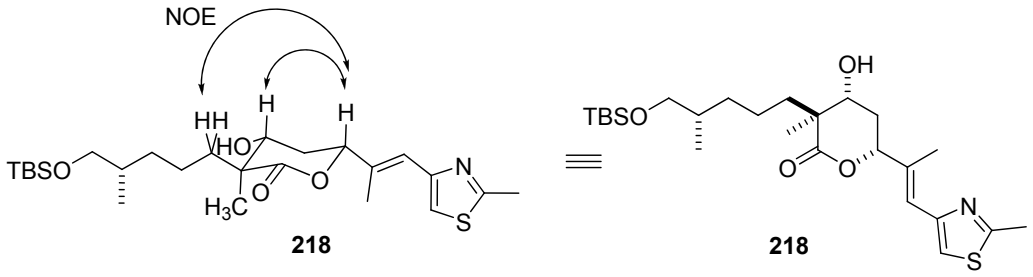
Scheme 57: Aldol addition.

Evans-Carreira *anti*-reduction with triacetoxy boronhydride to generate *anti* diol **217** was followed by hydrolysis of the methyl ester to the acid and the *δ*-lactone ring was closed to generate fragmentation precursor **181** (Scheme 58).[79]



Scheme 58: Conversion to the *δ*-lactone.

Now, structural determination by correlation NMR experiments was possible (Scheme 59). Surprisingly, careful interpretation of the NOESY spectra revealed the structure of the *δ*-lactone to be **218** and not **181** as assumed.

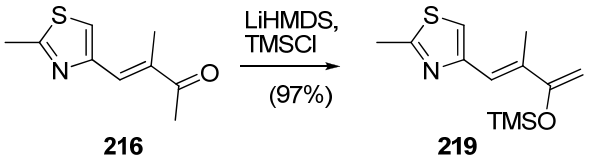


Scheme 59: Structural determination of the *δ*-lactone.

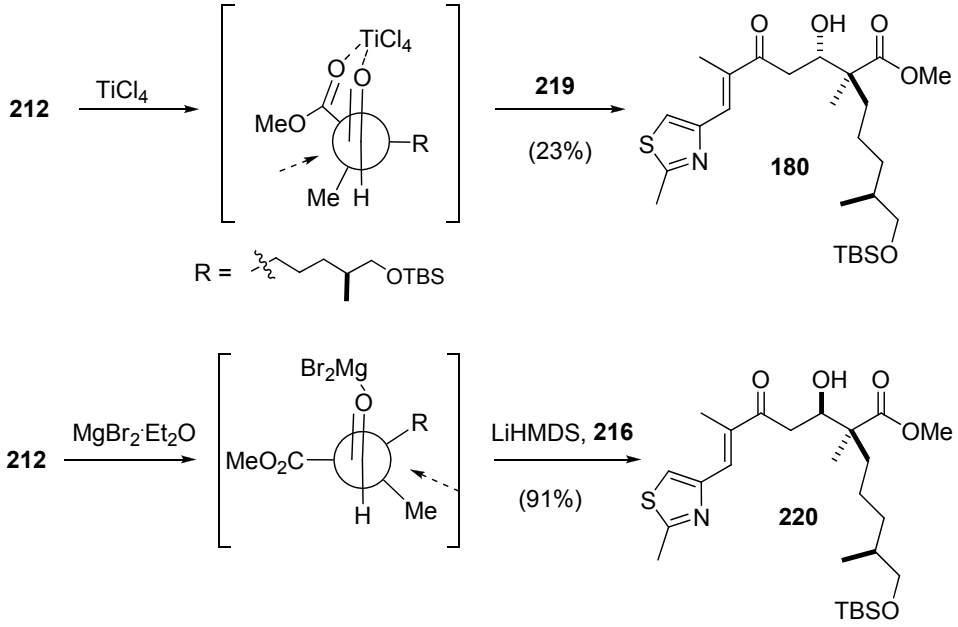
Thus, aldol addition did not proceed under Cram chelate control as assumed but the Felkin-Anh product was formed (Scheme 61). $MgBr_2 \cdot Et_2O$ was obviously only activating aldehyde **212** without forming a chelate complex, as longer reaction times were observed without its addition. Therefore different Lewis acids were tested: Et_2AlCl, $SnCl_4$, $ZnCl_2$, $TiCl_4$, $Ti(O\textit{i}Pr)_4$ with the lithium enolate of methyl ketone **216**; but the aldol addition always resulted in the Felkin-Anh product **220** in varying yields.

Mukaiyama aldol addition

Finally, when a Mukaiyama aldol addition was used the Cram chelate product **180** was isolated. However the best results never exceeded 23% yield, which were obtained with $TiCl_4$ and trimethyl silyl enol ether **219**.



Scheme 60: Silyl enol ether **219** of methyl ketone **216**.

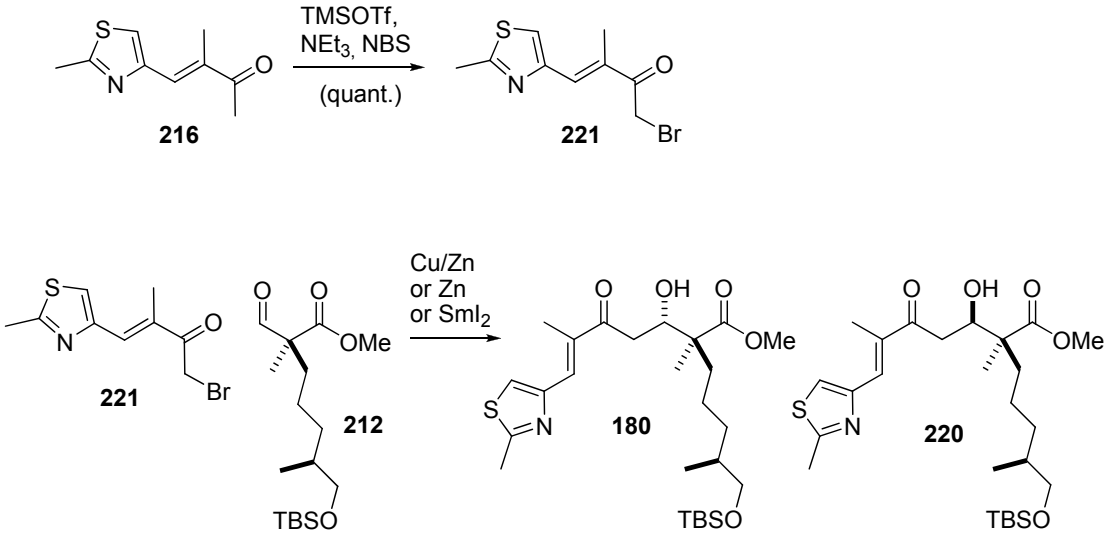


Scheme 61: Cram chelate vs. Felkin-Anh transition state.

Even though initial efforts were targeted on the Cram chelate aldol product, as it features the correct relative stereochemical arrangement between *α*- and *β*-center to form the fragmentation precursor for the (*Z*)-olefin. Felkin-Anh product **220** was used in the following synthesis, due to the better accessibility. Hence, the stereochemistry had to be corrected at a later stage.

Reformatsky reaction

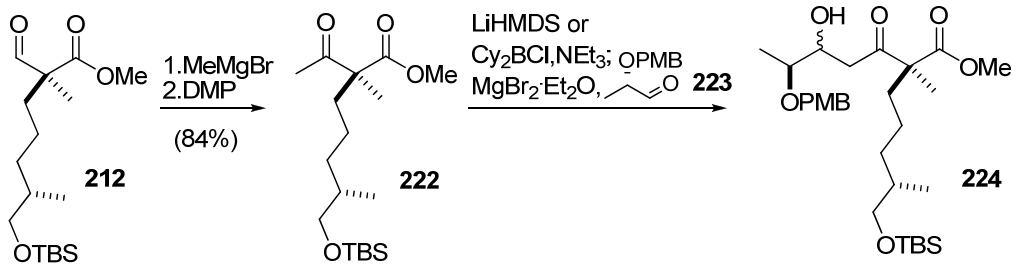
As an alternative C-C bond formation strategy, a Reformatsky reaction was investigated. Thus, *α*-bromo ketone **221** was prepared first,[80] and reacted with aldehyde **212**; unfortunately just the use of SmI_2 featured the Cram chelate product alas as the minor diastereoisomer in a 1:4 diastereomeric ratio (Scheme 62).



Scheme 62: Reformatsky reaction.

Alternative acetate aldol addition

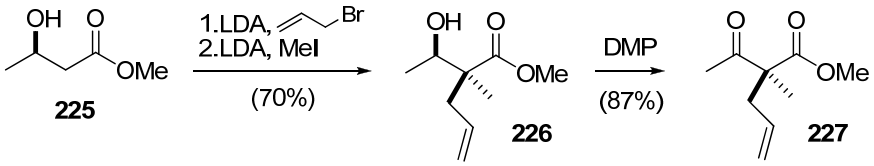
The unfavorable stereochemical outcome of the aldol addition between thiazole methyl ketone **216** and aldehyde **212** is only explicable by the strong influence of the quaternary center, which hinders the desired connection in the neopentyl position. Hence, the center of reaction was moved one carbon further away to an aldol addition between methyl ketone **222** with aldehyde **223**, derived from (*S*)-ethyl lactate and featuring a stereocenter in *α*-position to direct the stereochemical outcome by substrate control. Methyl ketone **222** was generated in two steps from aldehyde **212** by addition of methyl magnesium bromide and subsequent oxidation of the secondary alcohol. Aldehyde **223** was incubated with magnesium bromide etherate in advance and added to the enolate (Scheme 63). Here, several methods of enolization were investigated. The use of the lithium enolate mainly led to self-condensation of methyl ketone **222** and product mixtures in up to 50% yield; when the boron enolate was used, the reaction worked better concerning yields although the diastereomeric ratio was never higher than 3:2.



Scheme 63: Acetate aldol.

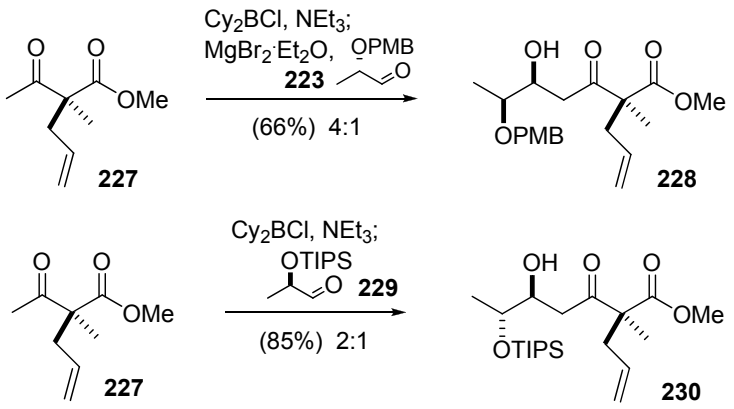
Building the quaternary center by double Frater-Seebach alkylation

To further investigate the above mentioned acetate aldol reaction on a maybe more favorable simpler substrate aceto acetate **227** was prepared, whose quaternary center originated from a double Frater-Seebach alkylation (Scheme 64).[81] The allyl moiety was introduced first by double deprotonation of methyl-3-hydroxybutanoate (**225**) with LDA and reaction with allyl bromide, in the second step methyl iodide was used as electrophile. NMR analyses showed only a single diastereoisomer. Dess-Martin oxidation gave aceto acetate **227** for additional investigations of the behavior in the acetate aldol addition.



Scheme 64: Synthesis of aceto acetate **227**.

The stereochemical outcome should be controlled by the chiral *α*-center of aldehyde **223** or **229** either under Cram chelate or Felkin-Anh control. Unfortunately the best results were a 4:1 diastereomeric ratio in modest yield under Cram chelate conditions. When the Felkin-Anh product was aimed for, yields were better but the selectivity dropped (Scheme 65).

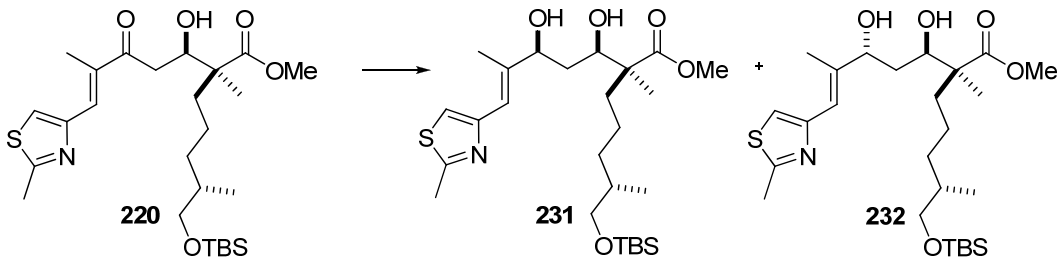


Scheme 65: Investigation of Cram chelate vs. Felkin-Anh control in acetate aldol addition.

In literature, high stereocontrol in acetate aldol additions is only observed when the acetated Crimmins' auxiliary is employed.[82] As other methyl ketones lead to moderate to bad selectivity our results were in accordance and therefore, not completely unexpected.

Correcting the stereochemistry of the fragmentation precursor

As alternative way to introduce the right relative stereochemistry inversion of the *β*-position by an oxidation-reduction sequence of the six-membered lactone was envisaged. With the use of a small hydride donor, attack on the carbonyl should be axial, leading to the equatorial hydroxyl group. Also the *δ*-position, the later C15, had to be inverted which is possible by simple generating *syn* diol **232** instead of *anti* diol **231** (Scheme 66). *Syn* reduction did work very well after some affords (Table 2), when catecholborane was found to convert hydroxy ketone **220** in good yields and high selectivity to *syn* diol **231**.[83]

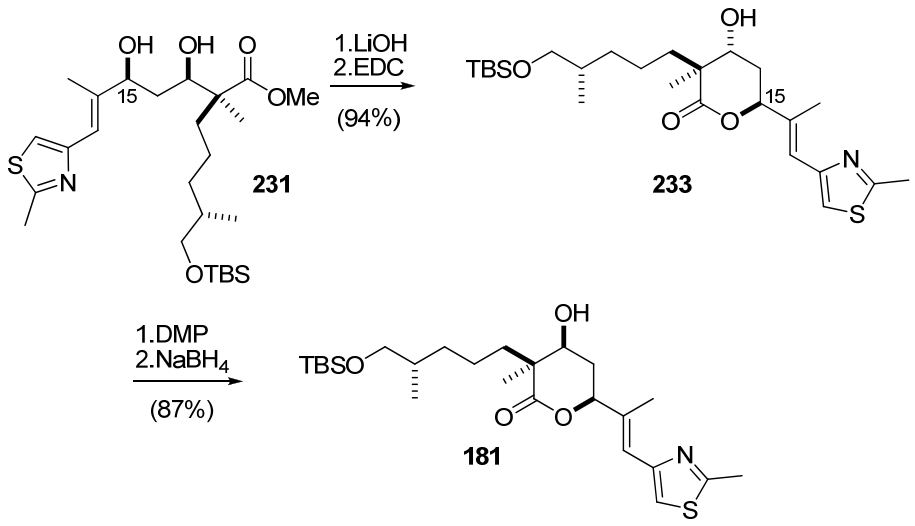


Scheme 66: *Syn* reduction of hydroxy ketone **220**.

reagent	product *syn*:*anti* (231:232)
BEt_3, MeOH, $NaBH_4$ (-30 °C)	3:1
BEt_3, MeOH, $NaBH_4$ (-78 °C)	4:1
BBu_3, MeOH, $NaBH_4$ (0 °C)	borane ester very stable
DIBALH	ester reduced, TBS deprotected
$Zn(BH_4)_2$	1:1, ester reduced
$LiBH_4$	1:1, ester reduced
SmI_2, NEt_3, H_2O	no reaction
catecholborane	86% only *syn* (**231**)

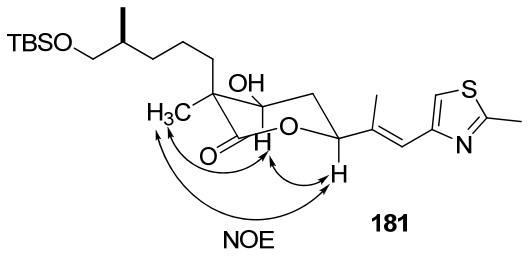
Table 2: Conditions for *syn* reduction of hyxdoxy ketone **220**.

With *syn* diol **231** in hand, saponification with lithium hydroxide in THF worked smoothly and was followed by lactonization under Steglich conditions to yield *δ*-lactone **233** with the desired absolute configuration at the later C15 (Scheme 67). Now the *β*-position had to be inverted. Therefore, the *β*-hydroxyl group was oxidized under neutral conditions using buffered Dess-Martin periodinane and subsequent reduction with $NaBH_4$ at low temperatures led exclusively to desired *δ*-lactone **181**.



Scheme 67: Fragmentation precursor **181**.

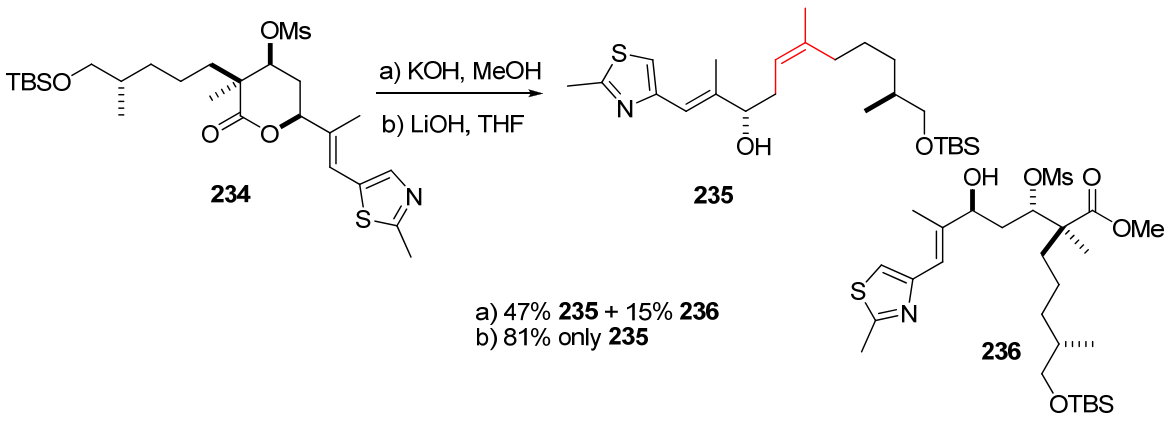
This time NOESY spectra verified the structure of δ-lactone **181**, showing clear NOE cross peaks (Scheme 68).



Scheme 68: NOE signals of fragmentation precursor **181**.

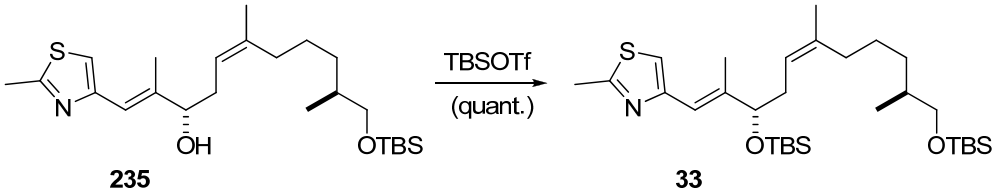
5.2.4. Fragmentation

Fragmentation precursor **234** was prepared by conversion of the hydroxyl group of **181** into the corresponding mesylate. First the well established conditions from the test system,[60] namely potassium hydroxide in methanol, were used, which gave apart from desired olefin **235**, methyl ester **236** as side product by lactone opening with methoxide (Scheme 69). Thus, when fragmentation conditions were switched to lithium hydroxide in THF the desired northern fragment **235** was formed smoothly as the only product in excellent yield and selectivity.



Scheme 69: Fragmentation of **181**.

To finish the formal synthesis, the free secondary alcohol was protected as silyl ether **33**.[25, 33, 84]

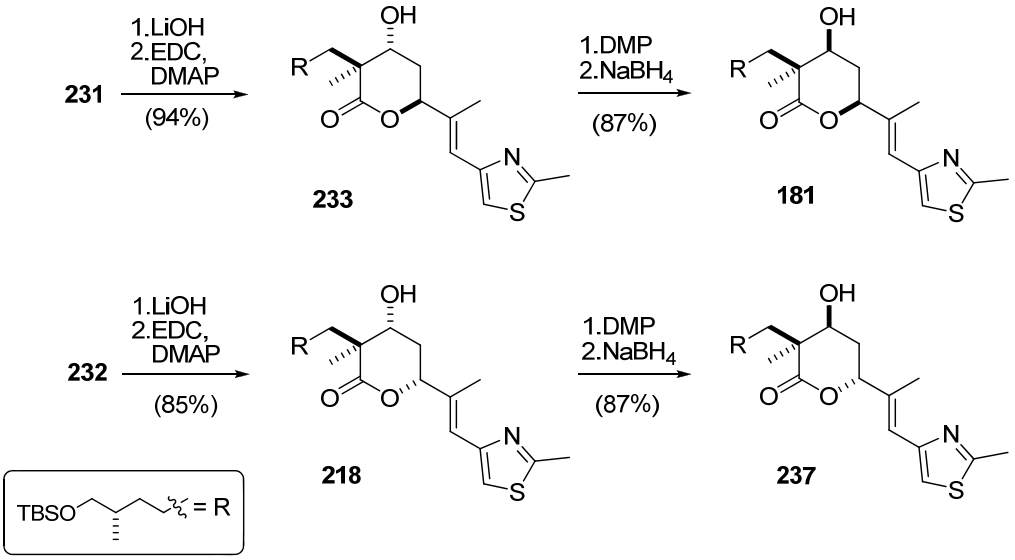


Scheme 70: Formal synthesis of the epothilone B northern fragment **33**.

5.2.5. Testing the Fragmentation Reaction of Different Diastereomeric Precursors

Fragmentation precursors

Starting from easily accessible *anti* and *syn* dihydroxy esters **231** and **232** all four diastereomeric *δ*-lactones **181**, **218**, **233** and **237** are available (Scheme 71).

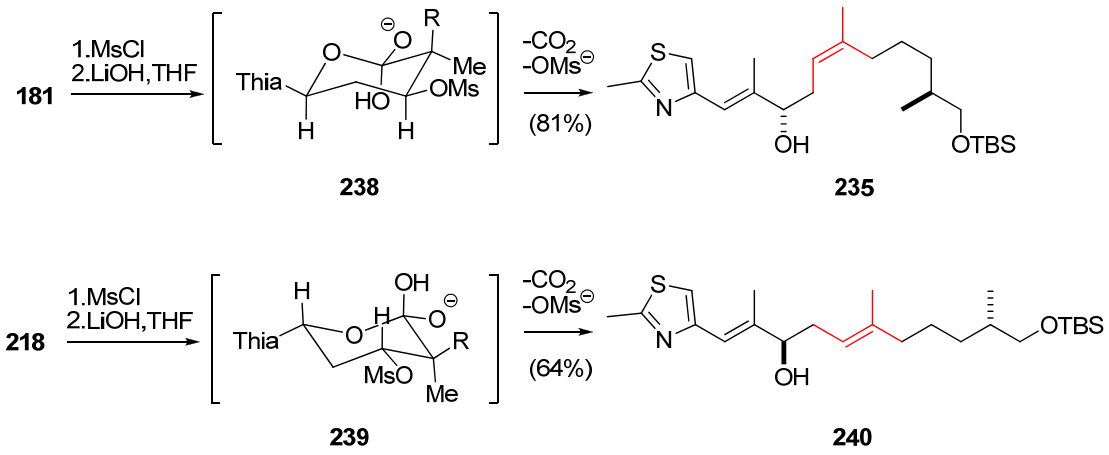


Scheme 71: Four diastereomeric precursors.

Fragmentations

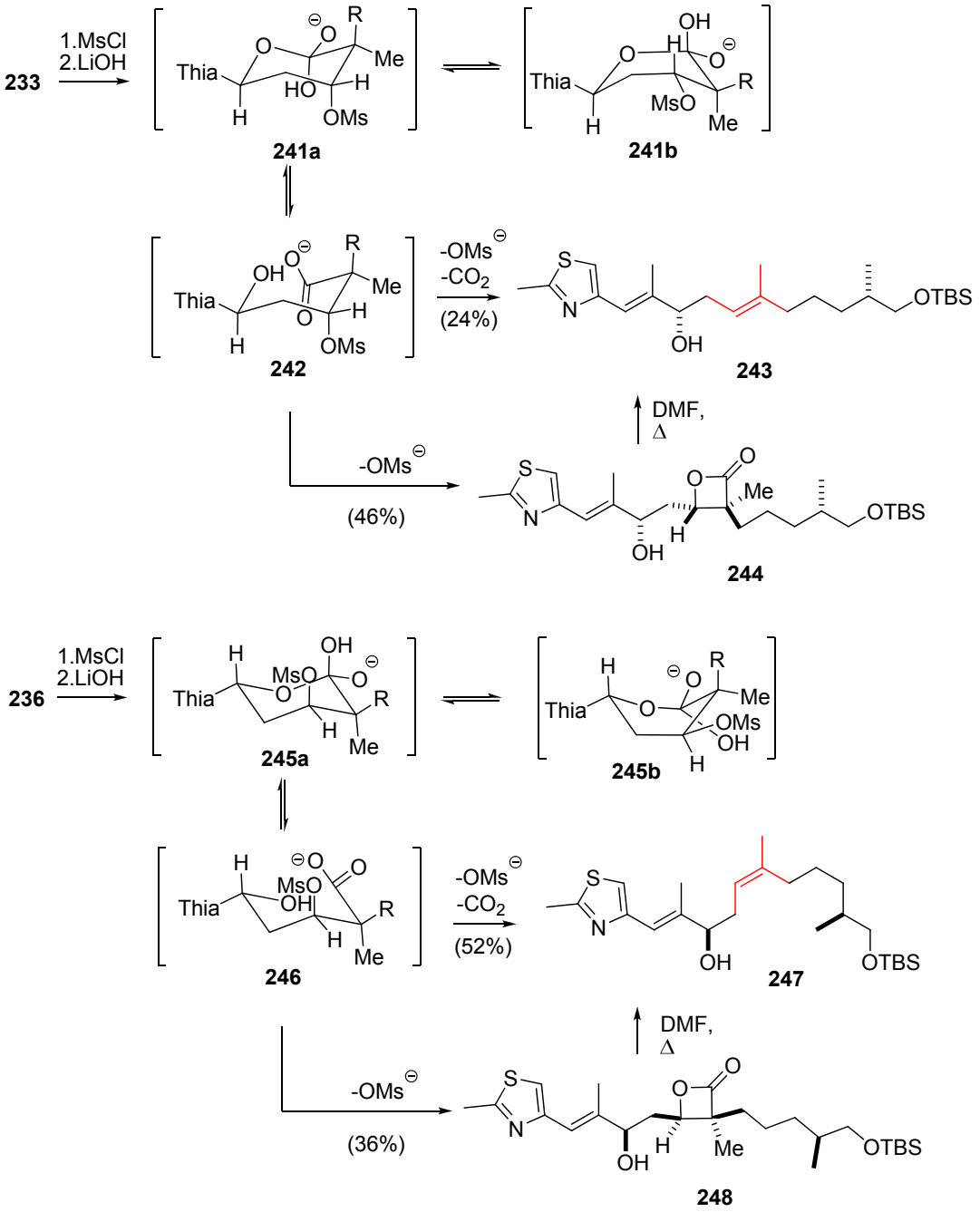
With all four diastereoisomers in hand, the leaving group in form of a mesylate was introduced under standard conditions, methansulfonyl chloride in Et_2O and triethylamine, and used directly in the following fragmentation reaction. Lactones **181** and **218** with a *syn*

arrangement of the *β*- and *δ*-hydroxyl group are able to react directly *via* the chair transition states and smoothly gave, depending on the relative configuration between *α*- and *β*-centers, (*E*)- or (*Z*)-olefins in good to excellent yields (Scheme 72). Also, the use of different hydroxides (LiOH, KOH, NaOH) in THF at 0 °C for the fragmentation of **181**, showed similar results and always gave olefin **235** as single product in about 80% yield.



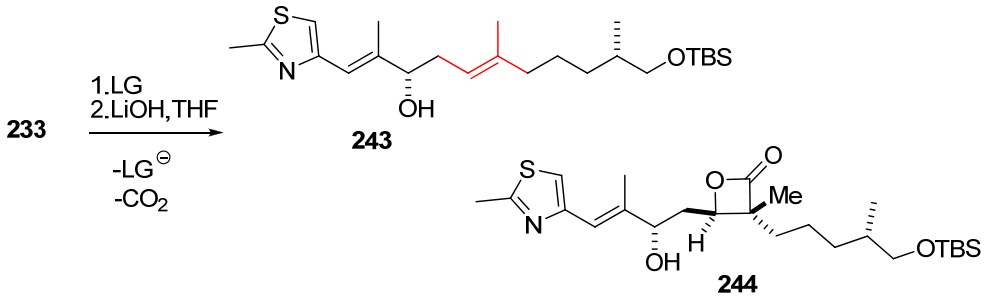
Scheme 72: Fragmentation reaction *via* the chair transition state.

Whereas, with the other two diastereoisomers featuring an *anti* arrangement of the *β*- and *δ*-hydroxyl group the mesylate adopts an axial configuration and a Grob-type fragmentation in a chair conformation should be impossible. On the other hand, a flip to the boat conformation **241b** and **245b** respectively might stereoelectronically be suitable to undergo fragmentation, however, the species itself is energetically unfavorable. Nevertheless, in both cases the olefin was obtained under the usual conditions, alongside the *β*-lactone. This result may be rationalized in terms of a ring opening to form carboxylate **242** and **246** respectively, which undergoes both fragmentation to the olefin and S_N2 cyclization to the *β*-lactone (Scheme 73). For the decarboxylation of *β*-lactone **244** and **248** to yield additional amounts of the corresponding olefin, various conditions were tested and thermal or microwave assisted decarboxylation in DMF or NMP worked best.



Scheme 73: Fragmentation reaction *via* an open or boat transition state.

Variation of the temperature in the fragmentation *via* the open chain or boat transition state led to slightly different amounts of olefin and *β*-lactone, with rising temperature the amount of the olefin increased (Scheme 74). Varying the leaving group showed similar product distribution with slightly lower yields in case of the instable triflate (Table 3).

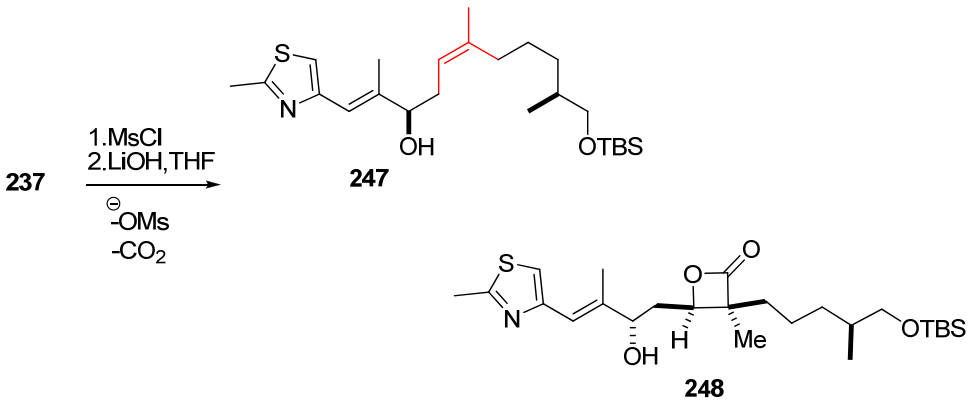


Scheme 74: Fragmentation reaction of **233**.

LG	T	243	244
OMs	0 °C	34%	36%
OMs	r.t.	24%	46%
OTf	0 °C	23%	21%
OTs	r.t.	35%	36%

Table 3: Varying temperature and LG in the Fragmentation of **233**.

The other diastereoisomer **237** which reacted *via* the open chain or boat transition state showed corresponding results giving (*Z*)-olefin **247** and *β*-lactone **248** (Scheme 75, Table 4).



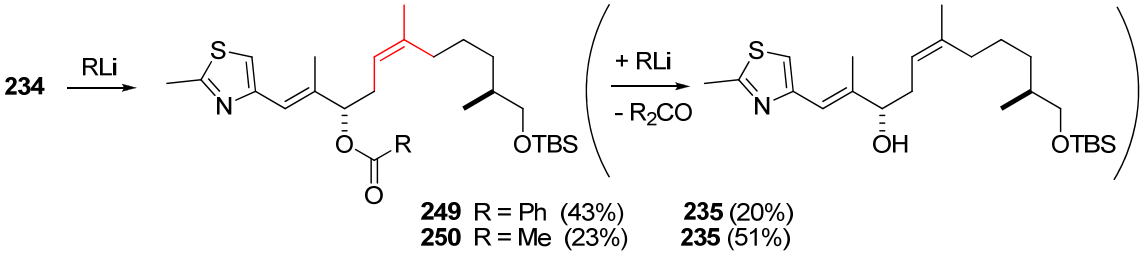
Scheme 75: Fragmentation reaction of **237**.

base	T	247	248
LiOH	r.t.	52%	36%
LiOH	0 °C	43%	34%

Table 4: Variation of the temperature in the fragmentation of **237**.

Fragmentation induced with carbon nucleophiles

Different carbon nucleophiles were also tested for the fragmentation of **234** and they turned out to induce the fragmentation reaction as well, always giving the (*Z*)-olefin either in form of carbonate **249** and **250** respectively or unprotected alcohol **235** (Scheme 76). Here, temperature control is very crucial, as yields dropped significantly at higher temperature. When fragmentation of **233** *via* the boat transition state was attempted with organo lithium species, only decomposition was observed.

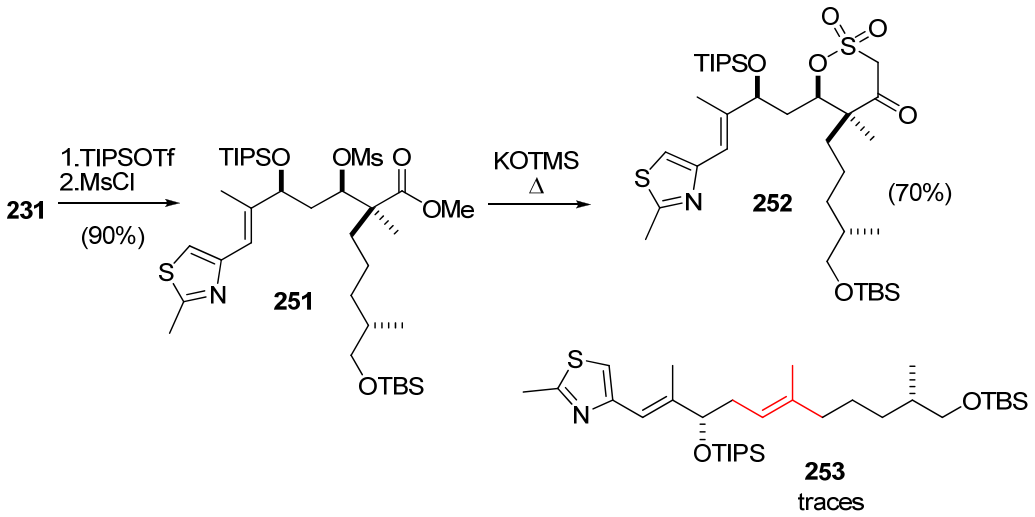


Scheme 76: Fragmentation using carbon nucleophiles.

5.2.6. Fragmentation of the Open Chain

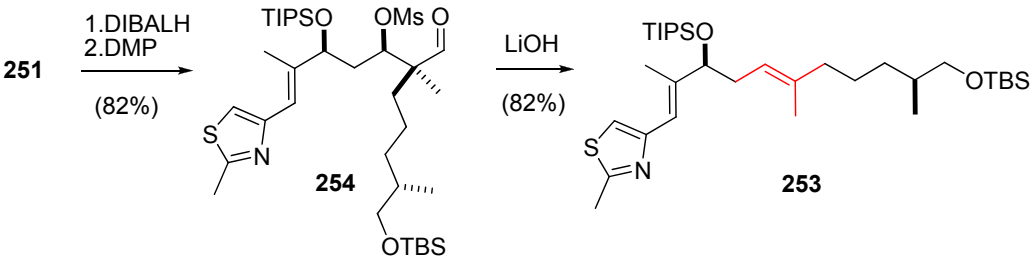
As we were able to show that fragmentation could be carried out successfully on the cyclic fragmentation precursors, the next step for a more general method was to move to a linear fragmentation precursor. Starting from dihydroxy ester **231** the *δ*-position had to be protected regioselectively as the corresponding silyl ether. First attempts were with a *tert*-butyldimethylsily ether, here the allylic alcohol in *δ*-position can be selectively protected with TBSCl but conversion is very slowly and the use of the more reactive TBSOTf only addresses the *β*-position, due to the different nucleophilicity of the two positions. Finally, the

bulky TIPS group was employed and the mesylate was introduced in *β*-position under standard conditions. All attempts to convert ester **251** into the carboxylate either by using various hydroxides, KOTMS or the Krapcho protocol failed (Scheme 77).[85, 86] The only base strong enough to bring forth a reaction was KOTMS in refluxing toluene. Unfortunately detailed NMR analyses revealed the major product to be the cyclic sulfite **252**, from deprotonation of the mesylate and attack on the ester to form the six-membered ring. To avoid this, a different leaving group should be installed, but the TIPS group proved to be sterically too demanding for any of the other groups (Tf, Ns, Ts) tested.



Scheme 77: Fragmentation of the open chain precursor **251**.

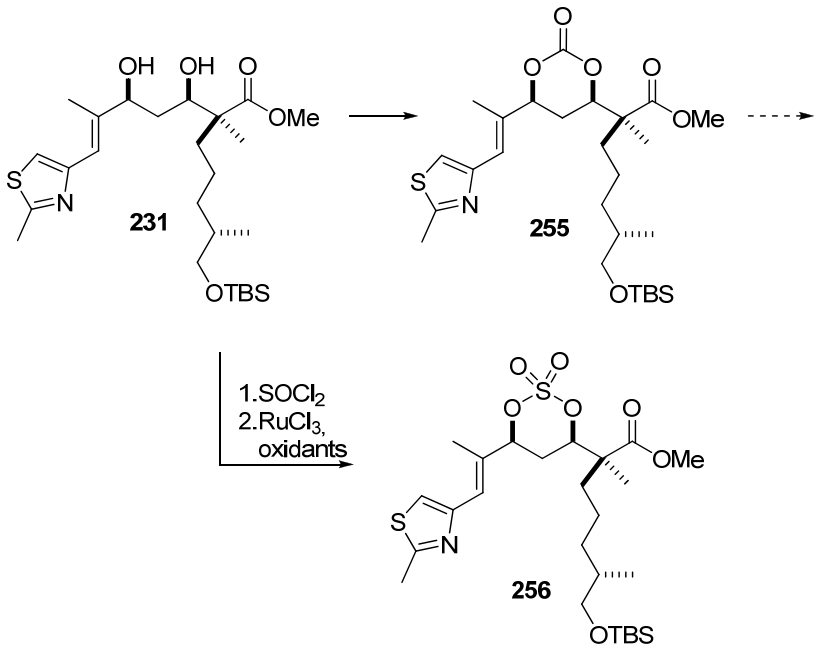
However, the ester could be reduced to the alcohol and was then reoxidized to aldehyde **254**, which upon treatment with hydroxide gave olefin **253** in excellent yield and selectivity (Scheme 79).



Scheme 78: Fragmentation of open chain aldehyde **254**.

Cyclic protecting and also leaving group

The protecting group in the *δ*-position seemed to present a problem, either through regioselectivity problems in the introduction or by presenting steric bulk, which prevented the hydroxide addition to the ester group. Thus, a cyclic protecting group between *β*- and *δ*-position, which should additionally serve as leaving group, was envisaged (Scheme 79). A cyclic carbonate could be introduced by standard methods with phosgene, triphosgene or carbonyldiimidazole. Alas, fragmentation did not give the expected product due to regioselectivity problems of the hydroxide attack. As alternative a cyclic sulfate should be generated by standard two step procedure. The cyclic sulfite was easily available but the oxidation step led either to decomposition with sodium periodate as oxidants or with NMO to no conversion. Also the direct use of sulfuryl chloride led only to decomposition, presumably through uncontrolled chlorination of the thiazole, and therefore proved unsuccessful.

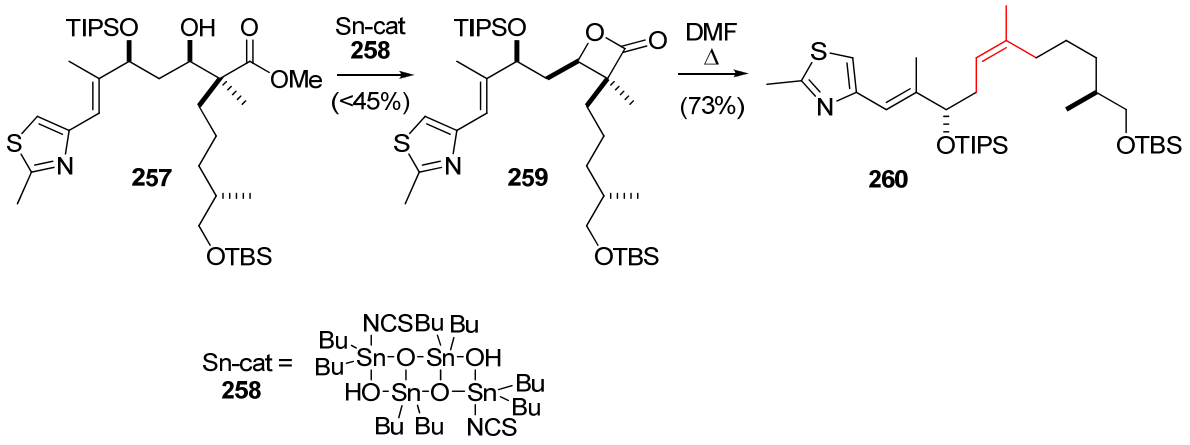


Scheme 79: Cyclic leaving group.

Decarboxylation of *β*-lactone 259

Another obvious route to the trisubstituted (*Z*)-olefin with **257** in hand was to form *β*-lactone **259** and afterwards decarboxylate (Scheme 80). Hence, saponification of **257** was attempted but unfortunately confirmed the disappointing results already observed in the above described fragmentation. No acid was isolated, presumably due to the steric bulk from the

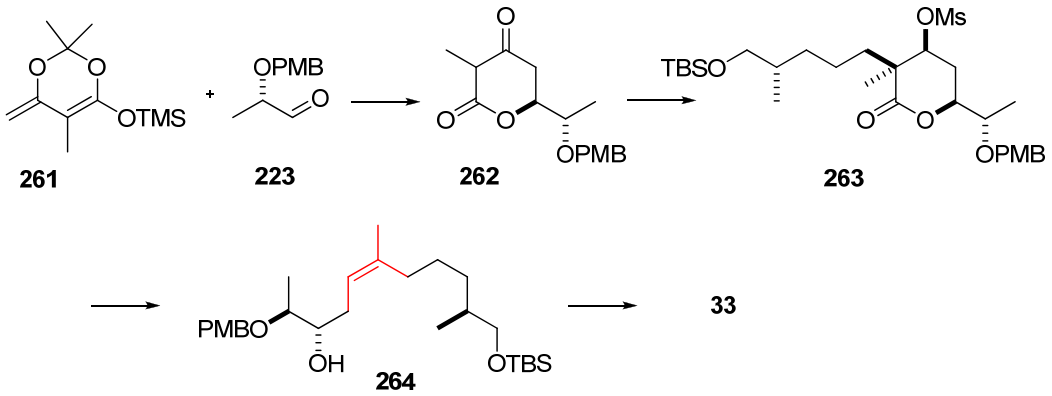
TIPS group. Thus, transesterification with Othera's catalyst **258** was investigated under numerous conditions by variation of the solvent (toluene, xylene, chlorobenzene, etc.), temperature and also using microwave irradiation but yields never exceeded 45%.[87, 88] However, thermal decarboxylation in DMF proceeded smoothly to the desired trisubstituted (*Z*)-olefin in the northern fragment **260** of epothilone B.



Scheme 80: (*Z*)-olefin **260** by decarboxylation of *β*-lactone **259**.

5.3. Second Approach: Lactate Route

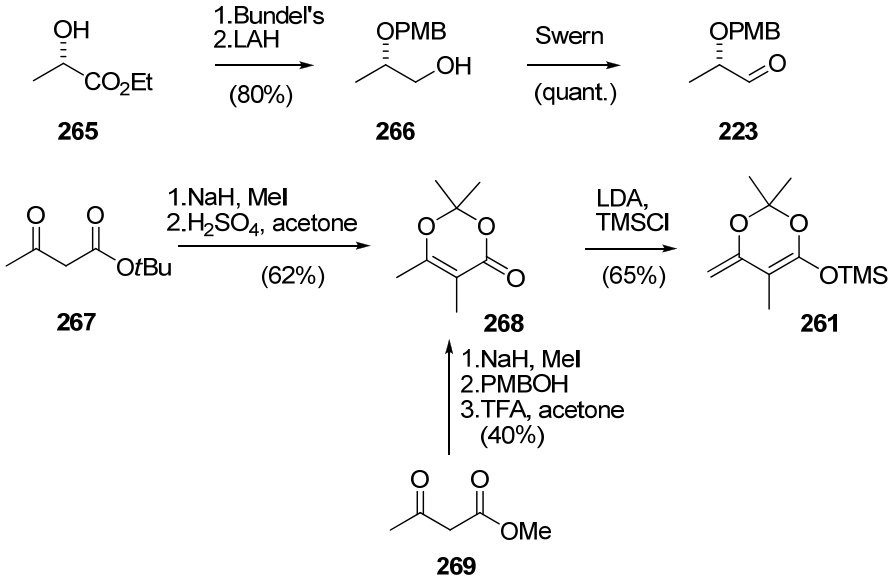
In this approach *β*-keto lactone **262** is synthesized enantioselectively by Mukaiyama aldol reaction between silyl enol ether **261** and aldehyde **223**, derived from (*S*)-ethyl lactate (**265**). The quaternary center is introduced by Tsuji-Trost allylation and the fragmentation takes place at an earlier stage in the synthesis (Scheme 81).



Scheme 81: Synthetic outline for the second approach to epothilone B (**1**).

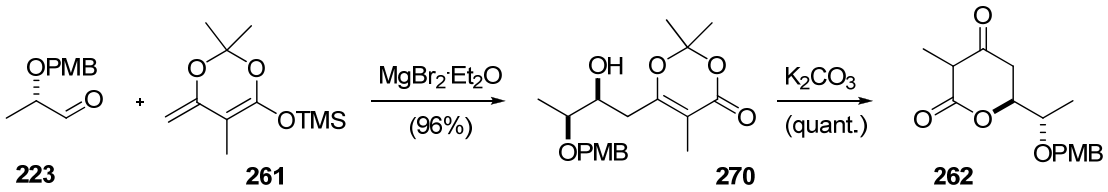
5.3.1. Building Lactone 262

To build up *β*-keto lactone **262** enantioselectively a Cram chelate controlled Mukaiyama aldol reaction was used with stereocontrol by 1,2 induction of chiral aldehyde **223**.[89] Thus, known aldehyde **223** was prepared by conversion of (*S*)-ethyl lactate (**265**) with Bundle's reagent into the corresponding PMB ether and reduction to alcohol **266**; subsequent Swern oxidation gave *α*-chiral aldehyde **223** (Scheme 82).[38] Dioxenone **268** was generated either from *tert*-butyl acetoacetate (**267**), after methylation, by treatment with sulfuric acid in acetone or from methyl acetoacetate (**269**) *via* conversion into the PMB ester and treatment with TFA in acetone.[90, 91] After deprotonation with freshly prepared LDA, the enolate was trapped as trimethylsilyl enol ether, which could be stored for some weeks in the fridge when purified by bulp-to-bulp distillation.



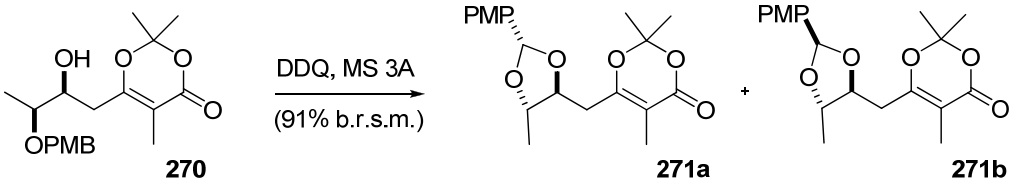
Scheme 82: Synthesis of aldehyde **223** and silyl enol ether **261**.

After some optimization the best results for the aldol addition proved to be two equivalent of the silyl enol ether and two equivalents of freshly prepared magnesium bromide etherate to give in almost quantitative yield **270** as single aldol adduct (Scheme 83).[92] Additional induction by a chiral Lewis acid was not necessary and stronger Lewis acids generally resulted in lower yields by attacking the dioxenone or cleaving the PMB ether. Subsequent treatment with potassium carbonate in methanol gave *β*-keto lactone **262** in quantitative yield as white crystals.



Scheme 83: Mukaiyama aldol addition.

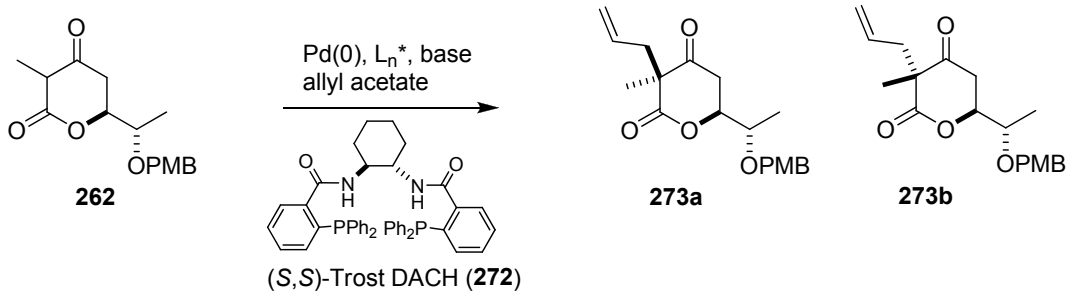
The *syn* configuration between the two hydroxyl groups was confirmed by conversion into the corresponding PMP-acetal through an oxidative shift of the PMB group (Scheme 84). Unfortunately, both acetals **271a** and **271b** were formed as is often observed in five-membered rings but interpretation of the NOESY spectra showed unambiguously the expected *syn* configuration.



Scheme 84: PMP acetals of Cram chelate product **270**.

5.3.2. Quaternary Center by Tsuji-Trost Allylation

The next obstacle was the introduction of the quaternary center by an asymmetric allylic alkylation, which was first tested with allyl acetate. Biphasic Tsuji-Trost allylation, developed for the test system,[60] without chiral induction using palladium-tetrakis(triphenylphosphine) gave in excellent yields a 3:1 ratio of diastereoisomers (Scheme 85); for structural determination these two diastereoisomers were separated by HPLC and NOE cross peaks confirmed the configuration of the two compounds.



Scheme 85: Tsuji-Trost allylation with allyl acetate.

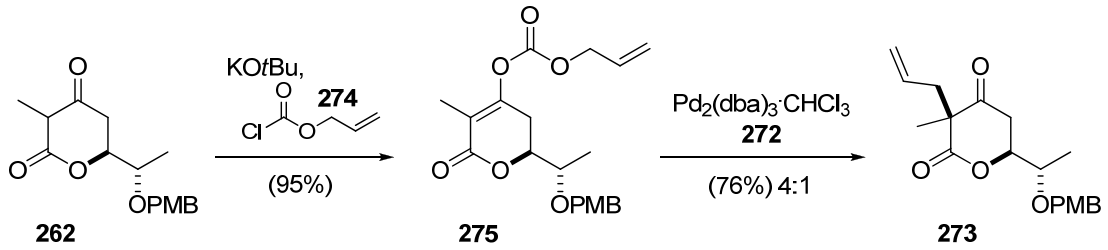
Alas, extensive optimization, concerning the choice of ligand, solvent, base and source of palladium proved not very successful. A small selection is shown in table 5.

Pd/L_n*	**base**	**solvent**	**yield**	**ax:eq 273a:273b**
$Pd(PPh_3)_4$	K_2CO_3	H_2O/EtOAc	98%	3:1
$Pd_2(dba)_3 \cdot CHCl_3$ (*R*,*R*)-Trost DACH	LDA	THF	lactone opening	-
$Pd_2(dba)_3 \cdot CHCl_3$ (*R*,*R*)-Trost DACH	LiHMDS	THF	82%	1:2
$Pd_2(dba)_3 \cdot CHCl_3$ (*R*,*R*)-Trost DACH	DBU	toluene	60%	2:3
$Pd_2(dba)_3 \cdot CHCl_3$ (*S*,*S*)-Trost DACH	LiHMDS	THF	75%	3:1
$Pd_2(dba)_3 \cdot CHCl_3$ (*S*,*S*)-Trost DACH	DBU	toluene	92%	7:2

Table 5: Conditions and results for Tsuji-Trost allylation with allyl acetate.

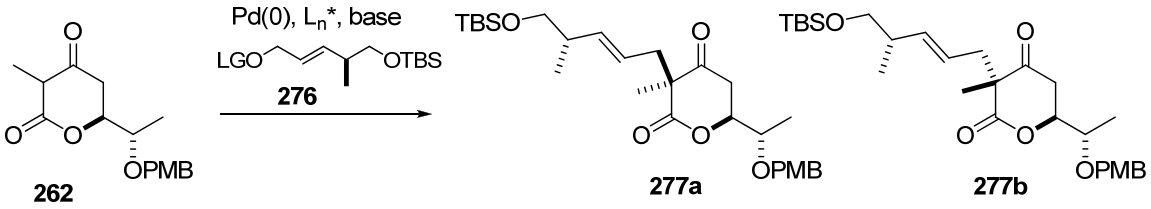
Intramolecular allylation, as described by Trost and Stoltz, was tested as well (Scheme 86).[93, 94] Therefore, the potassium enolate of **262** was trapped as allyl carbonate **275**, which

could be used in the allylation without any additional base or other additives, but no significant increase in diastereoselectivity was observed.



Scheme 86: Intramolecular Tsuji-Trost allylation.

Nevertheless, allylation with elaborated allylic carbonate **274** was tested; here additional different carbonates and acetates as leaving groups could be varied (Scheme 87, Table 6).



Scheme 87: Tsuji-Trost allylation with the elongated allylic carbonate **276.**

Surprisingly, the Trost ligands seemed to hinder smooth reaction, presumably through their additional steric bulk. Thus, best conditions were ethyl carbonate as leaving group in a biphasic system with palladium-tetrakis(triphenylphosphine) as catalyst and potassium carbonate as base, which yielded almost quantitatively allylation product **277** in a 4:1 diastereomeric ratio.

Pd/L_n*	**OLG**	**base**	**solvent**	**yield**	**ax:eq 377a:377b**
$Pd(PPh_3)_4$	OTroc	K_2CO_3	H_2O/EtOAc	97%	3:1
$Pd_2(dba)_3 \cdot CHCl_3$ (*R,R*)-Trost DACH	OTroc	DBU	toluene	60%	2:3
$Pd_2(dba)_3 \cdot CHCl_3$ (*S,S*)-Trost DACH	OTroc	DBU	toluene	54%	3:2
$Pd(PPh_3)_4$	OTroc	DBU	toluene	41%	3:1
$Pd(PPh_3)_4$	$OC(O)CH_2Cl$	DBU	toluene	17%	4:1
$Pd(PPh_3)_4$	OC(O)OEt	DBU	toluene	34%	4:1
$Pd(PPh_3)_4$	OC(O)OEt	-	H_2O/EtOAc	85%	4:1
$Pd(PPh_3)_4$	OC(O)OEt	K_2CO_3	H_2O/EtOAc	97%	4:1

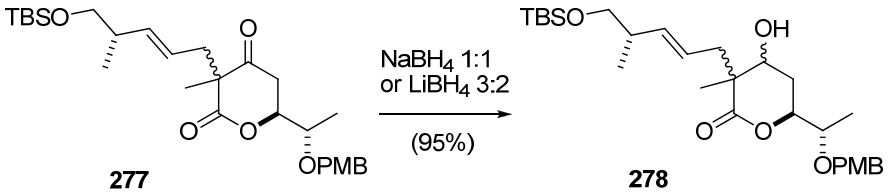
Table 6: Conditions and results for Tsuji-Trost allylation with elongated allyl carbonate.

Comparison with literature revealed the nucelophiles most common to be rather simple and achiral, like malonates or simple *β*-keto esters. This suggests that the use of more complex chiral nucleophiles has been neglected so fare as it presents a nontrivial problem in stereoselective Tsuji-Trost allylation. In literature examples chirality is always induced solely be the chiral ligands.[65, 66]

5.3.3. Fragmentation Precursor

Only reduction of the *β*-position and hydrogenation of the double bond was left to generate the fragmentation precursor. The seemingly trivial task of selectively reducing the *β*-position of **277** turned out to be more trouble than expected and always gave 1:1 mixtures. It was

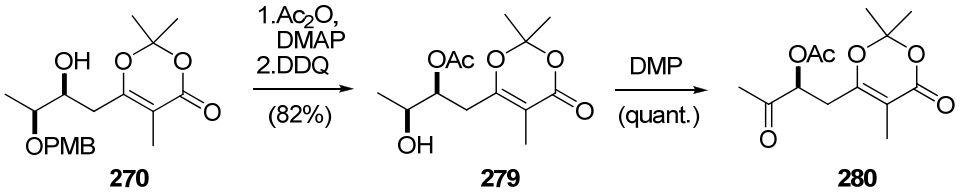
perceivable that the PMB protected moiety of the former lactates was too flexible and thus not adapt as conformative anchor (Scheme 88).



Scheme 88: Reduction of the *β*-position.

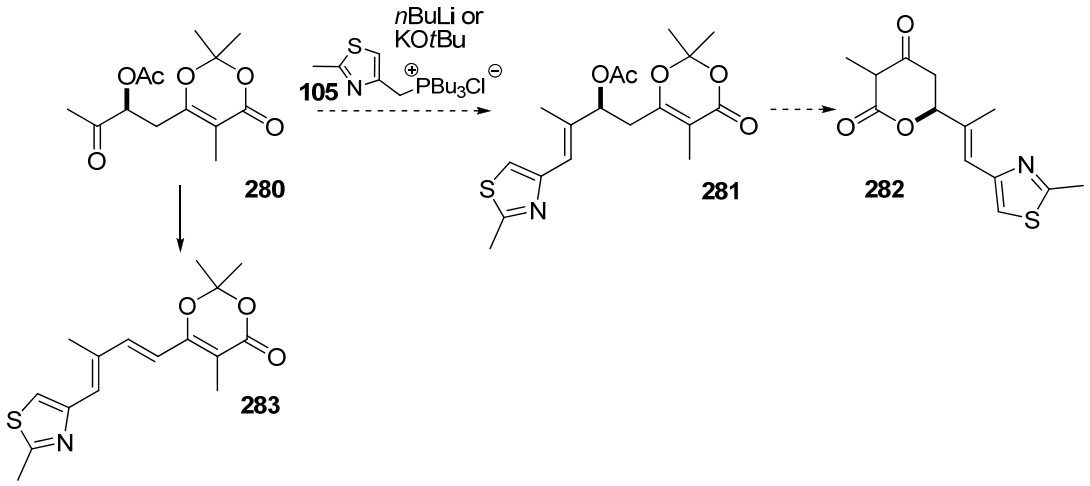
Alternative lactone for Tsuji-Trost reaction

To install a better conformative lock, efforts were made to introduce the thiazolalkylidene moiety earlier. Therefore, the free hydroxyl group was protected as acetate, based on the idea to cleave the acetate and the acetonide together with K_2CO_3 in one-pot, when the lactone is generated. The PMB ether was cleaved oxidatively with DDQ and the free alcohol was converted into methyl ketone **280** with buffered DMP (Scheme 89).



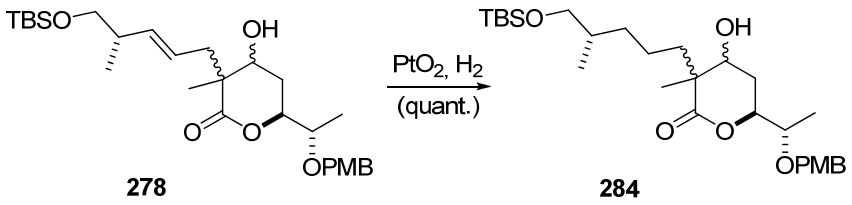
Scheme 89: Transformation of dioxenone **270**.

The next step was the Wittig reaction with thiazole salt **105**. Despite extensive optimization the only product ever isolated was **283** coming from acetate elimination to the conjugated aromatic system, before or after the Wittig reaction took place (Scheme 90). Problems were the good potential of acetate to act as leaving group and the high temperatures which were needed in the Wittig reaction to generate the double bond, due to the good stabilization of the betaine intermediate formed.



Scheme 90: Thiazole Wittig reaction.

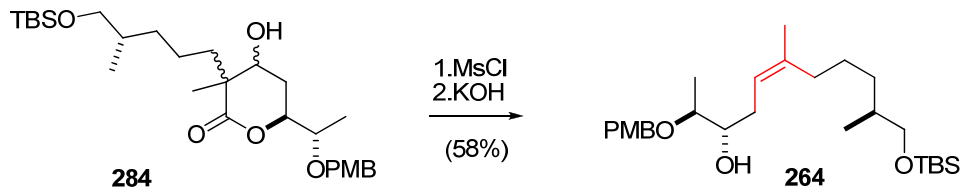
To generate fragmentation precursor **284** the double bond in **278** had to be hydrated. This could be achieved quantitatively under mild conditions by using Adam's catalyst (Scheme 92).



Scheme 91: Generation of fragmentation precursor **284**.

5.3.4. Fragmentation

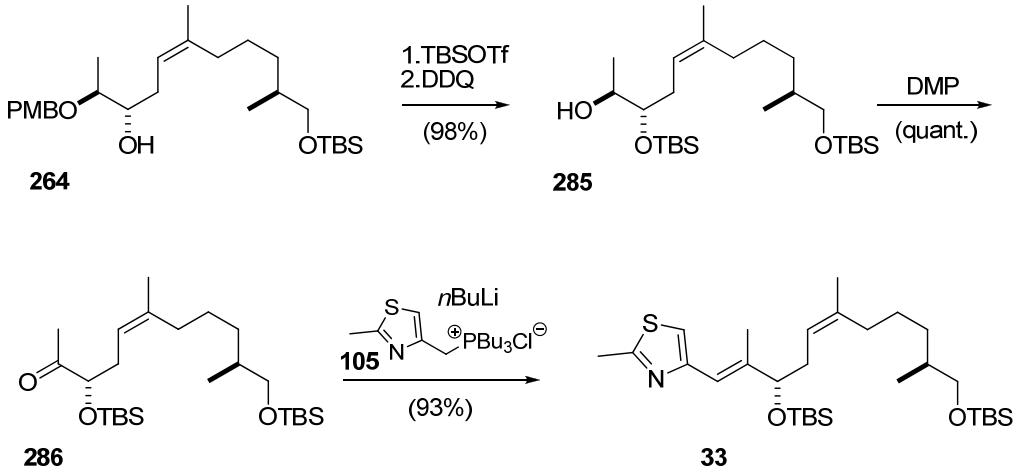
Going on with the epimeric mixture of lactone **284**, mesylation installed the required leaving group in *β*-position and treatment with potassium hydroxide in methanol at 0 °C gave desired (*Z*)-olefin **264** as only fragmentation product in 58% yield (Scheme 92). Obviously only the diastereoisomers with the correct relative configuration between *α*- and *β*-position, therefore fulfilling the stereochemical requirements for the fragmentation reaction take part in the reaction. This was proven by HPLC separation of the mixture and using only the diastereoisomer with the equatorial *β*-hydroxyl group and axial side chain in the fragmentation reaction, which produced **264** in 91% yield.



Scheme 92: Fragmentation of **284**.

5.3.5. Endgame

To complete the synthesis, the secondary alcohol group of **264** was protected with TBSOTf (Scheme 93). Then the PMB group was oxidatively removed using DDQ and the resulting free hydroxyl function of **285** was oxidized with DMP to give methyl ketone **286**, as precursor for attaching the thiazole ring *via* Wittig reaction. The Wittig salt **105** was deprotonated at 0 °C, using *n*BuLi and the resulting mixture was cooled to -78 °C, before adding ketone **286**. The reaction mixture was first warmed to room temperature, then slowly to 50 °C for 1 h. Thus, giving in nearly quantitative yield only the (*E*,*Z*)-isomer **33**, the northern fragment. The reaction temperature of the ketone addition was crucial, as at higher temperatures formation of a side product, the (*Z*,*Z*)-isomer was observed.



Scheme 93: Endgame.

With (*E*,*Z*)-diene **33** the same formal synthesis goal as from the PLE route was achieved, thus providing a second route for the a formal synthesis of epothilone B (**1**).

5.4. Summary – Epothilone B

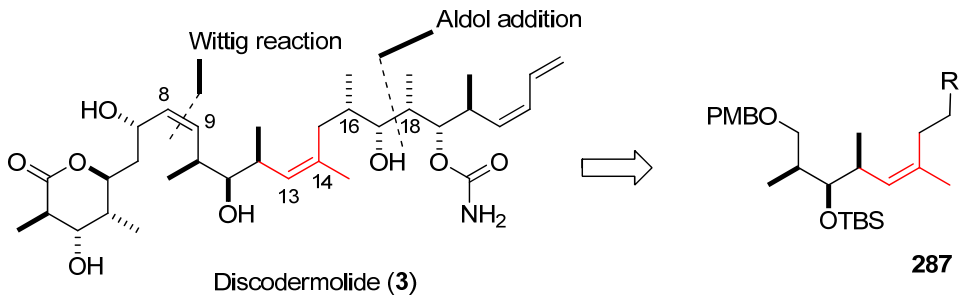
Two independent approaches to finish the formal synthesis of epothilone B were developed, using a new decarboxylative Grob-type fragmentation reaction to build up the trisubstituted C12,13-(*Z*)-double bond. The key to a successful synthesis lies in the stereoselective generation of the quaternary *α*-center of the fragmentation precursor.

In the PLE route this crucial step was performed at the beginning by enzymatic desymmetrization of *meso* malonate **193**. Thereby obtained stereoinformation was used as relay to generate the missing stereocenters along the chain by substrate control. An unexpected behavior of aldehyde **212** was observed, namely the strong hindrance of the quaternary *α*-center to induce Cram chelate controlled aldol addition, which on the other hand led to excellent stereocontrol for the Felkin-Anh adduct. The *δ*-lactone was closed at a late stage and fragmentation led to the desire (*Z*)-olefin as single product. Thus, the first formal synthesis was accomplished in 18 steps over the longest linear sequence and 24% yield. Additionally, aldol adduct **220** was transformed into four diastereomeric fragmentation precursors, whose behavior under fragmentation conditions was investigated and thus gave four diastereoisomers **235**, **240**, **243** and **247** of the epothilone B northern fragment. Fragmentation of the *δ*-lactones derived from *anti* dihydroxy esters proceeded *via* the chair transition state to the desired olefins. Whereas fragmentation of the *δ*-lactones derived from *syn* dihydroxy esters which bear the leaving group in axial position and thus make fragmentation *via* the chair transition state impossible, react presumably *via* the carboxylate to both olefin and *β*-lactone. The olefin geometry is determined by the relative configuration between *α*- and *β*-center and thus selectable during the synthesis of the fragmentation precursor. On thermolysis the *β*-lactones gave additional amounts of the olefin, so that overall fragmentation of the *syn* diols also gave the olefin in pure form and acceptable yield.

In the second approach, the lactate route, the quaternary center was installed by asymmetric allylic alkylation of enantiomerically pure *β*-keto lactone **262**. Despite intensive optimization best results were a 4:1 ratio in favor of the desired axial compound. Additionally, the selective reduction of the *β*-position provided always disappointing 1:1 mixtures as most probably the side chain, derived from the former lactate is not an efficient conformational anchor for the *δ*-lactone. However, after separation of the desired diastereoisomer fragmentation worked smoothly to provide desire (*Z*)-olefin **264**. Also the diastereomeric mixture could be employed to give only the desired olefinic product after fragmentation in correspondingly lower yield. A high yielding efficient endgame furnished the northern fragment **33** in 33% yield and 14 steps over the longest linear sequence.

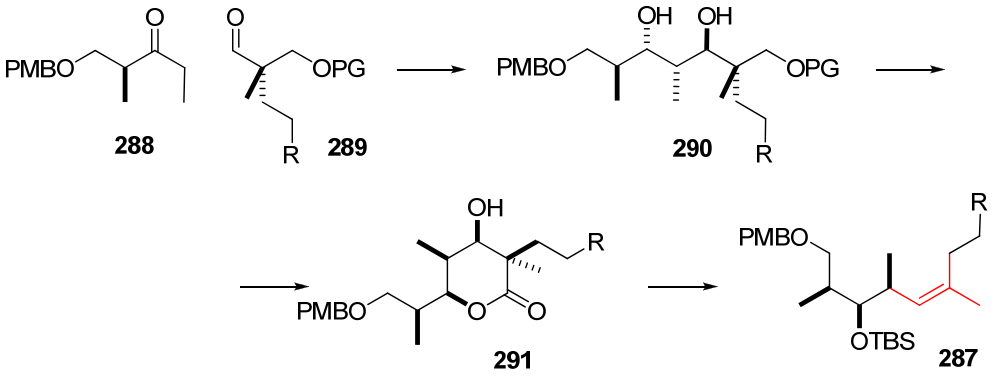
6. Results and Discussion - Discodermolide

6.1. General Retrosynthesis



Scheme 94: General retrosynthesis for discodermolide (**3**).

Discodermolide (**3**) is generally dissected in three rather equally complex building blocks (Scheme 95); one obvious disconnection is the Wittig reaction between C8 and C9 to generate the disubstituted C8,9-(*Z*)-olefin and the other cut is, depending on the strategy for the generation of the trisubstituted double bond, in the area between C14 and C18. The middle part contains the trisubstituted (*Z*)-double bond and thus should be prepared by the decarboxylative Grob-typ fragmentation. Fragmentation precursor **291** is led back to diprotected tetraol **290** with five successive stereocenters, which come from a Paterson aldol addition between chiral ethyl ketone **288** and aldehyde **289** containing the quaternary center (Scheme 96).

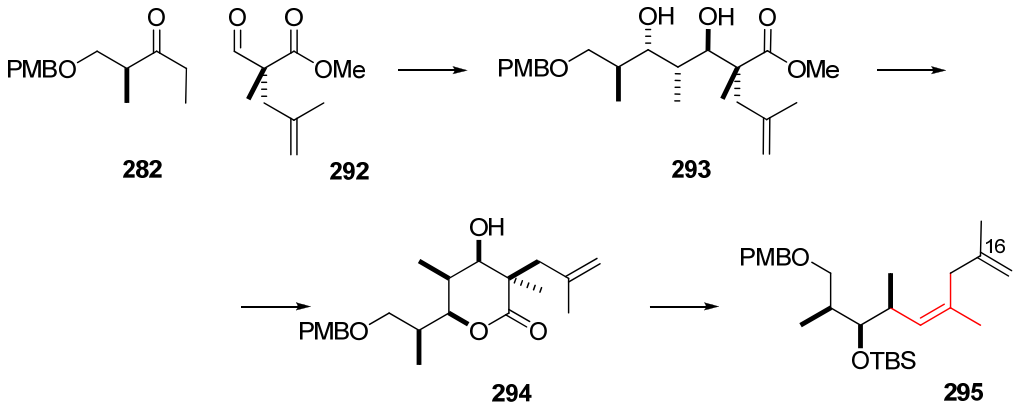


Scheme 95: Synthetic strategy for discodermolide (**3**).

In following the synthetic approaches to discodermolide (**3**) are described depending on the strategy to generate the quaternary center in aldehyde compound **289**.

6.2. Enzymatic Hydrolysis

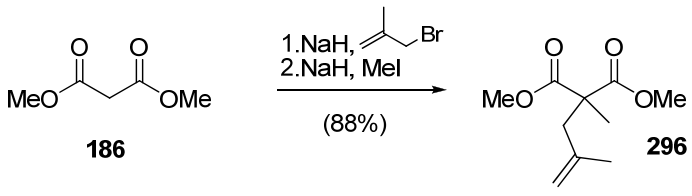
In analogy to the epothilone B PLE route (chapter 5.2.), aldehyde **292** should be gained from the mono acid derived from the corresponding *meso* malonate by enzymatic hydrolysis. A methallyl moiety was chosen as means to install the C16 center by enantioselective hydroboration after the fragmentation (Scheme 96). The *δ*-lactone as fragmentation precursor would be derived from dihydroxy ester **293** with all stereocenters already set correctly.



Scheme 96: Synthetic strategy for the PLE route.

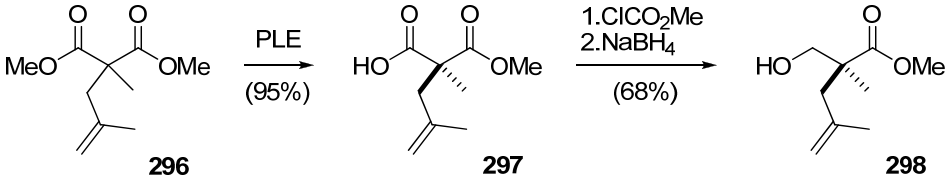
6.2.1. Quaternary Center by Desymmetrization

In the established fashion *meso* malonate **296** with a methallyl moiety was prepared by double alkylation of dimethyl malonate **186**, through deprotonation with sodium hydride and reaction with methallyl bromide followed by methylation to introduce the quaternary center (Scheme 97).



Scheme 97: Preparation of *meso* malonate **296**.

Meso malonate **296** was used in an enzymatic desymmetrization by hydrolysis with PLE, which worked now noticeably faster than for **193** and gave mono acid **297** in excellent yield (Scheme 98). Then the carboxylate was selectively reduced to the alcohol by a two step procedure *via* the mixed anhydride and alcohol **298** was used for the determination of the enantiomeric excess.

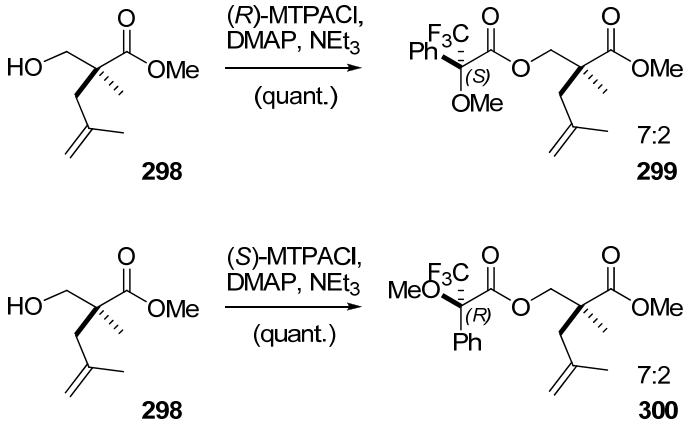


296 **297** **298**

Scheme 98: Enzymatic desymmetrization and reduction to alcohol **298**.

Determination of the enantiomeric ratio of 298

Alcohol **298** was converted into Mosher's ester **299** and **300** and HPLC analyses, ^{1}H-NMR and ^{19}F-NMR proved a 7:2 diastereomeric ratio (Scheme 99), due to poor selectivity in the enzymatic hydrolysis. The absolute configuration was assumed in analogy to the earlier gained mono acid **194** from the epothilone synthesis, as no literature known compounds were within easy reach.

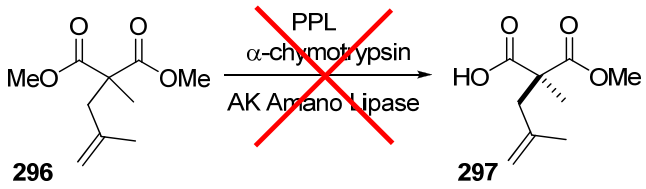


298 **299**

298 **300**

Scheme 99: Determination of the enantiomeric ratio of **298**.

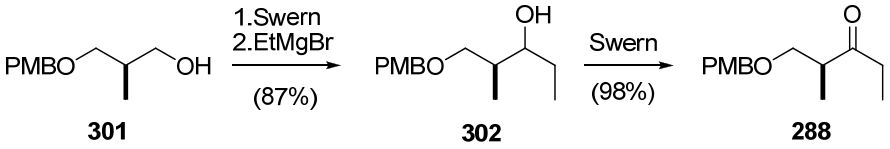
To obtain better selectivity in the enzymatic hydrolysis different enzymes were tested but no improvement was achieved (Scheme 100).



Scheme 100: Testing different enzymes for the hydrolysis of **296**.

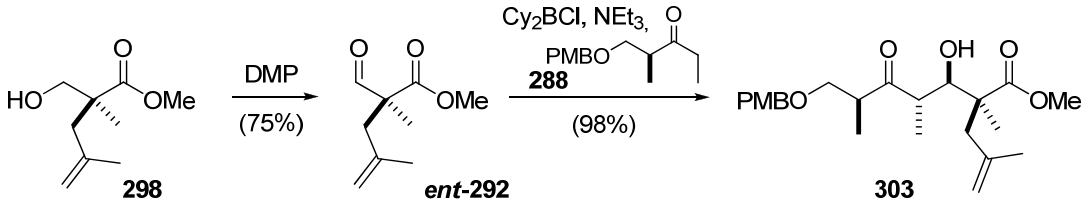
6.2.2. Fragmentation Precursor

First chiral ethyl ketone **288** was prepared starting from mono protected diol **301** (Scheme 101), derived from (*S*)-Roche ester (***ent*-182**) by protection with PMB Bundle's reagent followed by reduction. Swern oxidation led to the *α*-chiral aldehyde which was used in a Grignard addition with ethyl magnesium bromide to generate diol **302**. Subsequent Swern oxidation yielded ethyl ketone **288**, thus easily accessible from **301** on multi-gram scale in a three step procedure and 85% overall yield.[95]



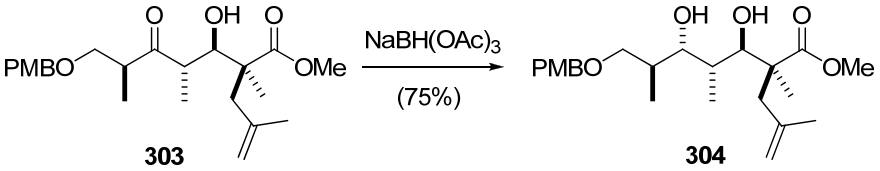
Scheme 101: Synthesis of chiral ethyl ketone **288**.

To obtain aldehyde ***ent*-292**, alcohol **298** was oxidized with Dess-Martin periodinane, which was then used in an *anti-anti*-selective Paterson aldol addition with dicyclohexylboron chloride (Scheme 102).[45, 96] Thus, ethyl ketone **288** was enolized with the Lewis acid and triethylamine at 0 °C and treated at -78 °C with the aldehyde. The desired aldol adduct was isolated in nearly quantitative yield and good selectivity.



Scheme 102: Paterson aldol addition.

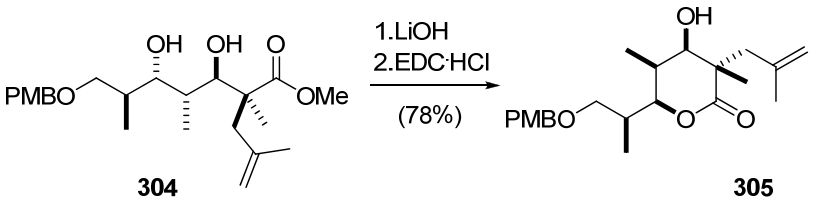
Evans-Carreira reduction to *anti* diol **304** was accomplished with the sodium salt of triacetoxy boronhydride in good yield (Scheme 103). At this stage the excellent selectivity of the aldol reaction and subsequent reduction step was confirmed by HPLC analysis, which still showed a 7:2 diastereomeric ratio, derived from the quaternary center.



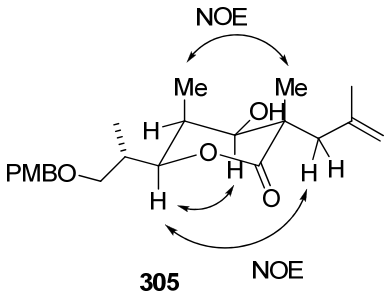
303 **304**

Scheme 103: Reduction to *anti* diol **304**.

Saponification with lithium hydroxide was followed by cyclization under Steglich conditions to *δ*-lactone **305** (Scheme 104). At this stage the diastereoisomers were easily separable by column chromatography and the NOESY experiments of the major compound confirmed the relative stereochemical arrangement of the fragmentation precursor, thereby supporting the assumption for the absolute configuration of the mono acid to be (*S*)-configuration, in accordance with the results observed earlier.



304 **305**

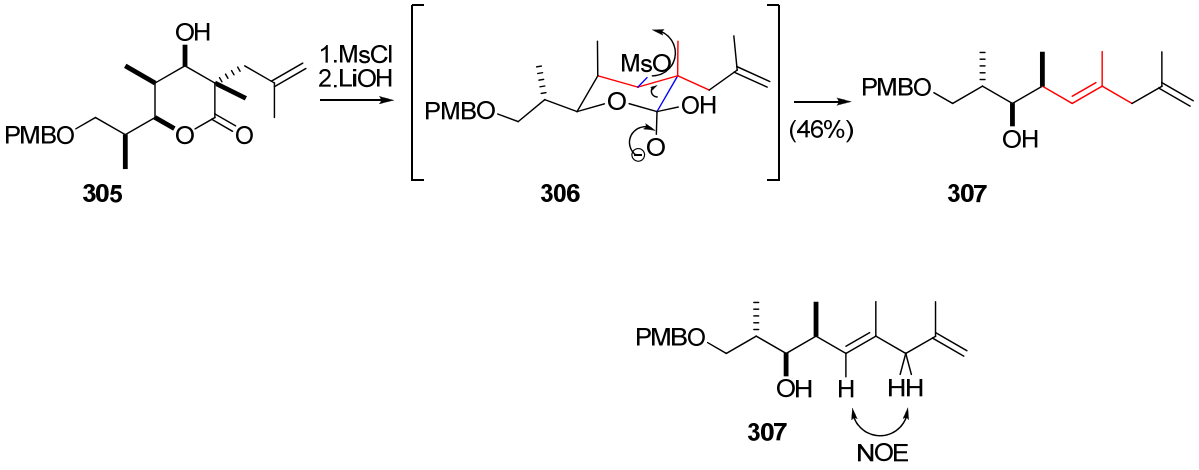


305

Scheme 104: Generation of *δ*-lactone **305**.

6.2.3. Fragmentation

The mesylate was installed under standard conditions and was directly treated with lithium hydroxide to give expected (*E*)-olefin **307** as only fragmentation product in moderate yield (Scheme 105). The low yield of the fragmentation reaction might result from an imperfect installation of the leaving group due to steric hindrance. Supported by the fact that lactone **305** was also isolated after the fragmentation. Thus, triflate was tested as leaving group but maximum yields never exceeded 45%. With the far more reactive triflate side reactions are also more likely.

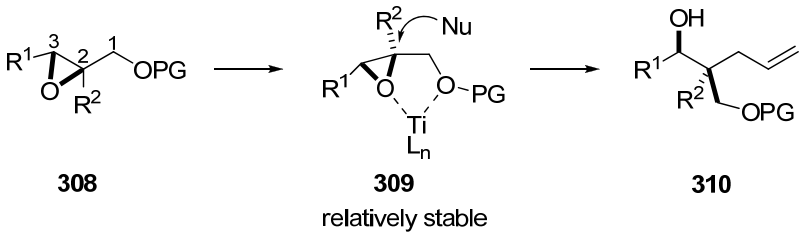


Scheme 105: Fragmentation of **305** to (*E*)-olefin **307**.

Due to the disappointing selectivity of the enzymatic desymmetrization no further attempts of correcting the relative stereochemical arrangement between *α*- and *β*-center to obtain the (*Z*)-olefin or optimization of the fragmentation reaction were made and this approach was abandoned.

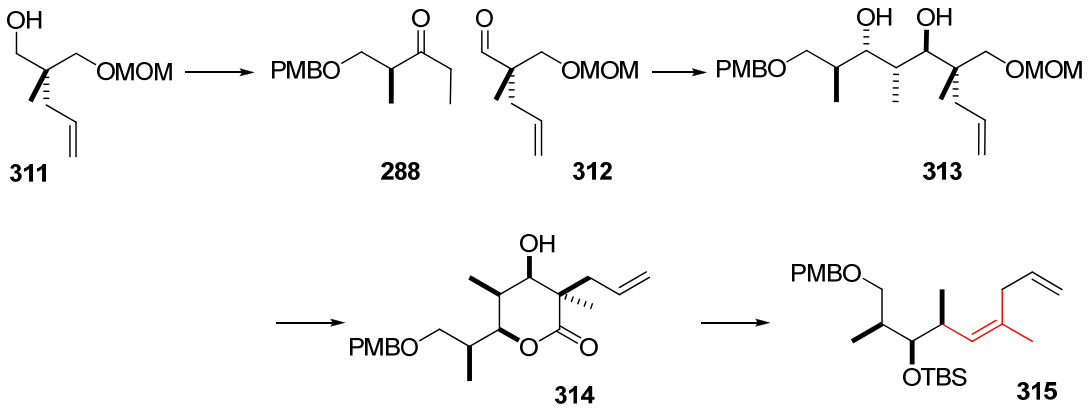
6.3. Introduction of the Quaternary Center by Regioselective Epoxide Opening

In a second approach Tanaka's titanium mediated ring opening of epoxides was tested.[97, 98] He reported the formation of chiral quaternary centers by opening of chiral epoxides on the more substituted carbon C2, which is achieved *via* a S_N2 *anti* attack of a nucleophile on a relatively stable intermediate **309** (Scheme 106). This was only observed when the C3 position had only one substituent R^1; with R^1= H attack was preferably on the C3 position due to the higher reactivity and with two substituents at C3 the tertiary carbocation was formed and a S_N1 like ring-opening gave in both cases a 1,2 diol. Yields for this epoxide opening were in general moderate.



Scheme 106: Tanaka's titanium mediated ring opening of epoxides.

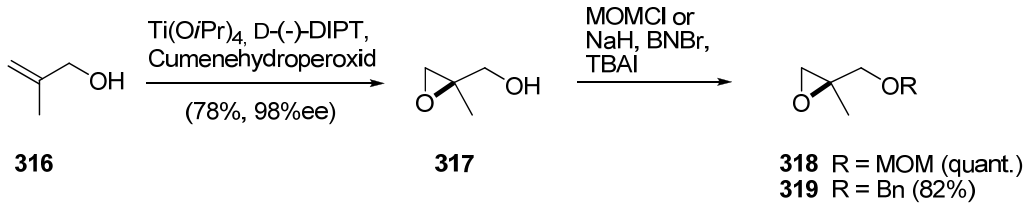
Thus, monoprotected diol **311** should be prepared and after oxidation used in a Paterson aldol addition which can easily be converted to fragmentation precursor **314** (Scheme 107). The terminal double bond of fragmentation product **315** can either be regioselectively and oxidatively cleaved or used in a hydroboration for further transformations.



Scheme 107: Synthetic strategy for the regioselective epoxide opening.

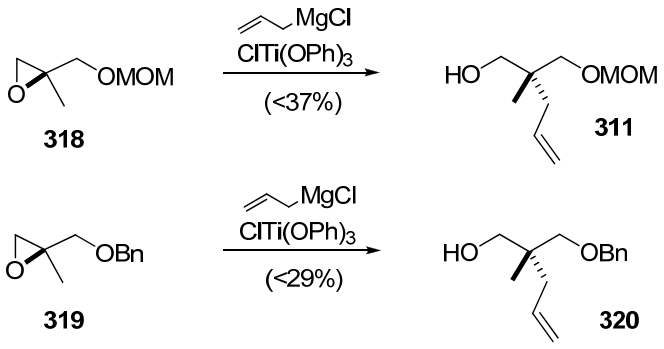
6.3.1. Epoxide Opening

Methallyl alcohol (**316**) was converted into epoxide **317** by a Sharpless epoxidation in good yield and high enantiomeric excess,[99] which was then further protected as MOM or benzyl ether both reported substrates for the epoxide opening (Scheme 108).



Scheme 108: Preparation of epoxide **318** and **319**.

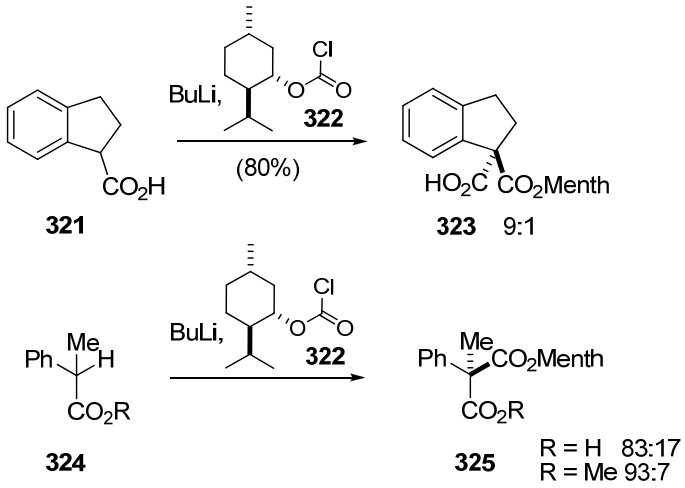
First obstacle of this reaction was the generation of the titanium species which can be achieved by conversion of the commercially available chlorotitanium triisopropoxide with phenol into the chlorotitanium triphenoxide, a dark red amorphous solid, which can be purified by bulp-to-bulp distillation at 250 °C.[100] As this distillation is not a trivial task, especially transferring the purified glass-like solid which is additionally very susceptible to oxidation, the purification protocol was changed to a repeated aceotropic distillation with toluene. Now the epoxide opening was attempted, here also the use of allyl magnesium chloride is of utmost importance as the bromide does not work. Depending on the substrate epoxide opening was achieved in 29% to 37% in contrast to 41% to 46% reported (Scheme 109). However, over 1.5 mmol reaction size the yields dropped significantly, thus the reaction was not upscale-able and therefore useless at the beginning of a synthetic route and hereupon abandoned.



Scheme 109: Investigation of the epoxide ring opening reaction.

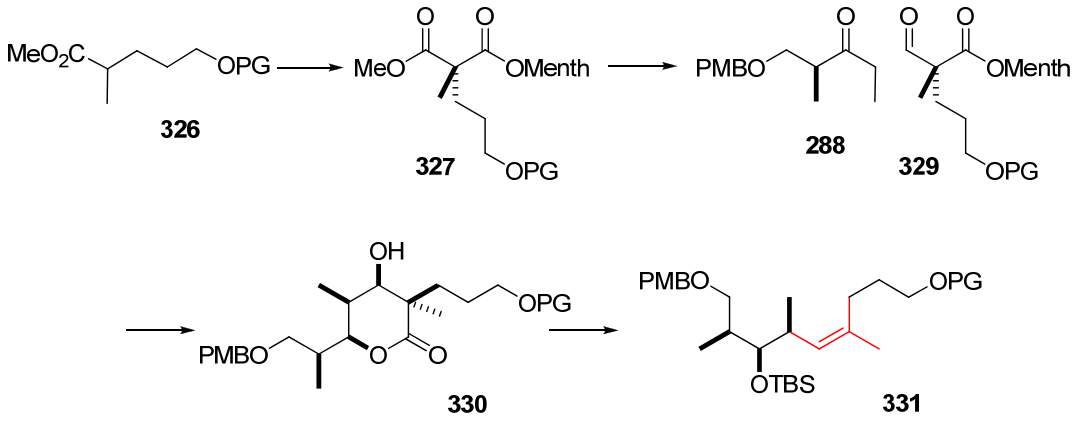
6.4. Diastereoselective Carboxalkylation of Enolates

Braun and co-workers reported the diastereoselective formation of quaternary carbon centers by a simple diastereoselective carboxalkylation of lithium enolates with (-)-menthyl chloroformate (**322**) (Scheme 110).[101, 102] They employed this strategy on cyclic and acyclic enolates generated from esters or acids and reached selectivity better than 9:1 very much depending on the solvent system. In acyclic systems esters were observed to give better results.



Scheme 110: Carboxalkylation of enolates with (-)-menthyl chloroformate (**322**).

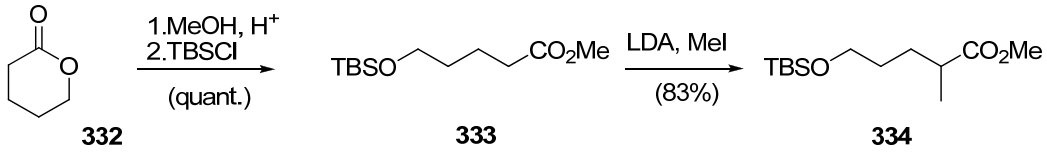
Methyl ester **326** featuring a methyl group and an alkyl chain in *α*-position should be subjected to the diastereoselective carboxalkylation to give diester **327**, which can be regioselectively converted to aldehyde **329** (Scheme 111). The protecting group PG has to be selectively modifiable in the fragmentation product **331**.



Scheme 111: Synthetic strategy for the asymmetric acylation.

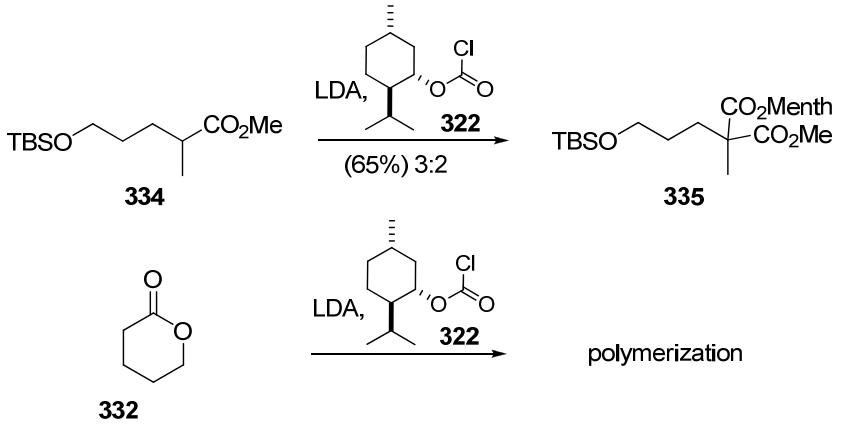
6.4.1. Quaternary Center by Acylation

Starting from *δ*-valerolactone (**332**) the methyl ester is easily accessible by acidic opening with methanol followed by *α*-methylation of the lithium enolate with methyliodide to give ester **334** as substrate for the acylation.



Scheme 112: Preparation of substrate **334**.

When ester **334** was subjected to carboxalkylation with (-)-menthyl chloroformate (**322**) the resulting diastereomeric ratio in the product mixture was disappointingly low (Scheme 113). Also the use of 8-phenylmenthol, which is generally known to improve selectivity, when employed instead of the simple menthol moiety, could not increase the diastereomeric ratio. Thus, direct carboxalkylation of *δ*-valerolactone (**332**) was attempted, assuming that the cyclic template might improve selectivity, unfortunately *δ*-valerolactone (**332**) polymerizes very easily under basic conditions.

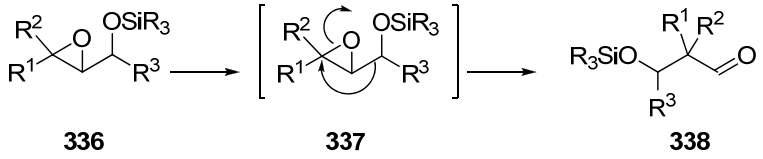


Scheme 113: Carboxalkylation of methyl ester **334** and *δ*-valerolactone (**332**).

These unfavorable results might be due to the similarity of the *α*-substituents of the substrate, two alkyl substituents were used in this case whereas the substrates described in literature always feature an alkyl and an aryl substituent.

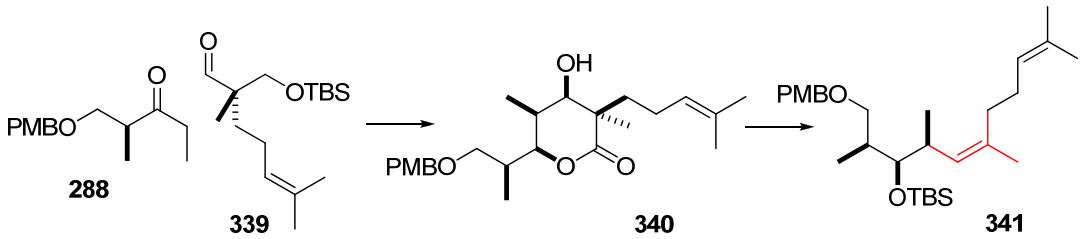
6.5. Wagner-Meerwein Rearrangement of Epoxide for the Generation of the Quaternary Center

Yamamoto described the stereocontrolled rearrangement of epoxy silyl ethers to *β*-siloxy aldehydes by Lewis acid catalyzes under mild conditions (Scheme 114).[103] His choice of catalyst fell on a sterically hindered, oxygenophilic organoaluminium reagent, as this compound will not react as base or nucelophile and its steric repulsion will promote the transfer of the siloxy methyl moiety.



Scheme 114: Organoaluminium-catalyzed rearrangement of epoxides.

Aldehyde **339** bearing the quaternary center is a known compound and will give the carbon skeleton for fragmentation precursor **340** upon aldolization with ethyl ketone **288** (Scheme 115). The terminal olefin can be further transformed regioselectively to intercept a formal synthesis intermediate.

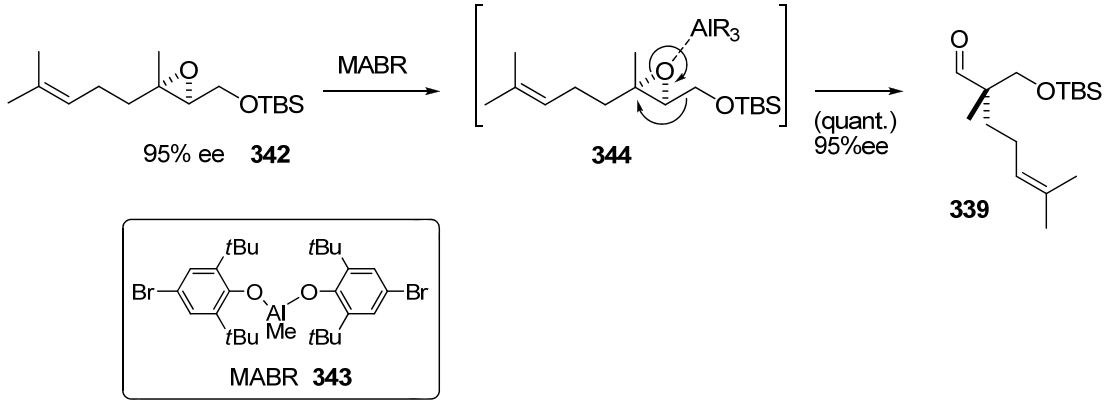


Scheme 115: Synthetic strategy to discodermolide (**3**).

6.5.1. Quaternary Center by Rearrangement

Yamamoto's organoaluminium-promoted rearrangement was first studied with *tert*-butyldimethylsilyl ether of epoxy geraniol (**342**) to construct a quaternary center. Here especial focus was on the stereochemical outcome of the reaction and it was found that the optical purity of the product matches the optical purity of the starting material; this chirality transfer comes from an *anti* migration of the siloxy methyl group (Scheme 116). Thus,

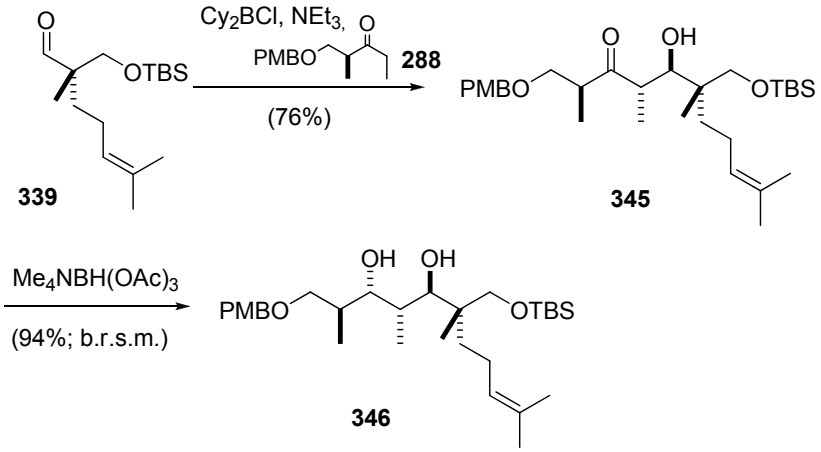
optically active epoxy silyl ether **342**, which was derived from Sharpless asymmetric epoxidation of geraniol using L-(+)-diethyl tartrate and subsequent conversion into its silyl ether, was treated with methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) (**343**) to provide aldehyde **339** in 97% yield and 95% ee.[99] This reaction can be performed with catalytic amounts of MABR on multi-gram scale.



Scheme 116: Yamamoto's organoaluminium-promoted rearrangement.

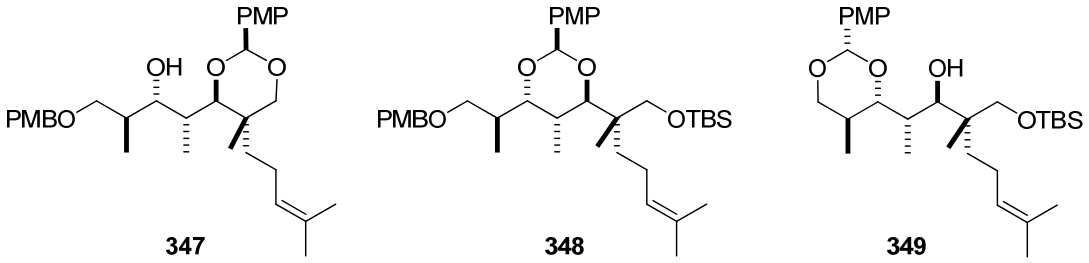
6.5.2. Fragmentation Precursor

The complete carbon skeleton of the fragmentation precursor was constructed in excellent yield and selectivity, also on big scale, using an *anti-anti*-selective Paterson boron aldol reaction between chiral ethyl ketone **288** and aldehyde **339**.[45] Thus, ethyl ketone **288** was enolized with dicyclohexylboron chloride and triethylamine at 0 °C and treated at -78 °C with aldehyde **339** (Scheme 117). The desired aldol adduct was isolated on small scale in nearly quantitative yield and good selectivity; when the reaction was preformed on 50 mmol scale the yields were still very good, around 75% to 80%. Then hydroxy ketone **345** was converted to diprotected tetraol **346** in an Evans-Carreira *anti*-reduction,[79] which proceeded very slowly and therefore was stopped after three days and 50% conversion.



Scheme 117: Paterson's *anti-anti*-selective boron aldol addition.

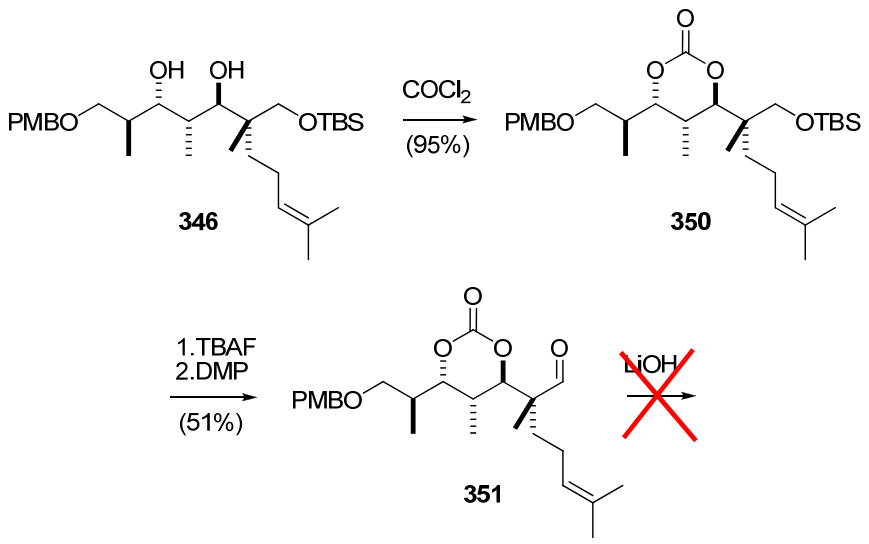
To confirm the stereochemical outcome of these two reactions and thus prove the configuration of the generated stereopentade the following three PMP acetals **347** to **349** were made and subjected to extensive NOE experiments (Scheme 118).



Scheme 118: PMP acetals of tetraol **346**.

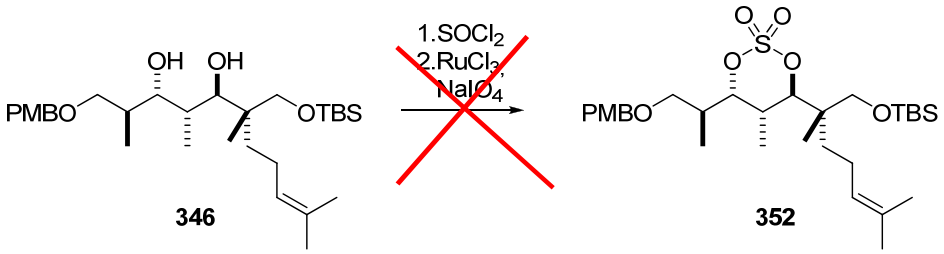
6.5.3. Fragmentation of the Open Chain Precursor

The cyclic carbonate could be introduced under standard conditions with phosgene. Then the silyl ether was cleaved with TBAF and oxidized to the corresponding aldehyde **351** in moderate 70% yield for each of the two steps. Next the fragmentation of aldehyde **351** was attempted in analogy to the fragmentation of aldehyde **254** from the epothilone route, but only decomposition was observed (Scheme 119). This might be due to several reasons: there is the regioselectivity problem of hydroxide attack, which might occure on the aldehyde or the carbonate. Additionally in aldehyde **254** the bulky TIPS group might have hampered the free rotation of the carbon chain and thus favored a conformation which fulfilled the stereochemical requirements for the fragmentation reaction to generate olefin **253**.



Scheme 119: Cyclic carbonate as leaving group.

Despite the negative results with the former cyclic sulfate, its introduction was attempted in a two step procedure. Again, the cyclic sulfite was easily available but the oxidation step led to decomposition (Scheme 120).

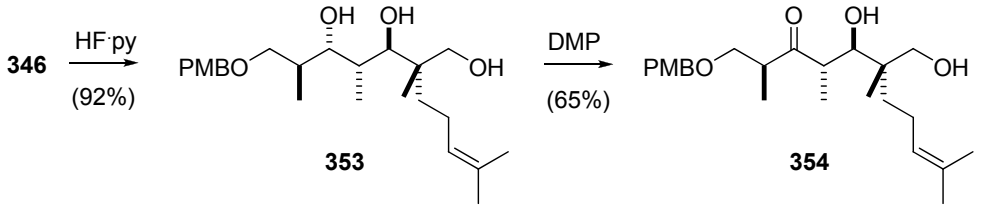


Scheme 120: Introduction of a cyclic sulfate as leaving group.

6.5.4. Conversion into δ-Lactone 340

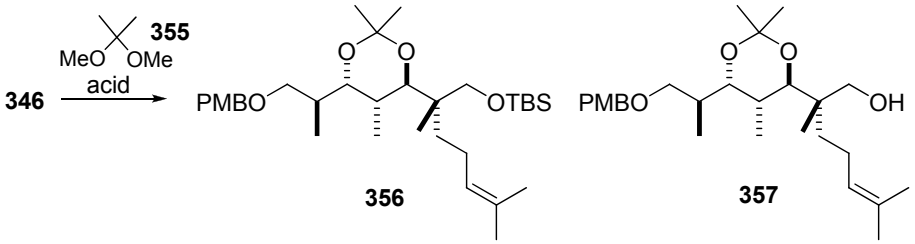
For the preparation of the δ-lactone the primary neopentyl position had to be oxidized to the acid and cyclized to the lactone. So the first attempt was to cleave the TBS ether with HF·pyridine and selectively oxidize the primary position of triol **353** with one equivalent of DMP (Scheme 121). As triol **353** is rather water soluble, the work-up of this reaction was a major issue and best results were achieved with HF·pyridine due to the ability of TBAF to act as phase transfer catalyst. The oxidation product was found to be ketone **354**, unambiguously determined by the ^{13}C-NMR, by selective oxidation of the sterically less

hindered secondary alcohol, which demonstrated very impressively the unpredictability of the reactivity of neopentyl positions.



Scheme 121: Selective oxidation of triol **353**.

As the primary position was not regioselectively oxidizable, the two secondary alcohols had to be protected first, which was accomplished with an acetonide. This seemingly trivial reaction required optimization efforts as the TBS group was very easily cleaved under acidic conditions (Scheme 122, Table 7). Thus, the first reaction provided as only products acetonide **356** and **357** with the free primary alcohol, which was very promising. Extensive optimization showed that the nature of the acid, the amount and the reaction time had to be adjusted very precisely to get useful products. In harsh conditions acetonide cleavage to the starting material **346** or free triol **353** was observed which led to a four component mixture, two of them inseparable, as the mixture of staring material **346** and acetonide **357** with the free hydroxyl group is not separable by column chromatography. In the end the reaction was carried out with only 10 mol% of CSA and stopped after 60% to 70% conversion. The recovered starting material could be easily recycled.

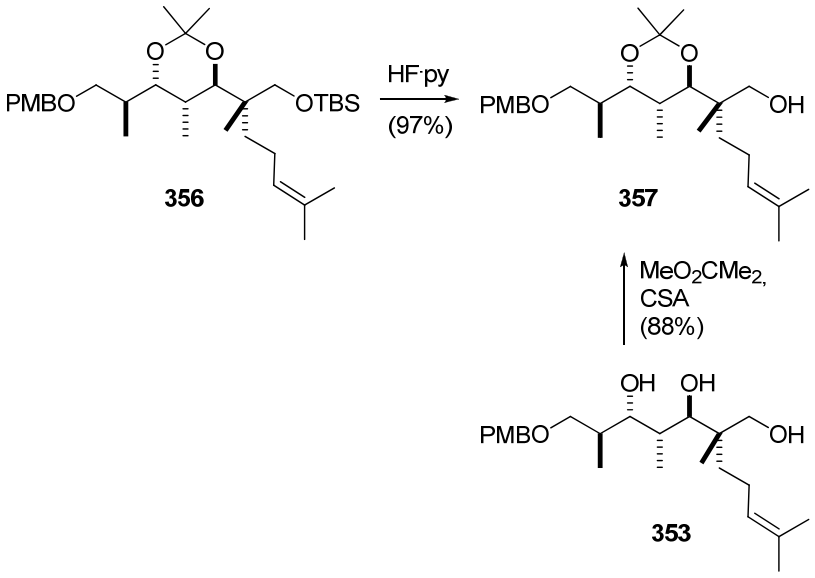


Scheme 122: Acetonide protection of diprotected tetraol **346**.

acid	eq.	rxn time	products
CSA	0.2	4 h	36% **356** and 38% **357**
CSA	0.1	2 h	68% **356** and 31% **346**
*p*TsOH	0.2	2 h	26% **356** and mixture of **346** and **357**
PPTS	0.5	8 h	58% **356** and mixture of **346** and **357**

Table 7: Conditions for acetonide protection of diprotected tetraol **346**.

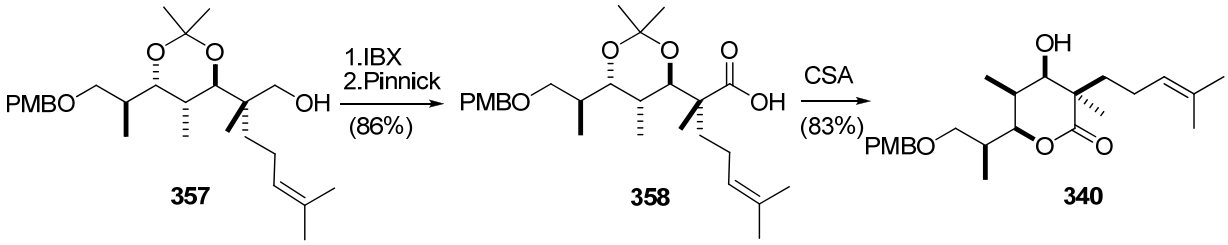
The silyl ether of **356** was cleaved in the next step with HF·pyridine to generate known acetonide **357** (Scheme 123). From experience with the oxidation of free triol **353**, the secondary alcohol was known to be the most reactive side. Thus, a second route to **357** was tested by directly installing the acetonide on the free triol **353**, which was accomplished regioselectively in good yields. Here also the reaction time is crucial as migration of the acetonide is observed at longer duration.



Scheme 123: Two ways to generate acetonide **357**.

Now the primary alcohol was oxidized in two steps to acid **358**; IBX oxidation led to the aldehyde and further treatment under Pinnick conditions gave acid **358**. In acidic conditions

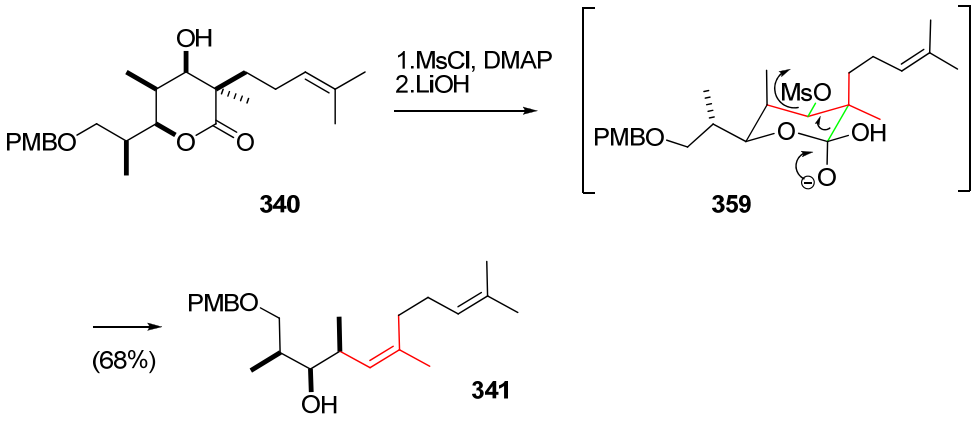
the acetonide was opened and the free dihydroxy acid cyclized spontaneously to *δ*-lactone **340** (Scheme 124).



Scheme 124: Building the fragmentation precursor.

6.5.5. Fragmentation

With *δ*-lactone **340** in hand the leaving group was installed in *β*-position, due to steric hindrance harsher conditions were needed than for the previous entries, namely stoichiometric amounts of DMAP in a 1:1 CH_2Cl_2:pyridine mixture with three to five equivalents of mesyl chloride. The generated mesylate was directly used in the following fragmentation reaction yielding desired (*Z*)-olefin **341** as single product *via* the chair transition state (Scheme 125).

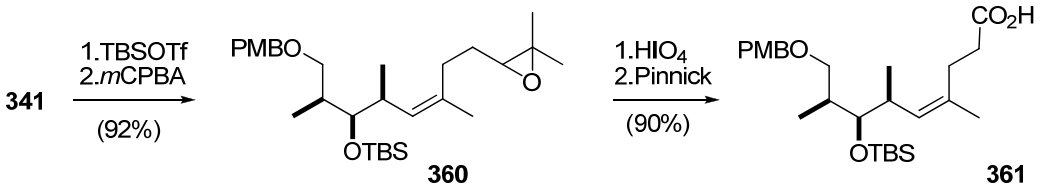


Scheme 125: Fragmentation reaction.

The somewhat lower yield in comparison to other examples can most likely be traced back to the problem of installing the leaving group. Different alternative leaving groups were investigated such as tosylate, nosylate and triflate; however, without success due to their even bigger sterical extension.

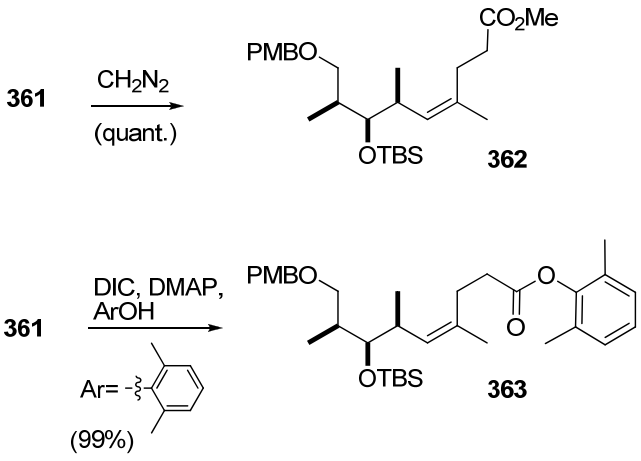
6.5.6. First Formal Synthesis Goal

To finish the formal synthesis and intersect one of Paterson's intermediates, the terminal olefin had to be converted into an ester. Thus, the homoallylic alcohol was protected as silyl ether and the terminal double bond was selectively epoxidized with *m*CPBA. In order to avoid epoxidation of the second double bond, adjustment of reaction times and temperature is crucial. Then the epoxide was cleaved to the aldehyde, which was oxidized to acid **361** (Scheme 126).



Scheme 126: Conversion of the terminal olefin into acid **361**.

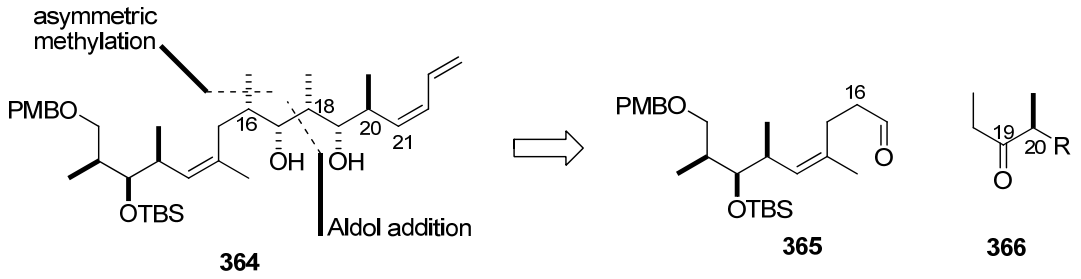
Now two formal synthesis goals were within reach, either conversion into methyl ester **362** by treatment with diazomethane or esterification under Steglich conditions with 2,6-dimethyl phenol to aromatic ester **363** (Scheme 127). Both esterifications worked very well and the analytical data matched perfectly with the reported ones.[45]



Scheme 127: Synthesis of Paterson's esters **362** and **363**.

6.5.7. Second Formal Synthesis Goal

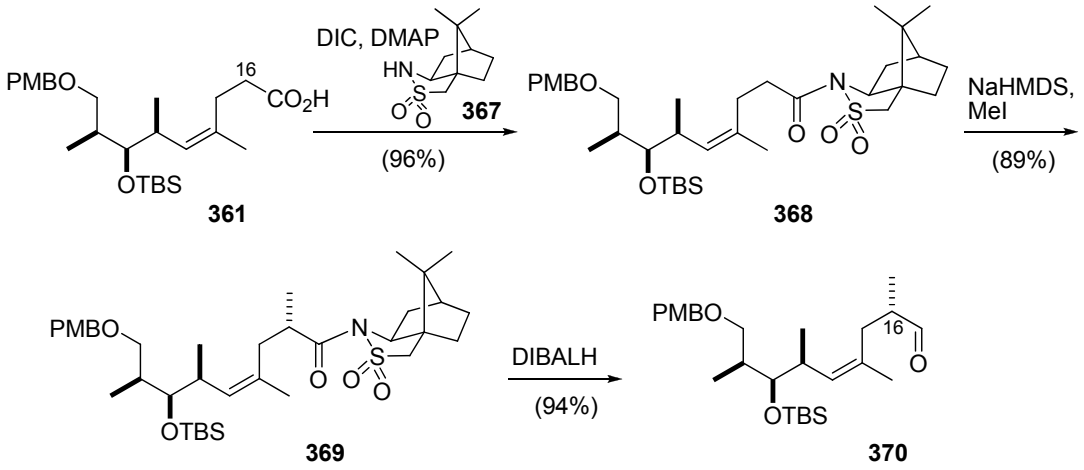
The second formal synthesis goal was an intermediate from Smith's synthesis with the eastern part of the molecule already attached. The C16 to C20 fragment contains five contiguous stereogenic centers from which four are *syn* and the last one *anti* to each other - an unusual configuration in polyketides (Scheme 128). The C16 methyl group should be installed by asymmetric methylation of a chiral auxiliary. Further dissection is between C17 and C18 which will be closed in a *syn* selective aldol addition. The ketone fragment **366** already contains the C20 stereocenter.



Scheme 128: Retrosynthetic analysis for the introduction of the eastern part.

6.5.8. Stereoselective Methylation at C16

Thus, the first task was to install Oppolzer's sultam as chiral auxiliary for the methylation of C16, which was easily possible using Steglich's reagent, acid **361** and sultam **367**.[104] The conversion *via* the acid chloride of **361** is also possible but yields are lower in the acylation reaction. Next the sodium enolate of **368** was formed and methyliodide introduced the desired C16 center in good yields and selectivity (Scheme 129). The auxiliary was reductively removed in the next step to provide *α*-chiral aldehyde **370** for the following aldol addition.

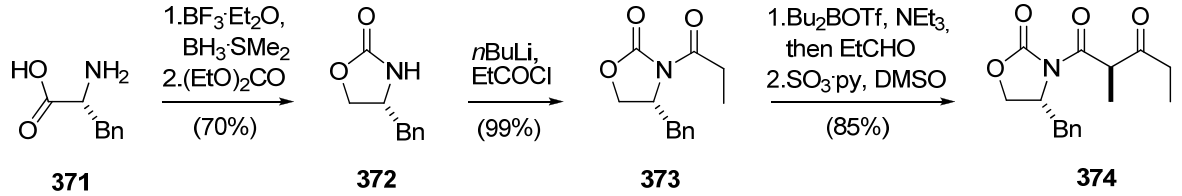


Scheme 129: Introduction of the C16 methyl group.

6.5.9. Attaching the C18 to C21 Fragment

Extended Evans' auxiliary

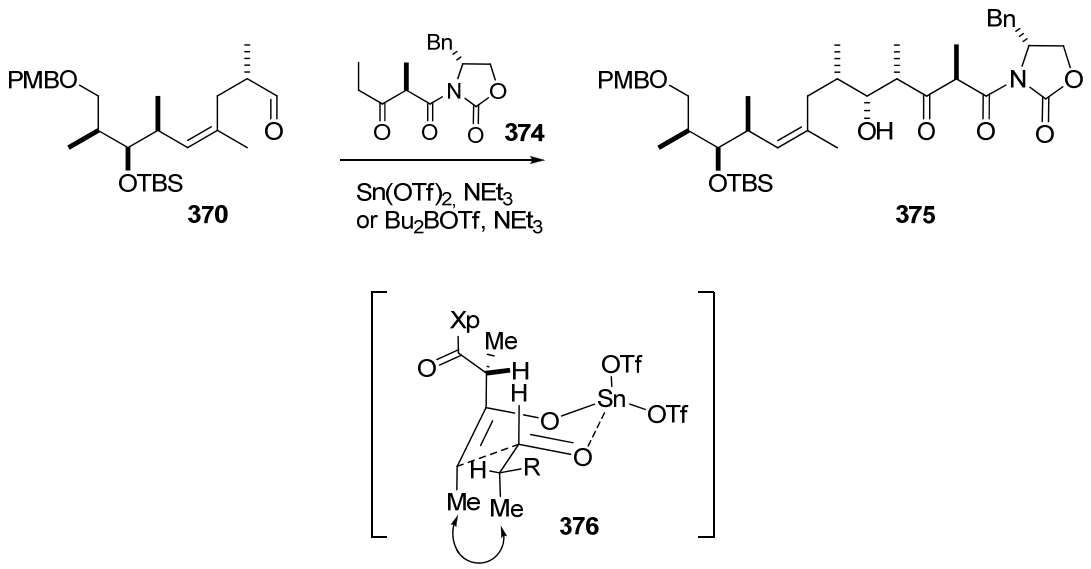
The most obvious building block for the C18-C21 fragment is *β*-ketoimide **374**, which already contains the C20 stereocenter. A *syn* selective aldolization should generate the required C17 and C18 stereocenters.[105, 106] Thus, *β*-ketoimide **374** was prepared according to the known literature procedure (Scheme 130).[107, 108] Starting from D-phenylalanin (**371**), reduction led to the amino alcohol which was carbonylated with diethylcarbonate to generate (4*R*)-benzyloxazolidinone (**372**), the Evans' auxiliary. Acylation with propionyl chloride gave **373** which was treated with dibutylboron triflate to form the *syn* aldol adduct with propanal. Subsequent Parikh-Doering oxidation to avoid epimerization of the *α*-methyl group, gave extended Evans' auxiliary **374**.



Scheme 130: Preparation of extended Evans' auxiliary **374**.

Hence, *β*-ketoimide **374** was subjected to the following aldolization reaction conditions using either tin(II) triflate or freshly prepared dibutylborontriflate to generate the (*Z*)-boron enolate

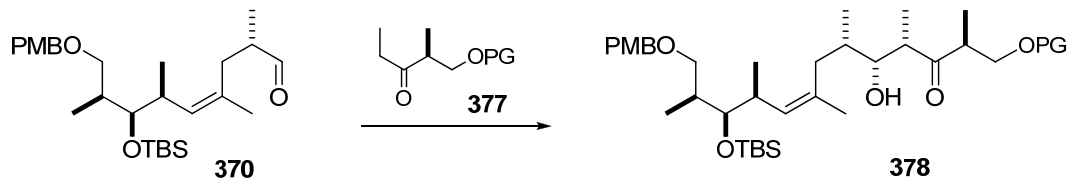
but no reaction with aldehyde **370** was observed (Scheme 131). A closer look at transition state **376** revealed it to be the stereochemically mismatched case due to *syn*-pentane interaction.



Scheme 131: Extended Evans aldol addition.

Paterson aldol addition

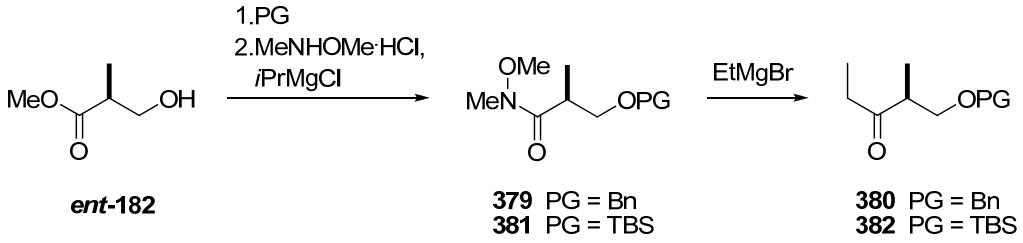
The next idea was to test Paterson aldol addition (Scheme 132). The ethyl ketones **377** employed are sterically less demanding than the extended Evans' auxiliary and might still be able to give aldol adducts despite the disfavored interaction between the two methyl groups. An additional advantage was the possibility of using ethyl ketone **388** with the terminal (*Z*)-diene already in place which would provide a very convergent approach and shorten the synthesis drastically.



Scheme 132: Paterson aldol addition.

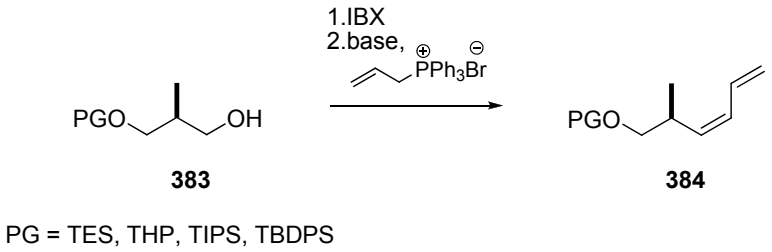
First the simple ethyl ketones **380** and **382** were prepared, starting from (*S*)-Roche ester (***ent*-182**) by protection either with benzyl Bundle's reagent or TBSCl and further conversion

into the corresponding Weinreb amide **379** and **381**. Addition of ethylmagnesium bromide gave ethyl ketones **380** and **382** (Scheme 133).



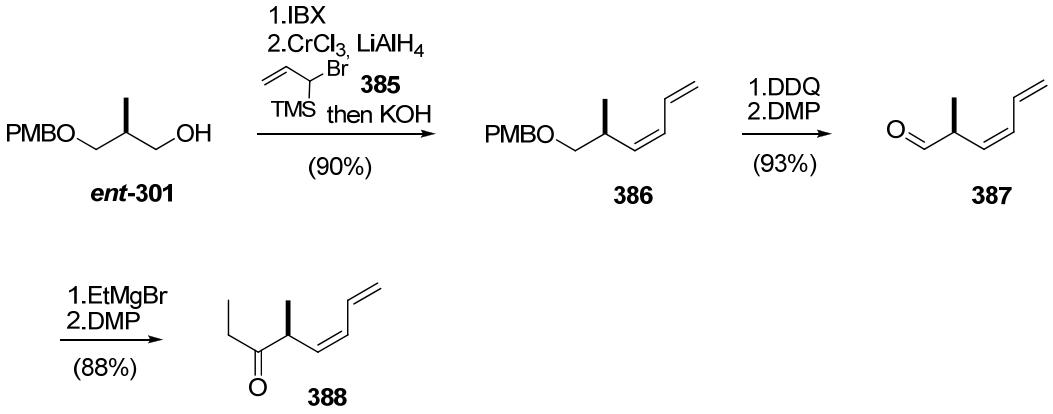
Scheme 133: Preparation of ethyl ketones **380** and **382**.

For the generation of ethyl ketone **388** featuring the (*Z*)-diene, the initial strategy was based on a (*Z*)-selective allyl Wittig reaction (Scheme 134). Thus, monoprotected diol **383**, derived from (*R*)-Roche ester (**182**) by protection and reduction, was oxidized to the corresponding aldehyde with IBX in DMSO at ambient temperature, which was directly employed in the following olefination reaction. Different bases for example NaHMDS, *t*BuOK or LDA were used and temperature was varied from low to ambient temperature, but no reaction was observed only deprotection and decomposition of the starting material.



Scheme 134: Preparation of the terminal (*Z*)-diene *via* Wittig reaction.

Then the strategy was changed to the Nozaki-Hiyama/Peterson protocol, first developed in the Paterson group and modified by Novartis to a one pot procedure (Scheme 135).[109] Thus, bromoallylsilane **385** was prepared and used in a chromium(II) mediated Nozaki-Hiyama coupling with the aldehyde derived from ***ent*-301**, basic workup with potassium hydroxide gave desired (*Z*)-diene **386** by a Peterson-type *syn* elimination. Now the PMB group was cleaved and the resulting alcohol was oxidized to aldehyde **387**. Grignard addition with ethylmagnesium bromide gave the corresponding secondary alcohol and Dess-Martin oxidation yielded ethyl ketone **388**.



Scheme 135: Ethyl ketone **388** featuring the (*Z*)-diene *via* Nozaki-Hiyama/Peterson protocol.

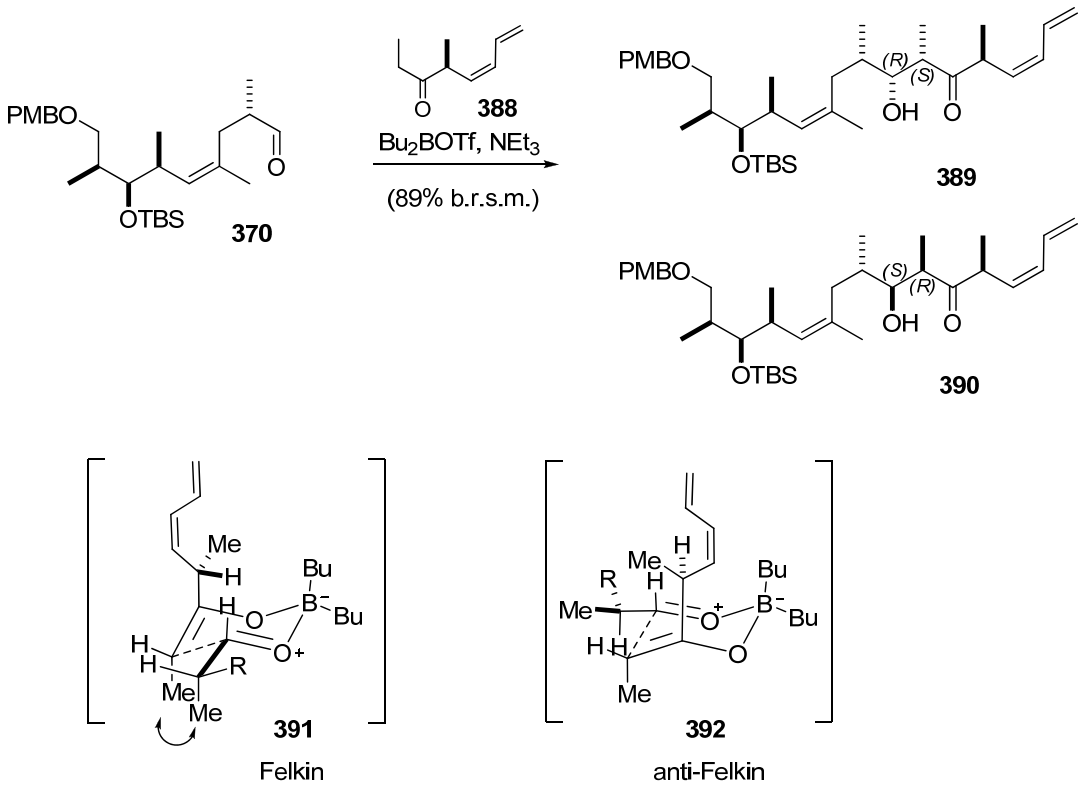
Now the aldol addition could be tested and the initial idea was to use (-)-diisopinocampheylboron triflate to generate the chiral (*Z*)-boron enolate which determines the stereochemical outcome of the reaction.[110] Alas, the isopinocampheyl moieties seemed to be too sterically demanding to lead to any reaction as the mismatched transition state had to be overcome. Also the use of lithium enolates only gave mixtures of diastereoisomers. So in the end simply employing freshly prepared dibutylboron triflate gave the aldol adduct as single diastereoisomer (Table 8).

ketone	LA, base	product
382	(-)-Ipc_2BOTf, DIPEA	no reaction
380	(-)-Ipc_2BOTf, DIPEA	no reaction
388	(-)-Ipc_2BOTf, DIPEA	no reaction
382	LiHMDS	1:1
388	LiHMDS	3:2
388	Bu_2BOTf, TEA	1 diast.
382	Bu_2BOTf, TEA	1 diast.

Table 8: Conditions for Paterson aldol addition.

Without chiral induction from the isopinocampheyl moieties two possible *syn* aldol adducts can be generated *via* the (*Z*)-boron enolate.[111] With *α*-chiral aldehydes, (*Z*)-boron enolates

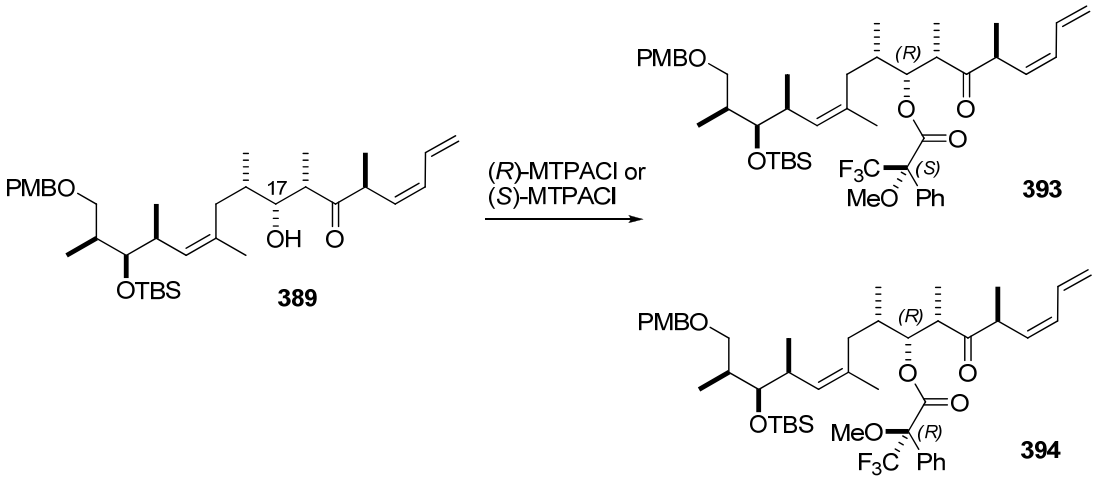
normally lead to anti-Felkin products through transition state **392** to avoid the destabilizing *syn*-pentane steric interaction in the cyclic chair transition state **391**.[96] Thus, aldolization to the undesired *syn* aldol adduct **390** is more likely (Scheme 136).



Scheme 136: Aldolization with dibutylboron triflate.

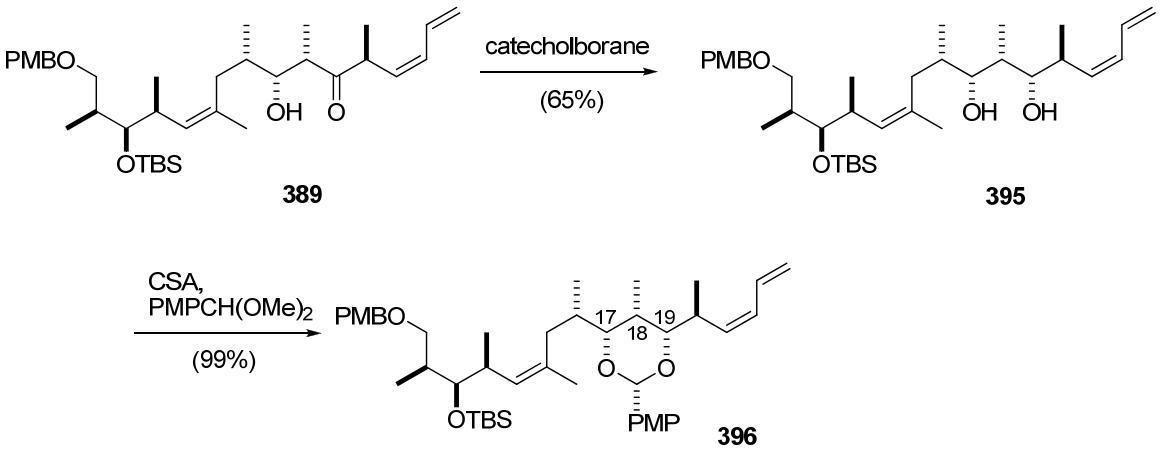
Determination of the configuration at C17 and C18

For the determination of the absolute configuration at C17 both (*R*)- and (*S*)-Mosher esters **393** and **394** were synthesized (Scheme 137) and the difference of the chemical shifts of both compounds provided evidence for the stereochemistry of the C17 center and the desired (*R*)-configuration could be deduced.[112, 113]



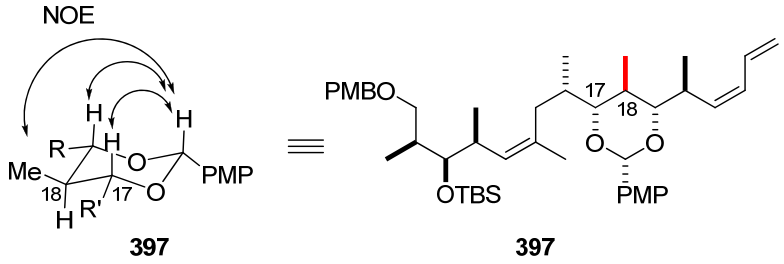
Scheme 137: Determination of the absolute configuration at C17.

To prove the *syn* selectivity of the aldol addition cyclic acetale **396** was prepared (Scheme 138) by substrate controlled *syn* reduction with catecholborane to diol **395** and subsequent acid mediated acetalization with anisaldehyde dimethyl acetal.



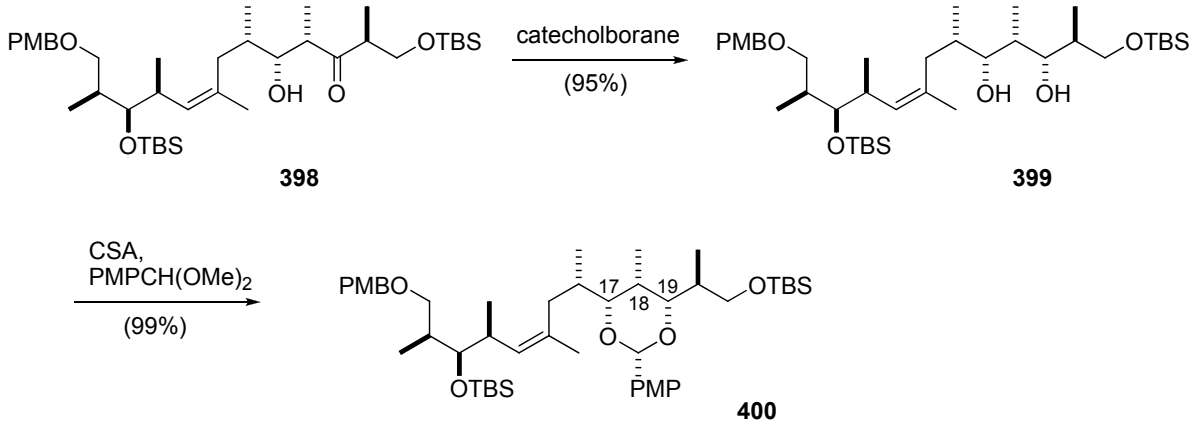
Scheme 138: Determination of the relative configuration between C17-C19 of **389**.

NMR correlation spectroscopy showed clearly NOE cross peaks between the methyl group at C18 and the acetal proton and thus revealed the configuration between C17 and C18 to be *anti* and not *syn* as assumed (Scheme 139).



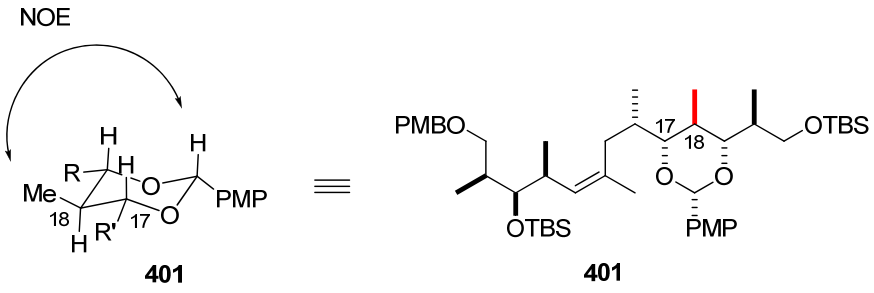
Scheme 139: Determination of the relative configuration between C17-C19 of **397**.

To validate this unexpected result, namely the aldol reaction *via* the (*E*)-enolate bespite using dibutylboron triflate, the relative configuration between C18-C20 in **398** was also investigated. Thus, after *syn* reduction to diol **399** treatment with anisaldehyde dimethyl acetal led to acetal **400** (Scheme 140).



Scheme 140: Determination of the relative configuration between C17-C19 of **398**.

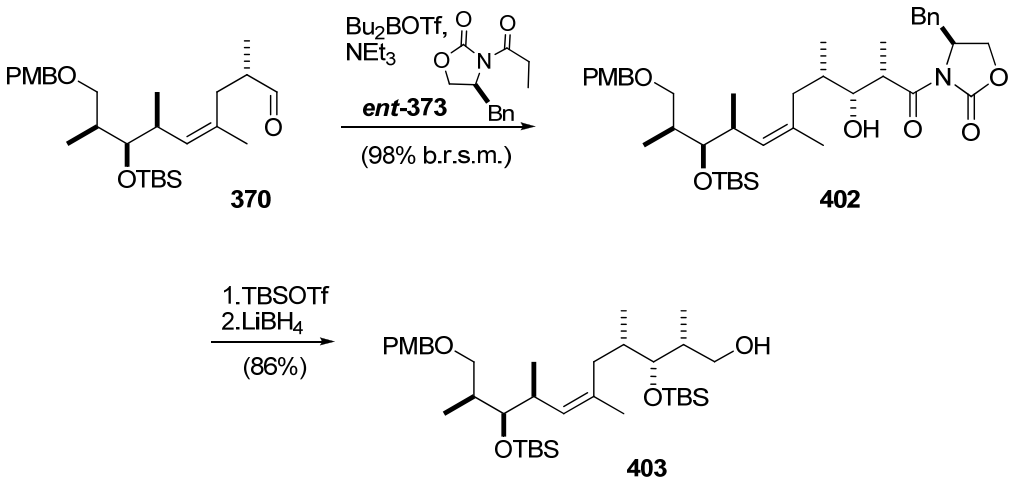
NOESY experiments confirmed the product of the aldol addition to feature the undesired *anti* arrangement between C17 and C18 (Scheme 141).



Scheme 141: Determination of the relative configuration between C17-C19 of **401**.

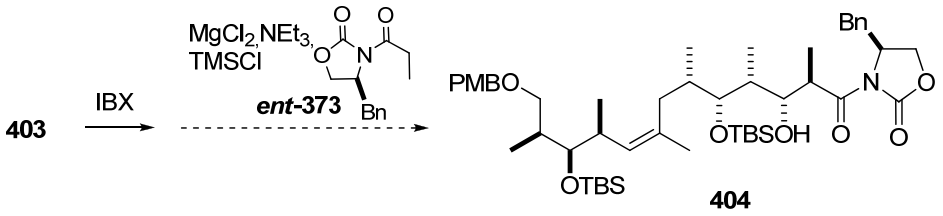
Stepwise elongation

Thus, the synthetic strategy was changed to a step wise installation of the C17-C20 stereocenters by reliable auxiliary chemistry. The first step was a classic *syn* selective Evans aldolization with oxazolidinone ***ent*-373**,[114] followed by protection of the generated alcohol as silyl ether and reductive removal of the auxiliary to generate alcohol **403** (Scheme 142).



Scheme 142: *Syn* selective Evans aldolization.

Then a second aldol addition should be perform, this time *anti* selective to install the missing C20 and C21 stereocenters in non-Evans *anti* product **404** (Scheme 143).[115] When the first few attempts appeared not to be successful, a simplified model substrate was prepared for further optimization.

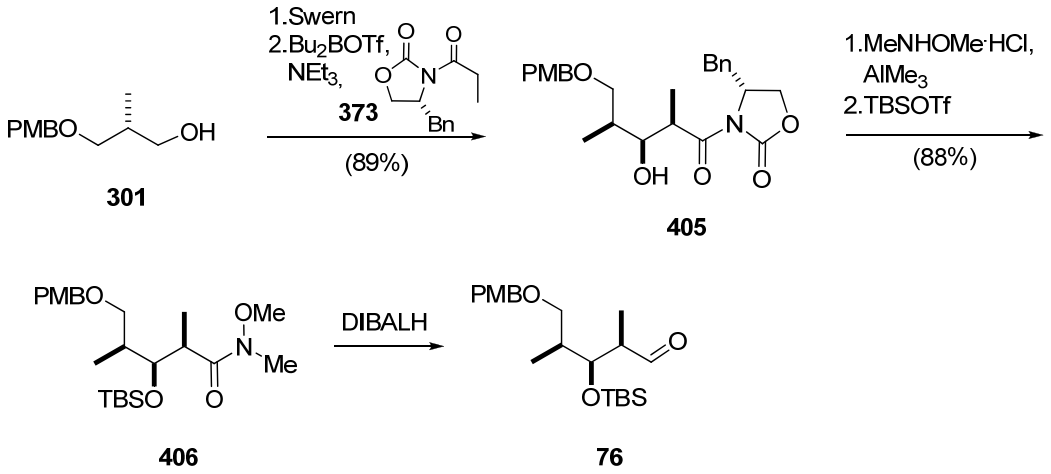


Scheme 143: Non-Evans *anti* aldol reaction.

Model substrate

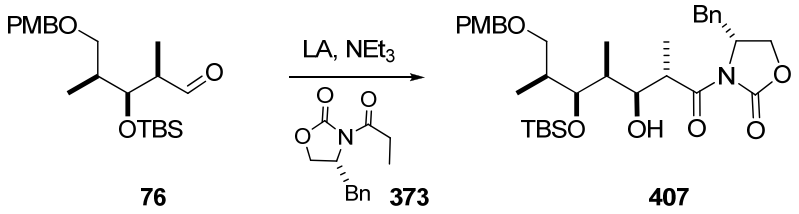
As model substrate stereotriade **76** was chosen, a common building block in many discodermolide syntheses, featuring a primary PMB ether, a secondary TBS group and the same relative configuration in *α*- and *β*-position of aldehyde **76** and **412** and thus able to

mimic the real substrate sufficiently well (Scheme 144). After oxidation of alcohol **301** to the corresponding aldehyde, *syn* selective aldolization with acylated Evans' auxiliary **373** gave aldol adduct **405**, which was converted into the Weinreb amide and the free hydroxyl group was protected as silyl ether **406**.[35] Aldehyde **76** can be easily gained by reduction with DIBALH.



Scheme 144: Synthesis of aldehyde **76** as model substrate.

Aldehyde **76** was now subjected to the non-Evans *anti* aldol reaction (Scheme 145) but despite many efforts an aldol adduct was observed only once alas with low yield and hardly any selectivity (Table 9).

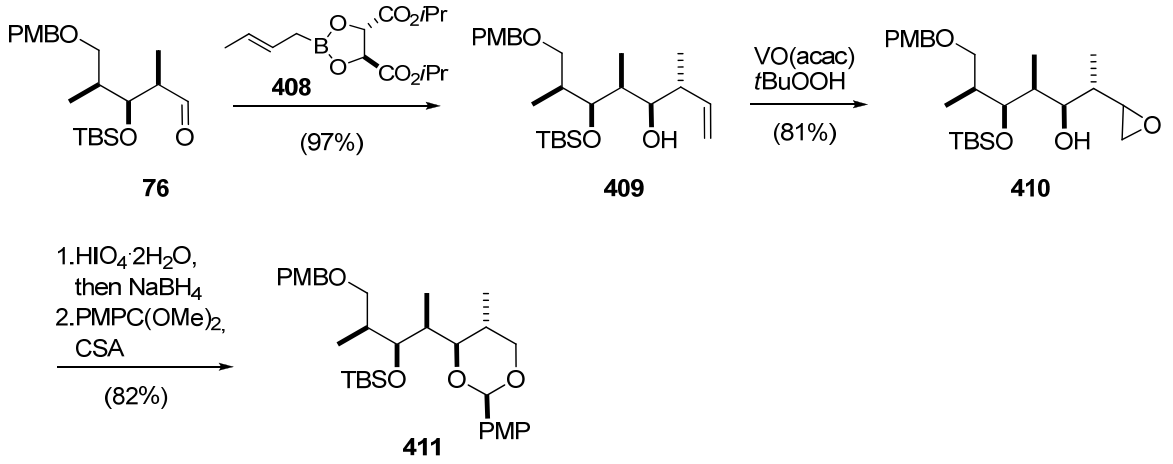


Scheme 145: Model substrate for non-Evans *anti* aldol reaction.

LA	eq.	additives	yield
$MgCl_2$	0.1 (in EtOAc)	TMSCl, $NaSbF_6$	63% sm
$MgCl_2$	0.1 (in THF)	TMSCl, $NaSbF_6$	50% sm
$MgCl_2$	0.2	TMSCl	52% sm
$MgCl_2$	2 + 20 eq. NEt_3	TMSCl	60% TMS enol ether of sm
$MgCl_2$	2 + 3 eq. NEt_3	TMSCl	35% 1:2 mix
Cy_2BCl	1.2	-	59% sm

Table 9: Conditions for non-Evans *anti* aldol reaction.

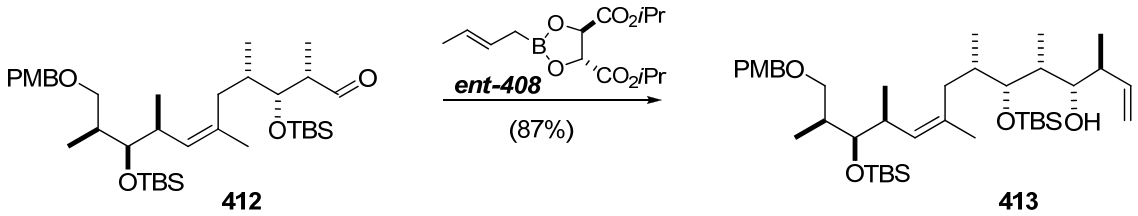
Thus, a new strategy for the missing two stereocenters at C19 and C20 was developed in form of a Roush crotylation which was first tested on model aldehyde **76** (Scheme 146).[116] A stock solution of (*S*,*S*)-diisopropyl tartrate (*E*)-crotylboronate (**408**) was prepared by deprotonation of *trans*-2-butene with Schlosser's base, formation of the boronate with triisopropylborate and followed by transesterification with (*S*,*S*)-diisopropyl tartrate. Treatment of aldehyde **76** with (*E*)-crotylboronate reagent **408** gave desired homoallylic alcohol **409** in excellent yield and selectivity over night. The terminal double bond was epoxidized under vanadium-catalysis. Here control of the reaction temperature is crucial to avoid oxidative cleavage of the PMB ether.[117] Now periodate cleavage of the epoxide moiety was directly followed by reduction of the generated aldehyde to the corresponding diol, which was easily converted into PMP acetal **411**.



Scheme 146: Roush crotylation of model aldehyde **76** and conversion into acetal **411**.

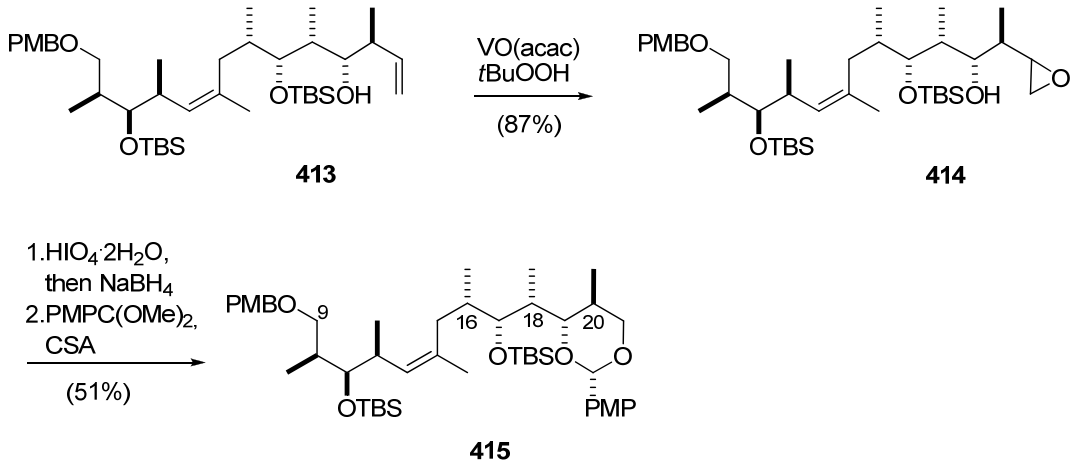
Smith's intermediate 415

Encouraged by this promising results the Roush crotylation was employed for the real system (Scheme 147). Thus, a stock solution of (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate (***ent*-408**) was prepared for the treatment of aldehyde **412** to generate desired allylic alcohol **413** in good yield and as a single diastereoisomer.



Scheme 147: Roush crotylation of the real system.

Regioselective epoxidation of the terminal homoallylic double bond was possible by vanadium-catalysis which yielded epoxide **414** in good yields without affecting the trisubstituted double bond. The following periodate cleavage of the epoxide moiety generated the corresponding aldehyde and was directly reduced to the diol. Its mediocre yields are not optimized. The diol was easily converted into PMP acetal **415** identical in every aspect with Smith's intermediate, thus finishing a second formal synthesis (Scheme 148).[35]



Scheme 148: Conversion of **413** into Smith's intermediate **415**.

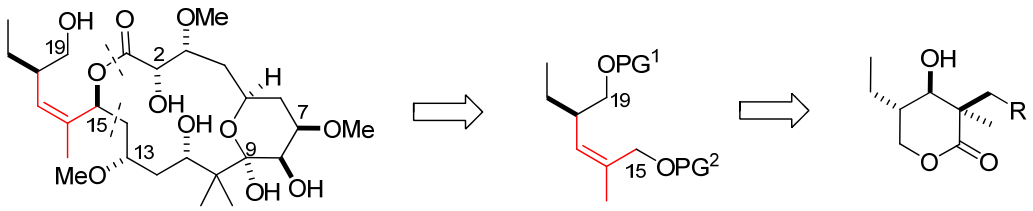
6.6. Summary – Discodermolide

The synthetic strategy to the discodermolide fragmentation precursor relied on an early introduction of the quaternary center. After investigation of several strategies, such as enzymatic desymmetrization, Tanaka's titanium mediated ring opening of epoxides or Braun's diastereoselective carboxalkylation of enolates with (-)-menthyl chloroformate (**322**), Yamamoto's organoaluminum-promoted rearrangement of TBS protected epoxy geraniol to aldehyde **339** proved to be the method of choice. A Paterson aldol addition generated the whole carbon skeleton of the fragmentation precursor and protecting group manipulations and oxidations led to *δ*-lacton **340**. The fragmentation reaction *via* the chair transition state furnished desired (*Z*)-olefin **341** in good yield and excellent selectivity. Esters **362** and **363**, both intermediates from Paterson's synthesis, were easily gained by oxidative cleavage of the terminal double bond, followed by esterification. Thus providing the first formal synthesis goal in 17 steps and 27% yield. Additionally, more highly advanced intermediate **415** from Smith's synthesis was generated by stepwise introduction of the five contiguous C16-C21 stereogenic centers when a more convergent approach failed due to a mismatched transition state in the aldol connection. Thus, the second formal synthesis goal was reached in 27 steps and 7.2% yield.

7. Results and Discussion - Peloruside A

7.1. Retrosynthetic Analysis

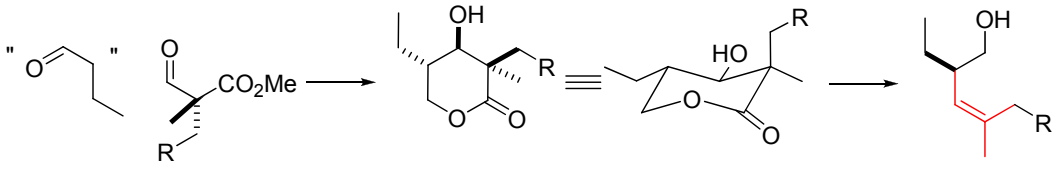
Peloruside A contains the trisubstituted (*Z*)-double bond between C16 and C17 in form of a methyl branched side chain. Thus, simple diol **416** featuring one stereogenic center and the trisubstituted (*Z*)-double bond was aimed for as formal synthesis goal (Scheme 149), which can be led back to *δ*-lactone **417** as fragmentation precursor.



2 **416** **417**

Scheme 149: Retrosynthethic analysis of peloruside A (**2**).

To synthesize *δ*-lactone **417** an aldehyde equivalent **418** and a 1,3-dicarbonyl compound **419** containing the quaternary stereocenter is required (Scheme 150). As fragmentation precursor the indicated configuration of *δ*-lactone **417** was chosen as the ethyl group in *γ*-position will be in equatorial position and thus make introduction of the mesyl group easier compared to the discodermolide precursor **340** with the axial *γ*-subsitutent.



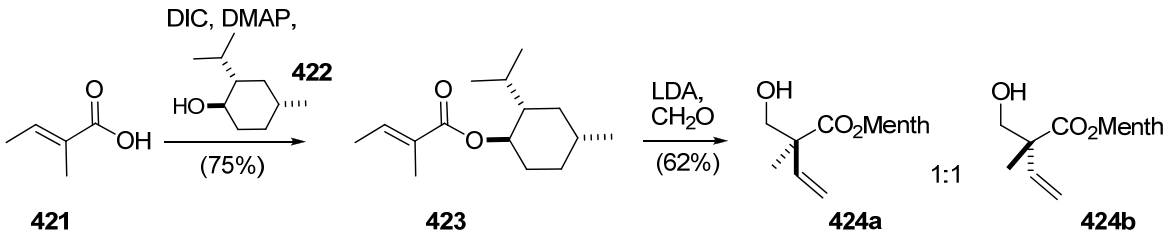
418 **419** **417** **417** **420**

Scheme 150: Synthetic strategy for peloruside A fragment **420**.

In following the synthetic approaches are mentioned depending on their strategy to introduce the stereogenic quaternary center.

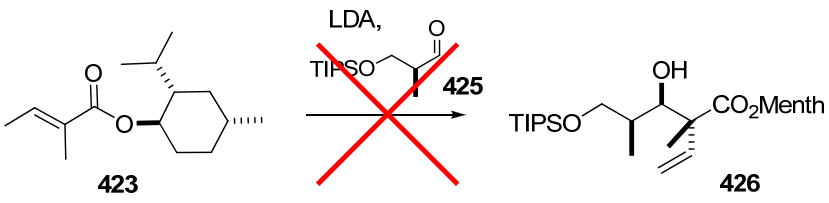
7.2. *α*-Alkylation of Menthyl Tiglate

A quaternary center containing a vinyl moiety can be gained by reaction of the lithium enolate of menthyl tiglate (**423**) with formaldehyde (Scheme 151).[118] In this case the menthyl group does not act as chiral auxiliary by inducing stereoselectivity as in Braun's generation of quaternary center (chapter 6.4.) but, as the authors claim, as an auxiliary to enable separation of the diastereomeric product mixture by chromatography. Thus, menthyl ester **423** was prepared under Steglich conditions in good yield and used in the following aldol addition. To accomplish acceptable yields paraformaldehyde had to be cracked thermally and introduced as gas into the reaction mixture containing the enolate at low temperatures. Unfortunately, separation of the diastereomeric product mixture is only possible by HPLC using chiral columns, which makes this strategy not viable due to the early stage where separation is necessary.



Scheme 151: Generation of the quaternary center.

Additionally, aldol addition with aldehyde **425** derived from (*S*)-Roche ester (***ent*-182**) was tested to gain aldol adduct **426** *via* a Felkin-Anh transition state in a hopefully double stereodifferentiating way. Regrettably, this reaction did not proceed at all presumably due to too much steric hindrance. When simple formylation with methyl formate was tested also no formylation product was observed.

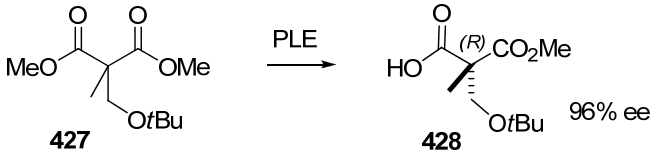


Scheme 152: Aldol addition of aldehyde **425** with menthyl ester **423**.

7.3. Enzymatic Desymmetrization with PLE

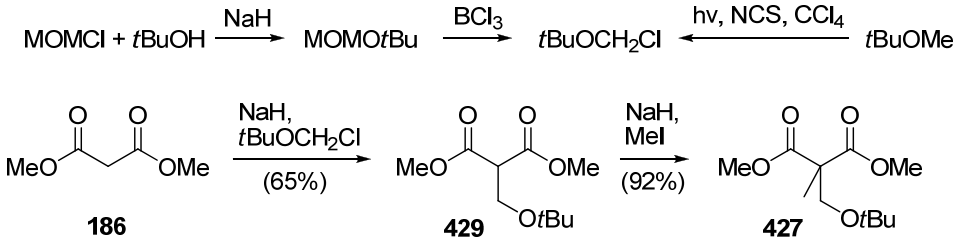
7.3.1. Quaternary Center by Desymmetrization

Mono acid **428** was known to be derived in excellent enantiomeric excess from incubation of *meso* malonate **427** with PLE (Scheme 153), which can be easily transformed into the corresponding aldehyde and used to build up the carbon skeleton of the fragmentation precursor in an aldol addition.[119]



Scheme 153: Known mono acid **428**.

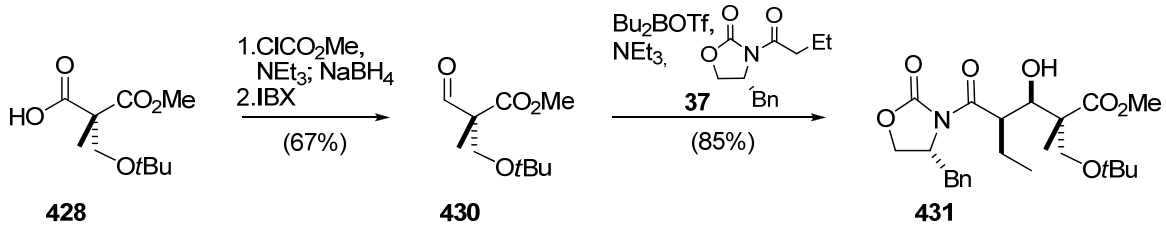
Thus, *meso* malonate **427** had to be prepared first and therefore *tert*-butyl chloromethyl ether was needed, which can be generated *via* free radical chlorination by irradiation of *tert*-butyl methyl ether with *N*-chlorosuccinimide or in a two step procedure *via* the *tert*-butyl methoxymethyl ether by cleavage with boron trichloride (Scheme 154).[120] Alkylation of dimethyl malonate **186** with *tert*-butyl chloromethyl ether gave malonate **429** in moderate yields and was followed by methylation to build up the quaternary center in malonate **427**. Enzymatic hydrolysis with PLE in aqueous buffer system to mono acid **428** worked smoothly and in excellent yield. Again it was observed that biphasic systems elongated the reaction times.



Scheme 154: Preparation of *meso* malonate **427**.

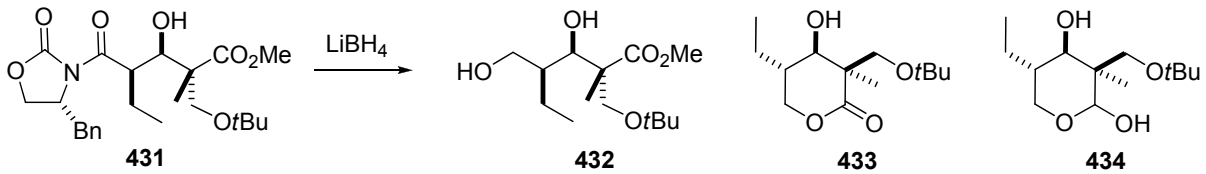
7.3.2. Fragmentation Precursor

The carboxylate was regioselectively reduced to the alcohol in the already known two step sequence *via* the mixed anhydride and oxidized to aldehyde **430** with IBX. To build up the complete carbon skeleton of the fragmentation precursor a *syn* selective Evans aldol reaction was designated (Scheme 155). Thus, Evans' auxiliary **372** was acylated with butyryl chloride to provide **37**, which was treated with freshly prepared dibutylboron triflate to generate the (*Z*)-enolate for the aldol addition with aldehyde **430**. Aldol adduct **431** could be gained in good yield as a single diastereoisomer despite a possible sterical clash between the alkyl group of the enolate and the bulky *α*-substituents of the aldehyde.[121, 122] The most crucial parameter was the concentration, as conversion stopped early in diluted reaction mixtures. Furthermore, freshly prepared dibutylboron triflate was essential as with aged stock solutions product mixtures were observed.



Scheme 155: *Syn* selective Evans aldol addition.

The reductive removal of the auxiliary turned out to be tricky as free diol **432** was prone to cyclize to lactone **433** which is then reduced by excess lithium boronhydride to lactol **434** (Scheme 156, Table 10). Lactone **433** and lactol **434** are inseparable by column chromatography. Lactol **434** can be reoxidized with manganese oxide in DCM in a very mild and selective way to lactone **433** without affecting the *β*-hydroxyl group, a huge excess of activated oxidants and long reaction times in the range of days are needed.

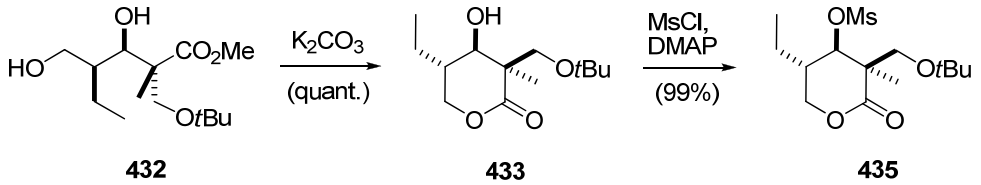


Scheme 156: Reductive removal of the auxiliary.

eq. ($LiBH_4$)	T	rxn time	solvent	products
2	-20 °C	3 h	Et_2O, 0.25% MeOH	21% **432**
1.5	-20 °C	4 h	Et_2O, 0.5% MeOH	28% **432**; 29% **434**
1.5	-20 °C	3 h	Et_2O, 0.5% H_2O	decomposition
1.5	-20 °C	3 h	THF	no rxn
1.3	-10 °C	0.5 h	Et_2O, 2% MeOH	66% **432**
1	0 °C	0.5 h	Et_2O, 2% MeOH	25% **432**, 27% **434**
1	0 °C	0.5 h	Et_2O, 1% MeOH	56% **432**, 12% **434**
1	0 °C	0.5 h	Et_2O, 0.5% MeOH	80% **432**
0.75	0 °C	0.5 h	Et_2O, 2% MeOH	26% **432**, 27% **434**, 25% **431**

Table 10: Conditions for reductive removal of the auxiliary.

Treatment of dihydroxy ester **432** with potassium carbonate in methanol gave desired *δ*-lactone **433** in quantitative yield, other bases such as lithium hydroxide in THF worked as well but in significantly lower yield. Introduction of the mesylate as leaving group was accomplished in almost quantitative yield with DMAP as additive (Scheme 157).

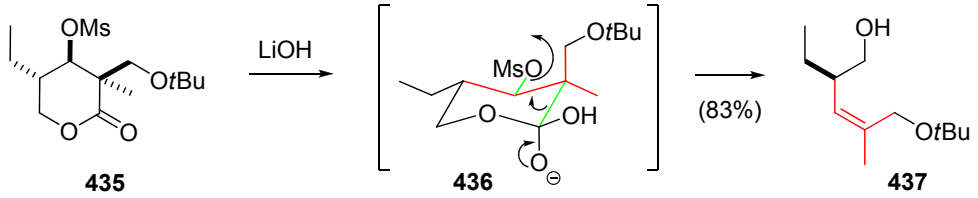


432 **433** **435**

Scheme 157: Synthesis of the fragmentation precursor **435**.

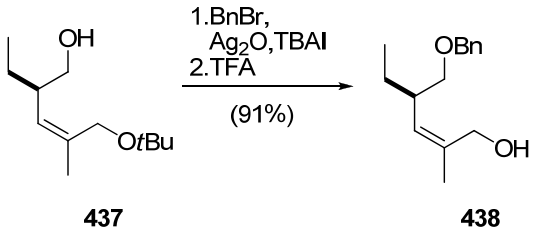
7.3.3. Fragmentation

The fragmentation reaction worked smoothly *via* the chair transition state to give desired (*Z*)-olefin **437** in high yields and as a single diastereoisomer (Scheme 158). Special attention had to be paid to the work up as homoallylic alcohol **437** is volatile.



Scheme 158: Fragmentation reaction.

To intercept a formal synthesis intermediate a protecting group change was necessary. Thus, the free alcohol was protected as TIPS ether and then the *tert*-butyl ether had to be cleaved selectively. Unfortunately, all attempts regenerated **437** or cleaved both ethers. Therefore benzyl was used as protecting group which could be installed by silver mediation in benzyl bromide as solvent.[123] Catalytic amounts of TFA yielded monoprotected diol **438** an intermediate form Gosh's synthesis (Scheme 159).[124]



Scheme 159: Protecting group manipulations.

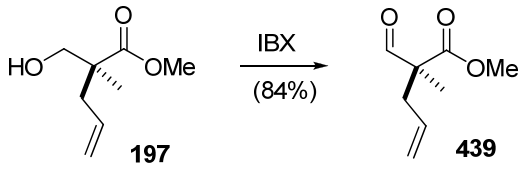
7.4. Summary – Peloruside A

For the generation of the simple peloruside A intermediate **438** from Ghosh's synthesis enzymatic desymmetrization was used again to install the quaternary center. Evans aldolization set the remaining stereocenters and built up the fragmentation precursor. Hydroxide induced fragmentation *via* the chair transition state provided desired (*Z*)-olefin **437**. Now only a change of protecting groups was necessary to finish the formal synthesis in 10 steps and 34% yield.

8. Results and Discussion - Nucleophile Additions to an Aldehyde with Quaternary *α*-Center

Due to the unanticipated behavior of aldehyde **212** in the aldol addition to generate the fragmentation precursor for epothilone B, the nucleophile addition to this kind of aldehydes with quaternary *α*-centers, where one of the substituents is an ester functionality, was investigated.

Thus, aldehyde **439** was generated as substrate from alcohol **197** by oxidation with IBX (Scheme 160).

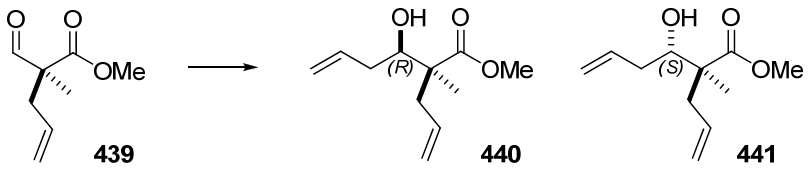


Scheme 160: Aldehyde **439** with quaternary *α*-center.

8.1. Allylation

8.1.1. Allylation with Chiral Allyl Reagents

The allylation methods developed by Roush and Brown use modified allyboronates featuring either enantiomerically pure tartrate or isopinocampheyl esters which are broadly used for the diastereo- and enantioselective addition to aldehydes.[125-127] Thus, the chiral allylboronates were prepared and used for the allyl addition to aldehyde **439** (Scheme 161). In general generation of the (*R*)-configured newly formed stereocenter was expected to be favored from experience with the aldol addition in the fragmentation precursor synthesis.



Scheme 161: Roush and Brown allylation of aldehyde **439**.

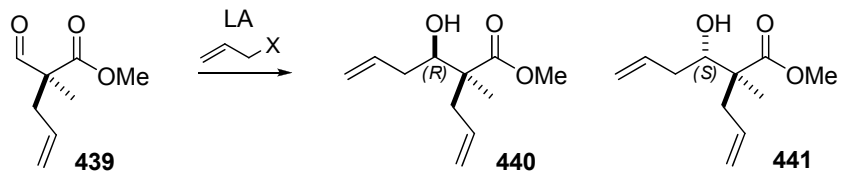
All allylation reactions were found to give as major diastereoisomer **440** in (*R*)-configuration (Table 11). This means that with aldehyde **439** substrate control completely overruled the reagent control of the reaction. When both, the substrate and reagent control, induced (*R*)-configuration yields and diastereomeric ratios were excellent. Only in the mismatched cases the diastereomeric ratio dropped still favoring product **440** as major diastereoisomer, despite reagent control for **441** and hence the (*S*)-configuration.

reagent (ligand)	yield	440:441
(-)-*i*Pc	51%	3:1
(+)-*i*Pc	quant.	20:1
L-(+)-DIPT	69%	8:1
D-(-)-DIPT	60%	20:1

Table 11: Roush and Brown allylation of aldehyde **439**.

8.1.2. Allylation with Achiral Allyl Reagents

The results of investigating the Sakurai reaction were exactly as described in all textbooks: the boron Lewis acid reacted *via* the open transition state to generate exclusively Felkin-Anh product **440**, whereas titanium tetrachloride induced the chelated transition state which led to (*S*)-product **441**.[128, 129] With allystannane and chelating Lewis acids (*S*)-product **441** was found again as the major product however in a lower diastereomeric ratio (Scheme 162, Table 12).

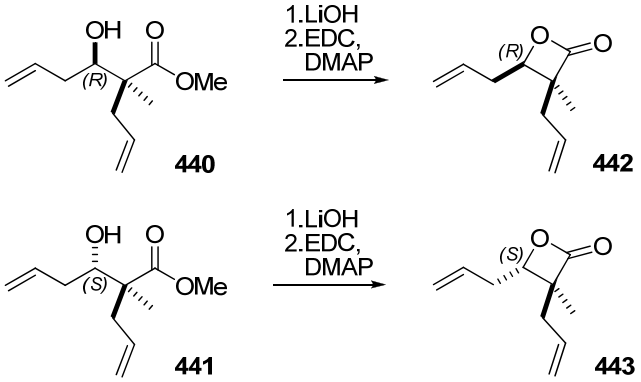


Scheme 162: Allyl addition to aldehyde **439**.

LA	T	X	yield	440:441
$BF_3{\cdot}Et_2O$	-78 °C	TMS	84%	**440**
$TiCl_4$	-78 °C	TMS	85%	**441**
$TiCl_4$	-78 °C	$SnBu_3$	quant.	1:2
$MgBr_2{\cdot}Et_2O$	r.t.	$SnBu_3$	87%	1:7

Table 12: Allyl addition to aldehyde **439**.

To prove the configuration of the newly formed stereogenic homoallyl centers, the hydroxy esters **440** and **441** were converted into the corresponding *β*-lactones **442** and **443** (Scheme 163) by saponification and esterification under carboxylate activation to retain the configuration of the *β*-position. NOE experiments confirmed the relative configuration between *α*- and *β*-position.



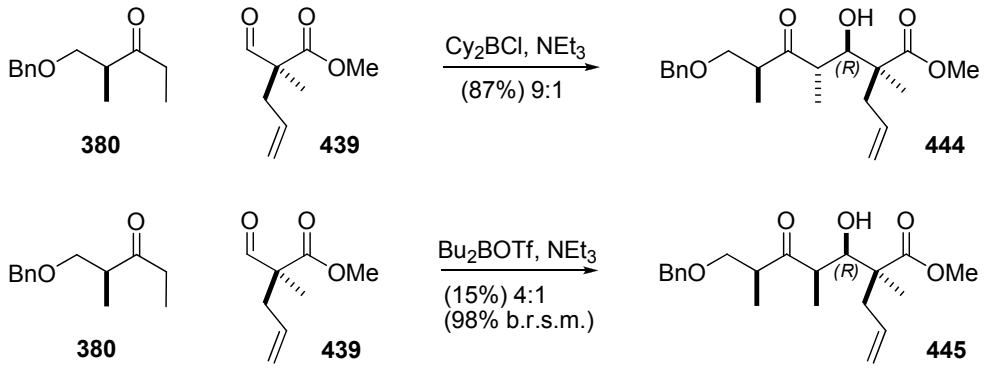
Scheme 163: Transformation into the *β*-lactones.

8.2. Aldol Additions

Next aldol additions were tested; here different ways of controlling the stereochemical outcome on the one hand from the aldehyde and on the other hand from the enol compound were investigated.

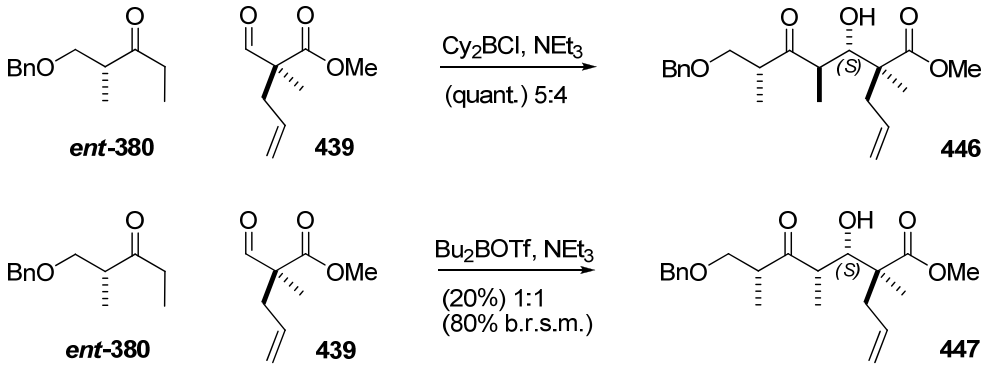
8.2.1. Boron Enolates[96]

In the Paterson aldol addition the stereocontrol comes from the methyl center of the ethyl ketone and the enolate geometry. Thus with ethyl ketone **380** in the *anti-anti*-selective as well as in the *syn-syn*-selective reaction the newly formed hydroxyl center has (*R*)-configuration, which is the matched double-stereodifferentiating case in accordance with substrate control from aldehyde **439** (Scheme 164). This was also found in the products, as there was in general a good diastereomeric ratio.



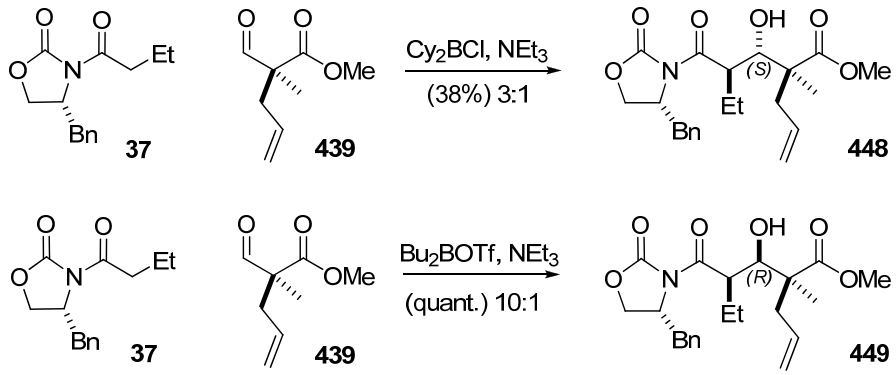
Scheme 164: Matched boron mediated aldol additions.

When ethyl ketone ***ent*-380** was used, the stereocontrol from the borone enolate induces the (*S*)-configuration, which is the unfavored outcome concerning the aldehyde. This mismatched constellation was clearly represented in the 1:1 diastereoisomeric mixture of the products (Scheme 165).



Scheme 165: Mismatched boron mediated aldol additions.

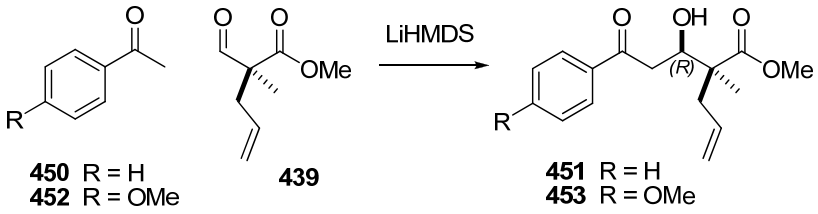
The aldol additions with acylated Evans' auxiliary **37** as enol compound further confirmed the above mentioned results. In the *syn*-selective aldol reaction, the matched case, product **449** with (*R*)-configuration of the newly formed hydroxyl group was obtained in a good diastereomeric ratio. Whereas the *anti*-selective Evans aldolization would lead to the (*S*)-configuration in product **448**, which is the mismatched configuration concerning the aldehyde compound, represented by a low diastereomeric ratio (Scheme 166).



Scheme 166: Evans aldol additions.

8.2.2. Lithium Enolates

Aldol addition between aldehyde **439** and the lithium enolates of methyl ketone **450** and **452**, very similar to the one already described in the epothilone precursor synthesis, was investigated (Scheme 167, Table 13). Here the (*R*)-configured product was the only product found. Despite the use of chelating Lewis acids only reactions *via* a Felkin-Anh transition state were observed.



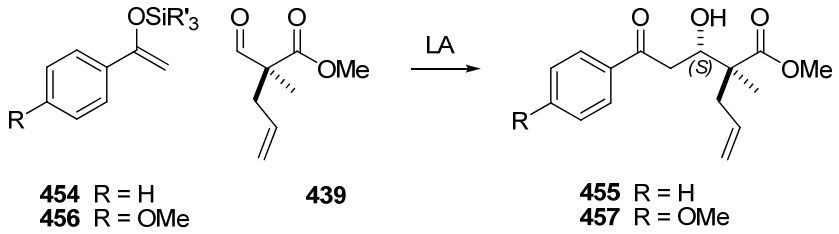
Scheme 167: Aldol addition with lithium enolates.

R	LA	yield
H	$MgBr_2 \cdot Et_2O$	91%
H	$TiCl_4$	no rxn
H	-	97%
OMe	$MgBr_2 \cdot Et_2O$	71%
OMe	$TiCl_4$	no rxn
OMe	-	72%

Table 13: Aldol addition with lithium enolates.

8.2.3. Mukaiyama Aldol reaction

Mukaiyama aldol reactions between various silyl enol ethers of methyl ketones **450** and **452** with aldehyde **439** were investigated (Scheme 168, Table 14). The *tert*-butyldimethyl silyl enol ethers proved to be very stable and induction of the reaction was only possible with the very strong Lewis acid titanium tetrachloride. The same was observed for the trimethyl silyl enol ethers. Selectivity of the reactions was excellent, as only a single product, the (*S*)-configured Cram chelate product was observed. However yields were low to moderate and dropped with longer reaction times.



454 R = H
456 R = OMe

439

455 R = H
457 R = OMe

Scheme 168: Mukaiyama aldol addition.

R	LA	SiR'_3	yield
H	$MgBr_2 \cdot Et_2O$	TBS	no rxn
H	$TiCl_4$	TBS	35%
H	$SnCl_4$	TBS	no rxn
H	$MgBr_2 \cdot Et_2O$	TMS	no rxn
H	$SnCl_4$	TMS	no rxn
H	$TiCl_4$	TMS	42% (1 h), 34% (2.5 h)
OMe	$TiCl_4$	TMS	59%

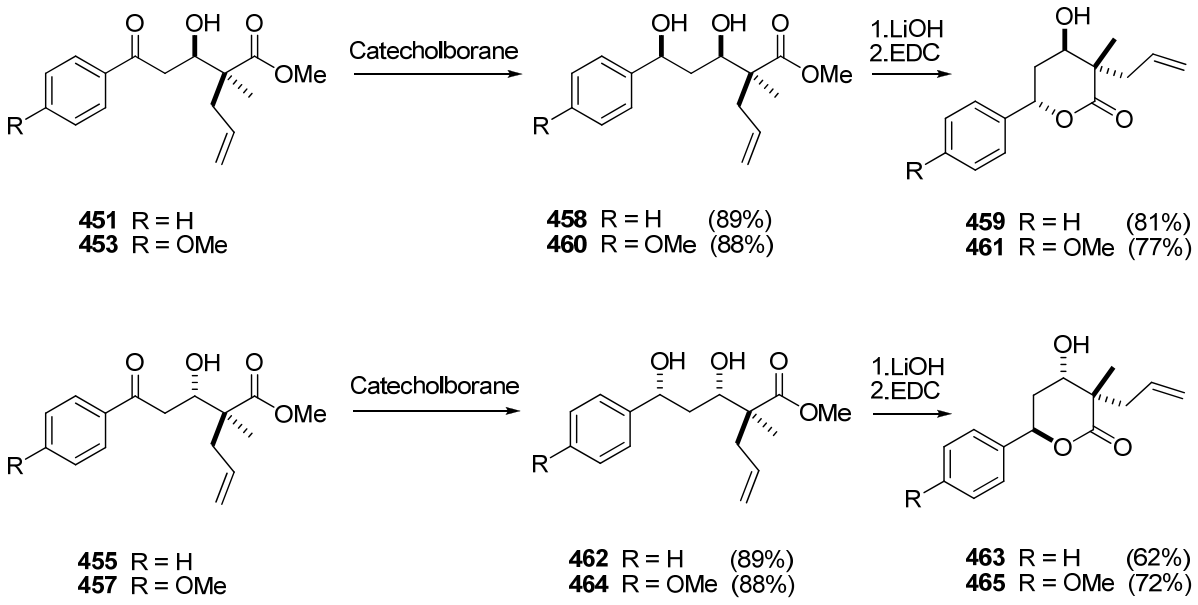
Table 14: Mukaiyama aldol addition.

8.3. Fragmentations

8.3.1. Fragmentation Precursors

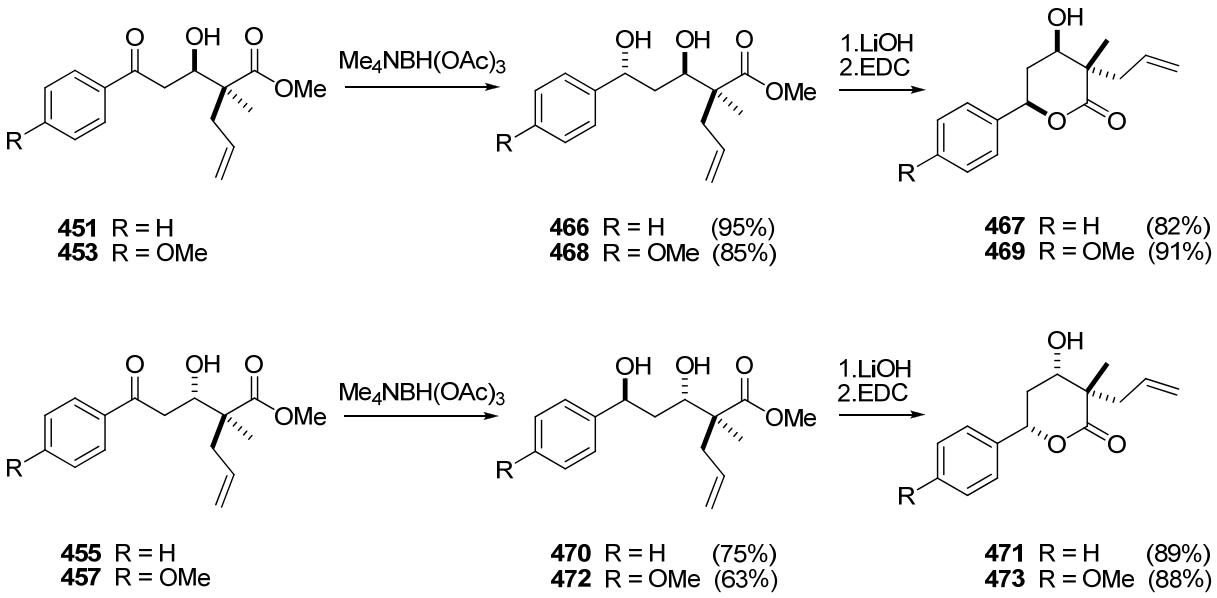
To prove the relative configuration between *α*- and *β*-center of the adducts gained in the aldol additions, the corresponding *δ*-lactones were prepared and NOE experiments verified the before assumed stereochemical arrangement.

Thus, all four diastereoisomers were reduced to the *syn* diols with catecholborane and saponification with lithium hydroxide in THF was followed by EDC mediated cyclization to the *δ*-lactones (Scheme 169).



Scheme 169: Fragmentation precursors from *syn* dihydroxy esters.

Evans-Carreira *anti*-reduction of the four diastereoisomers led to the *anti* diols and was followed by saponification with lithium hydroxide and cyclization to the *δ*-lactones (Scheme 170).

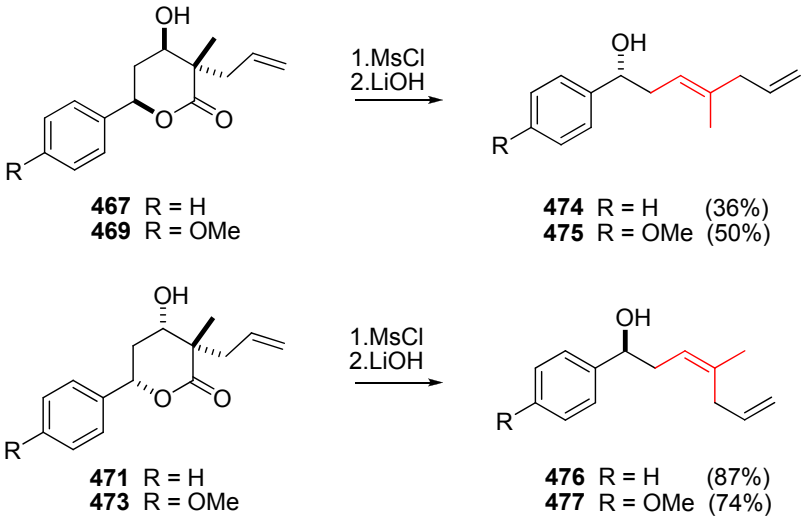


Scheme 170: Fragmentation precursors from *anti* dihydroxy esters.

8.3.2. Fragmentations

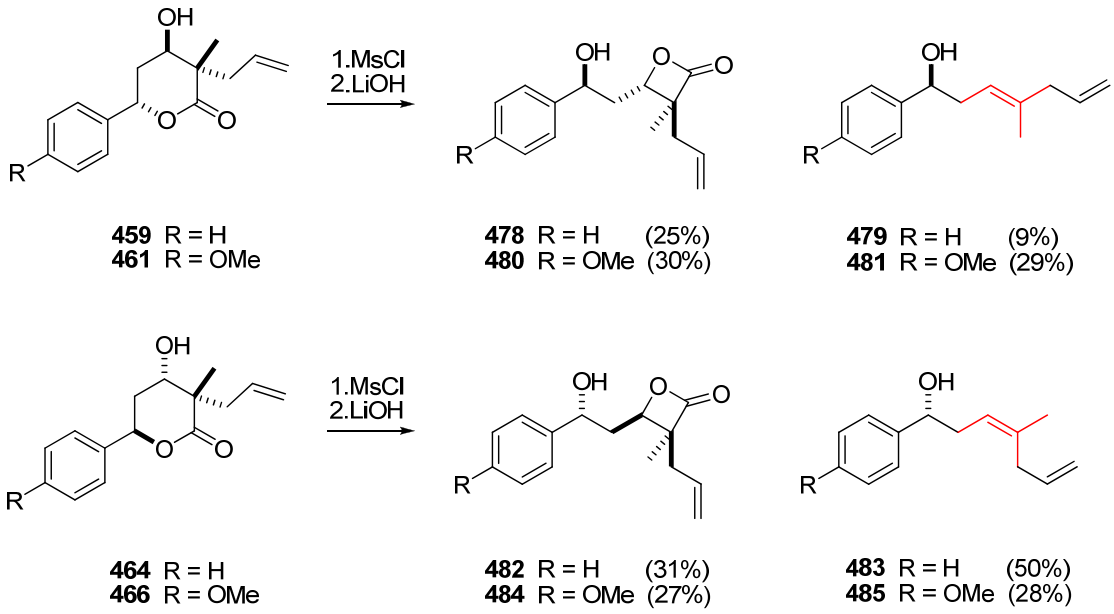
With the *δ*-lactones in hand installation of a mesylate as leaving group gave the fragmentation precursors, which were tested under fragmentation conditions.

The fragmentation precursors derived from the *anti* diols fulfill all stereochemical requirements for the fragmentation *via* the chair transition state and thus gave smoothly only the olefins (Scheme 171).



Scheme 171: Fragmentation *via* the chair transition state.

On the other hand, the fragmentation precursors derived from the *syn* diols have the leaving group in the axial position and thus make fragmentation *via* the chair transition state stereochemically impossible. However, fragmentation occurred again, presumably *via* the open carboxylate to form the olefin and *β*-lactone from S_N2 attack of the carboxylate on the leaving group, respectively (Scheme 172).



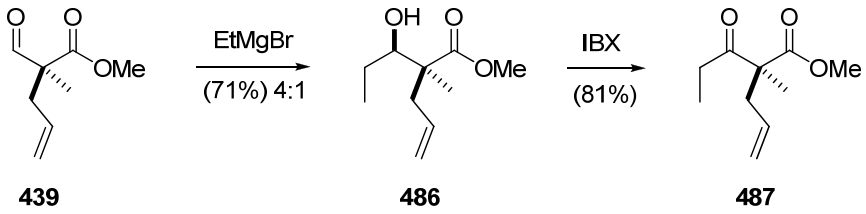
Scheme 172: Fragmentation *via* an open transition state.

It was observed that fragmentation precursors with all large substituents in equatorial position gave lower yields in the fragmentation reaction whereas when the allyl moiety was axial better yields were obtained. This might be due to saponification as side reaction

notwithstanding a dihydroxy acid was never isolated. As this is a very hydrophilic compound, this is not further surprising. With the allyl moiety in axial position the strain might be bigger and thus fragmentation might occur faster, suppressing side reactions.

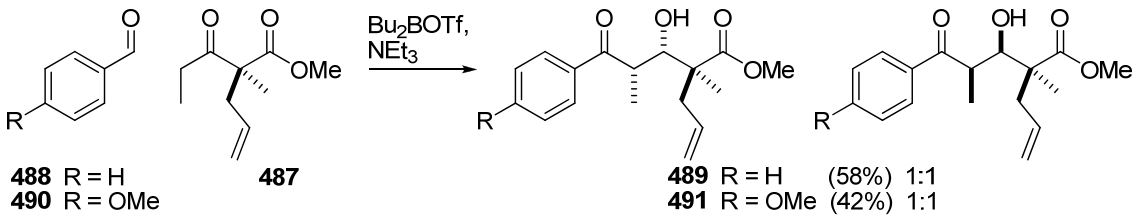
8.4. Aldol Addition of an Ethyl Ketone featuring a Quaternary *α*-Center

To further probe the influence of a quaternary *α*-center in aldol reaction, the connectivity was reversed. Thus, ethyl ketone **487** was prepared starting from known aldehyde **439** to give after Gringard addition secondary alcohol **486** in a 4:1 diastereomeric ratio, which was further oxidized to ethyl ketone **487** with IBX (Scheme 173).



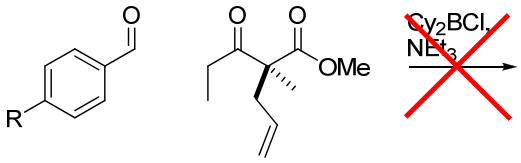
Scheme 173: Preparation of ethyl ketone **487**.

When ethyl ketone **487** was converted into the (*Z*)-enolate and treated with aromatic aldehyde **488** and **490** a 1:1 diastereomeric mixture of *syn*-aldol adducts was generated (Scheme 174). This implies that a quaternary *α*-center is not able to induce stereoselectivity in contrast to tertiary centers like the often used chiral *α*-methyl groups for the Paterson aldol addition demonstrates.



Scheme 174: Aldol addition of (Z)-boron enolates.

The aldol addition *via* the (*E*)-boron enolate was also attempted but did not give any results (Scheme 175).



488 R = H
490 R = OMe

487

Scheme 175: Aldol addition of (*E*)-boron enolates.

8.5. Summary - Nucleophile Additions

In the allylation of aldehyde **439** the stereochemical outcome correlated with the nature of the Lewis acid, giving the Cram chelate product with $TiCl_4$, $SnCl_4$ and $MgBr_2{\cdot}Et_2O$ and the Felkin-Anh product with $BF_3{\cdot}Et_2O$. When Brown or Roush allylation protocols were tested, substrate control overruled the reagent control and the chiral ligands were only able to modify this basic trend. This behavior was also observed in the Paterson aldol additions giving in the matched cases good to acceptable selectivity and in the mismatched cases 1:1 mixtures. The aldol additions of aldehyde **439** and the lithium enolates of methyl ketone gave in excellent selectivity always the Felkin-Anh adduct through substrate control. Whereas in Mukaiyama aldol reaction with chelating Lewis acids the Cram chelate products were isolated, although in moderate to low yields but in excellent selectivity. Conversion of the aldol adducts into the *δ*-lactones provided new fragmentation precursors which were tested under fragmentation conditions. The *δ*-lactones derived from the *anti* dihydroxy esters fulfill all stereochemical requirements for the fragmentation *via* the chair transition state and gave smoothly only the olefins. Whereas the *δ*-lactones derived from the *syn* dihydroxy esters reacted presumably *via* the open carboxylate and both olefin and *β*-lactone were obtained.

9. Conclusion and Outlook

The aim of this Ph.D. research was to establish a new hydroxide induced Grob-type fragmentation as methodology for the generation of methyl branched trisubstituted (*Z*)-olefins. Therefore, three formal syntheses with the fragmentation as olefination step were developed. Thus, *β*-mesyloxy lactones with three stereogenic centers, one of them quaternary, had to be prepared.

In the epothilone B synthesis two different strategies where developed one relying on the introduction of the quaternary center at an early stage and using this as relay to establish the remaining stereocenters and the other generated the quaternary center by *α*-allylation of *β*-keto lactone **262** (chapter 5). As the introduction of the quaternary center at the beginning of the synthesis proved more reliable, the formal synthesis of discodermolide (chapter 6) and peloruside A (chapter 7) employed this strategy. As means of enantioselective generation of the quaternary centers on the one hand enzymatic desymmetrization of *meso* malonates **193** and **427** was used and on the other hand organoaluminum-promoted rearrangement of chiral epoxide **342**. All fragmentation precursors were built up by aldol strategy. Fragmentation worked in all cases smoothly giving the desired (*Z*)-olefins in high yield and excellent selectivity. The olefin geometry was determined by the relative configuration between *α*- and *β*-center.

The scope of the fragmentation was tested by using different diastereomeric *δ*-lactones and acyclic fragmentation precursors (chapter 5 and 8). As general trend *δ*-lactones derived from the *anti* dihydroxy esters fulfill all stereochemical requirements for the fragmentation *via* the chair transition state and gave smoothly only the olefins. Whereas the *δ*-lactones derived from the *syn* dihydroxy esters reacted presumably *via* the open carboxylate to give the olefin and *β*-lactones from S_N2 attack of the carboxylate on the *β*-position. As thermolysis of the *β*-lactones generated additional amounts of the olefin a uniform product was obtained in both cases in excellent selectivity and good yields. For open chain fragmentation precursor **251** steric hindrance by the quaternary center was observed which had to be evaded by fragmentation of corresponding aldehyde **254**.

Based on the unusual behavior of aldehyde **212** nucleophilic additions to aldehyde **439** with quaternary *α*-center were briefly investigated. The results led to the conclusion that with this kind of 1,3-dicarbonyl compounds substrate control overrules reagent control in case of Brown or Roush allylation; whereas allylation with achiral reagents is predictable according to the nature of the Lewis acid. In boron aldol additions the induction from the enol compound is not sufficient. Chelation in aldol additions is only possible with very strong Lewis acids.

The hydroxide induced Grob-type fragmentation presents a versatile tool for the stereoselective synthesis of trisubstituted double bonds. The fragmentation is easy to perform, works very fast and the conditions are compatible with nearly all functional groups. The different substituents on the fragmentation precursors can be freely selected to give a broad range of olefins which can be transformed further into interesting synthetic intermediates.

To extend the scope of this method even further, it would be interesting to investigate fragmentation precursors with two elaborated *α*-substituents, to generate more complex trisubstituted olefins. The introduction of a second *β*-substituent, thereby generating two vicinal quaternary centers, to gain tetrasubstituted olefins would be a great challenge. Additionally more nucleophiles, different from hydroxide or carbon nucleophiles, to induce the fragmentation could be tested.

10. Experimental Section

10.1. General Experimental

Synthetic Methods

The following general procedures were used in all reactions unless otherwise noted. Reaction vessels were dried by repeated heating under vacuum (heat gun) followed by purging with dry argon. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure (balloon) and in dry solvents. Sensitive liquids and solutions were transferred by double tipped needle or syringe through rubber septa. All reactions were stirred magnetically. Solvents for palladium catalysed coupling reactions, cross metathesis and aluminium promoted rearrangement were degassed by “pump-freeze-thaw” method.

Solvents

All solvents (hexane, ethyl acetate, dichloromethane, diethyl ether) were distilled prior to use. Anhydrous solvents were stored under argon over molecular sieve (4 Å). Diethyl ether and tetrahydrofuran was distilled from sodium/benzophenone, toluene from sodium. Dichloromethane and acetone were dried over phosphorpentoxide. Acetonitrile, diisopropylamine, dimethylformamide, 2,6-lutidine and triethylamine were distilled from calcium hydride. Methanol was refluxed over magnesium filings for several hours and then distilled. Pyridine was distilled from potassium hydroxide. All other solvents were HPLC grade.

Chemicals

All commercially available reagents were used without further purification unless stated otherwise.

Chromatography

Thin-layer chromatography (TLC)

All reactions were monitored using Merck silica gel 60 F_{254} plates. UV active spots were detected at longwave UV (254 nm) and shortwave UV (180 nm). For visualizing the following reagents were use: *Anisaldehyde* [anisaldehyde (6 g) in ethanol (250 mL) and conc. H_2SO_4 (25 mL)], *Ceric(IV) sulfate* [$Ce(SO_4)_2$ (0.1 g), phosphormolybdic acid (20 g) in H_2SO_4 (10%, 400 mL)], *Vanilline* [vanilline (0.5 g) in ethanol (20 mL) and H_2SO_4 (15%, 80 mL)].

Column Chromatography

Preparative column chromatography was performed with silica gel 60 from Merck (0.040 - 0.063 µm, 240 - 400 mesh).

Analytic and preparative HPLC

For the determination of diastereomeric ratios in analytic scale a *Jasco* System (PU-980 pump, UV-975 UV detector, RI-930 RI detector) with a Nucleosil 50 column (5 µm, 4 mm x 241 mm) at ambient temperature was used. Preparative HPLC was preformed on a *Dynamix* System (SD-1 pump, UV-1 UV-detector (λ = 254 nm)) using a *Supersphere* 60 Si column (4 µm, 25 mm x 250 mm, Merck) at ambient temperature.

Spectroscopy

NMR Spectroscopy

NMR spectra were recorded on either a Bruker Avance DPX 250 MHz, a Bruker Avance DPX 400 MHz or a Bruker Avance DPX 600 MHz spectrometer, measured unless otherwise stated in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (δ_H = 7.26, δ_C = 77.00). All chemical shifts are given in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad) and all coupling constants *J* are given in Hz. Assignment of proton resonances were confirmed, when possible, by correlation spectroscopy.

Mass Spectroscopy

Mass spectra were measured on a *Micro Mass*, *Trio200 Fisions Instrument*. High resolution mass spectra (HRMS) were preformed with a *Finnigan* Mat 8230, with a resolution of 10000.

Infrared Spectroscopy

IR spectra were recorded as thin film on a silicon plate with a *Perkin-Elmer* 1600 FT-IR spectrometer.

Polarimetry

Optical rotations were measured on a P 341 *Perkin-Elmer* polarimeter in a 10 cm cell at 20 °C with 589 nm wavelength. The concentration *c* is given in g/100 mL.

$$[\alpha]_D^{20} = \frac{\alpha_{measured}}{d} \cdot \frac{100}{c}$$

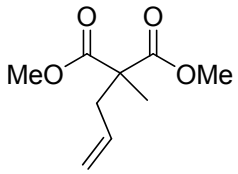
Melting points

Melting points (mp) were determined on a *Leica* Galen III apparatus and are uncorrected.

10.2. Experimental Procedures

10.2.1. Epothilone B: Pig Liver Esterase Route

2-Allyl-2-methyl-malonic acid dimethyl ester (193)



Malonate **192** (1.20 g, 69.60 mmol) in THF (50 mL) was added to a stirred suspension of NaH (3.05 g, 60% dispersion in mineral oil, 76.56 mmol) in THF (150 mL) at 0 °C and stirring was continued for 1 h. MeI (8.3 mL, 139.20 mmol) was added and the mixture warmed to r.t. over night. The reaction was quenched with saturated NH_4Cl solution, layers were separated and the aqueous solution was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (hexane:EtOAc = 5:1) to yield 1.20 g (93%) of **193** as pale yellow oil.

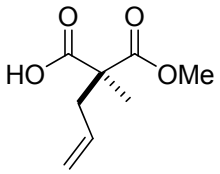
$\mathbf{R_f}$ = 0.64 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.74-5.63 (m, 1H), 5.12-5.08 (m, 2H), 3.72 (s, 6H), 2.61 (d, *J* = 7.36 Hz, 2H), 1.40 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.3, 132.5, 119.1, 53.6, 52.4, 40.2, 19.8.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_9H_{14}O_4$: 186.0892, found: 186.0888.

(*S*)-2-Allyl-2-methyl-malonic acid monomethyl ester (194)



To malonate **193** (3.00 g, 16 mmol) suspended in 0.05M KH_2PO_4 buffer (50 mL) at pH 7 was added PLE and *via* a pH-stat-controlled burette 0.5M NaOH (32 mL) was added over 48 h. After addition was completed, 1N NaOH was added to the mixture to reach pH 10 and by-products were removed with Et_2O. Upon acidification with 3N HCl to pH 1 mono acid **194**

was extracted with DCM, the organic layers were dried over $MgSO_4$ and the solvent was evaporated. For analytical purposes a sample was purified by column chromatography (hexane:EtOAc = 3:1 to 1:1) giving 2.48 g (90%) of mono acid **194**.

R_f = 0.08 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.76-5.66 (m, 1H), 5.15-5.11 (m, 2H), 3.75 (s, 3H), 2.66 (dd, *J* = 14.12, 7.40 Hz, 1H), 2.60 (dd, *J* = 14.10, 7.40 Hz, 1H), 1.44 (s, 3H).

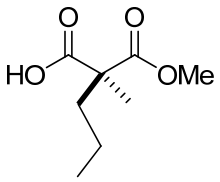
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 172.3, 132.2, 119.5, 53.5, 52.7, 40.2, 19.9.

IR (film): 2076, 1716, 1642, 1231, 1068 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_8H_{12}O_4$: 172.0736, found: 172.0734.

$[\alpha]_D^{20}$ 1.32 (*c* = 2.8, $CHCl_3$)

(*S*)-2-Methyl-2-propyl-malonic acid monomethyl ester (195)



Mono acid **194** (50 mg, 0.29 mmol) and Pd/C (10 mg, 5%) in ethyl acetate (2 mL) were stirred for 2 h under hydrogen atmosphere. The catalyst was filtered off over celite and the solvent was removed to yield 49 mg (98%) of hydrogenation product **195** as colorless oil.

R_f = 0.09 (hexane:EtOAc = 1:1)

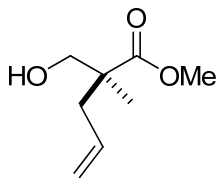
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 1.93-1.80 (m, 2H), 1.46 (s, 3H), 1.33-1.23 (m, 2H), 0.93 (t, *J* = 7.20 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.9, 172.2, 53.6, 52.7, 38.2, 20.3, 17.9, 14.2.

HRMS (ESI) (m/z): $[M\text{-}OCH_3]^+$ calcd for $C_7H_{11}O_3$: 143.0708, found: 143.0706.

$[\alpha]_D^{20}$ -1.92 (*c* = 2.45, $CHCl_3$)

(*S*)-2-Hydroxymethyl-2-methyl-pent-4-enoic acid methyl ester (197)



To a solution of mono acid **194** (4.20 g, 25.00 mmol) in THF (30 mL) at 0 °C, was added triethylamine (3.9 mL, 27.50 mmol) followed by methyl chloroformate (2.1 mL, 27.50 mmol). After 10 min at 0 °C, the reaction mixture was warmed to r.t. and stirred for 45 min. The white precipitate was filtered off, washed with Et_2O and the combined organic phase was concentrated. The residue was dissolved in methanol (25 mL) and cooled to 0 °C where $NaBH_4$ (1.88 g, 50.00 mmol) was added portion wise. After 1 h the reaction was carefully quenched with a saturated solution of NH_4Cl and extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) gave 2.95 g (75%) of alcohol **197**.

R_f = 0.34 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.80-5.69 (m, 1H), 5.11-5.07 (m, 2H), 3.71 (s, 3H), 3.68 (dd, *J* = 11.35, 6.85 Hz, 1H), 3.53 (dd, *J* = 11.36, 6.56 Hz, 1H), 2.34 (d, *J* = 7.56 Hz, 1H), 2.29 (t, *J* = 6.82 Hz, 1H), 1.17 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.1, 133.2, 118.5, 67.8, 51.9, 47.8, 39.9, 19.5.

IR (film): 3435, 2979, 1725, 1641, 1437, 1045 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_8H_{14}O_3$: 158.0943, found: 158.0933.

$[\alpha]_D^{20}$ -4.40 (*c* = 1.5, CH_2Cl_2)

MTPA esters of 197:

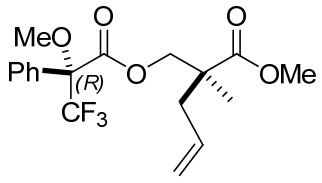
General Procedure:

To a solution of alcohol **197** (10 mg, 0.063 mmol) in DCM (1 mL) at r.t. was added triethylamine (0.1 mL) and a catalytic amount of DMAP. MTPACl (24 µL, 0.128 mmol) was added and the mixture was stirred for 1.5 h. A saturated NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted with DCM, the combined organic

layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 20 mg (90%) of the MTPA esters.

^{1}H-NMR, ^{19}F-NMR and HPLC analysis confirmed a 95:5 ratio of major to minor MTPA diastereoisomer.

(*R*)-MTPA ester (198)



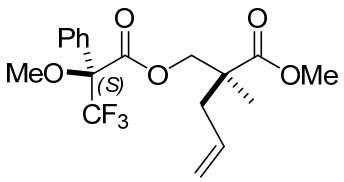
Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.49 (m, 2H), 7.39 (m, 3H), 5.71-5.60 (m, 1H), 5.10-5.00 (m, 2H), 4.42 (d, *J* = 10.84 Hz, 1H), 4.28 (d, *J* = 10.88 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 2.36 (dd, *J* = 14.04, 7.44 Hz, 1H), 2.31 (dd, *J* = 13.9, 7.58 Hz, 1H), 1.20 (s, 3H).

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.49 (m, 2H), 7.39 (m, 3H), 5.71-5.60 (m, 1H), 5.10-5.00 (m, 2H), 4.39 (d, *J* = 10.88 Hz, 1H), 4.31 (d, *J* = 10.88 Hz, 1H), 3.63 (s, 3H), 3.52 (s, 3H), 2.36 (dd, *J* = 14.04, 7.44 Hz, 1H), 2.31 (dd, *J* = 13.9, 7.58 Hz, 1H), 1.20 (s, 3H).

(*S*)-MTPA ester (199)



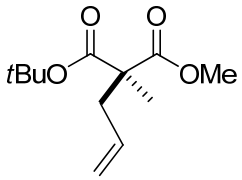
Major:

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.49 (m, 2H), 7.40 (m, 3H), 5.70-5.62 (m, 1H), 5.10-5.02 (m, 2H), 4,39 (d, *J* = 10.85 Hz, 1H), 4.31 (d, *J* = 10.85 Hz, 1H), 3.63 (s, 3H), 3.52 (s, 3H), 2.35 (dd, *J* = 13.91, 7.55 Hz, 1H), 2.31 (dd, *J* = 14.03, 7.67 Hz, 1H), 1.20 (s, 3H).

Minor:

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.49 (m, 2H), 7.40 (m, 3H), 5.70-5.62 (m, 1H), 5.10-5.02 (m, 2H), 4.42 (d, *J* = 10.85 Hz, 1H), 4.27 (d, *J* = 10.85 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 2.35 (dd, *J* = 13.91, 7.55 Hz, 1H), 2.31 (dd, *J* = 14.03, 7.67 Hz, 1H), 1.20 (s, 3H).

(*R*)-2-Allyl-2-methyl-malonic acid *tert*-butyl ester methyl ester (201)



To acid **194** (100 mg, 0.58 mmol) in DCM (2 mL) was added a catalytic amount of $H_2SO_{4conc.}$ and isobutene (1 mL) at -78 °C. The mixture was stirred in a sealed tube for 48 h at r.t.. The organic phase was washed with brine, saturated $NaHCO_3$ solution and brine and was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 100 mg (75%) of diester **201** and 25 mg (25%) of acid **194**.

R_f = 0.64 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.75-5.65 (m, 1H), 5.13-5.08 (m, 2H), 3.71 (s, 3H), 2.57 (d, *J* = 7.32 Hz, 2H), 1.43 (s, 9H), 1.35 (s, 3H).

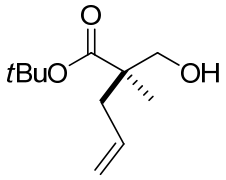
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.8, 170.8, 132.8, 118.9, 81.5, 54.1, 52.2, 40.1, 27.8, 19.7.

IR (film): 1732, 1369, 1296, 1253, 1146, 1114 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{11}H_{17}O_4$: 213.1127, found: 213.1131.

$[\alpha]_D^{20}$ 8.42 (*c* = 1.2, CH_2Cl_2)

(*R*)-2-Hydroxymethyl-2-methyl-pent-4-enoic acid *tert*-butyl ester (492)



To diester **201** (100 mg, 0.44 mmol) in THF (3 mL) at -78 °C was added DIBALH (0.67 mL, 1.5M in toluene, 1.01 mmol) and the mixture was allowed to reach -20 °C over 7 h. The reaction was quenched with methanol, a saturated sodium potassium tartrate solution was added and the mixture was stirred for 2 h. Layers were separated and the aqueous layer was extracted with hexane:Et_2O (1:1). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 5:1) yielded 43 mg (49%) of alcohol **492** and 25 mg (25%) of diester **201**.

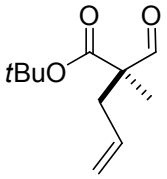
$\mathbf{R_f}$ = 0.27 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82-5.71 (m, 1H), 5.12-5.06 (m, 2H), 3.64 (dd, *J* = 11.24, 6.92 Hz, 1H), 3.48 (dd, *J* = 11.36, 6.56 Hz, 1H), 2.41 (t, *J* = 6.82 Hz, 1H (OH)), 2.30 (dd, *J* = 7.46, 3.42 Hz, 2H), 1.46 (s, 9H), 1.13 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1, 133.5, 118.2, 81.1, 67.9, 47.7, 40.2, 28.1, 19.7.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{10}H_{17}O_3$: 185.1178, found: 185.1175.

(*R*)-2-Formyl-2-methyl-pent-4-enoic acid *tert*-butyl ester (202)



Dess-Martin periodinane (824 mg, 2.16 mmol) was added portion wise to a solution of alcohol **492** (100 mg, 0.54 mmol) in DCM (2 mL) at 0 °C. After 4 h at r.t. a saturated solution of $NaHCO_3$ was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 75 mg (75%) of aldehyde **202** as colorless oil.

R_f = 0.74 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1H), 5.75-5.64 (m, 1H), 5.15-5.10 (m, 2H), 2.58 (dd, *J* = 14.02, 7.20 Hz, 1H), 2.46 (dd, *J* = 14.02, 7.45 Hz, 1H), 1.46 (s, 9H), 1.25 (s, 3H).

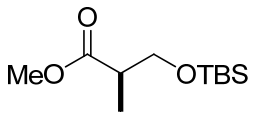
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.6, 170.8, 132.0, 119.2, 82.3, 57.8, 38.6, 28.0, 16.8.

IR (film): 1721, 1369, 1252, 1148 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{11}H_{18}O_3$: 198.1256, found: 198.1261.

$[\alpha]_D^{20}$ 7.11 (*c* = 0.45, CH_2Cl_2)

(-)-(2*R*)-3-(*tert*-Butyl-dimethyl-silyloxy)-2-methyl-propionic acid methyl ester (493)



To a stirred solution of (*R*)-methyl-2-hydroxy-2-methylpropionate (**182**) (2.0 g, 17.0 mmol) and imidazole (2.3 g, 34.0 mmol) in DMF (20 mL) was added TBSCl (2.9 g, 22.1 mmol) at 0 °C and stirring was continued at r.t. for 5 h. The reaction mixture was quenched with water and extracted with Et_2O. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) furnished 3.9 g (quant.) of the TBS ether **493** as colorless oil.

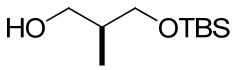
R_f = 0.70 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.76 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.66 (s, 3H), 3.63 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.63 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4, 65.2, 51.5, 42.5, 25.6, 18.2, 13.4, -5.5.

$[\alpha]_D^{20}$ -18.10 (*c* = 3.03, $CHCl_3$)

(-)-(2*S*)-3-(*tert*-Butyl-dimethyl-silyloxy)-2-methyl-propan-1-ol (183)



To a stirred solution of DIBALH (11.3 mL, 1.5 M in toluene, 17.0 mmol) in THF (20 mL) at -78 °C was added dropwise TBS protected ester **493** (1.9 g, 8.5 mmol). After 6 h the reaction mixture was quenched with saturated sodium potassium tartrate solution and the mixture was stirred over night. The layers were separated, the aqueous phase extracted with hexane:Et_2O (1:1) and the combined organic solution was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography (hexane:EtOAc = 9:1) to yield 1.47 g (85%) of alcohol **183** as colorless oil.

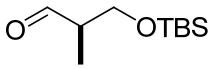
R_f = 0.23 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.72 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.61 (m, 2H), 3.53 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.78 (dd, Hz, *J* = 6.0, 4.5 Hz, 1H), 1.93 (m, 1H), 0.89 (s, 9H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.06 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 68.8, 68.3, 37.0, 25.9, 18.2, 13.1, -5.6.

$[\alpha]_D^{20}$ -20.60 (*c* = 0.8, $CHCl_3$)

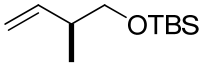
(-)-(2*R*)-3-(*tert*-Butyl-dimethyl-silyloxy)-2-methyl-propionaldehyde (494)



To a solution of oxalylchloride (1.26 mL, 14.7 mmol) in DCM (100 mL) at -78 °C was added DMSO (2.1 mL, 29.4 mmol) dropwise and the mixture was stirred for 30 min. Alcohol **183** (1.5 g, 7.35 mmol) in DCM (10 mL) was added and stirring was continued for 1 h before triethylamine (6.3 mL, 44.1 mmol) was added. The reaction mixture was shifted to an ice bath. After 45 min the reaction mixture was quenched with saturated NH_4Cl solution, the organic layer separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in hexane:EtOAc (5:1) and filtered over a short plug of silica gel to yield 1.5 g (quant.) of aldehyde **494** which was used without further purification.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 9.73 (d, *J* = 1.6 Hz, 1H), 3.86 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.80 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.60-2.46 (m, 1H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

tert-Butyl-dimethyl-((_S_)-2-methyl-but-3-enyloxy)-silane (203)



To a stirred suspension of methyltriphenylphosphoniumbromide (5.40 g, 14.8 mmol) in THF (30 mL) at 0 °C was added potassium *tert*-butoxide (1.70 g, 14.8 mmol) and stirring was continued for 1 h. Aldehyde **494** (1.4 g, 6.9 mmol) in THF (7 mL) was added and the reaction mixture was warmed to r.t.. After 2 h water was added the aqueous layer was extracted with DCM. After removal of the solvent olefin **203** (volatile!) was purified by column chromatography (pentane) to yield 1.20 g (87%).

R_f = 0.82 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.81-5.73 (m, 1H), 5.05-4.97 (m, 2H), 3.51 (dd, *J* = 9.72, 6.19 Hz, 1H), 3.41 (dd, *J* = 9.85, 7.07 Hz, 1H), 2.36-2.29 (m, 1H), 0.99 (d, *J* = 6.82 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

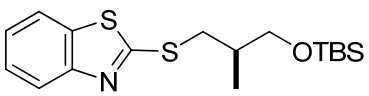
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 141.4, 113.9, 67.9, 40.4, 25.9, 14.1, 3.8, -5.3, -5.4.

IR (film): 2955, 2929, 1256, 1089 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{11}H_{24}OSi$: 200.1596, found: 200.1589.

$[\alpha]_D^{20}$ -6.00 (*c* = 1.15, CH_2Cl_2)

2-[(_R_)-3-(_tert_-Butyl-dimethyl-silanyloxy)-2-methyl-propylsulfanyl]-benzothiazole (495)



To a solution of DIAD (1 mL, 5.3 mmol) in THF (30 mL) at 0 °C, was added a solution of alcohol (**494**) (1.00 g, 4.9 mmol), 2-mercaptobenzothiazole (870 mg, 5.2 mmol) and triphenyl phosphine (1.41 g, 5.4 mmol) in THF (20 mL). After 4.5 h a saturated solution of $NaHCO_3$

was added and the mixture was filtered over celite. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (hexane:EtOAc = 15:1) gave 1.58 g (91%) of product **495** as yellow oil.

R_f = 0.79 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.08 Hz, 1H), 7.74 (d, *J* = 8.08 Hz, 1H), 7.40 (t, *J* = 7.18 Hz, 1H), 7.29 (d, *J* = 7.32 Hz, 1H), 3.65 (dd, *J* = 9.98, 5.18 Hz, 1H), 3.56 (dd, *J* = 10.08, 5.81 Hz, 1H), 3.51 (dd, *J* = 13.02, 6.18 Hz, 1H), 3.23 (dd, *J* = 13.00, 6.96 Hz, 1H), 2.17-2.09 (m, 1H), 1.07 (d, *J* = 6.80 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H).

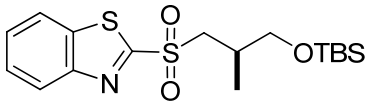
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.4, 153.4, 135.2, 125.9, 124.1, 121.5, 120.8, 74.3, 66.4, 37.0, 36.0, 25.9, 21.6, 16.2, -5.3 -5.4.

IR (film): 2955, 1461, 1428, 1250, 1095 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{17}H_{27}ONSiS_2$: 353.1303, found: 353.1314.

$[\alpha]_D^{20}$ -6.41 (*c* = 1.45, CH_2Cl_2)

2-[(*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propane-1-sulfonyl]-benzothiazole (206)



A solution of sulfide **495** (800 mg, 2.24 mmol) in ethanol (8 mL) was added to ammonium heptamolybdate tetrahydrate (560 mg, 0.44 mmol) in a 30% hydrogen peroxide solution (2 mL, 18.25 mmol) at 0 °C. After stirring for 4 h another portion of hydrogen peroxide (0.75 mL, 6.70 mmol) was added and stirring was continued for 3 h. Brine was added and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) gave 780 mg (90%) of sulfone **206** as pale yellow oil.

R_f = 0.39 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.08 Hz, 1H), 8.01 (d, *J* = 8.08 Hz, 1H), 7.66-7.57 (m, 2H), 3.83 (dd, *J* = 14.38, 4.54 Hz, 1H), 3.64 (dd, *J* = 9.84, 4.80 Hz, 1H), 3.44 (dd, *J*

= 9.82, 6.14 Hz, 1H), 3.29 (dd, *J* = 14.44, 7.88 Hz, 1H), 2.45-2.37 (m, 1H), 1.13 (d, *J* = 6.68 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H).

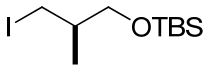
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.5, 152.8, 139.2, 136.8, 127.9, 127.6, 125.5, 122.3, 66.3, 57.6, 34.7, 31.6, 25.8, 16.7, 14.1, -5.5, -5.6.

IR (film): 3446, 1675, 1471, 1318, 1147 cm^{-1}

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{16}H_{22}O_3NSiS_2$: 370.0967, found: 370.0969.

$[\alpha]_D^{20}$ 0.56 (*c* = 1.25, CH_2Cl_2)

***tert*-Butyl-(3-iodo-2-methyl-propoxy)-dimethyl-silane (496)**



To a solution of alcohol **183** (200 mg, 0.98 mmol) in acetonitrile (6 mL) and Et_2O (5 mL) at 0 °C was added imidazole (125 mg, 1.93 mmol) followed by triphenyl phosphine (460 mg, 1.75 mmol) and iodide (465 mg, 1.83 mmol). After 10 min the cooling bath was removed and the mixture was stirred at r.t. for 2 h. The reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic phases were washed with a saturated $Na_2S_2O_3$ solution and dried over $MgSO_4$. After removal of the solvent, column chromatography (hexane:EtOAc = 40:1) yielded 306 mg (quant.) of iodide **496**.

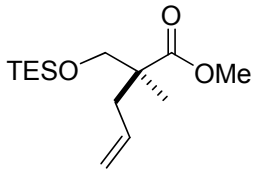
R_f = 0.90 (hexane:EtOAc = 20:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, *J* = 9.96, 9.92 Hz, 1H), 3.39 (dd, *J* = 9.96, 6.96 Hz, 1H), 3.31 (dd, *J* = 9.46, 5.18 Hz, 1H), 3.24 (dd, *J* = 9.60, 5.56 Hz, 1H), 1.64 (m, 1H), 0.95 (d, *J* = 6.82 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 66.7, 37.4, 25.9, 17.2, 13.8, -5.4.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_9H_{20}OISi$: 299.0328, found: 299.0325.

(*S*)-2-Methyl-2-triethylsilanyloxymethyl-pent-4-enoic acid methyl ester (208)



Triethylchlorosilane (2.4 mL, 12.54 mmol) was added to alcohol **197** (1.80 g, 11.4 mmol) in pyridine (20 mL) at r.t.. After 2 h water was added and the mixture was extracted with Et_2O. The combined ethereal phase was washed with water, dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) gave 3.10 g of silyl ether **208** as colorless oil.

R_f = 0.76 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.77-5.66 (m, 1H), 5.07-5.02 (m, 2H), 3.66 (s, 3H), 3.65 (d, *J* = 9.25 Hz, 1H), 3.58 (d, *J* = 9.40 Hz, 1H), 2.39 (dd, *J* = 13.52, 7.00 Hz, 1H), 2.22 (dd, *J* = 13.52, 7.72 Hz, 1H), 1.14 (s, 3H), 0.93 (t, *J* = 7.96 Hz, 9H), 0.57 (q, *J* = 8.00 Hz, 6H).

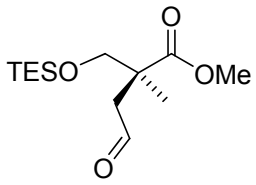
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.2, 133.9, 117.9, 67.9, 51.5, 48.5, 39.4, 19.1, 6.7, 4.3.

IR (film): 2954, 2877, 1736, 1458, 1149, 1101 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{13}H_{25}O_3Si$: 257.1573, found: 257.1571.

$[\alpha]_D^{20}$ -3.00 (*c* = 1.2, CH_2Cl_2)

(*S*)-2-Methyl-4-oxo-2-triethylsilanyloxymethyl-butyric acid methyl ester (210)



A steam of ozone was bubbled through a solution of **208** (1.50 g, 5.37 mmol) in DCM (100 mL) for 5 min at -78 °C. Triphenyl phospine (2.12 g, 8.06 mmol) and PPTS (129 mg, 0.54 mmol) were added to the solution and it was aged in the fridge over night. After removal of the solvent, the crude product was purified by quick column chromatography (hexane:EtOAc = 3:1) to yield 1.47 g of aldehyde **210** as colorless oil.

R_f = 0.50 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.77 (dd, *J* = 2.28, 1.76 Hz, 1H), 3.87 (d, *J* = 9.36 Hz, 1H), 3.71 (s, 3H), 3.55 (d, *J* = 9.60 Hz, 1H), 2.75 (dd, *J* = 16.68, 2.28 Hz, 1H), 2,60 (dd, *J* = 16.64, 1.76 Hz, 1H), 1.24 (s, 3H), 0.93 (t, *J* = 7.96 Hz, 9H), 0.57 (q, *J* = 7.92 Hz, 6H).

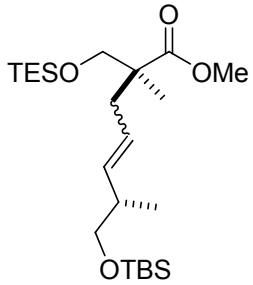
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.00, 175.4, 68.2, 52.0, 48.8, 46.7, 20.7, 6.6, 4.2.

IR (film): 2877, 1733, 1237, 1098 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_2H_5]^+$ calcd for $C_{11}H_{21}O_4Si$: 245.1209, found: 245.1205.

$[\alpha]_D^{20}$ 5.00 (*c* = 0.8, CH_2Cl_2)

(2*S*,6*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-2,6-dimethyl-2-triethylsilanyloxymethyl-hept-4-enoic acid methyl ester (209)



Cross metathesis:

To olefine **203** (96 mg, 0.48 mmol) and olefine **208** (195 mg, 0.720 mmol) in degassed DCM (2 mL) under argon at 40 °C was added Grubbs-Hoveyda catalyst (25 mg, 7 mol%, 0.035 mmol) in degassed DCM (0.5 mL) *via* syringe pump over 16 h. After the addition was completed, the mixture was stirred for an additional 5 h, cooled to r.t. and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 40:1) yielded 195 mg (98%) of olefin **209** as a 1:1 (*E:Z*) mixture.

R_f = 0.85 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41-5.32 (m, 2H), 3.64 (s, 3H), 3.65 (d, *J* = 9.36 Hz, 1H), 3.55 (d, *J* = 9.36 Hz, 1H), 3.47 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.35 (d, *J* = 7.32 Hz, 1H), 2.31 (dd, *J* = 13.01, 5.68 Hz, 1H), 2.28 (m, 1H), 2.15 (dd, *J* = 13.13, 6.31 Hz, 1H), 1.12 (s, 3H), 0.96 (d, *J* = 6.57 Hz, 3H), 0.94 (t, *J* = 7.96 Hz, 9H), 0.89 (s, 9H), 0.56 (q, *J* = 7.99 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.3, 136.7, 133.8, 124.7, 68.2, 67.8, 51.4, 48.7, 39.5, 38.2, 25.9, 19.1, 16.8, 6.7, 4.3, -5.3.

IR (film): 2955, 1735, 1654, 1560, 1458, 1251, 1091, 1006 cm^{-1}.

HRMS (ESI) (m/z): $[M-CH_3]^+$ calcd for $C_{22}H_{45}O_4Si_2$: 429.2856, found: 429.2864.

Julia-Lythgoe-Kocienski olefination:

To sulfone **206** (1.70 g, 4.35 mmol) in THF (45 mL) was added LiHMDS (4.8 mL, 1M in THF, 4.80 mmol) dropwise at -78 °C and stirred for 1 h. Aldehyde **210** (1.40 g, 5.27 mmol) was added in THF (15 mL). Stirring was continued for 1 h, and the reaction was gradually warmed to -20 °C over 4 h. Saturated NH_4Cl solution was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (hexane:EtOAc = 15:1) yielded 1.85 g (96%) of olefin **209** as a 1:1 (*E:Z*) mixture.

R_f = 0.85 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41-5.32 (m, 2H), 3.64 (s, 3H), 3.65 (d, *J* = 9.36 Hz, 1H), 3.55 (d, *J* = 9.36 Hz, 1H), 3.47 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.35 (d, *J* = 7.32 Hz, 1H), 2.31 (dd, *J* = 13.01, 5.68 Hz, 1H), 2.28 (m, 1H), 2.15 (dd, *J* = 13.13, 6.31 Hz, 1H), 1.12 (s, 3H), 0.96 (d, *J* = 6.57 Hz, 3H), 0.94 (t, *J* = 7.96 Hz, 9H), 0.89 (s, 9H), 0.56 (q, *J* = 7.99 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.3, 136.7, 133.8, 124.7, 68.2, 67.8, 51.4, 48.7, 39.5, 38.2, 25.9, 19.1, 16.8, 6.7, 4.3, -5.3.

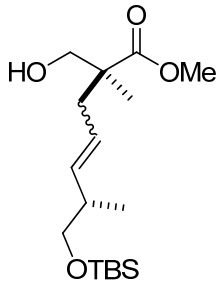
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.31-5.24 (m, 2H), 3.70 (d, *J* = 9.35 Hz, 1H), 3.64 (s, 3H), 3.56 (d, *J* = 9.35 Hz, 1H), 3.44 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.33 (d, *J* = 7.07 Hz, 1H), 2.62 (m, 1H), 2.44 (dd, *J* = 14.27 Hz, 6.69 Hz, 1H), 2.19 (dd, *J* = 14.46, 5.48 Hz, 1H), 1.16 (s, 3H), 0.94 (t, *J* = 7.96 Hz, 9H), 0.93 (d, *J* = 6.50 Hz, 3H), 0.89 (s, 9H), 0.57 (q, *J* = 7.58 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.2, 135.4, 133.6, 124.5, 68.1, 67.8, 51.5, 48.6, 34.7, 33.0, 25.9, 19.1, 17.3, 6.7, 4.3, -5.3.

IR (film): 2955, 1735, 1654, 1560, 1458, 1251, 1091, 1006 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_2H_5]^+$ calcd for $C_{21}H_{43}O_4Si_2$: 415.2700, found: 415.2693.

(2*S*,6*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxymethyl-2,6-dimethyl-hept-4-enoic acid methyl ester (497)



To a stirred solution of silyl ether **209** (1.34 g, 3.02 mmol) in methanol (25 mL) at 0 °C was added PPTS (380 mg, 1.51 mmol). After 2.5 h brine was added and the aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 920 mg (92%) of alcohol **497** as colorless oil.

R_f = 0.40 (hexane:EtOAc = 3:1)

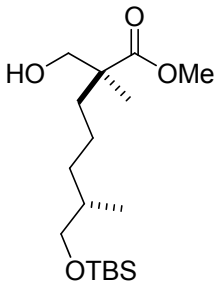
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.41-5.38 (m, 2H), 3.70 (s, 3H), 3.68 (dd, *J* = 11.24, 6.68 Hz, 1H), 3.51 (dd, *J* = 11.36, 6.84 Hz, 1H), 3.45 (dd, *J* = 9.72, 6.16 Hz, 1H), 3.37 (dd, *J* = 9.72, 6.68 Hz, 1H), 2.29-2.21 (m, 3H), 1.16 (s, 3H), 0.95 (d, *J* = 6.57 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.3, 137.4, 124.2, 68.1, 67.8, 51.8, 48.0, 39.5, 38.9, 32.7, 25.9, 19.6, 16.7, -5.3.

IR (film): 3468, 2955, 2857, 1731, 1463, 1255, 1089 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{16}H_{31}O_4Si$: 315.1992, found: 315.1999.

(2*S*,6*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxymethyl-2,6-dimethyl-heptanoic acid methyl ester (211)



Olefin **497** (930 mg, 2.8 mmol) and PtO_2 (43 mg, 0.2 mmol) in ethyl acetate (10 mL) were stirred under hydrogen atmosphere (1 bar) for 2 h. The catalyst was filtered off over celite and the solvent was removed under reduced pressure to yield 930 mg (99%) of product **211**, which was used without further purification.

R_f = 0.40 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.72 (dd, *J* = 11.24, 6.96 Hz, 1H), 3.71 (s, 3H), 3.42 (dd, *J* = 11.42, 6.44 Hz, 1H), 3.41 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.35 (dd, *J* = 9.72, 6.16 Hz, 1H), 2.25 (t, *J* = 6.69 Hz, 1H), 1.62-1.43 (m, 3H), 1.39-1.15 (m, 3H), 1.18 (s, 3H), 1.08-1.00 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 6.82 Hz, 3H), 0,03 (s, 6H).

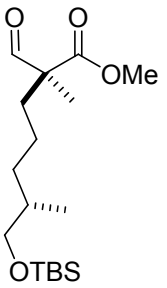
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.7, 68.3, 68.2, 51.8, 47.8, 36.2, 35.5, 33.6, 25.9, 21.6, 19.6, 16.6, -5.3.

IR (film): 2953, 1730, 1471, 1251, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{16}H_{33}O_4Si$: 317.2148, found: 317.2139.

$[\alpha]_D^{20}$ -2.48 (*c* = 1.25, CH_2Cl_2)

(2*S*,6*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-2-formyl-2,6-dimethyl-heptanoic acid methyl ester (212)



Dess-Martin periodinane (2.69 g, 6.3 mmol) was added portion wise to a solution of alcohol **211** (700 mg, 2.1 mmol) in DCM (20 mL) at 0 °C under argon. After 4 h a saturated solution of $NaHCO_3$ was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Comlumn chromatography (hexane:EtOAc = 3:1) yielded 635 mg (91%) of aldehyde **212** as colorless oil.

R_f = 0.78 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 3.75 (s, 3H), 3.41-3.34 (m, 2H), 1.88 (ddd, *J* = 11.61, 13.64, 5.31 Hz, 1H), 1.67 (ddd, *J* = 13.64, 11.75, 4.93 Hz, 1H), 1.63-1.53 (m, 1H), 1.44-1.32 (m, 1H), 1.30 (s, 3H), 1.32-1.17 (m, 2H), 1.11-1.01 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.84 Hz, 3H), 0.03 (s, 6H).

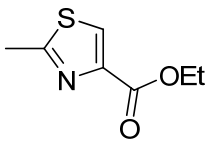
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.7, 172.8, 68.1, 57.8, 52.4, 35.4, 34.7, 33.4, 25.9, 21.7, 18.3, 16.7, 16.5, -5.4.

IR (film): 2954, 2856, 1725, 1463, 1356, 1094 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{16}H_{31}O_4Si$: 315.1992, found: 315.1997.

$[\alpha]_D^{20}$ -2.55 (*c* = 0.9, CH_2Cl_2)

2-Methyl-thiazole-4-carboxylic acid ethyl ester (213)



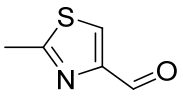
To a stirred solution of thioacetamide (1.7 g, 22.5 mmol) in ethanol (14 mL) was added ethyl bromopyruvate (90%, 2.7 mL, 19.4 mmol) over 10 min. A bright yellow solution formed, which was stirred for 16 h. 2 M HCl solution (25 mL) was added and the mixture was stirred for 40 min and extracted with Et_2O. The aqueous layer was cautiously neutralized with solid $NaHCO_3$ and extracted with DCM. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow solid. Purification by column chromatography (hexane:EtOAc = 2:1) yielded 3.1 g (93%) of thiazole ester **213** as white solid.

R_f = 0.25 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.77 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H)

mp = 58 °C

2-Methyl-thiazole-4-carbaldehyde (214)



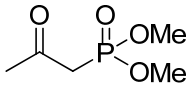
To a solution of ester **129** (3 g, 17.5 mmol) in DCM (150 mL) at -78 °C was added DIBALH (17.5 mL, 1.5 M in toluene, 26.3 mmol) over 45 min. After 2 h an additional portion of DIBALH (5.8 mL, 1.5 M in toluene, 8.7 mmol) was added over 20 min and stirring was continued for 3 h. The reaction was quenched by addition of methanol (1 mL) at -78 °C and the mixture was stirred with saturated sodium potassium tartrate solution over night. The aqueous layer was extracted with DCM and the combined organic solution was washed with brine, dried over $MgSO_4$ and the solvent was evaporated to yield 2.2 g (97%) of aldehyde **130** as a yellow powder.

R_f = 0.20 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 8.05 (s, 1H), 2.81 (s, 3H)

mp = 56 °C

(2-Oxo-propyl)-phosphonic acid dimethyl ester (498)

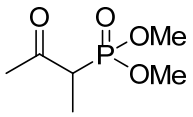


To a stirred suspension of KI (3.58 g, 21.60 mmol) in acetone (6 mL) and acetonitrile (5 mL) was added chloroacetone (1.72 mL, 21.60 mmol). The mixture was stirred for 10 min and trimethyl phosphite (2.45 mL, 21.60 mmol) was added. The reaction was stirred at r.t. for 5 h and at 50 °C for 4 h, followed by filtration and concentration. Purification by bulb-to-bulb-distillation yielded 1.12 g (32%) of phosphonate **498** as colorless liquid.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.79 (d, J_{HH} = 11.18 Hz, 6H), 3.10 (d, J_{PH} = 22.84 Hz, 2H), 2.33 (s, 3H)

bp = 97 °C / 5 mbar

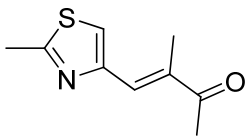
(1-Methyl-2-oxo-propyl)-phosphonic acid dimethyl ester (215)



Phosphonate **498** (300 mg, 1.8 mmol) in THF (5 mL) was slowly added to a stirred suspension of NaH (64 mg, 1.8 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at r.t. for 1.5 h. MeI (0.1 mL, 2.2 mmol) was added and stirring was continued over night at r.t.. The reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The combined extract was dried over $MgSO_4$ and the solvent was evaporated to give 280 mg (87%) of alkylated phosponate **215** as colorless liquid.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.78 (d, J_{HH} = 10.14 Hz, 6H), 3.23 (dq, J_{HH} = 6.93 Hz, J_{PH} = 24.90 Hz, 1H), 2.34 (s, 3H), 1.37 (dd, J_{HH} = 7.19 Hz, J_{PH} = 17.92 Hz, 3H).

(*E*)-2-Methyl-3-(2-methyl-thiazol-4-yl)-propenal (216)



A mixture of phosphonate **215** (250 mg, 1.4 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (440 mg, 1.4 mg) in THF (5 mL) was stirred for 1 h. The reaction was cooled to 0 °C and a solution of aldehyde **214** (149 mg, 1.2 mmol) in wet THF (1 mL) was added. After 1 h the cooling bath was removed and stirring was continued over night. The reaction was quenched with saturated NH_4Cl solution, the layers were separated and the aqueous phase was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 140 mg (64%) of enone **216** as white needles.

R_f = 0.50 (Hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 1.26 Hz, 1H), 7.34 (s, 1H), 2.75 (s, 3H), 2.45 (s, 3H), 2.21 (d, J = 1.26 Hz, 3H).

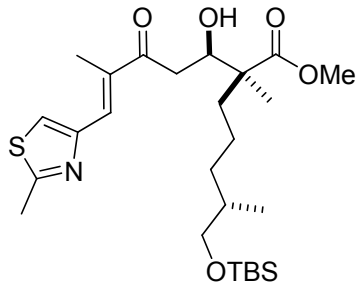
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.2, 161.5, 151.8, 137.7, 131.9, 121.2, 25.8, 19.2, 13.2.

IR (film): 3087, 2924, 1654, 1627, 1365, 1241, 1180 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_9H_{11}OSN$: 181.0561, found: 181.0554.

mp = 69°C

(*E*)-(2*S*,3*R*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-hydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-5-oxo-hept-6-enoic acid methyl ester (220)



LiHMDS (0.66 mL, 1M in THF, 0.66 mmol) was added to methyl ketone **216** (120 mg, 0.66 mmol) in THF (8 mL) at -78 °C. After 1 h a solution of aldehyde **212** (219 mg, 0.66 mmol) premixed with $MgBr_2 \cdot Et_2O$ (342 mg, 1.32 mmol) in THF (6 mL) at 0 °C for 1 h, was slowly added *via* canula. After 3.5 h a saturated NH_4Cl solution was added and the aqueous phase was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 312 mg (92%) of aldol adduct **220** as colorless oil.

R_f = 0.52 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.38 (s, 1H), 4.34-4.30 (m, 1H), 3.69 (s, 3H), 3.42 (dd, *J* = 9.86, 5.82 Hz, 1H), 3.35 (dd, *J* = 9.93, 6.64 Hz, 1H), 3.33 (d, *J* = 3.52 Hz, 1H), 2.92-2.89 (m, 2H), 2.75 (s, 3H), 2.23 (d, *J* = 1.00 Hz, 3H), 1.84-1.77 (m, 1H), 1.60-1.50 (m, 2H), 1.42-1.32 (m, 2H), 1.23-1.17 (m, 1H), 1.20 (s, 3H), 1.08-1.02 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 6.60 Hz, 3H), 0.03 (s, 6H).

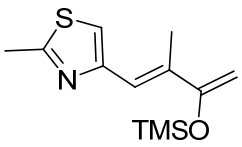
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.6, 176.3, 165.5, 151.6, 137.2, 131.2, 121.9, 71.6, 68.3, 51.7, 50.4, 39.8, 36.9, 35.5, 33.5, 25.9, 21.9, 19.3, 18.4, 16.6, 16.5, 13.2, -5.4.

IR (film): 3436, 2953, 1722, 1652, 1628, 1250, 1087 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{45}O_5NSSi$: 511.2788, found: 511.2776.

$[\alpha]_D^{20}$ 26.15 (*c* = 1.3, CH_2Cl_2)

2-Methyl-4-((*E*)-2-methyl-3-trimethylsilanyloxy-buta-1,3-dienyl)-thiazole (219)

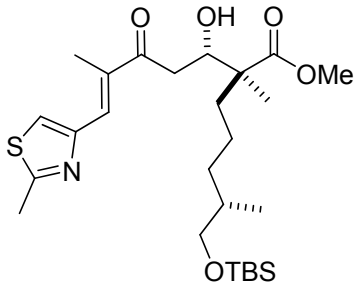


LiHMDS (1.22 mL, 1M in THF, 1.22 mmol) was added to methyl ketone **216** (150 mg, 0.82 mmol) in THF (3 mL) at -78 °C. After 1 h TMSCl (0.13 mL, 1.07 mmol), freshly distilled from CaH_2, was added and stirring was continued for 30 min. The mixture was warmed to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in hexane and filtered over celite. After evaporation of the solvent, crude enol ether **219** was used directly in the following reaction.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.35 (s, 1H), 6.54 (s, 1H), 4.73 (s, 1H), 4.52 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H), 0.22 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.2, 154.4, 120.5, 117.7, 93.6, 18.9, 15.1, 0.08.

(*E*)-(2*S*,3*S*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-hydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-5-oxo-hept-6-enoic acid methyl ester (180)



To aldehyde **212** (160 mg, 0.48 mmol) in DCM (5 mL) at -78 °C was added $TiCl_4$ (0.11 mL, 0.96 mmol). After 15 min silyl enol ether **219** (185 mg, 0.73 mmol) in DCM (2 mL) was added and stirring was continued for 2 h. A saturated $NaHCO_3$ solution was cautiously added and layers were separated. The aqueous layer was extracted with DCM, the combined DCM solution was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 34 mg (13%) of aldol adduct **180** as colorless oil.

R_f = 0.14 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.38 (s, 1H), 4.38 (ddd, *J* = 9.79, 4.36, 2.21 Hz, 1H), 3.72 (s, 3H), 3.41 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.36 (dd, *J* = 9.72, 6.19 Hz, 1H), 3.27 (d, *J* = 4.29 Hz, 1H (OH)), 2.95 (dd, *J* = 17.05, 2.40 Hz, 1H), 2.86 (dd, *J* = 17.05, 9.73 Hz, 1H), 2.76 (s, 3H), 2.23 (d, *J* = 1.01 Hz, 3H), 1.70-1.62 (m, 1H), 1.60-1.52 (m, 1H), 1.42-1.29 (m, 4H), 1.20 (s, 3H), 1.10-1.00 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

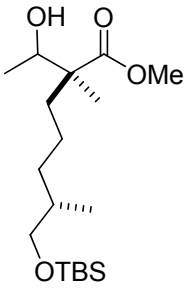
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.0, 176.6, 165.7, 150.1, 137.5, 132.0, 121.9, 72.56, 68.3, 51.9, 50.8, 38.8, 36.6, 35.5, 33.5, 26.0, 21.9, 19.3, 16.6, 16.4, 15.7, 13.2, -5.4.

IR (film): 2952, 1732, 1666, 1250, 1089 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{45}O_5NSSi$: 511.2788, found: 511.2786.

$[\alpha]_D^{20}$ -28.88 (*c* = 0.8, CH_2Cl_2)

(2*S*,6*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-2-(1-hydroxy-ethyl)-2,6-dimethyl-heptanoic acid methyl ester (499)

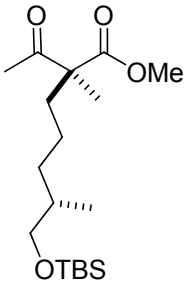


To aldehyde **212** (110 mg, 0.33 mmol) in THF (4 mL) at -78 °C was slowly added MeMgBr (0.35 mL, 1M in Et_2O, 0.35 mmol). After 1.5 h the reaction was quenched by the addition of a saturated NH_4Cl solution, the layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 81 mg (71%) of alcohol **99** as 1:1 mixture of diastereoisomers and 26 mg (24%) of recovered aldehyde **499**.

R_f = 0.66 (hexane:EtOAc = 3:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.89 (q, *J* = 6.39 Hz, 1H), 3.69 (s, 3H), 3.38 (ddd, *J* = 16.43, 10.05, 6.33 Hz, 2H), 2.13 (s, 3H), 1.75 (m, 1H), 1.62-1.52 (m, 2H), 1.44-1.32 (m, 2H), 1.14 (s, 3H), 1.12 (s, 3H), 1.16-1.00 (m, 2H), 0.89 (s, 9H), 0.85 (d, *J* = 6.72 Hz, 3H), 0.03 (s, 6H).

(2*S*,6*S*)-2-Acetyl-7-(*tert*-butyl-dimethyl-silanyloxy)-2,6-dimethyl-heptanoic acid methyl ester (222)

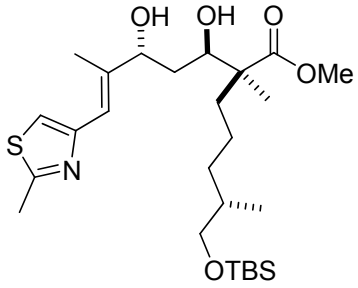


Dess-Martin periodinane (294 mg, 0.69 mmol) was added potionwise to alcohol **499** (80 mg, 0.23 mmol) in DCM (3 mL) at 0°C. After 4 h saturated $NaHCO_3$ solution was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 70 mg (88%) of methyl ketone **222**.

R_f = 0.73 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 3H), 3.38 (ddd, *J* = 15.85, 9.78, 6.12 Hz, 2H), 2.13 (s, 3H), 1.89 (ddd, *J* = 13.65, 12.25, 4.67 Hz, 1H), 1.70 (ddd, *J* = 13.84, 11.92, 4.62 Hz, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 1.33 (s, 3H), 1.28-1.03 (m, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.60 Hz, 3H), 0.02 (s, 6H)

(*E*)-(2*S*,3*R*,5*R*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3,5-dihydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-hept-6-enoic acid methyl ester (232)



To a solution of tetramethylammonium triacetoxyboron hydride (1.06 g, 3.88 mmol) in acetonitrile (7 mL) and acetic acid (5 mL) at -30 °C was slowly added a solution of **220** (260 mg, 0.48 mmol) in acetonitrile (5 mL). After stirring for 9 h a saturated solution of $NaHCO_3$ and solid $NaHCO_3$ were added very carefully till gas evolution ceased. The aqueous layer

was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 242 mg (97%) of dihydroxy ester **232** as colorless oil.

R_f = 0.41 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (s, 1H), 6.67 (s, 1H), 4.45 (dd, *J* = 6.44, 2.90 Hz, 1H), 4.00 (dd, *J* = 10.22, 1.13 Hz, 1H), 3.67 (s, 3H), 3.40 (dd, *J* = 9.73, 5.93 Hz, 1H), 3.34 (dd, *J* = 9.60, 6.32 Hz, 1H), 2.70 (s, 3H), 1.99 (d, *J* = 0.76 Hz, 3H), 1.81-1.63 (m, 3H), 1.60-1.52 (m, 1H), 1.46-1.37 (m, 1H), 1.36-1.23 (m, 2H), 1.15 (s, 3H), 1.16-0.98 (m, 2H), 0.88 (s, 9H), 0.83 (d, *J* = 6.57 Hz, 3H), 0.02 (s, 6H).

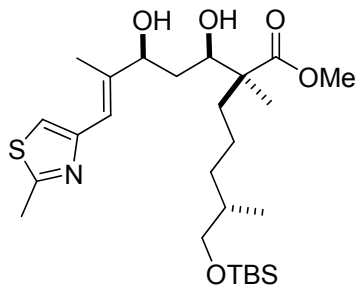
^{13}C-NMR (100M Hz, $CDCl_3$): δ = 177.1, 164.6, 153.0, 141.9, 118.0, 115.4, 74.4, 73.0, 68.3, 51.8, 50.6, 36.0, 35.8, 35.5, 33.6, 25.9, 21.9, 19.2, 18.4, 17.3, 16.6, 15.4, -5.4.

IR (film): 3400, 2952, 2989, 1731, 1256, 1091 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{47}O_5NSSi$: 513.2944, found: 513.2953.

$[\alpha]_D^{20}$ 14.60 (*c* = 0.5, CH_2Cl_2)

(*E*)-(2*S*,3*R*,5*R*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3,5-dihydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-hept-6-enoic acid methyl ester (231)



To a solution of **220** (950 mg, 1.90 mmol) in THF (20 mL) at -10 °C was added catecholborane (0.99 mL, 9.50 mmol) and stirred for 5 h. A saturated solution of potassium sodium tartrate was added and stirred for 1 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 835 mg (88%) of dihydroxy ester **231** as colorless oil

R_f = 0.15 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1H), 6.60 (s, 1H), 4.40 (dd, *J* = 9.22, 2.90 Hz, 1H), 4.02 (dd, *J* = 9.97, 1.64 Hz, 1H), 3.68 (s, 3H), 3.41 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.34 (dd, *J* = 9.72, 6.44 Hz, 1H), 2.75 (s, 3H), 2.01 (d, *J* = 1.01 Hz, 3H), 1.80-1.66 (m, 2H), 1.63-1.52 (m, 2H), 1.50-1.43 (m, 1H), 1.39-1.20 (m, 3H), 1.15 (s, 3H), 1.07-0.97 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.57 Hz, 3H), 0.03 (s, 6H).

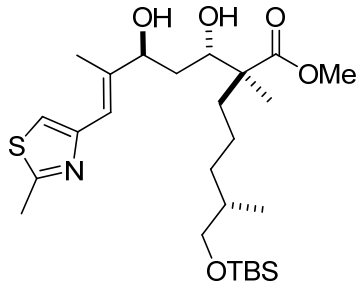
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.9, 165.3, 151.8, 142.8, 118.1, 115.7, 78.3, 76.3, 68.4, 51.8, 50.9, 36.9, 36.1, 35.5, 33.6, 25.9, 22.0, 18.8, 18.4, 16.9, 16.6, 14.4, -5.4.

IR (film): 2952, 1731, 1090, 837 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{47}O_5NSSi$: 513.2945, found: 513.2936.

$[\alpha]_D^{20}$ -0.40 (*c* = 0.5, CH_2Cl_2)

(*E*)-(2*S*,3*R*,5*R*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3,5-dihydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-hept-6-enoic acid methyl ester (217)



To a solution of tetramethylammonium triacetoxyboron hydride (123 mg, 0.420 mmol) in acetonitrile:acetic acid (1:1, 2 mL) at -30 °C was slowly added a solution of **180** (30 mg, 0.058 mmol) in acetonitrile (0.5 mL). After stirring for 7 h a saturated solution of $NaHCO_3$ and solid $NaHCO_3$ were added very carefully till gas evolution ceased. The aqueous layer was extracted with DCM, combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 26 mg (87%) of dihydroxy ester **217** as colorless oil.

R_f = 0.19 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (s, 1H), 6.66 (s, 1H), 4.48 (m, 1H), 4.03 (dd, *J* = 9.09, 6.57 Hz, 1H), 3.69 (s, 3H), 3.40 (dd, *J* = 9.73, 5.94 Hz, 1H), 3.34 (dd, *J* = 9.85, 6.32 Hz, 1H), 2.93 (d, *J* = 6.82 Hz, 1H (OH)), 2.71 (s, 3H), 2.66 (d, *J* = 4.80 Hz, 1H (OH)), 2.03 (d, *J* = 1.01 Hz, 3H), 1.76 (ddd, *J* = 14.21, 7.64, 1.70 Hz, 1H), 1.68-1.51 (m, 2H), 1.60 (s, 3H), 1.48-1.42

(m, 1H), 1.36-1.28 (m, 2H), 1.14 (s, 3H), 1.06-0.98 (m, 2H), 0,88 (s, 9H), 0.83 (d, *J* = 6.57 Hz, 3H), 0.02 (s, 6H).

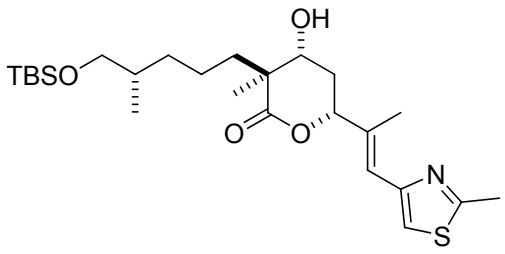
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 177.7, 164.5, 153.0, 142.0, 118.2, 115.5, 74.1, 72.4, 68.2, 51.9, 50.8, 36.9, 35.9, 35.5, 33.5, 25.9, 21.7, 19.2, 18.3, 17.3, 16.6, 15.3, -5.4.

IR (film): 2928, 2855, 1735, 1463, 1256, 1090 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{47}O_5NSSi$: 513.2944, found: 513.2951.

$[\alpha]_D^{20}$ -20.50 (*c* = 0.02, CH_2Cl_2)

(3*S*,4*R*,6*R*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-hydroxy-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-tetrahydro-pyran-2-one (218)



LiOH (1.5 mL, 1M in water, 1.5 mmol) was added to ester **232** (240 mg, 0.47 mmol) in THF (5 mL) at 0 °C and vigorously stirred for 4 h. Brine was added and the aqueous layer was acidified with 1N HCl and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to yield the crude dihydroxy acid.

R_f = 0.09 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.95 (s, 1H), 6.57 (s, 1H), 4.43 (t, *J* = 6.32 Hz, 1H), 4.03 (dd, *J* = 6.44, 5.16 Hz, 1H), 3.42 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.35 (dd, *J* = 9.98, 6.18 Hz, 1H), 2.71 (s, 3H), 2.,10 (s, 3H), 1.80-1.74 (m, 3H), 1.59 (m, 1H), 1.46-1.33 (m, 2H), 1.25 (m, 1H), 1.21 (s, 3H), 1.05 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.84 Hz, 3H), 0.03 (s, 6H).

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2664.

The residue was taken up in DCM (5 mL) and EDC·HCl (136 mg, 0.7 mmol) and DMAP (116 mg, 0.94 mmol) were added. After 3 h brine was added and the aqueous layer was extracted with DCM. The combined DCM phases were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 2:1) yielded 192 mg (85%) of lactone **218** as colorless oil.

R_f = 0.49 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.00 (s, 1H), 6,56 (s, 1H), 4.74 (dd, *J* = 9.60, 5.80 Hz, 1H), 4.20 (dd, *J* = 8.48, 6.93 Hz, 1H), 3.42 (dd, *J* = 9.86, 6.06 Hz, 1H), 3.38 (dd, *J* = 9.66, 6.26 Hz, 1H), 2.71 (s, 3H), 2.16-2.09 (m, 2H), 2.10 (d, *J* = 1.00 Hz, 3H), 1.85 (ddd, *J* = 13.72, 11.06, 4.98 Hz, 1H), 1.63 (ddd, *J* = 13.79, 11.00, 5.51 Hz, 1H), 1.59-1.54 (m, 1H), 1.45-1.26 (m, 3H), 1.29 (s, 3H), 1.26-1.17 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.80 Hz, 3H), 0.04 (s, 6H).

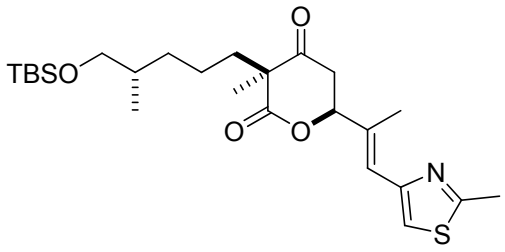
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.0, 165.0, 152.1, 136.4, 120.8, 116.9, 81.0, 68.4, 67.8, 48.7, 36.3, 35.7, 33.6, 33.3, 25.9, 22.3, 19.2, 16.7, 14.1, -5.4.

IR (film): 2953, 2928, 2856, 1712, 1250, 1087 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2671.

$[\alpha]_D^{20}$ -6.60 (*c* = 2, CH_2Cl_2)

(3*S*,6*S*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-dihydro-pyran-2,4-dione (500)



Dess-Martin periodinane (229 mg, 0.54 mmol) was added portionwise to a suspension of alcohol **218** (90 mg, 0.18 mmol) and $NaHCO_3$ (45 mg, 0.54 mmol) in DCM (3 mL) at 0 °C. After 4 h water was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 85 mg (94%) of ketone **500** as colorless oil

R_f = 0.66 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.04 (s, 1H), 6.61 (s, 1H), 4.97 (dd, *J* = 11.88, 2.28 Hz, 1H), 3.37 (dd, *J* = 9.84, 6.04 Hz, 1H), 3.33 (dd, *J* = 9.72, 6.16 Hz, 1H), 2.83 (dd, *J* = 16.31, 2.66 Hz, 1H), 2.75-2.68 (m, 1H), 2.71 (s, 3H), 2.17 (d, *J* = 1.00 Hz, 3H), 2.01-1.81 (m, 2H), 1.57-

1.49 (m, 1H), 1.46 (s, 1H), 1.40-1.17 (m, 3H), 1.07-1.00 (m, 1H), 0.88 (s, 9H), 0.81 (d, *J* = 6.84Hz, 3H), 0.02 (s, 6H).

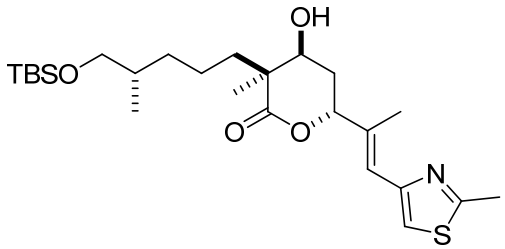
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 206.6, 173.6, 165.1, 151.7, 134.2, 122.0, 117.7, 78.2, 68.2, 56.4, 44.2, 38.4, 35.3, 33.3, 25.9, 23.6, 22.9, 19.3, 18.3, 16.5, 13.9, -5.4.

IR (film): 2928, 1751, 1718, 1257, 1140, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_4H_9]^+$ calcd for $C_{21}H_{32}O_4NSSi$: 422.1821, found: 422.1833.

$[\alpha]_D^{20}$ -23.40 (*c* = 1.0, CH_2Cl_2)

(3*S*,4*S*,6*R*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-hydroxy-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-tetrahydro-pyran-2-one (237)



Sodium boron hydride (1.5 mg, 0.041 mmol) was added to keto lactone **500** (20 mg, 0.041 mmol) in methanol (1 mL) at -78 °C. After 4 h brine was added, the mixture was warmed to r.t. and extracted with DCM. The combined DCM layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 1:1) yielded 18 mg (90%) of lactone **237** as colorless oil.

R_f = 0.68 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.99 (s, 1H), 6.58 (s, 1H), 5.23 (dd, *J* = 11.62, 3.79 Hz, 1H), 4.02 (dd, *J* = 4.03, 2.01 Hz, 1H), 3.47-3.36 (m, 2H), 2.72 (s, 3H), 2.24 (ddd, *J* = 14.00, 11.41, 2.20 Hz, 1H), 2.10 (d, *J* = 0.76 Hz, 3H), 2.02 (ddd, *J* = 14.00, 4.61, 3.79 Hz, 1H), 1.68-1.51 (m, 3H), 1.41-1.24 (m, 3H), 1.34 (s, 3H), 1.08-1.01 (m, 1H), 0.89 (s, 9H), 0.87 (d, *J* = 6.42 Hz, 3H), 0.05 (s, 6H).

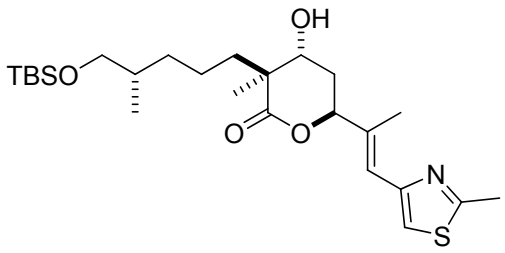
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.6, 165.0, 152.5, 136.8, 120.1, 116.7, 80.6, 70.5, 68.3, 47.2, 38.8, 35.6, 33.7, 31.4, 25.8, 21.6, 20.2, 19.1, 18.7, 16.9, 14.2, -5.3.

IR (film): 3400, 2928, 1712, 1462, 1251, 1182, 1088 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{25}H_{43}O_4NSSiNa$: 504.2580, found: 504.2589.

$[\alpha]_D^{20}$ 0.44 (*c* = 1.1, CH_2Cl_2)

(3*S*,4*R*,6*S*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-hydroxy-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-tetrahydro-pyran-2-one (233)



LiOH (2.4 mL, 1M in water, 2.4 mmol) was added to ester **231** (400 mg, 0.78 mmol) in THF (10 mL) at 0 °C and the mixture was stirred vigorously for 4 h. Brine was added and the aqueous layer was acidified with 1N HCl and extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in DCM (8 mL) and EDC·HCl (227 mg, 1.17 mmol) and DMAP (190 mg, 1.56 mmol) were added. After 4 h brine was added and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 2:1) yielded 350 mg (94%) of lactone **233** as colorless oil.

R_f = 0.56 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 6.56 (s, 1H), 5.21 (dd, *J* = 10.98, 3.92 Hz, 1H), 4.01 (dd, *J* = 4.55, 2.02 Hz, 1H), 3.40 (dd, *J* = 9.97, 6.19 Hz, 1H), 3.36 (dd, *J* = 9.85, 6.31 Hz, 1H), 2.73 (s, 3H), 2.27 (ddd, *J* = 14.11, 11.14, 2.05 Hz, 1H) 2.11 (d, *J* = 0.75 Hz, 3H), 2.04 (dt, *J* = 14.27, 4.48 Hz, 1H), 1.68-1.50 (m, 3H), 1.43-1.25 (m, 3H), 1.34 (s, 3H), 1.09-0.99 (m, 1H), 0.88 (s, 9H), 0.84 (d, *J* = 6.57 Hz, 3H), 0.02 (s, 6H).

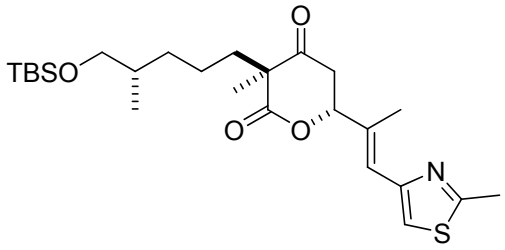
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1, 165.0, 152.1, 137.3, 119.9, 116.7, 80.6, 70.4, 68.2, 47.1, 38.7, 35.5, 33.5, 31.4, 25.9, 21.4, 19.2, 19.1, 18.3, 16.6, 14.4, -5.4.

IR (film): 2952, 1710, 1250, 1086 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2669.

$[\alpha]_D^{20}$ -0.54 (*c* = 1.4, CH_2Cl_2)

(3*S*,6*R*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-dihydro-pyran-2,4-dione (501)



Dess-Martin periodinane (178 mg, 0.42 mmol) was added potionwise to a suspension of alcohol **233** (70 mg, 0.14 mmol) and $NaHCO_3$ (35 mg, 0.42 mmol) in DCM (2 mL) at 0 °C. After 4 h water was added, layers were separated and the aqueous layer was extracted with DCM. The combined DCM phases were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 66 mg (94%) of ketone **501** as colorless oil.

R_f = 0.87 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1H), 6.60 (s, 1H), 5.01 (dd, *J* = 11.11, 3.03 Hz, 1H), 3.41-3.34 (m, 2H), 2.87 (dd, *J* = 16.17, 11.12 Hz, 1H), 2.77 (dd, *J* = 16.42, 3.28 Hz, 1H), 2.72 (s, 3H), 2,17 (d, *J* = 1.26 Hz, 3H), 1.99 (ddd, *J* = 13.20, 11.94, 4.48 Hz, 1H), 1.73 (ddd, *J* = 12.94, 12.94, 3.72 Hz, 1H), 1.60-1.52 (m, 2H), 1.42 (s, 1H), 1.43-1.17 (m, 3H), 1.10-1.02 (m, 1H), 0.89 (s, 9H), 0.84 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

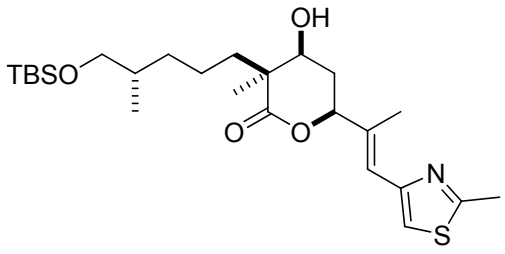
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.9, 173.7, 165.1, 151.8, 134.4, 121.9, 117.8, 78.0, 68.1, 57.0, 42.2, 37.6, 35.4, 33.1, 26.0, 22.7, 22.1, 19.3, 18.3, 16.6, 14.0, -5.4.

IR (film): 2953, 2928, 1749, 1716, 1256, 1090 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{24}H_{38}O_4NSSi$: 464.2281, found: 464.2279.

$[\alpha]_D^{20}$ 6.89 (*c* = 1.2, CH_2Cl_2)

(3*S*,4*S*,6*S*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-hydroxy-3-methyl-6-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-tetrahydro-pyran-2-one (181)



Sodium borohydride (13 mg, 0.3 mmol) was added to keto lactone **501** (150 mg, 0.3 mmol) in methanol (4 mL) at -78 °C. After 5 h brine was added, the mixture was warmed to r.t. and extracted with DCM. The combined DCM layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 1:1) yielded 140 mg (93%) of lactone **181** as colorless oil.

R_f = 0.48 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 6.55 (s, 1H), 4.75 (dd, *J* = 11.37, 4.04 Hz, 1H), 4.02 (dd, *J* = 11.11, 4.29 Hz, 1H), 3.42 (dd, *J* = 9.72, 5.94 Hz, 1H), 3.36 (dd, *J* = 9.72, 6.44 Hz, 1H), 2.71 (s, 3H), 2.27-2.18 (m, 1H) 2.10 (d, *J* = 1.01 Hz, 3H), 2.13-2.06 (m, 1H), 1.75-1.55 (m, 3H), 1.48-1.26 (m, 3H), 1.37 (s, 3H), 1.11-1.01 (m, 1H), 0.88 (s, 9H), 0.86 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.3, 165.0, 152.0, 136.5, 120.6, 116.9, 81.2, 72.5, 68.3, 47.7, 35.6, 33.7, 33.0, 32.7, 25.9, 21.8, 20.9, 19.2, 18.3, 16.6, 14.0, -5,4.

IR (film): 3420, 2954, 1727, 1250, 1127, 1078 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2676.

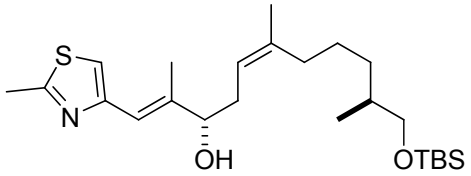
$[\alpha]_D^{20}$ -11.45 (*c* = 2.0, CH_2Cl_2)

General procedure for the fragmentation reactions:

To a 0.1M solution of *β*-hydroxy lactone (1 eq.) in Et_2O:Et_3N (10:1) at 0 °C under argon was added MsCl (1.5 eq.). After 1.5 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in THF (0.1M) and LiOH (3 eq., 1M in water) was added at 0 °C. After TLC showed completion, normally 1 to 2 h, a saturated

NH_4Cl solution was added, layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated.

(1*E*,5*Z*)-(3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-1-(2-methyl-thiazol-4-yl)-undeca-1,5-dien-3-ol (235)



To a solution of *β*-hydroxy lactone **181** (25 mg, 0.05 mmol) in Et_2O:Et_3N (10:1, 1 mL) at 0 °C under argon was added MsCl (6 µL, 0.07 mmol). After 1.5 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in THF (1 mL) and LiOH (0.15 mL, 1M in water, 0.15 mmol) was added at 0 °C. After 1 h a saturated NH_4Cl solution was added, the layers were separated and the aqueous phase was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 17.5 mg (81%) of di-olefin **235** as colorless oil.

R_f = 0.72 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.94 (s, 1H), 6.56 (s, 1H), 5.16 (t, *J* = 7.08 Hz, 1H), 4.14 (t, *J* = 6.30 Hz, 1H), 3.43 (dd, *J* = 9.46, 5.42 Hz, 1H), 3.35 (dd, *J* = 9.84, 6.56 Hz, 1H), 2.71 (s, 3H), 2.35 (t, *J* = 6.56 Hz, 2H), 2.05 (d, *J* = 1.28 Hz, 3H), 2.03 (t, *J* = 6.94 Hz, 2H), 1.71 (d, *J* = 1.24 Hz, 3H), 1.62-1.54 (m, 1H), 1.44-1.31 (m, 3H), 1.10-1.01 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.84 Hz, 3H), 0.02 (s, 6H).

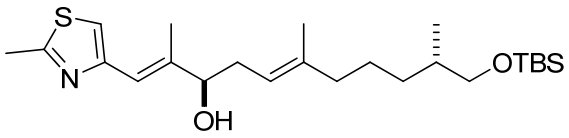
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 164.5, 152.9, 141.7, 139.5, 120.1, 118.8, 115.4, 77.2, 68.3, 65.8, 35.7, 34.1, 33.1, 32.3, 26.0, 25.5, 19.2, 18.4, 16.7, 15.2, 14.5, -5.3.

IR (film): 3390, 2955, 2928, 1256, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{43}O_2NSSi$: 437.2784, found: 437.2779.

$[\alpha]_D^{20}$ -8.20 (*c* = 0.5, CH_2Cl_2)

(1*E*,5*E*)-(3*R*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-1-(2-methyl-thiazol-4-yl)-undeca-1,5-dien-3-ol (240)



R_f = 0.39 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.56 (s, 1H), 5.17 (t, *J* = 7.34 Hz, 1H), 4.16 (t, *J* = 6.18 Hz, 1H), 3.42 (dd, *J* = 9.72, 5.96 Hz, 1H), 3.34 (dd, *J* = 9.82, 6.62 Hz, 1H), 2.71 (s, 3H), 2.36 (t, *J* = 6.82 Hz, 2H), 2.06 (s, 3H), 1.99 (t, *J* = 6.80 Hz, 2H), 1.64 (s, 3H), 1.61-1.53 (m, 1H), 1.46-1.23 (m, 3H), 1.06-0.96 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 6.56 Hz, 3H), 0.03 (s, 6H).

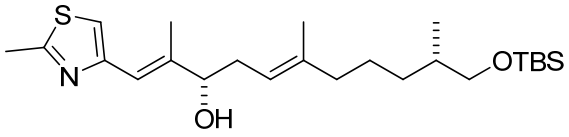
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.7, 153.0, 141.7, 139.3, 119.5, 118.9, 115.4, 77.2, 68.4, 40.2, 35.7, 34.4, 32.8, 29.7, 26.0, 25.4, 19.2, 16.7, 16.3, 14.4, -5.3.

IR (film): 2928, 2357, 1255, 1091 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{43}O_2NSSi$: 437.2784, found: 437.2776.

$[\alpha]_D^{20}$ 5.10 (*c* = 1.0, CH_2Cl_2)

(1*E*,5*E*)-(3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-1-(2-methyl-thiazol-4-yl)-undeca-1,5-dien-3-ol (243)



R_f = 0.36 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.56 (s, 1H), 5.17 (t, *J* = 7.20 Hz, 1H), 4.16 (t, *J* = 6.34 Hz, 1H), 3.42 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.34 (dd, *J* = 9.60, 6.06 Hz, 1H), 2.71 (s, 3H), 2.36 (t, *J* = 6.82 Hz, 2H), 2.06 (d, *J* = 1.26 Hz, 3H), 2.00 (t, *J* = 7.32 Hz, 2H), 1.78 (d, *J* = 3.28 Hz, 1H), 1.64 (s, 3H), 1.60-1.53 (m, 1H), 1.46-1.30 (m, 3H), 1.06-1.00 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

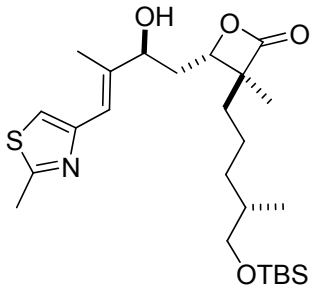
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.6, 153.0, 141.7, 139.4, 119.5, 118.9, 115.4, 77.2, 68.4, 40.2, 35.7, 34.4, 32.9, 26.0, 25.4, 19.2, 18.3, 16.7, 16.2, 14.5, -5.3.

IR (film): 2954, 2928, 1471, 1255, 1092 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{43}O_2NSSi$: 437.2784, found: 437.2785.

$[\alpha]_D^{20}$ -9.06 (*c* = 0.85, CH_2Cl_2)

(3*S*,4*S*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-[(*E*)-(*S*)-2-hydroxy-3-methyl-4-(2-methyl-thiazol-4-yl)-but-3-enyl]-3-methyl-oxetan-2-one (244)



R_f = 0.24 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 6.06 (s, 1H), 4.66 (dd, *J* = 9.35, 3.28 Hz, 1H), 4.36 (dt, *J* = 8.96, 3.09 Hz, 1H), 3.43-3.36 (m, 2H), 2.71 (s, 3H), 2.07 (d, *J* = 3.28 Hz, 1H), 2.06 (d, *J* =1.01 Hz, 3H), 2.00-1.86 (m, 2H), 1.74-1.67 (m, 2H), 1.62-1.56 (m, 2H), 1.49-1.34 (m, 3H), 1.26 (s, 3H), 1.14-1.05 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

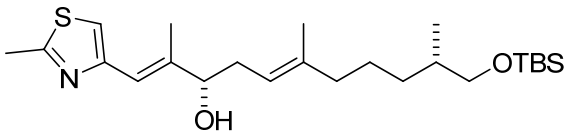
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.0, 164.8, 152.5, 141.5, 119.0, 116.1, 78.4, 73.6, 68.2, 57.4, 36.4, 36.1, 35.6, 33.3, 25.9, 21.7, 19.2, 18.3, 16.6, 14.8, 14.4, -5.4.

IR (film): 2954, 2528, 1820, 1094 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2672.

$[\alpha]_D^{20}$ -25.90 (*c* = 1.35, CH_2Cl_2)

(1*E*,5*E*)-(3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-1-(2-methyl-thiazol-4-yl)-undeca-1,5-dien-3-ol (243)



β-lactone **244** (10 mg, 0.02 mmol) in DMF (1 mL) was heated at reflux for 2 h. Water was added and the aqueous layer was extracted with hexane:Et_2O (1:1). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 5:1) yielded 5 mg (57%) of olefin **243**, whose data were identical with those of **243** obtained by fragmentation.

R_f = 0.35 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.94 (s, 1H), 6.56 (s, 1H), 5.17 (t, *J* = 7.20 Hz, 1H), 4.16 (t, *J* = 6.34 Hz, 1H), 3.42 (dd, *J* = 9.72, 5.92 Hz, 1H), 3.34 (dd, *J* = 9.60, 6.06 Hz, 1H), 2.71 (s, 3H), 2.36 (t, *J* = 6.82 Hz, 2H), 2.06 (d, *J* = 1.26 Hz, 3H), 2.00 (t, *J* = 7.32 Hz, 2H), 1.78 (d, *J* = 3.28 Hz, 1H), 1.64 (s, 3H), 1.60-1.53 (m, 1H), 1.46-1.30 (m, 3H), 1.06-1.00 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

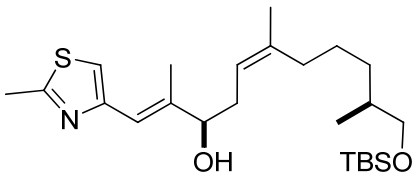
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 164.6, 153.0, 141.7, 139.4, 119.5, 118.9, 115.4, 77.2, 68.4, 40.2, 35.7, 34.4, 32.9, 26.0, 25.4, 19.2, 18.3, 16.7, 16.2, 14.5, -5.3.

IR (film): 2929, 1471, 1255, 1092 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{43}O_2NSSi$: 437.2784, found: 437.2776.

$[\alpha]_D^{20}$ -10.60 (*c* = 0.15, CH_2Cl_2)

(1*E*,5*Z*)-(3*R*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-1-(2-methyl-thiazol-4-yl)-undeca-1,5-dien-3-ol (248)



R_f = 0.36 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.56 (s, 1H), 5.17 (t, *J* = 7.20 Hz, 1H), 4.14 (dt, *J* = 6.60, 2.68 Hz, 1H), 3.43 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.36 (dd, *J* = 9.85, 6.57 Hz, 1H), 2.71 (s, 3H), 2.35 (t, *J* = 6.95 Hz, 2H), 2.05 (d, *J* = 1.26 Hz, 3H), 2.09-1.97 (m, 2H), 1.71 (d, *J* = 1.01 Hz, 1H), 1.61-1.53 (m, 1H), 1.46-1.26 (m, 3H), 1.09-1.00 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.57 Hz, 3H), 0.03 (s, 6H).

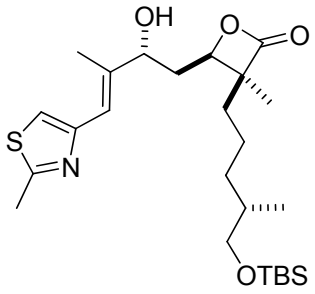
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 164.6, 153.0, 141.7, 139.5, 120.15, 118.9, 115.4, 77.3, 68.3, 40.2, 35.7, 34.1, 33.1, 32.3, 26.0, 25.4, 23.6, 22.7, 19.2, 18.3, 16.7, 14.5, -5.3.

IR (film): 2955, 2929, 1472, 1256, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{43}O_2NSSi$: 437.2784, found: 437.2783.

$[\alpha]_D^{20}$ 1.73 (*c* = 0.75, CH_2Cl_2)

(3*S*,4*R*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-[(*E*)-(*R*)-2-hydroxy-3-methyl-4-(2-methyl-thiazol-4-yl)-but-3-enyl]-3-methyl-oxetan-2-one (248)



R_f = 0.21 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 6.00 (s, 1H), 4.57 (dd, *J* = 8.46, 4.42 Hz, 1H), 4.37 (dd, *J* = 8.33, 4.56 Hz, 1H), 3.41 (dd, *J* = 9.90, 5.86 Hz, 1H), 3.37 (dd, *J* = 9.72, 6.20 Hz, 1H), 2.71 (s, 3H), 2.07 (s, 3H), 2.00-1.94 (m, 2H), 1.76-1.54 (m, 3H), 1.49-1.25 (m, 3H), 1.43 (s, 3H), 1.12-1.04 (m, 1H), 0.88 (s, 9H), 0.86 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

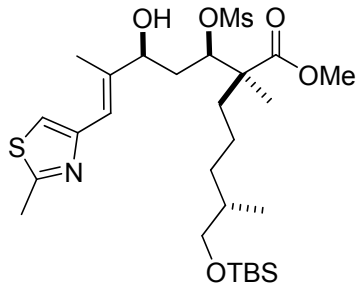
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8, 164.9, 152.5, 141.4, 119.0, 116.1, 80.7, 73.7, 56.8, 35.9, 35.5, 33.6, 25.9, 21.5, 19.6, 19.1, 18.3, 16.6, 14.4, -5.4.

IR (film): 2953, 1820, 1175, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2688.

$[\alpha]_D^{20}$ 14.40 (*c* = 0.5, CH_2Cl_2)

(*E*)-(2*S*,3*R*,5*s*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-5-hydroxy-2,6-dimethyl-3-(methylsulfonyloxy)-7-(2-methyl-thiazol-4-yl)-hept-6-enoic acid methyl ester (236)



To *β*-hydroxy lactone **234** (18 mg, 0.035 mmol) in Et_2O:NEt_3 (10:1, 1 mL) at 0 °C under argon was added MsCl (0.05 mL, 1M in Et_2O, 0.053 mmol). After 1.5 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in methanol (1 mL) and KOH (0.07 mL, 1M in water, 0.070 mmol) was added at 0 °C. After 1.5 h a saturated NH_4Cl solution was added, layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 1:1) furnished 15 mg (72%) of methyl ester **236**.

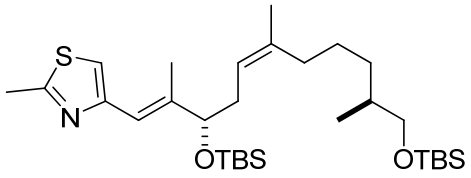
R_f = 0.38 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.97 (s, 1H), 6.61 (s, 1H), 5.13 (dd, *J* = 7.32, 3.28 Hz, 1H), 4.38 (dd, *J* = 7.32, 5.32 Hz, 1H), 3.70 (s, 3H), 3.37 (ddd, *J* = 14.49, 9.77, 5.97 Hz, 1H), 3.06 (s, 3H), 2.71 (s, 3H), 2.06 (s, 3H), 2.01 (m, 1H), 1.97-1.92 (m, 1H), 1.72-1.61 (m, 1H), 1.58-1.49 (m, 1H), 1.41-1.32 (m, 2H), 1.30-1.21 (m, 1H), 1.23 (s, 3H), 1.07-0.97 (m, 2H), 0.88 (s, 9H), 0.83 (d, *J* = 6.60 Hz, 3H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.7, 164.8, 152.5, 140.5, 120.1, 116.3, 85.1, 75.8, 68.0, 52.1, 51.6, 39.0, 36.8, 36.0, 35.4, 33.4, 25.9, 21.8, 19.2, 18.3, 16.5, 15.9, 13.8, -5.4.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{27}H_{49}O_7NS_2Si$: 591.2720, found: 591.2732.

4-[(1*E*,5*Z*)-(3*S*,10*S*)-3,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-undeca-1,5-dienyl]-2-methyl-thiazole (33)



To a stirred solution of alcohol **235** (15 mg, 0.034 mmol) in DCM (1 mL) was added 2,6-lutidine (9 µL, 0.051 mmol) and TBSOTf (10 µL, 0.041 mmol). After 1 h the reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 16 mg (85%) of protected **33** as colorless oil.

$\mathbf{R_f}$ = 0.45 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 6.45 (s, 1H), 5.13 (t, *J* = 7.07 Hz, 1H), 4.08 (t, *J* = 6.57 Hz, 1H), 3.44 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.34 (dd, *J* = 9.72, 6.69 Hz, 1H), 2.71 (s, 3H), 2.30-2.20 (m, 2H), 2.04-1.94 (m, 2H), 2.00 (d, *J* = 1.16 Hz, 3H), 1.66 (d, *J* = 1.01 Hz, 3H), 1.61-1.53 (m, 1H), 1.43-1.28 (m, 3H), 1.08-1.00 (m, 1H), 0.89 (s, 18H), 0.86 (d, *J* = 6.56 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H).

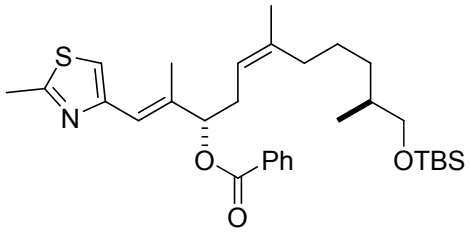
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.3, 153.3, 142.6, 136.9, 121.4, 118.7, 114.9, 79.1, 68.4, 35.8, 35.3, 33.2, 32.3, 25.9, 25.8, 25.4, 23.5, 19.2, 18.4, 18.2, 16.7, 13.9, -4.6, -4.9, -5.3.

IR (film): 2955, 2929, 1471, 1256, 1091 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{30}H_{57}O_2Si_2NS$: 551.3849, found: 551.3635.

$[\alpha]_D^{20}$ 3.50 (*c* = 1.1, CH_2Cl_2)

Benzoic acid (*Z*)-(1*S*,8*S*)-9-(*tert*-butyl-dimethyl-silanyloxy)-4,8-dimethyl-1-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-non-3-enyl ester (249)



To a solution of *β*-hydroxy lactone **234** (30 mg, 0.06 mmol) in Et_2O:NEt_3 (10:1, 1.5 mL) at 0 °C was added MsCl (17 µL, 0.09 mmol). After 1 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in THF (1 mL) and PhLi (0.18 ml, 1M in dibutyl ether, 0.18 mmol) was added at -78 °C. After 3 h a saturated NH_4Cl solution was added, layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 14 mg (43%) of product **249** and 5 mg (19%) of free alcohol **235**.

R_f = 0.88 (hexane:EtOAc = 3:1)

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* = 8.07 (m, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 6.95 (s, 1H), 6.60 (s, 1H), 5.47 (t, *J* = 6.78 Hz, 1H), 5.15 (t, *J* = 6.60 Hz, 1H), 3.43 (dd, *J* = 9.63, 5.85 Hz, 1H), 3.34 (dd, *J* = 9.60, 6.60 Hz, 1H), 2.70 (s, 3H), 2.64-2.59 (m, 1H), 2.54-2.50 (m, 1H), 2.15 (d, *J* = 1.51 Hz, 3H), 2.07-1.98 (m, 2H), 1.66 (d, *J* = 1.08 Hz, 3H), 1.56 (m, 1H), 1.42-1.24 (m, 3H), 1.07-1.02 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.78 Hz, 3H), 0.03 (s, 6H).

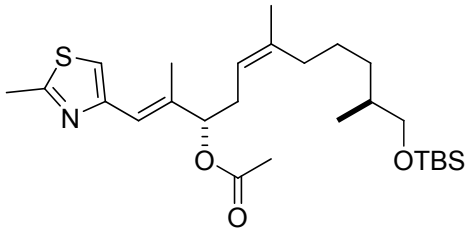
^{13}C-NMR (150 MHz, $CDCl_3$): *δ* = 165.7, 164.5, 152.6, 138.6, 137.6, 132.8, 130.6, 129.7, 128.3, 120.6, 119.3, 116.2, 79.6, 68.3, 35.8, 33.1, 32.3, 31.8, 25.9, 25.4, 23.5, 22.6, 19.2, 16.7, 14.9, -5.3.

IR (film): 2955, 2360, 2343, 1718, 1654, 1458, 1271 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{31}H_{47}O_3SiNS$: 541.3046, found: 541.3055.

$[\alpha]_D^{20}$ 5.20 (*c* = 0.25, CH_2Cl_2)

Acetic acid (*Z*)-(1*S*,8*S*)-9-(*tert*-butyl-dimethyl-silanyloxy)-4,8-dimethyl-1-[(*E*)-1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-non-3-enyl ester (250)



To a solution of *β*-hydroxy lactone **234** (18 mg, 0.036 mmol)) in Et_2O:NEt_3 (10:1, 1 mL) at 0 °C under argon was added MsCl (4 µL, 0.052 mmol). After 1 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in THF (1 mL) and MeLi (36 µL, 1.6 M in Et_2O, 0.054 mmol) was added at -78 °C. After 5 h a saturated NH_4Cl solution was added, layers were separated and the aqueous extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 4 mg (23%) of product **250** and 8 mg (51%) of free alcohol **235**.

R_f = 0.70 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.94 (s, 1H), 6.51 (s, 1H), 5.23 (t, *J* = 6.78 Hz, 1H), 5.07 (t, *J* = 6.76 Hz, 1H), 3.44 (dd, *J* = 9.78, 6.02 Hz, 1H), 3.35 (dd, *J* = 9.65, 6.64 Hz, 1H), 2.70 (s, 3H), 2.49-2.34 (m, 2H), 2.08 (d, *J* = 1.20 Hz, 3H), 2.06 (s, 3H), 2.00 (t, *J* = 7.02 Hz, 2H), 1.67 (d, *J* = 1.24 Hz, 3H), 1.57 (m, 1H), 1.42-1.32 (m, 3H), 1.05 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.52 Hz, 3H), 0.03 (s, 6H).

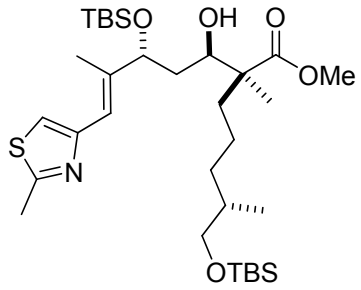
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 170.2, 164.5, 152.7, 138.5, 137.6, 120.5, 119.3, 116.1, 78.9, 68.3, 35.7, 33.1, 32.3, 31.7, 29.7, 25.9, 25.4, 23.5, 21.2, 19.2, 18.3, 16.7, 14.9, -5.3.

IR (film): 2929, 1508, 1458, 1238.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{26}H_{45}O_3SiNS$: 479.2889, found: 479.2899.

$[\alpha]_D^{20}$ -12.00 (*c* = 0.1, CH_2Cl_2)

(*E*)-(2*S*,3*R*,5*S*)- 5-tert-butyldimethylsilanyloxy-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-hydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-hept-6-enoic acid methyl ester (502)



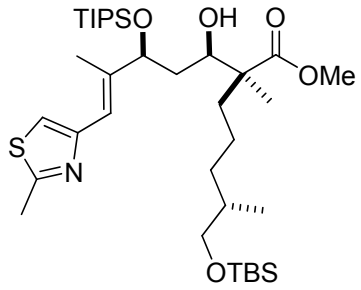
To a stirred solution of diol **232** (30 mg, 0.058 mmol) and imidazole (8 mg, 0.120 mmol) in DMF (1 mL) at r.t. was added TBSCl (8 mg, 0.063 mmol) and stirring was continued for 48 h. The reaction mixture was quenched with water and extracted with Et_2O. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) furnished 15 mg (41%) of monoprotected product **502**.

R_f = 0.60 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.46 (s, 1H), 4.41 (dd, *J* = 8.84, 4.52 Hz, 1H), 3.92 (d, *J* = 10.12 Hz, 1H), 3.65 (s, 3H), 3.41 (dd, *J* = 9.72, 5.68 Hz, 1H), 3.33 (dd, *J* = 9.72, 6.44 Hz, 1H), 2.70 (s, 3H), 1.99 (d, *J* = 0.76 Hz, 3H), 1.77-1.68 (m, 2H), 1.58 (m, 1H), 1.53-1.44 (m, 2H), 1.38-1.21 (m, 2H), 1.12 (s, 3H), 1.10-0.97 (m, 2H), 0.91 (s, 9H), 0.88 (s, 9H), 0.83 (d, *J* = 6.56 Hz, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.6, 164.5, 152.7, 141.4, 119.7, 115,.6, 79.9, 74.7, 68.3, 51.5, 51.1, 38.9, 36.8, 35.5, 33.5, 25.9, 25.8, 21.9, 19.2, 18.3, 18.1, 16.6, 15.9, 13.7, -4.4, -5.1, -5.4.

(*E*)-(2*S*,3*R*,5*S*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-hydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-5-triisopropylsilanyloxy-hept-6-enoic acid methyl ester (257)



To a stirred solution of dihydroxy ester **231** (110 mg, 0.22 mmol) in DCM (4 mL) was added 2,6-lutidine (58 µL, 0.48 mmol) and TIPSOTf (68 µL, 0.24 mmol). After 1.5 h the reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 125 mg (85%) of **257** as colorless oil.

R_f = 0.70 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 6.52 (s, 1H), 4.55 (t, *J* = 6.82 Hz, 1H), 3.79 (dd, *J* = 9.73, 3.92 Hz, 1H), 3.65 (s, 3H), 3.39 (dd, *J* = 9.60, 5.81 Hz, 1H), 3.32 (dd, *J* = 9.73, 6.44 Hz, 1H), 2.75 (d, *J* = 3.74 Hz,1H), 2.71 (s, 3H), 1.99 (d, *J* = 1.01 Hz, 3H), 1.78-1.66 (m, 2H), 1.61-1.50 (m, 2H), 1.48-1.40 (m, 1H), 1.36-1.21 (m, 3H), 1.12 (s, 3H), 1.06 (s, 21H), 1.07-0.97 (m, 1H), 0.88 (s, 9H), 0.82 (d, *J* = 6.57 Hz, 3H), 0.02 (s, 6H).

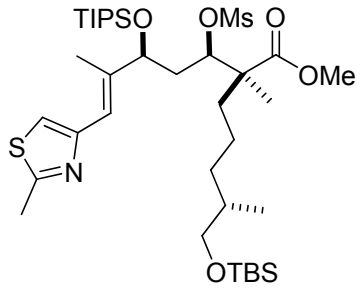
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8, 168.4, 152.9, 141.3, 120.1, 115.4, 78.3, 73.6, 68.4, 51.7, 50.9, 40.5, 39.0, 36.5, 35.5, 33.5, 25.9, 22.0, 19.2, 18.1, 16.5, 13.6, 12.5, -0.4, -5.4.

IR (film): 2948, 2865, 1734, 1465, 1256, 1088 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{43}O_4NSSi$: 481.2682, found: 481.2688.

$[\alpha]_D^{20}$ -0.22 (*c* = 0.9, CH_2Cl_2)

(*E*)-(2*S*,3*R*,5*S*)-2-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-methanesulfonyloxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-5-triisopropylsilanyloxy-hept-6-enoic acid methyl ester (251)



To alcohol **257** (95 mg, 0.14 mmol) in Et_2O:NEt_3 (10:1, 3 mL) at r.t. was added mesyl chloride (38 µL, 0.42 mmol) and the mixture was stirred for 2 h. Brine was added, the layers were separated and the aqueous layer was extracted with Et_2O. The ethereal layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 100 mg (96%) of **251** as colorless oil.

R_f = 0.41 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1H), 6.63 (s, 1H), 4.84 (t, *J* = 8.84 Hz, 1H), 4.59 (dd, *J* = 10.74, 3.66 Hz, 1H), 3.61 (s, 3H), 3.38 (dd, *J* = 9.73, 5.94 Hz, 1H), 3.31 (dd, *J* = 9.85, 6.31 Hz, 1H), 3.05 (s, 3H), 2.71 (s, 3H), 2.03-1.94 (m, 1H), 1.98 (d, *J* = 1.01 Hz, 3H), 1.84-1.74 (m, 2H), 1.56-1.48 (m, 2H), 1.46-1.23 (m, 3H), 1.17 (s, 3H), 1.05 (s, 21H), 1.07-0.97 (m, 1H), 0.87 (s, 9H), 0.81 (d, *J* = 6.57 Hz, 3H), 0.01 (s, 6H).

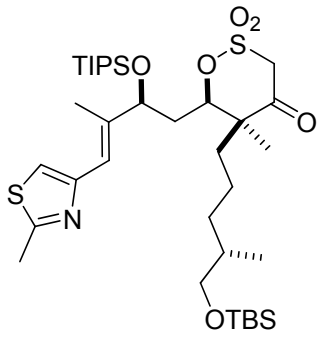
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4, 164.2, 153.8, 144.9, 138.8, 121.9, 116.2, 83.3, 79.9, 75.2, 68.4, 63.1, 52.1, 51.5, 36.7, 35.6, 33.4, 32.8, 25.9, 19.4, 18.1, 16.7, 15.9, 12.2, -5.4.

IR (film): 2951, 2865, 1736, 1340, 1174 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{36}H_{69}O_7NS_2Si_2Na$: 770.3952, found: 770.3968.

$[\alpha]_D^{20}$ 14.27 (*c* = 0.55, CH_2Cl_2)

(5*S*,6*R*)-5-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-5-methyl-6-[(*E*)-(*S*)-3-methyl-4-(2-methyl-thiazol-4-yl)-2-triisopropylsilanyloxy-but-3-enyl]-2,2-dioxo-2λ^6-[1,2]oxathian-4-one (252)



Ester **251** (15 mg, 0.02 mmol) in toluene (1 mL) was treated with KOTMS (5 mg, 0.04 mmol) and heated under reflux for 1 h. After cooling to r.t. a saturated solution of NH_4Cl was added and layers were separated. The aqueous layer was repeatedly extracted with DCM, combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 10 mg (70%) of cyclic product **252** and traces of olefin **253**.

R_f = 0.50 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.95 (s, 1H), 6.44 (s, 1H), 4.52 (dd, *J* = 9.86, 3.78 Hz, 1H), 4.24 (d, *J* = 9.84 Hz, 1H), 4.08 (d, *J* = 13.92 Hz, 1H), 3.96 (d, *J* = 13.65 Hz, 1H), 3.37 (dd, *J* = 5.94, 2.40 Hz, 2H), 2.70 (s, 3H), 2.14-1.91 (m, 3H), 2.06 (s, 3H), 1.64-1.48 (m, 2H), 1.34-1.23 (m, 2H), 1.07 (s, 3H), 1.06 (s, 21H), 0.89 (s, 9H), 0.83 (d, *J* = 6.56 Hz, 3H), 0.03 (s, 6H).

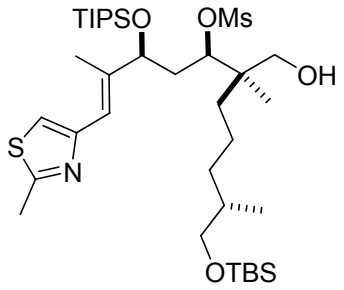
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 197.2, 164.5, 152.7, 137.8, 121.7, 116.8, 83.2, 75.7, 67.9, 59.7, 52.0, 35,5, 34.6, 33.6, 31.5, 25.9, 22.6, 19.4, 18.1, 18.0, 16.6, 16.3, 12.2, -5.4.

IR (film): 2945, 2360, 1726, 1383, 1085 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{35}H_{65}O_6NS_2Si_2Na$: 738.3690, found: 738.3695.

$[\alpha]_D^{20}$ 52.86 (*c* = 0.35, CH_2Cl_2)

Methanesulfonic acid (1*R*,2*R*,6*S*)-7-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxymethyl-2,6-dimethyl-1-[(*E*)-(*S*)-3-methyl-4-(2-methyl-thiazol-4-yl)-2-triisopropylsilanyloxy-but-3-enyl]-heptyl ester (503)



To a solution of ester **251** (90 mg, 0.12 mmol) in toluene (2 mL) at -78 °C was slowly added DIBALH (0.1 mL, 1.5M in toluene, 0.14 mmol). After 3 h the reaction mixture was quenched by the addition of methanol and potassium sodium tartrate solution was added and stirring was continued for 2 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 75 mg (87%) of alcohol **503** as colorless oil.

R_f = 0.23 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.64 (s, 1H), 4.70 (d, *J* = 7.56 Hz, 1H), 4.66 (dd, *J* = 10.34, 3.78 Hz, 1H), 3.57 (d, *J* = 11.88 Hz, 1H), 3.42 (dd, *J* = 9.84, 6.04 Hz, 1H), 3.34 (dd, *J* = 9.72, 6.44 Hz, 1H), 3.33 (d, *J* = 12.64 Hz, 1H), 3.07 (s, 3H), 2.70 (s, 3H), 2.07 (m, 1H), 2.02 (s, 3H), 1.91 (ddd, *J* = 15.40, 8.72, 3.92 Hz, 1H), 1.56 (m, 1H), 1.40-1.19 (m, 5H), 1.07 (s, 3H), 1,05 (s, 21H), 0.99 (m, 1H), 0.89 (s, 9H), 0.84 (d, *J* = 6.80 Hz, 3H), 0.03 (s, 6H).

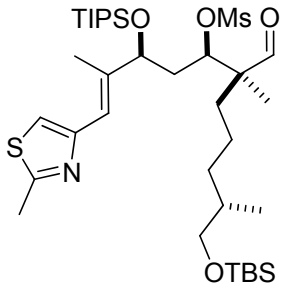
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.4, 152.9, 139.3, 121.9, 116.1, 83.9, 75.4, 68.3, 66.5, 42.4, 38.6, 37.4, 35.6, 34.3, 32.8, 25.9, 20.7, 19.4, 19.2, 18.1, 18.0, 16.6, 12.2, -5.4.

IR (film): 3368, 2944, 2893, 2865, 1464, 1334, 1171, 1083, 1062 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{35}H_{69}O_6NS_2Si_2$: 719.4105, found: 719.4112.

$[\alpha]_D^{20}$ 20.17 (*c* = 1.2, CH_2Cl_2)

Methanesulfonic acid (1*R*,2*S*,6*S*)-7-(*tert*-butyl-dimethyl-silanyloxy)-2-formyl-2,6-dimethyl-1-[(*E*)-(*S*)-3-methyl-4-(2-methyl-thiazol-4-yl)-2-triisopropylsilanyloxy-but-3-enyl]-heptyl ester (254)



Dess-Martin periodinane (87 mg, 0.21 mmol) was added portion wise to a suspension of alcohol **503** (50 mg, 0.07 mmol) and $NaHCO_3$ (52 mg, 0.63 mmol) in DCM (3 mL) at 0 °C. After 2 h water was added, layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 47 mg (94%) of aldehyde **254** as colorless oil.

R_f = 0.59 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H), 6.98 (s, 1H), 6.65 (s, 1H), 4.78 (dd, *J* = 5.82, 4.54 Hz, 1H), 4.62 (dd, *J* = 7.84, 6.32 Hz, 1H), 3.37 (dd, *J* = 9.98, 6.18 Hz, 1H), 3.32 (dd, *J* = 9.72, 6.20 Hz, 1H), 3.03 (s, 3H), 2.70 (s, 3H), 2.02 (s,3H), 1.95 (dd, *J* = 6.82, 5.58 Hz, 2H), 1.71 (dq, *J* = 12.96, 4.60 Hz, 1H), 1.52 (m, 1H), 1.46-1.32 (m, 4H), 1.27-1.14 (m, 2H), 1.08 (s, 3H), 1.04 (s, 21H), 0.88 (s, 9H), 0.80 (d, *J* = 6.80 Hz, 3H), 0.02 (s, 6H).

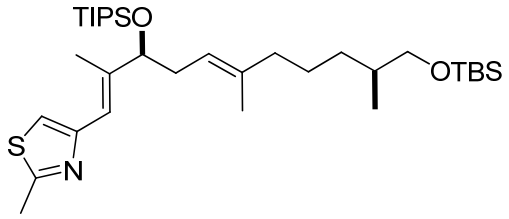
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.2, 164.3, 153.0, 138.6, 122.4, 116.5, 81.6, 75.2, 68.2, 53.5, 38.9, 37.9, 35.5, 33.8, 32.4, 25.9, 21.2, 19.3, 18.1, 17.9, 16.6, 16.0, 12.5, 12.2, -5.4.

IR (film): 2945, 2865, 1731, 1463, 1339, 1174, 1085, 1064 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{35}H_{67}O_6NS_2Si_2$: 717.3948, found: 717.3943.

$[\alpha]_D^{20}$ 23.58 (*c* = 0.95, CH_2Cl_2)

4-[(1*E*,5*E*)-(3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-3-triisopropylsilanyloxy-undeca-1,5-dienyl]-2-methyl-thiazole (253)



To aldehyde **254** (25 mg, 0.035 mmol) in THF (1 mL) was added LiOH (0.1 mL, 1M in water, 0.1 mmol) at 0 °C. After 6 h a saturated NH_4Cl solution was added, layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 17 mg (82%) of olefin **253** as colorless oil.

R_f = 0.60 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.90 (s, 1H), 6,43 (s, 1H), 5.09 (t, *J* = 7.17 Hz, 1H), 4.24 (t, *J* = 6.60 Hz, 1H), 3.40 (dd, *J* = 9.81, 6.03 Hz, 1H), 3.30 (dd, *J* = 9.84, 6.78 Hz, 1H), 2.70 (s, 3H), 2.38-2.34 (m, 1H), 2.33-2.28 (m, 1H), 2.00 (d, *J* = 1.14 Hz, 3H), 1.94-1.88 (m, 2H), 1.57 (s, 3H), 1.52 (m, 1H), 1.39-1.35 (m, 1H), 1.32-1.25 (m, 3H), 1.06 (s, 11H), 1.04 (s, 10H), 1.00-0.95 (m, 1H), 0.88 (s, 9H), 0.81 (d, *J* = 6.78 Hz, 3H), 0.02 (s, 6H).

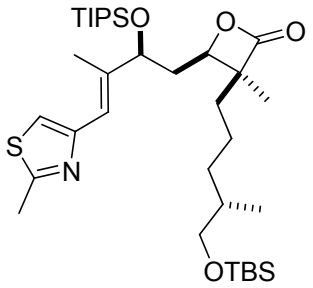
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 164.1, 153.2, 142.2, 136.8, 120.2, 119.1, 114.7, 78.8, 68.4, 40.2, 35.7, 35.6, 32.9, 29.7, 25.9, 25.4, 19.2, 18.3, 18.1, 18.0, 16.7, 16.2, 12.4, -5.3.

IR (film): 2928, 2864, 1463, 1255, 1091, 1064 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{33}H_{63}O_2NSSi_2$: 593.4118, found: 593.4125.

$[\alpha]_D^{20}$ 8.12 (*c* = 0.85, CH_2Cl_2)

(3*S*,4*R*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-3-methyl-4-[(*E*)-(*S*)-3-methyl-4-(2-methyl-thiazol-4-yl)-2-triisopropylsilanyloxy-but-3-enyl]-oxetan-2-one (259)



β-Hydroxy ester **257** (25 mg, 0.036 mmol) and 1-hydroxy-3-(isothiocyanato) tetrabutyldistannane (**258**) (4 mg, 0.007 mmol) in toluene (1 mL) were refluxed for 48 h. The solvent was removed under reduced pressure and column chromatography (hexane:EtOAc = 10 : 1) gave 15 mg (65%) of *β*-lactone **259** and additionally 2 mg (9%) of olefin **260**.

R_f = 0.36 (hexane:EtOAc = 10:1)

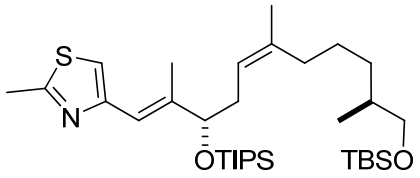
^{1}H-NMR (600 MHz, $CDCl_3$): *δ* = 6.96 (s, 1H), 6.50 (s, 1H), 4.46 (dd, *J* = 8.85, 3.99 Hz, 1H), 4.18 (dd, *J* = 10.20, 2.64 Hz, 1H), 3.42 (dd, *J* = 9.81, 6.03 Hz, 1H), 3.38 (dd, *J* = 9.81, 6.03 Hz, 1H), 2.71 (s, 3H), 2.10-1.99 (m, 2H), 2.05 (d, *J* = 1.50 Hz, 3H), 1.74 (m, 1H), 1.60-1.49 (m, 2H), 1.48-1.40 (m, 4H), 1.34 (s, 3H), 1.10 (m, 1H), 1.06 (s, 11H), 1.05 (s, 10H), 0.89 (s, 9H), 0.86 (d, *J* = 6.78 Hz, 3H), 0.03 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): *δ* = 174.9, 164.6, 152.8, 139.7, 120.4, 115.9, 80.1, 75.2, 68.1, 56.8, 36.9, 35.5, 33.6, 30.9, 21.6, 19.6, 18.0, 16.6, 13.4, 12.2, -5.4.

IR (film): 2946, 1827, 1698, 1651, 1574, 1463, 1091 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{34}H_{63}O_4NSSi_2$:637.4016, found: 637.4011.

4-[(1*E*,5*Z*)-(3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-3-triisopropylsilanyloxy-undeca-1,5-dienyl]-2-methyl-thiazole (260)w



β-lactone **259** (15 mg, 0.023 mmol) was heated in DMF (1 mL) at 160 °C for 1.5 h. Brine was added and the aqueous phase was extracted with hexane:Et_2O (1:1). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 10 mg (73%) of olefin **260**.

R_f = 0.60 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* = 6.92 (s, 1H), 6.44 (s, 1H), 5.08 (t, *J* = 7.77 Hz, 1H), 4.21 (t, *J* = 6.42 Hz, 1H), 3.43 (dd, *J* = 9.84, 5.64 Hz, 1H), 3.33 (dd, *J* = 9,63, 6.63 Hz, 1H), 2.70 (s, 3H), 2.38-2.32 (m, 1H), 2.31-2.26 (m, 1H), 1.99 (d, *J* = 1.50 Hz, 3H), 1.97 (m, 2H), 1.71-1.66 (m, 1H) 1.64 (s, 3H), 1.54 (m, 1H), 1.42-1.35 (m, 2H), 1.32-1.22 (m, 1H), 1.06 (s, 11H), 1.04 (s, 10H), 0.89 (s, 9H), 0.84 (d, *J* = 6.78 Hz, 3H), 0.03 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): *δ* = 164.1, 153.5, 142.2, 134.1, 120.6, 118.9, 114.8, 68.4, 35.8, 28.1, 25.9, 23.5, 19.2, 18.3, 18.1, 18.0, 16.7, 13.6, 12.4, -5.3.

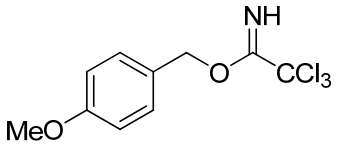
IR (film): 2925, 1456, 1249, 1098 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{33}H_{63}O_6NSSi_2$: 593.4118, found: 593.4125.

$[\alpha]_D^{20}$ 6.28 (*c* = 0.175, CH_2Cl_2)

10.2.2. Epothilone B: Lactate Route

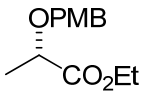
_p_-Methoxybenzyl-trichloroacatimidate (504)



To a suspension of NaH (35 mg, 1.5 mmol) in Et_2O (7 mL) was added a solution of *p*-methoxybenzylalcohol (2 g, 14.5 mmol) in Et_2O (5 mL) and the mixture was stirred for 30 min at r.t.. The reaction mixture was cooled down to -5 °C, trichloroacetonitrile (1.5 mL, 14.5 mmol) was added and the reaction was allowed to warm to r.t. over 2 h. Et_2O was removed under reduced pressure (cold water bath), the residue treated with hexane:methanol (98:2, 15 mL), filtered over Celite and the solvent was evaporated to yield 3.7 g (90%) of the Bundle's reagent.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.31 (s, 2H), 3.82 (s, 3H).

(2*S*)-2-(4-Methoxy-benzyloxy)-propionic acid ethyl ester (505)



To a stirred solution of *p*-methoxybenzyl-trichloroacatimidate (**504**) (3.70 g, 13 mmol) in cyclohexane (14 mL) was added (*S*)-(-)-ethyllactate (**265**) (0.97 mL, 8.50 mmol) in DCM (10 mL). The mixture was cooled to 0 °C and a catalytic amount of trifluoromethanesulfonic acid was added. After 45 min the ice bath was removed and stirring was continued for 3 h at r.t.. The reaction mixture was diluted with pentane, the precipitate filtered off over celite and washed with saturated $NaHCO_3$ solution. The combined aqueous solution was extracted with hexane:Et_2O (1:1) and the combined organic solution was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 5:1) to yield 1.50 g (75%) of protected lactate **505**.

$\mathbf{R_f}$ = 0.47 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 4.62 (d, *J* = 11.37 Hz, 1H), 4.39 (d, *J* = 11.37 Hz, 1H), 3.80 (s, 3H), 4.21 (dq, *J* = 7.12, 2.33 Hz, 1H), 4.02 (q, *J* = 6.90 Hz, 1H), 1.41 (d, *J* = 6.82 Hz, 3H), 1.30 (t, *J* = 7.20 Hz, 3H).

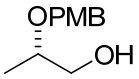
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.3, 159.4, 129.7, 129.6, 113.8, 73.7, 71.6, 60.8, 55.3, 18.7, 14.3.

IR (film): 2981, 1732, 1614, 1514, 1030 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{13}H_{18}O_4$: 238.1205, found: 238.1197.

$[\alpha]_D^{20}$ -64.46 (c = 1.3, CH_2Cl_2)

(2*S*)-2-(4-Methoxy-benzyloxy)-propan-1-ol (266)



A stirred solution of ester **505** (500 mg, 2.1 mmol) in THF (30 mL) was cooled to 0 °C and $LiAlH_4$ powder (66 mg, 1.7 mmol) was added in small portions. The mixture was stirred over night. The reaction was quenched with methanol and diluted with saturated NH_4Cl solution. The organic layer was separated, the aqueous layer was acidified with 1 N HCl solution to pH 4 and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 1:1) to yield 390 mg (96%) of alcohol **266** as pale yellow oil.

R_f = 0.30 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 4.59 (d, *J* = 11.12 Hz, 1H), 4.42 (d, *J* = 11.12 Hz, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 3.60 (ddd, *J* = 11.37, 3.28, 0.1o Hz, 1H), 3.48 (ddd, *J* = 11.37, 6.95, 4.42 Hz, 1H), 2.02 (dd, *J* = 7.58, 4.55 Hz, 1H), 1.16 (d, *J* = 6.31 Hz, 3H).

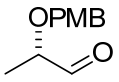
^{13}C-NMR (100 MHz, $CDCl_3$): δ =159.3, 130.5, 129.3, 113.9, 75.2, 70.5, 66.4, 55.3, 15.9.

IR (film): 3431, 2930, 1612, 1513, 1247, 1034 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{11}H_{16}O_3$: 196.1099, found: 196.1088.

$[\alpha]_D^{20}$ 46.22 (c = 1.2, CH_2Cl_2)

(2*S*)-2-(4-Methoxy-benzyloxy)-propionaldehyde (223)

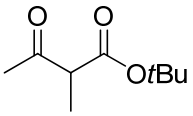


To a solution of oxalylchloride (0.3 mL, 3.6 mmol) in DCM (20 mL) at -78 °C was dropwise added DMSO (0.5 mL, 7.1 mmol) and the mixture was stirred for 30 min. Alcohol **266** (350 mg, 1.8 mmol) in DCM (10 mL) was added and stirring was continued for 1 h before triethylamine (1.5 mL, 10.7 mmol) was added. The reaction mixture was shifted to an ice bath. After 45 min the reaction mixture was quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. The residue was taken up in hexane:EtOAc (3:1) and filtered over a short plug of silica gel to yield 350 mg (quant.) of aldehyde **223** which was used without further purification.

$\mathbf{R_f}$ = 0.81 (hexane:EtOAc = 1:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.8 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.56 (s, 2H), 3.86 (dq, *J* = 6.9, 1.4 Hz, 1H), 3.80 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H).

2-Methyl-3-oxo-butyric acid *tert*-butyl ester (506)

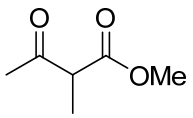


To a stirred suspension of NaH (794 mg, 19.8 mmol) in THF (70 mL) at 0 °C was added 3-oxo-butyric acid *tert*-butyl ester (**267**) (3.1 mL, 18.9 mmol) and the mixture was stirred for 1 h. MeI (2.35 mL, 37.8 mmol) was added slowly and the solution was stirred at r.t. over night. The reaction was quenched with a saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) of the crude product yielded 3.13 g (96%) of **506** as colorless liquid.

$\mathbf{R_f}$ = 0.60 (hexane:EtOAc = 5:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.40 (q, *J* = 7.12 Hz, 1H), 2.23 (s, 3H), 1.46 (s, 9H), 1.29 (d, *J* = 7.20 Hz, 3H).

2-Methyl-3-oxo-butyric acid methyl ester (507)

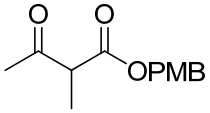


To a stirred suspension of NaH (717 mg, 19.4 mmol) in THF (40 mL) at 0 °C was added 3-oxo-butyric acid methyl ester (**269**) (2 mL, 18.5 mmol) and the mixture was stirred for 1 h. MeI (3.6 mL, 55.5 mmol) was added slowly and the solution was stirred at r.t. over night. The reaction was quenched with a saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 3:1) of the crude product yielded 1.95 g (81%) of **507** as colorless liquid.

$\mathbf{R_f}$ = 0.58 (hexane:EtOAc = 3:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.62 (s, 3H), 3.42 (q, J = 1.61 Hz, 1H), 2.12 (s, 3H), 1.24 (d, J = 1.61 Hz, 3H).

2-Methyl-3-oxo-butyric acid 4-methoxy-benzyl ester (508)



A solution of methyl ester **507** (5 g, 10.6 mmol) and 4-methoxybenzyl alcohol (10.6 g, 76.8 mmol) in toluene (50 mL) was refluxed with a Dean-Stark trap for 48 h. After cooling to r.t. the solvent was removed under reduced pressure and column chromatography (hexane:EtOAc = 5:1) yielded 7.3 g (80%) of PMB ester **508**.

$\mathbf{R_f}$ = 0.57 (hexane:EtOAc = 3:1)

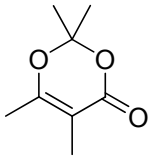
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.60 Hz, 2H), 6.88 (d, J = 8.60 Hz, 2H), 5.11 (s, 2H), 3.81 (s, 3H), 3.51 (q, J = 7.16 Hz, 1H), 2.17 (s, 3H), 1.34 (d, J = 7.08 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.4, 170.4, 159.7, 130.2, 127.5, 114.0, 66.9, 55.3, 53.7, 28.4, 12.7.

IR (film): 2943, 1716, 1248 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{13}H_{16}O_4$: 236.1049, found: 236.1052.

2,2,5,6-tetramethyl-4H-1,3-dioxin-4-one (268)



To aceto acetate **506** (2.4 g, 13.9 mmol) in acetone (8 mL) at -10 °C was added Ac_2O (5.3 mL, 55.7 mmol) and a catalytic amount of conc. H_2SO_4. The mixture was allowed to warm to r.t. over night. Ice water was added and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with DCM. The combined organic layer was washed with brine and dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 1.3 g (60%) of **268**.

$\mathbf{R_f}$ = 0.62 (hexane:EtOAc = 1:1)

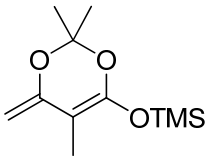
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.97 (d, J = 0.76 Hz, 3H), 1.81 (d, J = 1.00 Hz, 3H), 1.64 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.6, 104.7, 100.3, 25.1, 17.4, 10.3.

IR (film): 1728, 1654, 1399, 1348, 1270, 1238, 1207, 1155 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_8H_{12}O_3$: 156.0786, 156.0793.

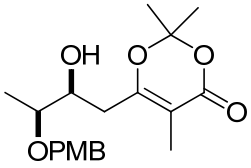
Trimethyl-(2,2,5-trimethyl-6-methylene-6H-[1,3]dioxin-4-yloxy)-silane (261)



A stirred solution of LDA (24.6 mmol), prepared by adding *n*BuLi (9.8 mL, 2.5M in hexane, 24.6 mmol) dropwise to diisopropylamine (3.4 mL, 24.6 mmol) in THF (15 mL) at 0 °C and stirring for 15 min, was cooled to -78 °C and dioxenone **268** (3.2 g, 20.5 mmol) in THF (7 mL) was added dropwise. After 1 h TMSCl (2.9 mL, 22.6 mmol), freshly distilled from CaH_2, was added. The mixture was stirred for 3 h at -78 °C; then warmed to r.t. and the solvent was removed under reduced pressure. The residue was purified by bulb-to-bulb distillation to yield 3.1 g (65%) of silylether **261** as colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 4.52 (d, *J* = 1.00 Hz, 1H), 4.16 (d, *J* = 1.04 Hz, 1H), 1.81 (s, 3H), 1.39 (s, 6H), 0.14 (s, 9H).

6-[(2*S*,3*S*)-2-Hydroxy-3-(4-methoxy-benzyloxy)-butyl]-2,2,5-trimethyl-[1,3]dioxin-4-one (270)



Aldehyde **223** (800 mg, 4 mmol) in DCM (12 mL) at -10 °C was incubated with $MgBr_2 \cdot Et_2O$ (2.1 g, 8 mmol) for 30 min. Silyl enol ether **261** (1.42 g, 6 mmol) in DCM (5 mL) was added and stirring continued for 1 h. A saturated NH_4Cl solution was added, layers were separated and the aqueous layer was extracted with DCM. The combined DCM layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) to yield 1.34 g (96%) of aldol adduct **270** as pale yellow oil.

R_f = 0.55 (Hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.59 Hz, 2H), 6.89 (d, *J* = 8.84 Hz, 2H), 4.62 (d, *J* = 11.11 Hz, 1H), 4.36 (d, *J* = 11.11 Hz, 1H), 3.81 (s, 3H), 3.75-3.70 (m, 1H), 3.43 (dt, *J* = 11.62, 6.18 Hz, 1H), 2.53 (dd, *J* = 14.16, 6.18 Hz, 1H), 2.44 (m, 1H), 2.35 (dd, *J* = 14.27, 9.09 Hz, 1H), 1.84 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.24 (d, *J* = 6.32 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.9, 159.4, 129.9, 113.9, 104.9, 102.3, 76.8, 72.5, 70.7, 55.3, 34.9, 25.8, 24.4, 15.5, 10.3.

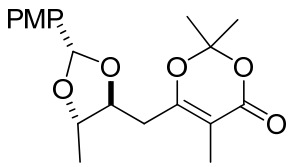
IR (film): 3468, 2936, 1721, 1647, 1514, 1248 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{19}H_{26}O_6$: 350.1729, found: 350.1737.

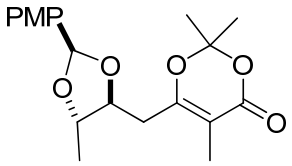
$[\alpha]_D^{20}$ 15.83 (c = 1.2, CH_2Cl_2)

6-{[(2*S*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxolan-4-yl]methyl}-2,2,5-trimethyl-4H-1,3-dioxin-4-one (271a)

6-{[(2*R*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxolan-4-yl]methyl}-2,2,5-trimethyl-4H-1,3-dioxin-4-one (271b)



a



b

A suspension of monoprotected diol **270** (55 mg, 0.16 mmol) and MS 3 Å (100 mg) in Et_2O (6 mL) under argon at r.t. was stirred for 1 h before a suspension of DDQ (181 mg, 0.8 mmol) in Et_2O (6 mL) also stirred for 1 h was added. After 2 h the reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution and the MS was filtered off over celite. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic solvent was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 10 mg (18%) of acetale **271** and 40 mg (73%) of the educt.

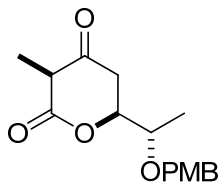
271a: ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.56 Hz, 2H), 6.89 (d, J = 7.84 Hz, 2H), 5.91 (s, 1H), 4.03 (q, J = 6.32 Hz, 1H), 3.95 (m, 1H), 3.81 (s, 3H), 2.74 (dd, J = 14.12, 4.04 Hz, 1H), 2.51 (dd, J = 14.40, 4.80 Hz, 1H), 1.84 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.36 (d, J = 6.04 Hz, 3H).

^{13}**C-NMR** (100 MHz, $CDCl_3$): δ = 161.5, 160.4, 127.7, 113.8, 102.6, 80.3, 78.6, 55.3, 34.6, 25.7, 24.6, 17.8, 10.4.

271b: ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.56 Hz, 2H), 6.89 (d, J = 7.84 Hz, 2H), 5.88 (s, 1H), 4.00 (q, J = 5.72 Hz, 1H), 3.95 (m, 1H), 3.81 (s, 3H), 2.76 (dd, J = 14.16, 3.80 Hz, 1H), 2.45 (dd, J = 14.28, 4.44 Hz, 1H), 1.88 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.41 (d, J = 5.80 Hz, 3H).

^{13}**C-NMR** (100 MHz, $CDCl_3$): δ = 161.6, 160.4, 127.8, 113.7, 102.9, 80.3, 79.3, 55.3, 34.2, 25.8, 24.5, 17.7, 10.3.

(*S*)-6-[(*S*)-1-(4-Methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (262)



To a solution of lactone **270** (650 mg, 1.85 mmol) in methanol (12 mL) was added K_2CO_3 (385 mg, 2.78 mmol) and the mixture was stirred over night. The solvent was evaporated and ice and 2N HCl were added to the residue. The acidic layer was extracted with Et_2O repeatedly and the combined ethereal phase was dried over $MgSO_4$. After removal of the solvent under reduced pressure 550 mg (quant.) of lactone **262** as yellow solid was isolated, in 3:1 mixture of diastereoisomers in *α*-position, and used without further purification.

R_f = 0.15 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.23 (d, *J* = 8.56 Hz, 2H), 6.88 (d, *J* = 8.56 Hz, 2H), 4.64 (dt, *J* = 8.84, 4.04 Hz, 1H), 4.58 (d, *J* = 11.36 Hz, 1H), 4.42 (d, *J* = 11.36 Hz, 1H), 3.80 (s, 3H), 3.70 (ddd, *J* = 12.68, 6.38, 3.84 Hz, 1H), 3.41 (q, *J* = 6.64 Hz, 1H), 2.72 (dd, *J* = 18.05, 4.16 Hz, 1H), 2.60 (dd, *J* = 18.04, 8.96 Hz, 1H), 1.31 (d, *J* = 6.80 Hz, 3H), 1.29 (d, *J* = 6.32 Hz, 3H).

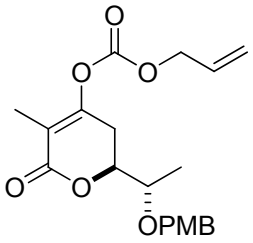
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 200.8, 169.7, 159.0, 129.8, 129.4, 113.9, 76.5, 73.8, 71.1, 55.3, 51.5, 39.4, 14.9, 8.3.

IR (film): 2926, 1726, 1654, 1613, 1513, 1400, 1248, 1115 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_5$: 292.1311, found: 292.1307.

$[\alpha]_D^{20}$ -29.50 (*c* = 0.8, $CHCl_3$)

Carbonic acid allyl ester (*S*)-2-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-5-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl ester (275)



To a stirred solution of *β*-keto lactone **262** (230 mg, 0.74 mmol) in THF (6 mL) at -78 °C was slowly added a solution of potassium *tert*-butoxide (91 mg, 0.81 mmol) in THF (2 mL) and stirring was continued for 2.5 h. Allyl chloroformate (0.18 mL, 1.48 mmol) was added and after an additional 2.5 h the reaction was quenched by the addition of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to afford 172 mg (95%) of **275** as colorless oil.

R_f = 0.29 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.25 (d, *J* = 8.56 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 5.96 (ddt, *J* = 17.15, 11.13, 5.57 Hz, 1H), 5.44-5.33 (m, 2H), 4.71 (dt, *J* = 6.04, 1.26 Hz, 2H), 4.59 (d, *J* = 11.36 Hz, 1H), 4.48 (d, *J* = 11.60 Hz, 1H), 4.49 (m, 1H), 3.80 (s, 3H), 3.76 (ddd, *J* = 12.74, 4.68, 0.02 Hz, 1H), 2.91 (m, 1H), 2.43 (ddd, *J* = 17.56, 3.91, 1.15 Hz, 1H), 1.83 (s, 3H), 1.26 (d, *J* = 6.56 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 166.2, 159.3, 157.5, 150.9, 130.5, 130.1, 129.4, 120.1, 115.8, 113.8, 77.5, 73.6, 71.1, 69.7, 55.3, 27.3, 14.7, 9.8.

IR (film): 2930, 1764, 1744, 1722, 1612, 1514, 1228, 1125, 1053 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{20}H_{24}O_7Na$: 399.1420, found: 399,1416.

$[\alpha]_D^{20}$ -58.73 (*c* = 0.95, CH_2Cl_2)

Tsuji-Trost in biphasic system:

To $Pd(PPh_3)_4$ (7.5 mg, 0.006 mmol) under argon atmosphere was added benzyl-triethyl-ammonium chloride (3 mg, 0.012 mmol) in degassed water (1 mL) and cooled to 0 °C. Allyl acetate (14 µL, 0.13 mmol) was added and the mixture was stirred for 15 min. A degassed suspension of **262** (50 mg, 0.170 mmol) in ethyl acetate (1 mL) was added and stirring was continued for 15 min, then K_2CO_3 (25 mg, 0.180 mmol) in degassed water (0.5 mL) was added. After stirring for 2 h, the reaction mixture was quenched with saturated NH_4Cl solution and phases were separated. The aqueous phase was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to afford 43 mg (97%) of **273** in a d.r. of 3:1 (ax:eq).

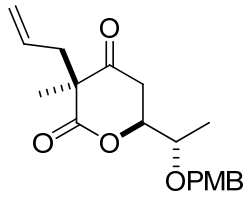
Tsuji-Trost with Trost-DACH ligand:

$Pd_2(dba)_3$ (5 mg, 0.005 mmol) and (*S*,*S*)-Trost-DACH ligand (**272**) (7 mg, 0.010 mmol) were stirred in degassed toluene (1.5 mL) at r.t. to form a dark red solution, which turned orange and a precipitate formed upon the addition of allyl acetate (40 µL, 0.400 mmol). Then DBU (36 µL, 0.240 mmol) was added giving a clear yellow solution, which was cooled to -78 °C. A degassed solution of **262** (58 mg, 0.2 mmol) in toluene (0.5 mL) was added The reaction was quenched after 6 h with saturated NH_4Cl solution, layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to yield 61 mg (92%) of **273** in a d.r. of 7:2 (ax:eq) as colorless oil.

Intramolecular Tsuji-Trost with allyl carbonate 275:

$Pd_2(dba)_3$ (7 mg, 0.0066 mmol) and (*S*,*S*)-Trost-DACH ligand (**272**) (9 mg, 0.0130 mmol) were stirred in degassed toluene (1 mL) for 20 min during which time the dark red solution turned orange. This solution was added *via* double needle to **275** (50 mg, 0.1300 mmol) in degassed toluene (1 mL) whereupon the solution turned yellow. After 1 h the solution was orange again and the solvent was evaporated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to yield 33 mg (76%) of **273** in a d.r. of 4:1 (ax:eq) as colorless oil.

(3*S*,6*S*)-3-Allyl-6-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (273a)



R_f = 0.21 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.74-5.64 (m, 1H), 5.10-5.03 (m, 2H), 4.45 (d, *J* = 11.62 Hz, 1H), 4.47-4.43 (m, 1H), 4.42 (d, *J* = 11.36 Hz, 1H), 3.80 (s, 3H), 3.65 (ddd, *J* = 12.63, 3.79, 3.79 Hz, 1H), 2.72 (dd, *J* = 16.16, 3.54 Hz, 1H), 2.69 (dd, *J* = 13.33, 6.82 Hz, 1H), 2.53 (dd, *J* = 13.64, 8.33 Hz, 1H), 2.51 (dd, *J* = 16.16, 10.10 Hz, 1H), 1.40 (s, 3H), 1.29 (d, *J* = 6.31 Hz, 3H).

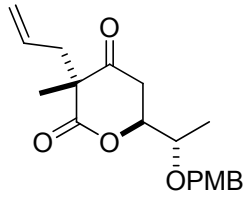
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.8, 173.2, 159.4, 132.6, 129.7, 129.5, 119.5, 113.9, 75.9, 73.8, 70.9, 56.5, 55.3, 40.9, 40.5, 23.7, 14.6.

IR (film): 1749, 1713, 1513, 1246, 1031 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{19}H_{24}O_5$: 332.1624, found: 332.1619.

$[\alpha]_D^{20}$ -19.41 (*c* = 0.85, CH_2Cl_2)

(3*R*,6*S*)-3-Allyl-6-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (273b)



R_f = 0.21 (Hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.69-5.59 (m, 1H), 5.12-5.06 (m, 2H), 4.49 (d, *J* = 11.62 Hz, 1H), 4.47-4.45 (m, 1H), 4.32 (d, *J* = 11.62 Hz, 1H), 3.80 (s, 3H), 3.49 (ddd, *J* = 12.69, 6.38, 2.08 Hz, 1H), 2.79 (dd, *J* = 16.04,

6.19 Hz, 1H), 2.56-2.43 (m, 2H), 2.52 (dd, *J* = 15.91, 4.54 Hz, 1H), 1.29 (d, *J* = 6.02 Hz, 3H), 1.27 (s, 3H).

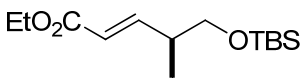
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 204.3, 174.1, 159.5, 131.9, 130.2, 128.8, 119.9, 113.8, 76.8, 74.4, 70.6, 57.6, 55.3, 44.5, 40.5, 20.4, 15.2.

IR (film): 1745, 1713, 1514, 1247, 1030 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{19}H_{24}O_5$: 332.1624, found: 332.1619.

$[\alpha]_D^{20}$ 60.20 (*c* = 0.45, CH_2Cl_2)

(-)-(4*S*)-(*E*)-5-(*tert*-Butyl-dimethyl-silyloxy)-4-methyl-pent-2-enoic acid ethyl ester (184)



To a stirred suspension of anhydrous LiCl (251 mg, 5.93 mmol) in acetonitrile (40 mL) at r.t. was added triethylphosponoacetate (0.99 mL, 4.94 mmol) and DBU (0.88 mL, 5.93 mmol). The mixture was stirred for 10 min to form a clear solution, then aldehyde **494** (1 g, 4.94 mmol) in acetonitrile (15 mL) was added and stirring was continued over night. The reaction mixture was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 1.18 g (84%) of **184** as colorless oil.

R_f = 0.50 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 6.92 (dd, *J* = 15.80, 7.20 Hz, 1H), 5.83 (dd, *J* = 15.78, 1.38 Hz, 1H), 4.19 (q, *J* = 7.08 Hz, 2H), 3.55 (dd, *J* = 9.86, 6.58 Hz, 1H), 3.51 (dd, *J* = 9.96, 6.44 Hz, 1H), 2.50 (m, 1H), 1.28 (t, *J* = 7.06 Hz, 3H), 1.05 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

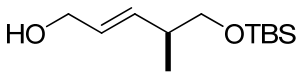
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 173.5, 151.4, 120.9, 66.9, 60.1, 39.1, 25.9, 15.5, 14.3, -5.4.

IR (film): 2956, 2929, 1723, 1258, 1183, 1097 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{14}H_{28}O_3Si$: 272.1808, found: 272.1801.

$[\alpha]_D^{20}$ -11.80 (*c* = 1.5, $CHCl_3$), **$[\alpha]_D^{20}$** -18.72 (*c* = 1.25, CH_2Cl_2)

(-)-(4*S*)-(*E*)-5-(*tert*-Butyl-dimethyl-silyloxy)-4-methyl-pent-2-en-1-ol (509)



To a stirred solution of DIBALH (5.7 mL, 1.5 M in toluene, 8.5 mmol) in THF (15 mL) at -78 °C was dropwise added ester **186** (1.2 g, 4.0 mmol). After 5 h the reaction mixture was quenched with saturated sodium potassium tartrate solution and stirred for 2 h. The layers were separated, the aqueous phase was extracted with hexane:Et_2O (1:1) and the combined organic solution was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography (hexane:EtOAc = 10:1) to yield 875 mg (95%) of alcohol **509** as colorless oil.

R_f = 0.23 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70-5.60 (m, 2H), 4.10 (t, *J* = 5.32 Hz, 2H), 3.50 (dd, *J* = 9.72, 6.20 Hz, 1H), 3.41 (dd, *J* = 9.70, 6.94 Hz, 1H), 2.34 (m, 1H), 1.26 (t, *J* = 5.80 Hz, 1H (OH)), 1.00 (d, *J* = 6.56 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

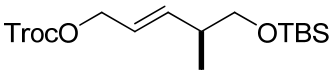
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.6, 128.7, 67.9, 63.9, 38.9, 25.9, 18.3, 16.4, -5.3.

IR (film): 3328, 2956, 2929, 2857, 1256, 1104, 1089 cm^{-1}.

HRMS (ESI) (m/z): $[M - t\text{Bu}]^+$ calcd for $C_8H_{17}O_2Si$: 173.0998, found: 173.1002.

$[\alpha]_D^{20}$ -7.44 (*c* = 1.3, $CHCl_3$), **$[\alpha]_D^{20}$** -9.91 (*c* = 1.15, CH_2Cl_2)

Carbonic acid (-)-(4*S*)-(*E*)-5-(*tert*-butyl-dimethyl-silyloxy)-4-methyl-pent-2-enyl ester 2,2,2-trichloro-ethyl ester (185)



In a stirred solution of alcohol **509** (760 mg, 3.13 mmol) in pyridine (22 mL) was dissolved a catalytic amount of DMAP and 2,2,2-trichloroethyl chloroformate (0.47 mL, 3.45 mmol) was added. The mixture was stirred at r.t. for 1 h, quenched with brine and the layers were separated. The aqueous phase was extracted with Et_2O, the combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1, 1% NEt_3) yielded 1.4 g (quant.) of carbonate **185** as colorless oil.

R_f = 0.71 (hexane:EtOAc = 10:1)

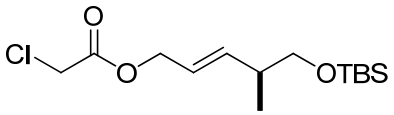
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82 (dd, *J* = 15.64, 7.08 Hz, 1H), 5.64 (ddt, *J* =14.88, 6.82, 1.30 Hz, 1H), 4.76 (s, 2H), 4.67 (d, *J* = 6.56 Hz, 2H), 3.49 (dd, *J* = 9.84, 6.32 Hz, 1H), 3.43 (dd, *J* = 9.70, 6.70 Hz, 1H), 2.40-2.34 (m, 1H), 1.00 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.97, 140.61, 122.43, 69.96, 67.67, 39.16, 26.06, 26.02, 18.48, 16.21, -5.21.

HRMS (ESI) (m/z): $[M - tBu]^+$ calcd for $C_{11}H_{18}O_4SiCl_3$: 349.0012, found: 349.0008.

$[\alpha]_D^{20}$ -6.15 (*c* = 2.1, $CHCl_3$)

Chloro-acetic acid (*E*)-(4*S*)-5-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl ester (510)



To stirred solution of alcohol **509** (100 mg, 0.43 mmol) in pyridine (4 mL) was added chloroacetic anhydride (88 mg, 0.52 mmol). The mixture was stirred at r.t. for 1 h, quenched with brine and the layers were separated. The aqueous phase was extracted with Et_2O, the combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 130 mg (99%) of chloroactate **510**.

R_f = 0.65 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, *J* = 15.41, 7.08 Hz, 1H), 5.60 (dtd, *J* = 15.47, 6.48, 1.09 Hz, 1H), 4,64 (d, *J* = 6.32 Hz, 2H), 4.06 (s, 2H), 3.48 (dd, *J* = 9.88, 6.56 Hz, 1H), 3.44 (dd, *J* = 9.72, 6.44 Hz, 1H), 2.36 (m, 1H), 1.00 (d, *J* = 6.80 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

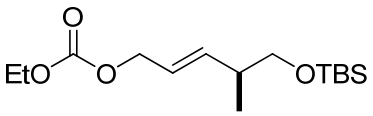
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.1, 140.0, 122.6, 118.1, 67.5, 66.9, 40.9, 39.0, 25.9, 18.3, 16.1, -5.4.

IR (film): 2956, 2857, 1762, 1257, 1168, 1107 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{14}H_{27}O_3SiClNa$: 329,1316, found: 329,1323.

$[\alpha]_D^{20}$ -9.80 (*c* = 1.5, CH_2Cl_2)

Carbonic acid (*E*)-(*S*)-5-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl ester ethyl ester (511)



To stirred solution of alcohol **509** (150 mg, 0.64 mmol) in pyridine (5 mL) was added ethyl chloroformate (73 µL, 0.76 mmol). The mixture was stirred at r.t. for 20 min, quenched with brine and the layers were separated. The aqueous phase was extracted with Et_2O, the combined organic solution was washed with water, dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 170 mg (88%) of ethyl carbonate **511**.

R_f = 0.64 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.76 (d, *J* = 15.52, 6.96 Hz, 1H), 5.61 (dtd, *J* = 15.58, 6.41, 1.08 Hz, 1H), 4.57 (d, *J* = 6.32 Hz, 2H), 4.19 (q, *J* = 7.16 Hz, 2H), 3.49 (dd, *J* = 9.86, 6.30 Hz, 1H), 3.41 (dd, *J* = 9.86, 6.82 Hz, 1H), 2.35 (m, 1H), 1.30 (t, *J* = 7.20 Hz, 3H), 1.00 (d, *J* = 6.60 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

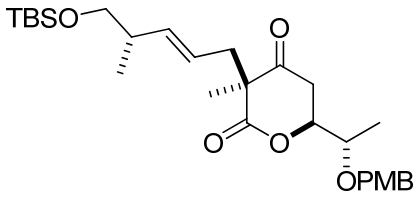
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.0, 139.3, 123.0, 68.5, 67.6, 63.9, 39.0, 25.9, 18.3, 16.1, 14.3, -5.4.

IR (film): 2956, 2930, 2857, 1747, 1258, 1105 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{15}H_{30}O_4SiNa$: 325.1811, found: 325.1817.

$[\alpha]_D^{20}$ -9.20 (*c* = 1.25, CH_2Cl_2)

(3*S*,6*S*)-3-[(*E*)-(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl]-6-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (277)



To $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and benzyl-triethyl-ammonium chloride (34 mg, 0.150 mmol) in degassed water (4 mL) at 0 °C was added ethyl carbonate **511** (453 mg, 1.500 mmol) in ethyl acetate (3 mL) and the mixture was stirred for 15 min. A degassed suspension of **23** (650 mg, 1.800 mmol) in ethyl acetate (3 mL) was added and stirring was continued for 15 min before K_2CO_3 (270 mg, 1.950 mmol) in degassed water (2 mL) was added. After stirring for 3 h, the reaction mixture was quenched with saturated NH_4Cl solution and phases were separated. The aqueous phase was extracted with DCM and the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to afford 730 mg (97%) of **277** as 3:1 mixture as pale yellow oil.

Major: **277a**

R_f = 0.24 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.44 (dd, *J* = 15.42, 7.06 Hz, 1H), 5.32 (dt, *J* = 14.76, 7.38 Hz, 1H), 4.58 (d, *J* = 11.60 Hz, 1H), 4.43 (d, *J* = 11.60 Hz, 1H), 4.42 (m, 1H), 3.80 (s, 3H), 3.69 (dd, *J* = 6.30, 3.78 Hz, 1H), 3.66 (dd, *J* = 6.32, 3.80 Hz, 1H), 3.43 (dd, *J* = 9.70, 5.94 Hz, 1H), 3.31 (dd, *J* = 9.73, 7.20 Hz, 1H), 2.68 (dd, *J* = 15.93, 3.28 Hz, 1H), 2.64 (dd, *J* = 13.24, 6.68 Hz, 1H), 2.49 (dd, *J* = 15.90, 10.86 Hz, 1H), 2.45 (dd, *J* = 13.14, 8.06 Hz, 1H), 2.22 (m,1H), 1.37 (s, 3H), 1.26 (d, *J* = 6.32 Hz, 3H), 0.92 (d, *J* = 6.56 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H).

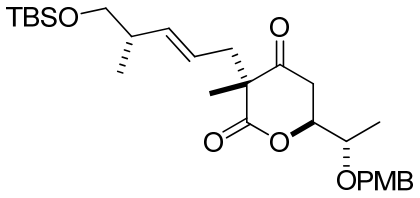
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.2, 173.4, 159.4, 138.5, 129.6, 129.5, 123.3, 113.9, 75.6, 73.8, 71.0, 67.9, 56.7, 55.3, 40.7, 40.6, 39.3, 25.9, 23.0, 18.3, 16.6, 14.5, -5.3, -5.4.

IR (film): 2955, 2930, 1717, 1635, 1615, 1250 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_4H_9]^+$ calcd for $C_{24}H_{35}O_6Si$: 447.2203, found: 447.2212.

$[\alpha]_D^{20}$ -35.33 (*c* = 0.3, CH_2Cl_2)

Minor: **277b**



R_f = 0.24 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.43 (dd, *J* = 15.54, 6.95 Hz, 1H), 5.28 (dt, *J* = 15.28, 7.52Hz, 1H), 4.48 (d, *J* = 11.34 Hz, 1H), 4.44 (m, 1H), 4.31 (d, *J* = 11.62 Hz, 1H), 3.80 (s, 3H), 3.48 (m, 1H), 3.44 (dd, *J* = 9.85, 6.06 Hz, 1H), 3.35 (dd, *J* = 9.72, 6.95 Hz, 1H), 2.78 (dd, *J* = 16.01, 6.19 Hz, 1H), 2.50 (dd, *J* = 16.16, 4.54 Hz, 1H), 2.49 (m,1H), 2.39 (dd, *J* = 13.51, 8.21 Hz, 1H), 2.26 (m, 1H), 1.28 (d, *J* = 6.31 Hz, 3H), 1.26 (s, 3H), 0.94 (d, *J* = 6.82 Hz, 3H), 0.87 (s, 9H), 0,01 (s, 6H).

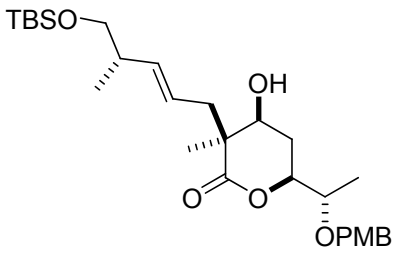
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.5, 174.3, 159.5, 138.7, 130.2, 128.8, 123.0, 113.8, 76.8, 74.4, 70.5, 67.8, 57.9, 55.2, 43.6, 40.6, 39.2, 25.9, 20.3, 18.3, 16.6, 15.2, -5.3, -5.4.

IR (film): 2955, 2930, 1716, 1613, 1514, 1250, 1082 .cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}C_4H_9]^+$ calcd for $C_{24}H_{35}O_6Si$: 447.2203, found: 447.2210.

$[\alpha]_D^{20}$ 38.31 (*c* = 0.95, CH_2Cl_2)

(3*S*,4*S*,6*S*)-3-[(*E*)-(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl]-4-hydroxy-6-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-tetrahydro-pyran-2-one (278)



To ß-keto lactone **277** (220 mg, 0.44 mmol) in methanol (9 mL) at 0 °C was added $NaBH_4$ (17 mg, 0.44 mmol) and the solution was stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and

the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 3:1) yielded 218 mg (98%) of reduction product **278**.

R_f = 0.30 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.84 Hz, 2H), 5.47 (m, 2H), 4.63 (d, *J* = 11.40 Hz, 1H), 4.43 (d, *J* = 11.36 Hz, 1H), 4.42 (m, 1H), 3.82 (m, 1H), 3.80 (s, 3H), 3.56 (ddd, *J* = 12.63, 6.31, 3.28 Hz, 1H), 3.46 (dd, *J* = 9.60, 6.31 Hz, 1H), 3.39 (dd, *J* = 9.85, 6.82 Hz, 1H), 2.55 (dd, *J* = 13.64, 5.81 Hz, 1H), 2.40 (dd, *J* = 13.89, 6.06 Hz, 1H), 2.29 (m, 1H), 2.16 (ddd, *J* = 14.21, 7.14, 4.35 Hz, 1H), 1.98 (dt, *J* = 14.14, 7.07 Hz, 1H), 1.20 (d, *J* = 6.56 Hz, 3H), 1.20 (s, 3H), 0.96 (d, *J* = 6.82 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H).

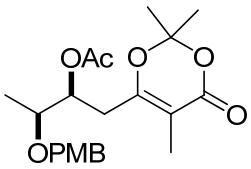
^{13}C-NMR (100 MHz, $CDCl_3$): δ =175.2, 159.4, 137.4, 129.7, 129.4, 129.2, 124.7, 113.9, 78.3, 75.0, 70.8, 70.4, 68.0, 55.2, 47.1, 39.4, 37.4, 28.9, 25.9, 21.0, 18.3, 16.6, 14.6, -5.3, -5.4.

IR (film): 3435, 2956, 2856, 1732, 1514, 1463, 1250, 1089, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{28}H_{46}O_6$: 506.3069, found: 506.3055.

$[\alpha]_D^{20}$ 23.41 (*c* = 0.85, CH_2Cl_2)

(2*R*,3*R*)-3-(4-methoxybenzyloxy)-1-(2,2,5-trimethyl-4-oxo-4H-[1,3]-dioxin-6-yl)butan-2-yl acetate (512)



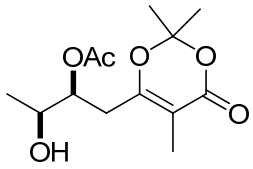
To alcohol **270** (100 mg, 0.28 mmol) in pyridine (1.5 mL) in at r.t. was added acetic anhydride (0.13 mL, 1.40 mmol) and a catalytic amount of DMAP. After 1 h the reaction was quenched by the addition of a saturated $NaHCO_3$ solution and the aqueous layer was extracted with Et_2O. The combined ethereal phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 2:1) yielded 95 mg (86%) of acetate **512**.

R_f = 0.53 (Hexane:EtOAc = 1:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.55 Hz, 2H), 6.88 (d, *J* = 8.67 Hz, 2H), 5.21 (dt, *J* = 9.59, 3.77 Hz, 1H), 4.58 (d, *J* = 11.43 Hz, 1H), 4.42 (d, *J* = 11.53 Hz, 1H), 3.80 (s, 3H),

3.63 (m, 1H), 2.76 (dt, *J* = 14.73, 9.48 Hz, 1H), 2.46 (dd, *J* = 14.78, 3.47 Hz, 1H), 2.04 (s, 3H), 1.83 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H), 1.17 (d, *J* = 6.40 Hz, 3H).

(2*R*,3*R*)-3-hydroxy-1-(2,2,5-trimethyl-4-oxo-4H-[1,3]-dioxin-6-yl)butan-2-yl acetate (279)



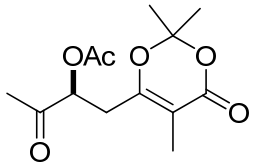
To a stirred solution of diprotected diol **512** (300 mg, 0.75 mmol) in wet DCM (6 mL) was added DDQ (198 mg, 0.83 mmol) in small portions and the mixture was stirred vigorously for 4 h. The reaction was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 1:1) to yield 203 mg (quant.) of monoprotected diol **279**.

R_f = 0.28 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.06 (m, 1H), 3.86 (ddd, *J* = 12.49, 6.33, 4.05 Hz, 1H), 2.79 (dd, *J* = 14.40, 8.60 Hz, 1H), 2.55 (dd, *J* = 14.52, 4.68 Hz, 1H), 2.08 (d, *J* = 1.28 Hz, 3H), 1.85 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 1.22 (dd, *J* = 6.56, 1.28 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 170.2, 105.0, 73.8, 68.5, 32.4, 25.6, 24.6, 21.1, 19.4, 10.3.

(*R*)-3-oxo-1-(2,2,5-trimethyl-4-oxo-4H-[1,3]-dioxin-6-yl)butan-2-yl acetate (280)



To a stirred solution of alcohol **279** (110 mg, 0.41 mmol) in DCM (6 mL) was added Dess-Martin periodinane (514 mg, 1.24 mmol) in small portions and the suspension was stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 1:1) to yield 110 mg (quant.) of ketone **280**.

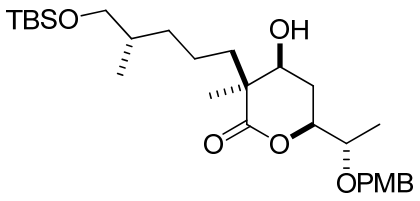
R_f = 0.13 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.28 (t, *J* = 6.32 Hz, 1H), 2.82 (d, *J* = 6.32 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.85 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.4, 169.8, 105.3, 40.9, 31.6, 26.1, 25.2, 24.7, 20.5, 10.2.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{13}H_{18}O_6$: 270.1103, found: 270.1094.

(3*S*,4*S*,6*S*)-3-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-4-hydroxy-6-[(*S*)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-tetrahydro-pyran-2-one (284)



To *β*-hydroxyl lactone **278** (350 mg, 0.65 mmol) in ethyl acetate (6 mL) was added PtO_2 (12 mg, 0.07 mmol) and the resulting suspension was stirred under an atmosphere of hydrogen. After 1.5 h the reaction mixture was filtered through Celite and the filtrate was evaporated to yield 350 mg (quant.) of **284** as colorless oil.

R_f = 0.30 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.84 Hz, 2H), 6.87 (d, *J* = 8.84 Hz, 2H), 4.63 (d, *J* = 11.64 Hz, 1H), 4.42 (d, *J* = 11.60 Hz, 1H), 4.39 (m, 1H), 3.86 (ddd, *J* = 6.95, 6.69, 4.29 Hz, 1H), 3.80 (s, 3H), 3.56 (ddd, *J* = 12.67, 6.39, 3.21 Hz, 1H), 3.42 (dd, *J* = 9.84, 5.80 Hz, 1H), 3.34 (dd, *J* = 9.84, 6.56 Hz, 1H), 2.83 (d, *J* = 6.32 Hz, 1H), 2.14 (ddd, *J* = 14.07, 6.75, 4.23 Hz, 1H), 2.01 (dt, *J* = 14.22, 7.65 Hz, 1H), 1.75-1.67 (m, 2H), 1.59 (m, 1H), 1.33-1.28 (m, 2H), 1.31 (d, *J* = 6.28 Hz, 3H), 1.25 (s, 3H), 1.05 (m, 1H), 0.84 (d, *J* = 6.80 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

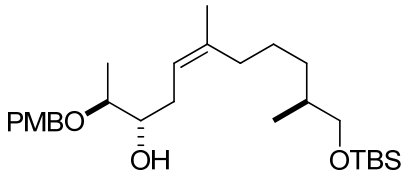
^{13}C-NMR (100 MHz, $CDCl_3$): δ =175.3, 159.4, 129.7, 129.5, 113.9, 78.1, 74.9, 70.8, 70.7, 68.4, 55.3, 47.0, 35.6, 33.7, 33.1, 28.6, 25.9, 21.1, 18.3, 16.7, 14.6, -5,4.

IR (film): 2953, 1732, 1514, 1463, 1250, 1092 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{28}H_{48}O_6Si$: 508.3220, found: 508.3224.

$[\alpha]_D^{20}$ 24.75 (*c* = 0.4, CH_2Cl_2)

(*Z*)-(2*S*,3*S*,10*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzyloxy)-6,10-dimethyl-undec-5-en-3-ol (264)



Alcohol **284** (60 mg, 0.12 mmol) was dissolved in Et_2O (3 mL), triethylamine (0.30 mL) was added at 0 °C and the mixture was stirred for 15 min. Methanesulfonyl chloride (10 µL, 0.13 mmol) was added and stirring was continued. After 1.5 h the reaction mixture was quenched with brine, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. This yielded 80 mg of the crude mesylate which was used without further purification.

To a stirred solution of the mesylate (70 mg, 0.10 mmol) in methanol (3 mL) at 0 °C was added 1 M KOH (0.2 mL, 0.20 mmol) and the solution was stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 15:1) yielded 42 mg (91%) of **264** as colorless oil.

R_f = 0.20 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.84 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 5.21 (t, *J* = 7.07 Hz, 1H), 4.59 (d, *J* = 11.11 Hz, 1H), 4.38 (d, *J* = 11.11 Hz, 1H), 3.80 (s, 3H), 3.46-3.40 (m, 3H), 3.35 (dd, *J* = 9.85, 6.57 Hz, 1H), 2.47 (d, *J* = 3.54 Hz, 1H), 2.28-2.21 (m, 1H), 2.19-2.11 (m, 1H), 2.00 (t, *J* = 7.96 Hz, 2H), 1.70 (d, *J* = 1.01 Hz, 3H), 1.61-1.53 (m, 1H), 1.45-1.31 (m, 3H), 1.18 (d, *J* = 5.81 Hz, 3H), 1.08-1.01 (m, 1H), 0.90 (s, 9H), 0.86 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H).

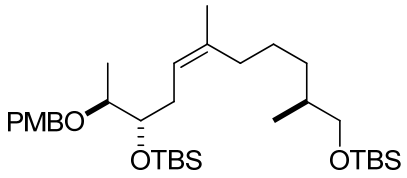
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.3, 137.9, 130.5, 129.3, 120.5, 113.9, 77.3, 75.1, 70.7, 68.3, 55.3, 35.7, 33.1, 32.2, 25.9, 25.3, 23.5, 18.3, 16.7, 15.7, -5.3.

IR (film): 2929, 1726, 1514, 1249, 1180, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_4H_9]^+$ calcd for $C_{23}H_{39}O_4Si$: 407.2617, found: 407.2610.

$[\alpha]_D^{20}$ 20.00 (*c* = 1.9, CH_2Cl_2)

1-[(*Z*)-(1*S*,2*S*,9*S*)-2,10-Bis-(*tert*-butyl-dimethyl-silanyloxy)-1,5,9-trimethyl-dec-4-enyloxymethyl]-4-methoxy-benzene (513)



To a stirred solution of alcohol **264** (150 mg, 0.32 mmol) in DCM (4 mL) was added 2,6-lutidine (58 µL, 0.48 mmol) and TBSOTf (92 µL, 0.38 mmol). After 1 h the reaction was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 185 mg (quant.) of protected triole **513** as colorless oil.

R_f = 0.62 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.50 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.15 (t, *J* = 7.33 Hz, 1H), 4.51 (d, *J* = 11.62 Hz, 1H), 4.44 (d, *J* = 11.62 Hz, 1H), 3.80 (s, 3H), 3.69-3.65 (m, 1H), 3.47-3.44 (m, 1H), 3.44 (dd, *J* = 11.87, 6.06 Hz, 1H), 3.34 (dd, *J* = 9.72, 6.69 Hz, 1H), 2.31-2.23 (m, 1H), 2.12-1.93 (m, 3H), 1.67 (s, 3H), 1.61-1.54 (m, 1H), 1.42-1.28 (m, 3H), 1.12 (d, *J* = 6.32 Hz, 3H), 1.08-1.00 (m, 1H), 0.89 (s, 9H), 0.86 (s, 9H), 0.86 (d, *J* = 6.82 Hz, 3H), 0.03 (s, 6H), 0.00 (s, 3H), -0.02 (s, 3H).

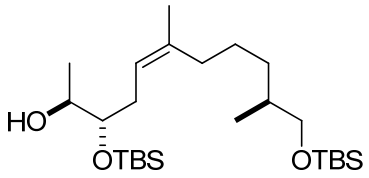
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.1, 136.5, 131.3, 129.1, 122.3, 113.8, 77.0, 74.4, 70.6, 68.4, 55.3, 35.8, 33.2, 32.3, 29.9, 25.9, 25.8, 25.5, 23.5, 18.1, 16.7, 14.1, -4.5, -4.6 -5.3.

IR (film): 2856, 1513, 1472, 1249, 1249, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}C_4H_9]^+$ calcd for $C_{29}H_{53}O_4Si_2$: 521.3482, found: 521.3489.

$[\alpha]_D^{20}$ -2.66 (*c* = 1.2, CH_2Cl_2)

(*Z*)-(2*S*,3*S*,10*S*)-3,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-6,10-dimethyl-undec-5-en-2-ol (283)



To a stirred solution of triol **513** (85 mg, 0.14 mmol) in DCM (2 mL) and water (0.5 mL) was added DDQ (37 mg, 0.16 mmol) in small portions and the mixture was stirred vigorously for 20 min. The reaction was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 20:1) to yield 63 mg (98%) of **283**.

R_f = 0.45 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.13 (t, *J* = 7.20 Hz, 1H), 3.66-3.58 (m, 1H), 3.42 (m, 1H), 3.43 (dd, *J* = 9.73, 5.94 Hz, 1H), 3.36 (dd, *J* = 9.85, 6.57 Hz, 1H), 2.34-2.27 (m, 1H), 2.17 (d, *J* = 6.56 Hz, 1H), 2.17-2.11 (m, 1H), 2.05-1.95 (m, 2H), 1.68 (d, *J* = 1.01 Hz, 3H), 1.62-1.54 (m, 1H), 1.45-1.27 (m, 3H), 1.12 (d, *J* = 6.30 Hz, 3H), 1.08-1.01 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (d, *J* = 6.82 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.03 (s, 6H).

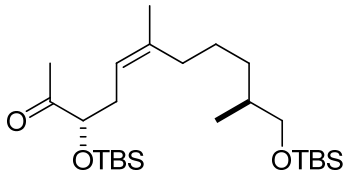
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.7, 120.3, 76.7, 68.7, 68.3, 35.7, 33.2, 32.4, 32.2, 25.9, 25.8, 25.4, 23.5, 19.9, 18.1, 16.7, -4.1, -4.7, -5.3.

IR (film): 2929, 2857, 1472, 1256, 1094 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{54}O_3Si_2$: 458.3612, found: 458.3618.

$[\alpha]_D^{20}$ 11.81 (*c* = 1.05, CH_2Cl_2)

(*Z*)-(3*S*,10*S*)-3,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-6,10-dimethyl-undec-5-en-2-one (284)



To a stirred solution of alcohol **283** (40 mg, 0.087 mmol) in DCM (2 mL) was added Dess-Martin periodinane (74 mg, 0.170 mmol) and the suspension was stirred for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 20:1) to yield 39 mg (quant.) of ketone **284**.

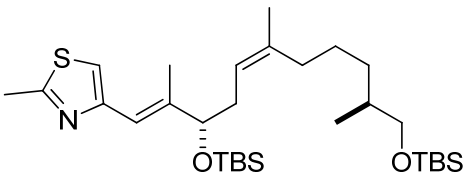
R_f = 0.57 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.11 (t, *J* = 7.32 Hz, 1H), 3.97 (dd, *J* = 6.82, 5.58 Hz, 1H), 3.43 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.35 (dd, *J* = 9.72, 6.44 Hz, 1H), 2.38-2.22 (m, 2H), 2.15 (s, 3H), 2.04-1.91 (m, 2H), 1.68 (d, *J* = 1.01 Hz, 3H), 1.61-1.53 (m, 1H), 1.39-1.27 (m, 3H), 1.08-1.00 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.86 (d, *J* = 6.57 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.0, 138.6, 119.0, 79.2, 68.3, 35.7, 33.4, 33.1, 32.2, 25.9, 25.7, 25.4, 25.3, 23.5, 16.7, 14.1, -4.9, -5.0, -5.3.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{52}O_3Si_2$: 456.3455, found: 456.3461.

4-[(1*E*,5*Z*)-(3*S*,10*S*)-3,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-undeca-1,5-dienyl]-2-methyl-thiazole (33)



To a stirred solution of (2-methyl-thiazol-4-yl)methyltributylphosphonium chloride (115 mg, 0.330 mmol) in THF (1 mL) at 0 °C was added *n*BuLi (130 µL, 2.5 M in hexane, 0.330 mmol) to form a bright red solution, which was stirred for 1 h. The mixture was cooled to -78 °C and

ketone **284** (15 mg, 0.033 mmol) in THF (0.5 mL) was slowly added. The cooling bath was removed and the mixture was stirred at 60 °C for 1.5 h. After cooling down to r.t., the reaction was quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (hexane:EtOAc = 20:1) to yield 17 mg (93%) of northern fragment **33**.

R_f = 0.36 (hexane:EtOAc = 15:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 6.45 (s, 1H), 5.13 (t, *J* = 6.82 Hz, 1H), 4.08 (t, *J* = 6.44 Hz, 1H), 3.44 (dd, *J* = 9.85, 5.81 Hz, 1H), 3.34 (dd, *J* = 9.85, 6.57 Hz, 1H), 2.71 (s, 3H), 2.29-2.20 (m, 2H), 2.05-1.94 (m, 2H), 2.00 (d, *J* = 1.26 Hz, 3H), 1.66 (d, *J* = 1.26 Hz, 3H), 1.61-1.53 (m, 1H), 1.45-1.28 (m, 3H), 1.08-1.00 (m, 1H), 0.89 (s, 18H), 0.86 (d, *J* = 6.56 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.3, 153.3, 142.6, 136.9, 121.4, 118.7, 114.9, 79.1, 68.4, 35.8, 35.3, 33.2, 32.3, 25.9, 25.8, 25.4, 23.5, 19.2, 16.7, 13.9, -4.6, -4.9, -5.3.

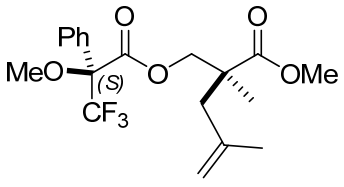
IR (film): 2929, 1472, 1257, 1090 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{30}H_{57}O_2Si_2NS$: 551.3849, found: 551.3635.

$[\alpha]_D^{20}$ 0.66 (*c* = 0.3, CH_2Cl_2)

10.2.3. Discodermolide

(*S*)-MTPA ester (299)



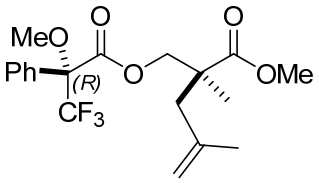
Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2H), 7.39 (m, 3H), 4.84 (s, 1H), 4.62 (s, 1H), 4.47 (d, *J* = 10.60 Hz, 1H), 4.26 (d, *J* = 10.84 Hz, 1H), 3.64 (s, 3H), 3.52 (s, 3H), 2.32 (q, *J* = 14.56 Hz, 2H), 1.64 (s, 3H), 1.21 (s, 3H).

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2H), 7.39 (m, 3H), 4.84 (s, 1H), 4.62 (s, 1H), 4.52 (d, *J* = 10.84 Hz, 1H), 4.22 (d, *J* = 10.60 Hz, 1H), 3.60 (s, 3H), 3.52 (s, 3H), 2.33 (q, *J* = 14.48 Hz, 2H), 1.64 (s, 3H), 1.21 (s, 3H).

(*R*)-MTPA ester (300)



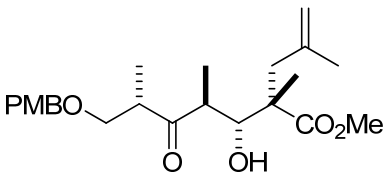
Major:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2H), 7.40 (m, 3H), 4.85 (s, 1H), 4.64 (s, 1H), 4.51 (d, *J* = 10.84 Hz, 1H), 4.22 (d, *J* = 10.84 Hz, 1H), 3.60 (s, 3H), 3.52 (s, 3H), 2.37 (d, *J* = 13.12 Hz, 1H), 2.30 (d, *J* = 13.64 Hz, 1H), 1.64 (s, 3H), 1.21 (s, 3H).

Minor:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2H), 7.40 (m, 3H), 4.85 (s, 1H), 4.64 (s, 1H), 4.47 (d, *J* = 10.84 Hz, 1H), 4.26 (d, *J* = 10.84 Hz, 1H), 3.64 (s, 3H), 3.52 (s, 3H), 2.36 (d, *J* = 13.16 Hz, 1H), 2.29 (d, *J* = 13.64 Hz, 1H), 1.64 (s, 3H), 1.21 (s, 3H).

(2*S*,3*R*,4*S*,6*S*)-3-Hydroxy-7-(4-methoxy-benzyloxy)-2,4,6-trimethyl-2-(2-methyl-allyl)-5-oxo-heptanoic acid methyl ester (303)



To a solution of chlorodicyclohexylborane (0.94 mL, 1M in hexane, 0.94 mmol) in Et_2O (1 mL) at 0 °C was added triethylamine (0.14 mL, 1.00 mmol). After 15 min a solution of ethyl ketone **288** (148 mg, 0.63 mmol) in Et_2O (1 mL) was slowly added. Stirring was continued for 1 h and then cooled to -78 °C where a solution of aldehyde ***ent*-292** (160 mg, 0.94 mmol) in Et_2O (1 mL) was added. The reaction was kept at -78 °C for 3.5 h, then it was warmed to 0

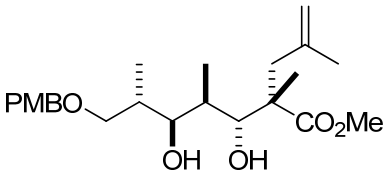
°C for 15 min and pH 7 buffer solution (5 mL), methanol (1 mL) and H_2O_2 (1 mL, 30% aqueous) were added. After stirring for 1 h at room temperature the mixture was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 5:1) to yield 250 mg (98%) of **303**.

$\mathbf{R_f}$ = 0.48 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.60 Hz, 2H), 6.86 (d, *J* = 8.60 Hz, 2H), 4.81 (s, 1H), 4.65 (s, 1H), 4.42 (d, *J* = 11.12 Hz, 1H), 4.38 (d, *J* = 11.60 Hz, 1H), 3.90 (dd, *J* = 8.08, 4.52 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.61 (t, *J* = 8.60 Hz, 1H), 3,40 (dd, *J* = 9.10, 4.54 Hz, 1H), 3.01 (m, 1H), 2.75 (ddd, *J* = 14.40, 7.20, 4.40 Hz, 1H), 2.50 (d, *J* = 13.40 Hz, 1H), 2.40 (d, *J* = 13.40 Hz, 1H), 1.63 (s, 3H), 1.16 (d, *J* = 7.32 Hz, 3H), 1.07 (d, *J* = 7.08 Hz, 3H), 1.03 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 219.0, 141.9, 129.8, 129.2, 114.9, 113.8, 79.4, 73.0, 71.6, 70.3, 55.2, 51.5, 51.1, 46.4, 45.5, 23.6, 15.6, 15.0, 13.8.

(2*S*,3*R*,4*R*,5*S*,6*S*)-3,5-Dihydroxy-7-(4-methoxy-benzyloxy)-2,4,6-trimethyl-2-(2-methyl-allyl)-heptanoic acid methyl ester (304)



To a solution of tetramethylammonium triacetoxyboron hydride (1.09 g, 4.96 mmol) in acetonitrile:acetic acid (1:1, 14 mL) at -30 °C was slowly added a solution of hydroxyketone **303** (250 mg, 0.62 mmol) in acetonitrile (3 mL). After stirring for 9 h a saturated solution of $NaHCO_3$ and solid $NaHCO_3$ was added very carefully till gas evolution ceased. The aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) yielded 95 mg (38%) of dihydroxy ester **304** and 22 mg (9%) of the wrong diastereoisomer and 110 mg (44%) of educt **303**.

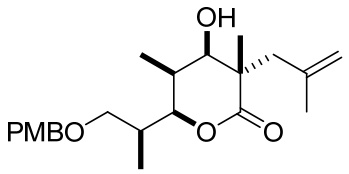
$\mathbf{R_f}$ = 0.31 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.56 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 4.80 (s, 1H), 4.68 s, 1H), 4.45 (s, 2H), 4.41 (s, 1H (OH)), 4.17 (d, *J* = 6.32 Hz, 1H (OH)), 3.96 (d, *J* =

9.36 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, *J* = 6.30, 3.54 Hz, 1H), 3.64 (s, 3H), 3.55 (dd, *J* = 9.08, 4.04 Hz, 1H), 3.43 (t, *J* = 9.34 Hz, 1H), 2.58 (d, *J* = 13.60 Hz, 1H), 2.48 (d, *J* = 13.64 Hz, 1H), 2.01-1.94 (m, 1H), 1.72-1.67 (m, 1H), 1.63 (s, 3H), 1.22 (s, 3H), 1.00 (d, *J* = 7.08 Hz, 3H), 0.69 (d, *J* = 7.08 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.9, 159.4, 142.3, 129.4, 114.5, 113.9, 81.2, 77.9, 76.8, 73.2, 55.3, 51.5, 51.3, 46.3, 35.9, 35.6, 23.4, 15.1, 12.7, 12.3.

(3*S*,4*R*,5*S*,6*S*)-4-hydroxy-6-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-3,5-dimethyl-3-(2-methylallyl)tetrahydro-2H-pyran-2-one (305)



LiOH (1.8 mL, 1M in water, 1.76 mmol) was added to ester **304** (237 mg, 0.58 mmol) in THF (5 mL) at 0 °C and vigorously stirred for 4 h. Brine was added and the aqueous layer was acidified with 1N HCl and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated.

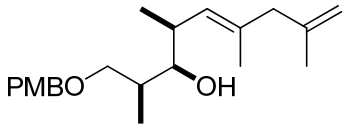
The residue was taken up in DCM (6 mL) and EDC·HCl (171 mg, 0.88 mmol) and DMAP (138 mg, 1.16 mmol) were added and stirred over night. Brine was added and the aqueous layer was extracted with DCM. The combined DCM phasewas dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 172 mg (79%) of lactone **305** as colorless oil.

R_f = 0.50 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.23 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.56 Hz, 2H), 4.91 (s, 1H), 4.80 (s, 1H), 4.44 (s, 2H), 4.17 (bs, 1H), 4.11 (dd, *J* = 10.36, 2.00 Hz, 1H), 3.80 (s, 3H), 3.64 (dd, *J* = 8.98, 5.18 Hz, 1H), 3.57 (dd, *J* = 8.84, 2.80 Hz, 1H), 2.61 (d, *J* = 13.40 Hz, 1H), 2.35 (d, *J* = 13.36 Hz, 1H), 2.23 (m, 1H), 2.01 (m, 1H), 1.71 (s, 3H), 1.35 (s, 3H), 1.00 (d, *J* = 7.32 Hz, 3H), 0.98 (d, *J* = 7.56 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.9, 142.5, 130.7, 129.1, 116.1, 113.7, 79.2, 72.9, 71.1, 70.6, 55.3, 48.2, 46.8, 35.2, 35.1, 23.4, 23.0, 13.2, 5.7.

(*E*)-(2*S*,3*R*,4*S*)- 1-(4-methoxybenzyloxy)-2,4,6,8-tetramethylnona-5,8-dien-3-ol (307)



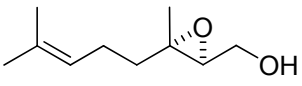
To lactone **305** (80 mg, 0.21 mmol) in Et_2O:trietyhlamine (10:1, 2 mL) at 0 °C was added methanesulfonyl chloride (0.025 mL, 0.32 mmol). After 2 h brine was added, the layers were separated and the aqueous layer extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in THF (2 mL) and LiOH (0.63 mL, 1M in water, 0.63 mmol) was added. After 2 h the reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 25 mg (36%) of fragmentation product **307**.

R_f = 0.83 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.26 (d, *J* = 8.56 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.10 (d, *J* = 9.60 Hz, 1H), 4.77 (s, 1H), 4.71 (s, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.52 (dd, *J* = 8.84, 6.32 Hz, 1H), 3.45 (dd, *J* = 10.02, 8.14 Hz, 1H), 3.42 (dd, *J* = 8.96, 5.96 Hz, 1H), 3.00 (s, 1H (OH)), 2.71 (s, 2H), 2.54 (m, 1H), 1.99 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 0.95 (d, *J* = 7.08 Hz, 3H), 0.90 (d, *J* = 6.84 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.1, 143.7, 135.0, 130.6, 129.9, 129.2, 113.7, 111.8, 76.1, 74.2, 72.9, 55.3, 48.9, 36.3, 35.0, 21.7, 17.1, 15.9, 9.9.

((2S,3S)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (514)



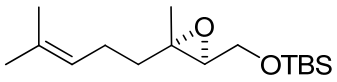
To a suspension of MS 4 Å (900 mg) in DCM (25 mL), freshly distilled from P_2O_5, at 0 °C was added L-(+)-DET (0.41 mL, 2.4 mmol) followed by freshly distilled Ti(O*i*Pr)$_4$ (0.48 mL, 1.6 mmol) and the mixture was cooled to -20 °C. *tert*-Butylhydroperoxide (8.80 mL, 5.5M in octane, 48.5 mmol) was added slowly and stirring was continued for 40 min. Geraniol (5.70 mL, 32.5 mmol) was slowly added and the mixture was kept at -20 °C for 1 h before it was warmed to 0 °C over 45 min. Water (10 mL) was added and after 1 h 30% aqueous NaOH saturated with NaCl (3 mL) was added and the mixture was stirred for further 45 min. The

MS was filtered off over celite and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by bulb-to-bulb distillation yielded at 100 °C 5.90 g (quant.) of epoxide **514**.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.08 (tt, *J* = 7.08, 1.26 Hz, 1H), 3.81 (ddd, *J* = 11.87, 7.07, 4.54 Hz, 1H), 3.67 (ddd, *J* = 11.83, 6.98, 4.51 Hz, 1H), 2.97 (dd, *J* = 6.82, 4.29 Hz, 1H), 2.08 (q, *J* = 7.66 Hz, 2H), 1.72-1.64 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.47 (ddd, *J* = 13.70, 8.65, 7.76 Hz, 1H), 1.29 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 132.1, 123.3, 62.9, 61.5, 38.5, 25.7, 23.7, 17.6, 16.7.

tert-butyldimethyl[((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methoxy]silane (342)

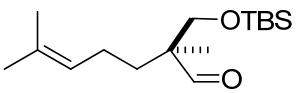


To a stirred solution of epoxide **514** (5.4 g, 32.0 mmol) and imidazole (4.35 g, 64.0 mmol) in DMF (40 mL) was added TBSCl (4.6 g, 35.2 mmol) at 0 °C and stirring was continued at r.t. for 3 h. The reaction mixture was quenched with water and extracted with hexane:Et_2O (1:1). The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 50:1) furnished 9.1 g (quant.) of TBS ether **342** as colorless oil.

R_f = 0.78 (hexane:EtOAc = 10:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.09 (bt, *J* = 7.01 Hz, 1H), 3.73 (d, *J* = 5.25 Hz, 2H), 2.90 (t, *J* = 5.49 Hz, 1H), 2.13-2.03 (m, 2H), 1.68 (s, 3H), 1.64 (m, 1H), 1.60 (s, 3H), 1.52-1.41 (m, 1H), 1.26 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

(*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-2,6-dimethylhept-5-enal (339)



To 4-bromo-2,6-di*tert*-butylphenol (3.18 g, 11.2 mmol) in degassed DCM (130 mL), distilled from P_2O_5, at r.t. was added $AlMe_3$ (2.80 mL, 2M in hexane, 5.6 mmol) under gas evolution

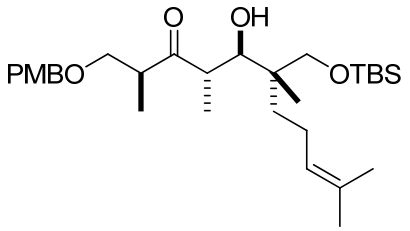
and the mixture was stirred for 1 h. TBS epoxide **342** (8.00 g. 28.1 mmol) in degassed DCM (40 mL) was added at -78 °C over 45 min *via* cannula and stirring was continued for 30 min. Then the mixture was brought to 0 °C over 30 min and KF (651 mg, 11.2 mmol) and water (152 µL, 8.4 mmol) were added and stirring was continued for 30 min. After warming to r.t. the mixture was filtered over celite and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 50:1) furnished 8.00 g (quant.) of aldehyde **339**.

$\mathbf{R_f}$ = 0.88 (hexane:EtOAc = 20:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.55 (s, 1H), 5.01 (tt, *J* = 7.14, 1.44 Hz, 1H), 3.68 (d, *J* = 9.84 Hz, 1H), 3.56 (d, *J* = 10.08 Hz, 1H), 1.97-1.83 (m, 2H), 1.67 (s, 3H), 1.60 (m, 1H), 1.58 (s, 3H), 1.46 (m, 1H), 1.04 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{32}O_2Si$: 284.2172, found: 284.2153.

(2*S*,4*S*,5*R*,6*S*)-6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-1-(4-methoxy-benzyloxy)-2,4,6,10-tetramethyl-undec-9-en-3-one (345)



To a solution of chlorodicyclohexylborane (55 mL, 1M in hexane, 54.6 mmol) in Et_2O (200 mL) at 0 °C under argon atmosphere was added triethylamine (8 mL, 58.2 mmol). After 15 min a solution of ethyl ketone **288** (8.60 g, 36.4 mmol) in Et_2O (50 mL) was added dropwise. Stirring was continued for 1 h and then the mixture was cooled to -78 °C and a solution of aldehyde **339** (11.38 g, 40.0 mmol) in Et_2O (70 mL) was added over 25 min. After the addition was completed the reaction was kept at -78 °C for 3 h, then it was warmed to 0 °C over 15 min and pH 7 buffer solution (500 mL), methanol (100 mL) and H_2O_2 (50 mL, 30% aqueous) were added. After stirring for 1.5 h at room temperature the mixture was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 50:1 to 10:1) to yield 14.30 g (75%) of **345** as a pale yellow oil. At smaller scales (5 mmol) the yield was quantitative.

$\mathbf{R_f}$ = 0.35 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.07 (bt, *J* = 7.07 Hz, 1H), 4.43 (d, *J* = 11.37 Hz, 1H), 4.39 (d, *J* = 11.62 Hz, 1H), 3.98 (d, *J* = 8.08 Hz, 1H (OH)), 3.80 (s, 3H), 3.62-3.55 (m, 3H), 3.44-3.37 (m, 2H), 3.09-3.00 (m, 2H), 1.97-1.88 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.45-1.37 (m, 1H), 1.26-1.18 (m, 1H), 1.21 (d, *J* = 7.07 Hz, 3H), 1.07 (d, *J* = 7.32 Hz, 3H), 0.89 (s, 9H), 0.77 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

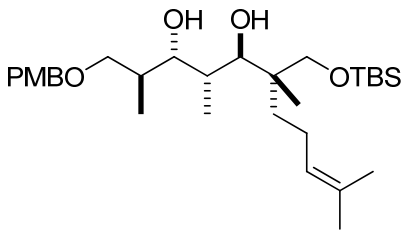
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 219.0, 159.2, 131.3, 130.1, 129.2, 124.9, 113.8, 79.9, 73.0, 72.0, 67.9, 55.3, 47.5, 45.5, 42.5, 35.0, 25.9, 22.1, 18.2, 16.7, 13.6, -5.6.

IR (film): 3474, 2931, 1696, 1613, 1514, 1463, 1249, 1092 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{30}H_{52}O_5SiNa$: 543.3482, found: 543.3476.

$[\alpha]_D^{20}$ 16.23 (*c* = 1.4, CH_2Cl_2).

(2*S*,3*S*,4*R*,5*R*,6*S*)-6-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-(4-methoxy-benzyloxy)-2,4,6,10-tetramethyl-undec-9-ene-3,5-diol (346)



To a solution of tetramethylammonium triacetoxyboron hydride (17.07 g, 102.90 mmol) in acetonitrile:acetic acid (1:1, 120 mL) at -30 °C was slowly added a solution of **345** (6.70 g, 12.86 mmol) in acetonitrile (30 mL). After stirring for 7 h, the reaction was kept in the freezer (-25 °C) for 96 h, then a saturated solution of $NaHCO_3$ and solid $NaHCO_3$ was added very carefully until the gas evolution ceased. The aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 4.30 g (64%) of dihydroxy ester **346** and 2.01 g (30%) of educt **345**.

R_f = 0.12 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.69 Hz, 2H), 6.86 (d, *J* = 8.69 Hz, 2H), 5.07 (bt, *J* = 6.99 Hz, 1H), 4.46 (d, *J* = 11.33 Hz, 1H), 4.43 (d, *J* = 11.33 Hz, 1H), 3.86 (d, *J* = 9.82 Hz, 1H), 3.80 (s, 3H), 3.65-3.60 (m, 2H), 3.57 (m, 1H), 3.49-3.40 (m, 2H), 1.98-1.87 (m, 4H), 1.68

(s, 3H), 1.60 (s, 3H), 1.45-1.40 (m, 1H), 1.33-1.25 (m, 1H), 1.04 (d, *J* = 7.17 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.79 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

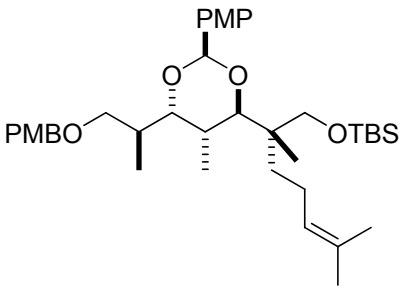
^{13}C-NMR (150 MHz, $CDCl_3$): *δ* = 159.0, 131.3, 130.5, 129.2, 124.7, 113.7, 82.4, 74.8, 74.3, 70.2, 55.2, 41.7, 36.3, 35.5, 25.8, 22.0, 18.0, 17.7, 13.8, 13.4, -5.7, -5.8.

IR (film): 3447, 2930, 2856, 1513, 1406, 1249, 1094 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{30}H_{54}O_5SiNa$: 545.3638, found: 545.3632.

$[\alpha]_D^{20}$ -2.98 (*c* = 1.5, CH_2Cl_2).

***tert*-butyl{(*S*)-2-[(2*R*,4*R*,5*R*,6*S*)-6-[(*S*)-1-(4-methoxybenzyloxy)propan-2-yl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-2,6-dimethylhept-5-enyloxy}dimethylsilane (348)**



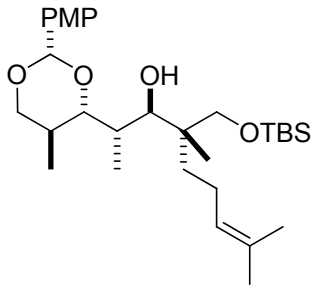
To diol **346** (45 mg, 0.086 mmol) in DCM (2 mL) was added anisaldehyde dimethyl acetal (22 µL, 0.130 mmol) and CSA (cat.) at r.t. and the mixture was stirred for 1.5 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 43 mg (75%) of acetal **348** as colorless oil.

R_f = 0.54 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.36 (d, *J* = 8.84 Hz, 2H), 7.20 (d, *J* = 8.60 Hz, 2H), 6.86 (d, *J* = 7.60 Hz, 2H), 6.85 (d, *J* = 8.60 Hz, 2H), 5.64 (s, 1H), 5.11 (bt, *J* = 7.06 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.73 (dd, *J* = 10.05, 2.90 Hz, 1H), 3.63 (dd, *J* = 8.96, 3.16 Hz, 1H), 3.58 (d, *J* = 9.60 Hz, 1H), 3.41-3.38 (m, 2H), 3.32 (dd, *J* = 8.76, 6.64 Hz, 1H), 2.15 (m, 1H), 2.01-1.88 (m, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.46-1.37 (m, 1H), 1.32-1.21 (m, 1H), 1.00 (d, *J* = 6.80 Hz, 3H), 0.95 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.6, 159.0, 133.7, 131.1, 129.1, 127.3, 125.2, 113.7, 113.3, 98.1, 83.8, 72.8, 72.5, 70.7, 65.1, 55.2, 42.5, 34.4, 32.5, 31.4, 26.0, 25.7, 22.0, 17.6, 16.1, 14.2, -5.6.

(2*S*,3*R*,4*S*)-4-[(*tert*-butyldimethylsilyloxy)methyl)-2-[(2*S*,4*S*,5*S*)-2-(4-methoxyphenyl]-5-methyl-[1,3]-dioxan-4-yl]-4,8-dimethylnon-7-en-3-ol (349)



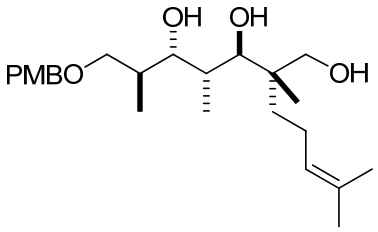
To a suspension of diol **346** (45 mg, 0.086 mmol) and MS 3Å (50 mg) in DCM (1.5 mL) under argon at r.t. was added DDQ (23 mg, 0.103 mmol). After 2.5 h another equivalent of DDQ was added and stirring was continued for 2 h. The reaction was quenched by the addition of a saturated $Na_2S_2O_3$ solution and the MS was filtered off over celite. The layers were separated and the aqueous layer was extracted with DCM. The combined organic slayer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 18 mg (38%) of acetale **349**.

R_f = 0.28 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.56 Hz, 2H), 6.87 (d, *J* = 8.84 Hz, 2H), 5.45 (s, 1H), 5.10 (bt, *J* = 6.96 Hz, 1H), 4.10 (dd, *J* = 11.24, 4.68 Hz, 1H), 3.99 (dd, *J* = 10.24, 1.64 Hz, 1H), 3.79 (s, 3H), 3.58 (d, *J* = 9.84 Hz, 1H), 3.56 (m, 1H), 3.52 (t, *J* = 11.00 Hz, 1H), 3.36 (d, *J* = 9.60 Hz, 1H), 3.20 (d, *J* = 6.80 Hz, 1H (OH)), 2.17-2.09 (m, 2H), 2.00-1.94 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.43-1.27 (m, 2H), 1.15 (d, *J* = 7.08 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 3H), 0.77 (d, *J* = 6.84 Hz, 3H), 0.04 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.9, 131.1, 130.9, 127.3, 125.2, 113.6, 101.1, 84.4, 78.5, 73.4, 66.9, 55.3, 42.7, 34.4, 33.4, 30.5, 25.9, 25.7, 22.3, 18.2, 17.5, 13.8, 11.9, -5.6.

(2*S*,3*R*,4*R*,5*S*,6*S*)-7-(4-Methoxy-benzyloxy)-2,4,6-trimethyl-2-(4-methyl-pent-3-enyl)-heptane-1,3,5-triol (353)



To a stirred solution of silyl ether **346** (1.1 g, 2.1 mmol) in acetonitrile (8 mL) and pyridine (4 mL) in a plastic vessel was added HF·pyridine (2 mL, 70%) and stirring was continued for 4 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and DCM was added. The aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 790 mg (92%) of triol **353** as colorless oil.

R_f = 0.26 (hexane:EtOAc = 3:1)

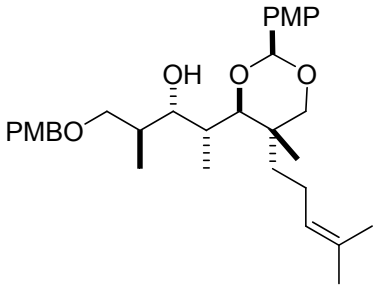
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.56 Hz, 2H), 6.88 (d, *J* = 8.56 Hz, 2H), 5.10 (tt, *J* = 6.73, 1.01 Hz, 1H), 4.68 (d, *J* = 3.28 Hz, 1H (OH)), 4.46 (d, *J* = 2.52 Hz, 2H), 3.96 (d, *J* = 9.32 Hz, 1H), 3.81 (s, 3H), 3.64-3.51 (m, 4H), 3.46 (m, 1H), 2.07-1.92 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.41-1.37 (m, 2H), 1.03 (d, *J* = 7.04 Hz, 3H), 0.91 (s, 3H), 0.77 (d, *J* = 7.08 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.5, 131.4, 129.4, 124.8, 113.9, 83.7, 78.0, 76.8, 73.3, 70.6, 55.3, 41.6, 35.9, 35.6, 33.9, 25.7, 22.0, 17.6, 17.4, 13.5, 12.9.

IR (film): 3392, 2964, 2928, 1613, 1513, 1463, 1377, 1305, 1248, 1173, 1076, 1038 cm^{-1}.

$[\alpha]_D^{20}$ 43.50 (*c* = 0.6, CH_2Cl_2)

(2*S*,3*S*,4*R*)-1-(4-methoxybenzyloxy)-4-[(2*S*,4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl-5-(4-methylpent-3-enyl)-[1,3]-dioxan-4-yl]-2-methylpentan-3-ol (347)



To diol **353** (20 mg, 0.049 mmol) in DCM (1 mL) was added anisaldehyde dimethyl acetal (12 µL, 0.073 mmol) and CSA (cat.) at r.t. under argon. The mixture was stirred for 1 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 23 mg (84%) of acetal **347** as colorless oil.

R_f = 0.71 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.38 (d, *J* = 8.84 Hz, 2H), 7.25 (d, *J* = 8.60 Hz, 2H), 6.88 (d, *J* = 8.60 Hz, 2H), 6.85 (d, *J* = 8.60 Hz, 2H), 5.41 (s, 1H), 5.06 (bt, *J* = 6.94 Hz, 1H), 4.44 (q, *J* = 12.04 Hz, 2H), 3.90 (d, *J* = 10.12 Hz, 1H), 3.83 (d, *J* = 11.12 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.71 (d, *J* = 11.08 Hz, 1H), 3.68-3.64 (m, 2H), 3.36 (dd, *J* = 8.96, 7.20 Hz, 1H), 2.99 (d, *J* = 1.76 Hz, 1H (OH)), 2.05-1.96 (m, 2H), 1.94-1.84 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.34-1.18 (m, 2H), 1.24 (s, 3H), 1.05 (d, *J* = 7.08 Hz, 3H), 0.92 (d, *J* = 6.80 Hz, 3H).

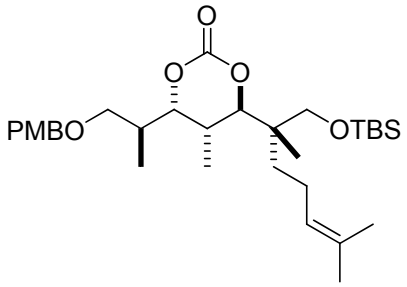
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 160.0, 159.1, 132.0, 131.0, 130.9, 129.1, 127.3, 124.1, 113.8, 113.7, 102.2, 89.3, 77.8, 73.5, 72.8, 72.7, 55.3, 55.2, 36.6, 36.5, 36,2, 33.8, 25.7, 21.4, 17.6, 14.3, 13.2.

IR (film): 2963, 1614, 1515, 1249, 1171, 1093, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{32}H_{46}O_6$: 526.3294, found: 526.3289.

$[\alpha]_D^{20}$ 6.22 (*c* = 0.45, CH_2Cl_2)

(4*R*,5*R*,6*S*)-4-[(*S*)-1-(tert-butyldimethylsilyloxy)-2,6-dimethylhept-5-en-2-yl]-6-[(*S*)-1-(4-methoxybenzyloxy)propan-2-yl]-5-methyl-1,3-dioxan-2-one (350)



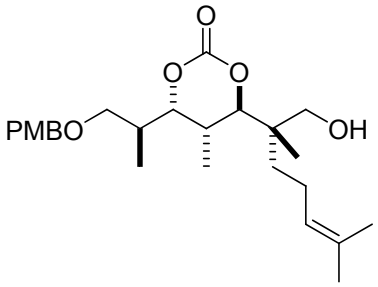
To a stirred solution of diol **346** (30 mg, 0.057 mmol) in DCM (1 mL) at r.t. was added pyridine (0.1 mL) and phosgene (43 µL, 2M in toluene, 0.085 mmol) and stirring was continued for 1 h. A saturated NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) yielded 31 mg (quant.) of carbonate **350**.

$\mathbf{R_f}$ = 0.35 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.60 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.07 (m, 1H), 4.44 (m, 2H), 4.11 (dd, *J* = 10.26, 2.64 Hz, 1H), 4.02 (d, *J* = 2.56 Hz, 1H), 3.81 (s, 3H), 3.61-3.50 (m, 3H), 3.44 (d, *J* = 10.10 Hz, 1H), 2.38 (m, 1H), 2.02-1.90 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.36-1.26 (m, 2H), 1.04 (d, *J* = 7.04 Hz, 3H), 0.98 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.3, 151.7, 131.8, 130.6, 129.3, 124.2, 113.8, 88.8, 79.1, 73.1, 70.7, 65.3, 55.2, 42.5, 34.6, 32.5, 28.7, 25.9, 21.9, 17.8, 16.9, 13.9, 13.0, -5.6.

(4*R*,5*R*,6*S*)-4-[(*S*)-1-hydroxy-2,6-dimethylhept-5-en-2-yl]-6-[(*S*)-1-(4-methoxybenzyloxy)propan-2-yl]-5-methyl-1,3-dioxan-2-one (515)

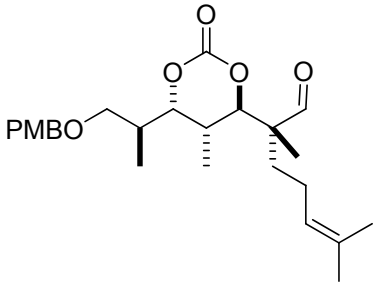


Silyl ether **350** (80 mg, 0.14 mmol) in THF (3 mL) at r.t. was treated with TBAF (0.17 mL, 1M in THF, 0.17 mmol) and the mixture was stirred for 12 h. Brine was added and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 50 mg (83%) of **515**.

$\mathbf{R_f}$ = 0.38 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.56 Hz, 2H), 6.87 (d, *J* = 8.56 Hz, 2H), 5.07 (bt, *J* = 7.06 Hz, 1H), 4.44 (s, 2H), 4.16 (dd, *J* = 10.61, 2.77 Hz, 1H), 4.08 (d, *J* = 2.52 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 11.12, 3.28 Hz, 1H), 3.59-3.50 (m, 3H), 2.37 (m, 1H), 2.04-1.95 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.42-1.26 (m, 2H), 1.06 (d, *J* = 7.08 Hz, 3H), 0.99 (d, *J* = 7.08 Hz, 3H), 0.90 (s, 3H).

(*R*)-2-[(4*R*,5*R*,6*S*)-6-((*S*)-1-(4-methoxybenzyloxy)propan-2-yl)-5-methyl-2-oxo-[1,3]-dioxan-4-yl]-2,6-dimethylhept-5-enal (351)



Dess-Martin periodinane (117 mg, 0.270 mmol) was added portion wise to a solution of alcohol **515** (40 mg, 0.088 mmol) in DCM (2 mL) at 0 °C under argon. After 2.5 h a saturated $NaHCO_3$ solution was added, the layers were separated and the aqueous layer was

extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 27 mg (68%) of aldehyde **351** as colorless oil.

R_f = 0.45 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.03 (bt, *J* = 6.96 Hz, 1H), 4.43 (s, 2H), 4.21 (d, *J* = 2.80 Hz, 1H), 4.06 (dd, *J* = 10.48, 2.88 Hz, 1H), 3.80 (s, 3H), 3.53 (d, *J* = 4.04 Hz, 2H), 2.25 (m, 1H), 2.04-1.94 (m, 2H), 1.86 (m, 1H), 1.67 (m, 1H), 1.67 (s, 3H), 1.60 (m, 1H), 1.58 (s, 3H), 1.15 (s, 3H), 1.10 (d, *J* = 7.32 Hz, 3H), 0.98 (d, *J* = 6.80 Hz, 3H).

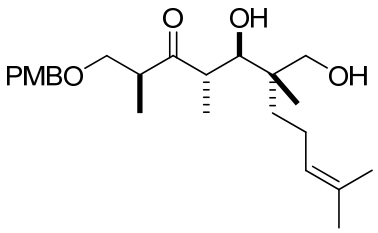
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.0, 159.2, 150.5, 133.3, 130.5, 129.2, 122.8, 113.9, 88.0, 78.8, 73.0, 70.4, 55.3, 53.4, 34.3, 32.6, 29.3, 25.8, 22.1, 17.7, 13.6, 12.9.

IR (film): 2929, 1766, 1613, 1513, 1462, 1247, 1098 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{36}O_6Na$: 455.2410, found: 455.2400.

$[\alpha]_D^{20}$ -19.67 (*c* = 0.3, CH_2Cl_2)

(2*S*,4*S*,5*R*,6*S*)-5-hydroxy-6-(hydroxymethyl)-1-(4-methoxybenzyloxy)-2,4,6,10-tetramethylundec-9-en-3-one (354)



Dess-Martin periodinane (19 mg, 0.04 mmol) was added potion wise to a solution of alcohol **353** (15 mg, 0.038 mmol) in DCM (1 mL) at 0 °C. After 1.5 h saturated $NaHCO_3$ solution was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 9 mg (60%) of ketone **354** as colorless oil.

R_f = 0.28 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.60 Hz, 2H), 6.86 (d, *J* = 8.60 Hz, 2H), 5.04 (bt, *J* = 6.94 Hz 1H), 4.45 (d, *J* = 11.64 Hz, 1H), 4.42 (d, *J* = 11.64 Hz, 1H), 3.80 (s, 3H), 3.74

(dd, *J* = 11.36, 5.80 Hz, 1H), 3.67-3.63 (m, 1H), 3.60-3.56 (m, 1H+1H (OH)), 3.51-3.45 (m, 1H), 3.17 (dq, J = 6.85, 2.59 Hz, 1H), 2.26 (t, *J* = 6.56 Hz, 1H (OH)), 1.94-1.85 (m, 3H), 1.67 (s, 3H), 1.61-1.47 (m, 2H), 1.58 (s, 3H), 1.22 (s, 3H),1.07 (d, *J* = 6.84 Hz, 3H), 0.94 (d, *J* = 6.80 Hz, 3H).

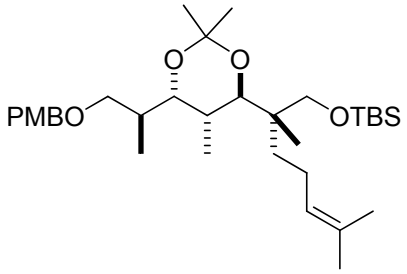
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 221.6, 159.2, 132.3, 130.3, 129.4, 123.6, 113.9, 73.4, 73.1, 72.9, 67.8, 55.3, 53.8, 41.8, 36.1, 35.2, 25.6, 22.7, 17.6, 14.1, 10.2.

IR (film): 3468, 2930, 1682, 1513, 1455, 1302, 1248, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{24}H_{38}O_5Na$: 429.2617, found: 429.2621.

$[\alpha]_D^{20}$ -28.00 (*c* = 0.45, CH_2Cl_2)

***tert*-Butyl-((*S*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl}-2,6-dimethyl-hept-5-enyloxy)-dimethyl-silane (356)**



To a stirred solution of **346** (2.50 g, 4.75 mmol) in DCM (50 mL) at r.t. under argon was added 2,2-dimethoxypropane (2.25 mL, 14.25 mmol) followed by CSA (110 mg, 0.47 mmol). After 2 h brine was added and the aqueous layer was extracted with DCM, the combined DCM layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 1.82 g (68%) of acetonide **356** as colorless oil and 0.78 g (31%) of starting material **346**.

R_f = 0.66 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.25 (d, *J* = 7.83 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 5.08 (bt, *J* = 6.57 Hz, 1H), 4.45-4.38 (m, 2H), 3.80 (s, 3H), 3.56 (dd, *J* = 8.82, 3.03 Hz, 1H), 3.48 (dd, *J* = 10.36, 2.78 Hz, 1H), 3.46 (d, *J* = 9.35 Hz, 1H), 3.40-3.32 (m, 3H), 1.99-1.89 (m, 3H), 1.84-1.76 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.36-1.18 (m, 2H), 1.29 (s, 3H), 1.22 (s, 3H), 0.92 (d, *J* = 6.57 Hz, 3H), 0.88 (s, 12H), 0.80 (s, 3H), 0.03 (s, 6H).

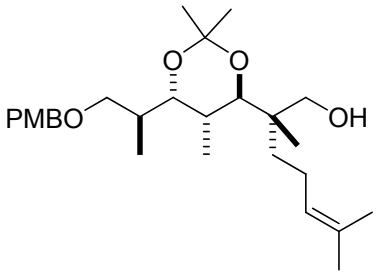
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 131.1, 129.1, 125.3, 113.7, 99.9, 76.9, 72.8, 72.5, 70.5, 65.2, 55.3, 41.9, 33.8, 32.7, 32.0, 25.9, 23.5, 22.0, 18.2, 17.6, 16.1, 13.4, 13.3, -5.5, -5.6.

IR (film): 2932, 1614, 1513, 1458, 1376, 1248, 1098 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{33}H_{58}O_5Si$: 562.4054, found: 562.4049.

$[\alpha]_D^{20}$ 6.90 (*c* = 0.86, CH_2Cl_2).

(*S*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-Methoxy-benzyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl}-2,6-dimethyl-hept-5-en-1-ol (357)



To a stirred solution of silyl ether **356** (1.20 g, 2.07 mmol) in acetonitrile (8 mL) and pyridine (3 mL) in a plastic vessel was added HF·pyridine (2 mL, 70%) and stirring was continued over night. HF·pyridine (1 mL, 70%) was added and the mixture was stirred for another 5 h, the reaction was quenched by addition of saturated $NaHCO_3$ solution and DCM was added. The aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) yielded 900 mg (97%) of alcohol **357** as colorless oil.

R_f = 0.39 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.56 Hz, 2H), 5.11 (bt, *J* = 6.94 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.72 (dd, *J* = 11.36, 3.80 Hz, 1H), 3.59 (dd, *J* = 10.74, 3.42 Hz, 1H), 3.53 (dd, *J* = 8.71, 2.90 Hz, 1H), 3.39-3.32 (m, 3H), 2.01-1.94 (m, 3H), 1.86-1.79 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.53-1.38 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 0.95 (d, *J* = 6.82 Hz, 3H), 0.92 (d, *J* = 6.57 Hz, 3H), 0.81 (s, 3H).

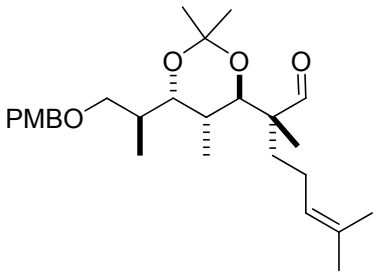
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 131.4, 130.9, 129.2, 124.7, 113.7, 100.6, 81.9, 72.9, 72.1, 70.6, 68.6, 55.3, 40.8, 34.8, 33.7, 32.5, 25.7, 23.2, 21.9, 17.0, 13.4, 13.2.

IR (film): 3509, 2967, 2933, 1513, 1377, 1247, 1085, 1038 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{27}H_{44}O_5$: 448.3189, found: 448.3192.

$[\alpha]_D^{20}$ 10.72 (*c* = 0.97, CH_2Cl_2).

(*R*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-Methoxy-benzyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl}-2,6-dimethyl-hept-5-enal (516)



To a solution of alcohol **357** (2.1 g, 4.68 mmol) in ethyl acetate (40 mL) was added IBX (2.62 g, 9.35 mmol). The mixture was heated under reflux for 2 h, then the white precipitate was filtered off and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 1.78 g (86%) of aldehyde **516** as colorless oil.

R_f = 0.76 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 7.24 (d, *J* = 8.59 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 5.03 (tt, *J* = 7.04, 1.33 Hz, 1H), 4.40 (s, 2H), 3.80 (s, 3H), 3.54-3.49 (m, 3H), 3.36 (dd, *J* = 8.71, 6.19 Hz, 1H), 1.98-1.85 (m, 2H), 1.83-1.71 (m, 2H), 1.67 (s, 3H), 1.64-1.46 (m, 2H), 1.57 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H), 1.06 (s, 3H), 0.94 (d, *J* = 6.57 Hz, 3H), 0.91 (d, *J* = 6.82 Hz, 3H).

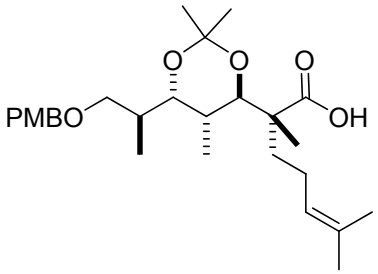
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.1, 159.0, 132.3, 130.9, 129.2, 123.7, 113.7, 100.5, 78.3, 72.9, 72.0, 70.1, 55.3, 53.3, 33.6, 32.8, 32.6, 25.7, 25.3, 23.2, 22.2, 17.7, 13.6, 13.2, 13.0.

IR (film): 2969, 2935, 1726, 1515, 1456, 1378, 1247, 1096, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{27}H_{42}O_5$: 446.3032, found: 446.3028.

$[\alpha]_D^{20}$ 4.56 (*c* = 1.36, CH_2Cl_2).

(*R*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-Methoxy-benzyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl}-2,6-dimethyl-hept-5-enoic acid (358)



To a solution of aldehyde **516** (1.65 g, 3.69 mmol) in *tert*-butanol (25 mL) with 2-methyl-2-butene (5 mL) was added dropwise a solution of $NaClO_2$ (4.95 g, 55.00 mmol) and NaH_2PO_4 (4.95 g) in water (15 mL). After 3 h 0.01N NaOH was added and the aqueous layer was extracted with Et_2O, 1N HCl was added until pH 2 was reached and the aqueous layer was extracted with DCM. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 1.71 g (quant.) of acid **358**.

R_f = 0.25 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.56 Hz, 2H), 5.06 (bt, *J* = 6.96 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.56 (dd, *J* = 10.74, 3.42 Hz, 1H), 3.49 (dd, *J* = 8.60, 2.80 Hz, 1H), 3.48 (d, *J* = 6.08 Hz, 1H), 3.37 (dd, *J* = 8.58, 6.06 Hz, 1H), 2.08-1.96 (m, 3H), 1.89-1.70 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.48-1.38 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.19 (s, 3H), 0.97 (d, *J* = 6.57 Hz, 3H), 0.91 (d, *J* = 6.82 Hz, 3H).

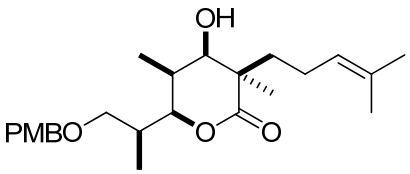
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.4, 159.0, 132.4, 130.9, 129.1, 123.4, 113.7, 101.5, 79.1, 72.9, 71.9, 70.6, 55.3, 50.8, 35.9, 33.9, 33.6, 25.6, 25.2, 23.3, 22.7, 17.6, 16.5, 13.6, 13.2, 13.0.

IR (film): 2981, 2935, 1701, 1513, 1226 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{27}H_{42}O_6Na$: 485.2879, found: 485.2896.

$[\alpha]_D^{20}$ 14.26 (*c* = 1.36, CH_2Cl_2).

(3*R*,4*R*,5*S*,6*S*)-4-Hydroxy-6-[(*S*)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl]-3,5-dimethyl-3-(4-methyl-pent-3-enyl)-tetrahydro-pyran-2-one (340)



To a stirred solution of acid **358** (1.66 mg, 3.5 mmol) in DCM (35 mL) at r.t. under argon was added CSA (783 mg, 3.5 mmol) and stirring was continued for 6 h. Brine was added and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 1.18 g (83%) of lactone **340** as colorless oil.

R_f = 0.16 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.01 (bt, *J* = 7.20 Hz, 1H), 4.45 (d, *J* = 11.37 Hz, 1H), 4.36 (d, *J* = 11.62 Hz, 1H), 4.18 (dd, *J* = 7.70, 4.42 Hz, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 4.04 Hz, 1H), 3.62 (dd, *J* = 8.84, 6.06 Hz, 1H), 3.60 (m, 1H), 3.49 (dd, *J* = 8.97, 4.67 Hz, 1H), 2.42-2.29 (m, 2H), 2.07-1.97 (m, 3H), 1.69-1.59 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.31 (s, 3H), 1.08 (d, *J* = 7.07 Hz, 3H), 0.96 (d, *J* = 7.07 Hz, 3H).

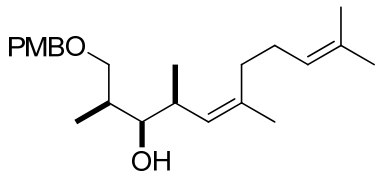
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1, 159.3, 131.7, 129.9, 129.6, 124.3, 113.7, 81.3, 76.0, 72.9, 71.6, 55.2, 46.5, 34.4, 34.1, 33.8, 25.8, 25.6, 22.8, 15.9, 8.8.

IR (film): 3435, 2968, 1706, 1513, 1248, 1102 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{36}O_5$: 404.2563, found: 404.2559.

$[\alpha]_D^{20}$ -23.50 (*c* = 0.92, CH_2Cl_2).

(*Z*)-(2*S*,3*R*,4*S*)-1-(4-Methoxy-benzyloxy)-2,4,6,10-tetramethyl-undeca-5,9-dien-3-ol (341)



To lactone **340** (450 mg, 1.05 mmol) in 1:1 DCM:pyridine (10 mL) at r.t. was added methanesulfonyl chloride (0.25 mL, 3.15 mmol) and DMAP (136 mg, 1.05 mmol). After 3 h brine was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in THF (10 mL) and LiOH (3.15 mL, 1M in water, 3.15 mmol) was added. After 2 h the reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 333 mg (88%) of olefin **341**.

R_f = 0.60 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.59 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 5.10 (m, 2H), 4.46-4.39 (m, 2H), 3.80 (s, 3H), 3.59 (dd, *J* = 9.09, 4.04 Hz, 1H), 3.41 (dd, *J* = 9.09, 6.32 Hz, 1H), 3.30-3.23 (m, 1H + 1H (OH)), 2.53-2.44 (m, 1H), 2.08-1.94 (m, 4H), 1.93-1.86 (m, 2H), 1.68 (s, 6H), 1.61 (s, 3H), 0.96 (d, *J* = 6.82 Hz, 6H).

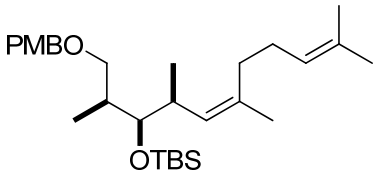
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.3, 134.0, 129.9, 129.3, 129.1, 124.3, 113.8, 80.4, 74.5, 73.2, 55.3, 35.7, 35.6, 32.2, 26.6, 25.7, 23.4, 22.6, 15.4, 14.8.

IR (film): 3503, 2930, 1513, 1248, 1083, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{23}H_{36}O_3$: 360.2664, found: 360.2671.

$[\alpha]_D^{20}$ 18.42 (*c* = 1.14, CH_2Cl_2).

***tert*-Butyl-{(*Z*)-(1*R*,2*S*)-1-[(*S*)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl]-2,4,8-trimethyl-nona-3,7-dienyloxy}-dimethyl-silane (517)**



To a stirred solution of alcohol **341** (240 mg, 0.65 mmol) in DCM (6 mL) was added 2,6-lutidine (120 µL, 0.98 mmol) and TBSOTf (160 µL, 0.72 mmol). After 1 h the reaction was quenched with saturated NH_4Cl solution and the layers were separated. The aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 320 mg (quant.) of protected diol **517** as colorless oil.

$\mathbf{R_f}$ = 0.55 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.59 Hz, 2H), 5.10 (t, *J* = 6.06 Hz, 1H), 4.98 (d, *J* = 9.85 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.51 (dd, *J* = 9.09, 4.80 Hz, 1H), 3.39 (t, *J* = 5.30 Hz, 1H), 3.20 (t, *J* = 8.72 Hz, 1H), 2.59-2.50 (m, 1H), 2.12-1.91 (m, 5H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 0.96 (d, *J* = 6.82 Hz, 3H), 0.89 (d, *J* = 6.06 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 6H).

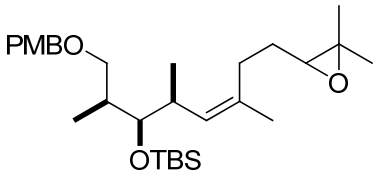
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 133.3, 131.5, 130.2, 129.1, 124.1, 113.7, 78.6, 72.7, 72.6, 55.3, 38.5, 35.5, 32.2, 26.6, 26.1, 25.7, 23.3, 18.4, 17.6, 16.9, 14.8, -3.8, -3.9.

IR (film): 2957, 2929, 1462, 1249, 1083, 1040 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{29}H_{50}O_3Si$: 474.3529, found: 474.3532.

$[\alpha]_D^{20}$ 6.64 (*c* = 1.28, CH_2Cl_2).

***tert*-Butyl-{(*Z*)-(1*R*,2*S*)-6-dimethyloxIRanyl-1-[(*S*)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl]-2,4-dimethyl-hex-3-enyloxy}-dimethyl-silane (360)**



To a stirred solution of **517** (320 mg, 0.65 mmol) in DCM (7 mL) at -20 °C NaOAc (60 mg, 0.68 mmol) and *m*CPBA (168 mg, 80% of weight, 0.68 mmol) was added. The mixture was warmed to 0 °C over 2 h and saturated $NaHCO_3$ solution was added. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 293 mg (92%) of epoxide **360** as 1:1 mixture of diastereoisomers.

$\mathbf{R_f}$ = 0.25 (hexane:EtOAc = 10:1)

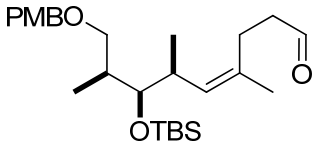
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.34 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 5.03 (d, *J* = 9.85 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.51 (dd, *J* = 8.84, 4.80 Hz, 1H), 3.40 (t, *J* = 5.43 Hz, 1H), 3.21 (t, *J* = 8.59 Hz, 1H), 2.68 or 2.67 (t, *J* = 6.19 Hz, 1H), 2.60-2.54 (m, 1H), 2.30-2.16 (m, 2H), 2.10-1.93 (m, 3H), 1.66 (s, 3H), 1.64-1.53 (m, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 0.96 (d, *J* = 6.82 Hz, 3H), 0.90 (d, *J* = 6.90 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 132.5, 130.9, 130.8/130.7, 129.1/129.0, 113.7, 78.6, 72.6, 72.5/72.4, 64.1/64.0, 58.3/58.2, 55.3, 38.4, 36.5/36.4, 35.6/35.5, 28.8, 27.6/27.5, 26.2, 24.9/24.8, 23.3, 18.7/18.6, 18.4, 17.0/16.9, 14.9/14.8, -3.8, -3.9.

IR (film): 2952, 1612, 1513, 1458, 1376, 1248, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_4H_9]^+$ calcd for $C_{25}H_{41}O_4Si$: 433.2774, found: 433.2768.

(*Z*)-(6*S*,7*R*,8*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-4,6,8-trimethyl-non-4-enal (365)



To a stirred solution of epoxide **360** (190 mg, 0.38 mmol) in Et_2O (3 mL) at 0 °C was added dropwise a solution of $HIO_4 \cdot 2H_2O$ (97 mg, 0.42 mmol) in THF (2 mL). The mixture was stirred for 2.5 h and then a saturated $NaHCO_3$ solution was added. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 155 mg (90%) of aldehyde **365** as colorless oil.

$\mathbf{R_f}$ = 0.24 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.70 (t, *J* = 1.64 Hz, 1H), 7.24 (d, *J* = 8.59 Hz, 2H), 6.87 (d, *J* = 8.84 Hz, 2H), 5.03 (d, *J* = 9.85 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.50 (dd, *J* = 9.09, 5.05 Hz, 1H), 3.39 (dd, *J* = 6.06, 4.29 Hz, 1H), 3.20 (dd, *J* = 9.15, 7.78 Hz, 1H), 2.60-2.53 (m, 1H), 2.47-2.33 (m, 2H), 2.26-2.17 (m, 1H), 2.01-1.93 (m, 1H), 1.63 (s, 3H), 0.96 (d, *J* = 7.07 Hz, 3H), 0.90 (d, *J* = 5.30 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

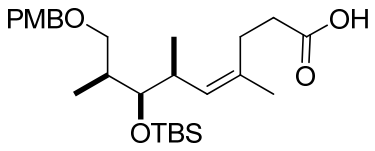
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.1, 159.0, 132.5, 131.4, 131.4, 130.7, 129.1, 113.7, 78.7, 72.7, 72.4, 55.3, 42.2, 38.3, 35.8, 28.8, 27.5, 26.2, 24.4, 23.1, 18.4, 17.3, 15.1, -3.8, -3.9.

IR (film): 2958, 2930, 2856, 1725, 1513, 1249, 1089, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}C_4H_9]^+$ calcd for $C_{22}H_{35}O_4Si$: 391.2305, found: 391.2308.

$[\alpha]_D^{20}$ 2.20 (*c* = 1.00, CH_2Cl_2).

(*Z*)-(6*S*,7*R*,8*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-4,6,8-trimethyl-non-4-enoic acid (361)

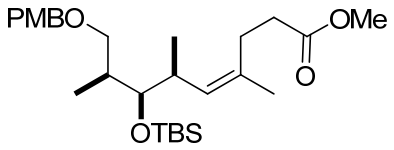


To a solution of aldehyde **365** (155 mg, 0.34 mmol) in *tert*-butanol (3 mL) with 2-methyl-2-butene (0.5 mL) was added dropwise a solution of $NaClO_2$ (465 mg, 5.2 mmol) and NaH_2PO_4 (465 mg) in water (2 mL). After 3 h 0.01N NaOH was added and the aqueous layer was extracted with Et_2O. 1N HCl was added until pH 2 was reached and the aqueous layer was extracted with DCM. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 160 mg of crude acid **361** which was directly used for the following reaction.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.27 (d, *J* = 8.56 Hz, 2H), 6.82 (d, *J* = 8.59 Hz, 2H), 5.11 (d, *J* = 10.10 Hz, 1H), 4.40 (d, *J* = 2.00 Hz, 2H), 3.60 (dd, *J* = 9.09, 5.30 Hz, 1H), 3.53 (dd, *J* = 6.30, 4.30 Hz, 1H), 3.33 (s, 3H), 3.32 (m, 1H), 2.81-2.72 (m, 1H), 2.37-2.20 (m, 4H), 2.18-2.11 (m, 1H), 1.53 (d, *J* = 1.26 Hz, 3H), 1.08 (d, *J* = 7.07 Hz, 3H), 1.04 (d, *J* = 6.57 Hz, 3H), 1.01 (s, 9H), 0.10 (s, 6H).

^{13}C-NMR (100 MHz, C_6D_6): δ = 179.1, 159.7, 132.1, 131.8, 131.2, 129.6, 114.1, 79.1, 73.0, 72.6, 54.8, 39.0, 36.0, 32.7, 27.6, 26.4, 22.9, 18.7, 17.5, 15.4, -3.6, -3.7.

(Z)-(6S,7R,8S)-7-(tert-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4,6,8-trimethylnon-4- enoic acid methyl ester (362)



Crude acid **361** (10 mg, 0.022 mmol) in methanol (1 mL) was treated with diazomethane (0.5 mL, ~0.1M in Et_2O) until the solution stayed yellow. Acetic acid was added to quench excess diazomethane and the solution was colorless again. The solvent was removed under reduced pressure and purification by column chromatography (hexane:EtOAc = 10:1) yielded 11 mg (quant.) of methyl ester **362**.

R_f = 0.40 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CHCl_3$): δ = 7.24 (d, *J* = 8.59 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 5.02 (d, *J* = 9.85 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.50 (dd, *J* = 9.09, 4.80 Hz, 1H), 3.39 (dd, *J* = 5.94, 4.67 Hz, 1H), 3.20 (t, *J* = 8.59 Hz, 1H), 2.61-2.52 (m, 1H), 2.43-2.33 (m, 3H), 2.29-2.20 (m, 1H), 2.02-1.93 (m, 1H), 1.64 (d, *J* = 1.26 Hz, 3H), 0.96 (d, *J* = 6.82 Hz, 3H), 0.89 (d, *J* = 6.06 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 6H).

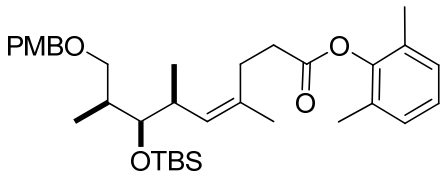
^{13}C-NMR (100 MHz, $CHCl_3$): δ = 173.7, 159.0, 131.5, 131.4, 131.0, 129.2, 113.7, 78.6, 72.6, 72.5, 55.3, 51.5, 38.4, 35.7, 32.7, 27.4, 26.1, 22.9, 18.4, 17.2, 14.9, -3.8, -3.9.

IR (film): 2957, 1741, 1513, 1249, 1087, 1038 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{27}H_{46}O_5Si$: 478.3115, found: 478.3107.

$[\alpha]_D^{20}$ 2.20 (*c* = 0.5, CH_2Cl_2)

(*Z*)-(6*S*,7*R*,8*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-4,6,8-trimethyl-non-4-enoic acid 2,6-dimethyl-phenyl ester (363)



To acid **361** (5 mg, 0.010 mmol) in DCM (1 mL) at r.t. was added 2,6-dimethylphenol (2 mg, 0.015 mmol) followed by DMAP (1.5 mg, 0.011 mmol) and DIC (2 µL, 0.011 mmol) and the mixture was stirred for 18 h. Brine was added and the organic layer was separated. The aqueous layer was extracted with DCM, the combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 6 mg (99%) of aromatic ester **363**.

R_f = 0.39 (hexane:EtOAc = 20:1)

^{1}H-NMR (400 MHz, $CHCl_3$): δ = 7.23 (d, *J* = 8.56 Hz, 2H), 7.05 (s, 3H), 6.85 (d, *J* = 8.56 Hz, 2H), 5.09 (d, *J* = 9.60 Hz, 1H), 4.41 (d, *J* = 11.36 Hz, 1H), 4.37 (d, *J* = 11.60 Hz, 1H), 3.78 (s, 3H), 3.51 (dd, *J* = 9.10, 5.06 Hz, 1H), 3.42 (t, *J* = 5.16 Hz, 1H), 3.21 (dd, *J* = 8.93, 8.20 Hz, 1H), 2.68-2.55 (m, 4H), 2.44-2.36 (m, 1H), 2.12 (s, 6H), 2.02-1.95 (m, 1H), 1.64 (d, *J* = 1.26 Hz, 3H), 0.97 (d, *J* = 6.84 Hz, 3H), 0.92 (d, *J* = 6.56 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

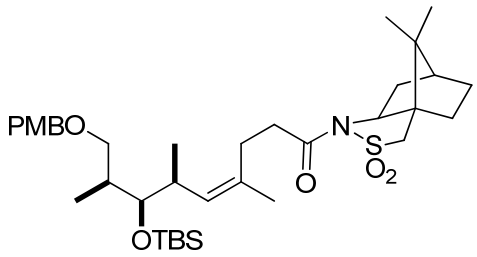
^{13}C-NMR (100 MHz, $CHCl_3$): δ = 171.0, 159.0, 148.2, 131.8, 131.3, 131.0, 129.1, 128.6, 125.8, 113.7, 78.6, 72.6, 72.5, 55.3, 38.4, 35.7, 32.6, 27.5, 26.2, 23.0, 18.4, 16.9, 16.3, 14.9, -3.8, -3.9.

IR (film): 2928, 1757, 1249 cm^{-1}.

HRMS (ESI) (m/z): $[M-C_4H_9]^+$ calcd for $C_{30}H_{43}O_5Si$: 511.2880, found: 511.2875.

$[\alpha]_D^{20}$ 10.40 (*c* = 0.25, CH_2Cl_2)

(*Z*)-(6*S*,7*R*,8*S*)-*N*-[7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-4,6,8-trimethyl-non-4-enoyl]-(1'*R*)-bornan-2',10'-sultam (368)



To a stirred solution of crude acid **361** (60 mg, 0.13 mmol), DMAP (16 mg, 0.13 mmol) and (1*R*)-camphore-2,10-sultam (**367**) (29 mg, 0.13 mmol) in DCM (2 mL) under argon at r.t. was slowly added DIC (23 µL. 0.14 mmol). Stirring was continued for 2 h, brine was added and the layers were separated. The aqueous layer was extracted with DCM and the combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 3:1) yielded 83 mg (96%) of *N*-acyl sultam **368**.

R_f = 0.28 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CHCl_3$): δ = 7.25 (d, *J* = 8.84 Hz, 2H), 6.86 (d, *J* = 8.60 Hz, 2H), 5.03 (d, *J* = 9.32 Hz, 1H), 4.39 (s, 2H), 3.85 (dd, *J* = 7.58, 5.54 Hz, 1H), 3.80 (s, 3H), 3.51 (dd, *J* = 9.34, 5.06 Hz, 1H), 3.48 (d, *J* = 13.92 Hz, 1H), 3.41 (d, *J* = 13.36 Hz, 1H), 3.39 (t, *J* = 5.30 Hz, 1H), 3.19 (t, *J* = 8.72 Hz, 1H), 2.82-2.69 (m, 2H), 2.64-2.55 (m, 1H), 2.53-2.46 (m, 1H), 2.32-2.20 (m, 1H), 2.15-2.02 (m, 2H), 1.99-1.84 (m, 4H), 1.65 (d, *J* = 1.28 Hz, 3H), 1.43-1.25 (m, 3H), 1.15 (s, 3H), 0.97 (s, 3H), 0.96 (d, *J* = 7.07 Hz, 3H), 0.89 (d, *J* = 6.82 Hz, 3H), 0.88 (s, 9H), 0.01 (s, 6H).

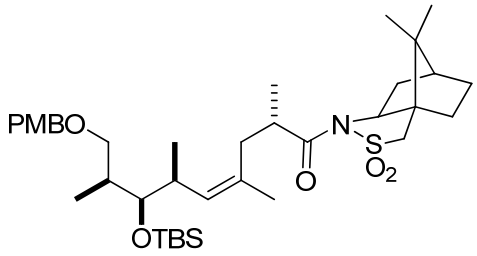
^{13}C-NMR (100 MHz, $CHCl_3$): δ = 171.5, 159.0, 131.3, 131.1, 129.1, 113.7, 78.5, 72.6, 72.5, 65.2, 55.3, 52.9, 48.4, 47.7, 44.7, 38.6, 38.5, 35.4, 34.0, 32.9, 26.9, 26.5, 26.2, 23.0, 20.9, 19.9, 18.4, 16.8, 14.7, -3.8, -3.9.

IR (film): 2958, 2855, 1698, 1513, 1461, 1332, 1248, 1212, 1171, 1133, 1085 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{36}H_{59}O_6SNSiNa$: 684.3730, found: 684.3736.

$[\alpha]_D^{20}$ 34.95 (*c* = 1.58, CH_2Cl_2)

(*Z*)-(2*S*,6*S*,7*R*,8*S*)-N-[7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-2,4,6,8-tetramethyl-non-4-enoyl]-(1'*R*)-bornan-2',10'-sultam (369)



To *N*-acyl sultam **368** (35 mg, 0.050 mmol) in THF (1 mL) at -78 °C was slowly added NaHMDS (55 µL, 1M in THF, 0.055 mmol) and the solution was stirred for 1 h. MeI (9 µL, 0.100 mmol) was added and stirring was continued for 1.5 h. The reaction was quenched by the addition of a saturated NH_4Cl solution and the layers were separated. The aqueous layer was extracted with DCM and the combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 5:1) yielded 30 mg (89%) of *α*-methylated *N*-acyl sultam **369**.

R_f = 0.29 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CHCl_3$): *δ* = 7.25 (d, *J* = 8.59 Hz, 2H), 6.86 (d, *J* = 8.56 Hz, 2H), 5.09 (d, *J* = 9.88 Hz, 1H), 4.39 (d, *J* = 1.76 Hz, 2H), 3.87 (t, *J* = 6.32 Hz, 1H), 3.80 (s, 3H), 3.49 (dd, *J* = 14.78, 9.72 Hz, 1H), 3.49 (d, *J* = 13.64 Hz, 1H), 3.42 (d, *J* = 13.64 Hz, 1H), 3.40 (t, *J* = 5.18 Hz, 1H), 3.19 (t, *J* = 8.72 Hz, 1H), 2.65-2.56 (m, 1H), 2.40 (dd, *J* = 13.52, 9.47 Hz, 1H), 2.23 (dd, *J* = 13.16, 4.79 Hz, 1H), 2.08-1.93 (m, 3H), 1.91-1.79 (m, 3H), 1.64 (s, 3H), 1.44-1.23 (m, 3H), 1.16 (s, 3H), 1.12 (d, *J* = 6.82 Hz, 3H), 0.97 (s, 3H), 0.96 (d, *J* = 6.82 Hz, 3H), 0.90 (d, *J* = 7.07 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

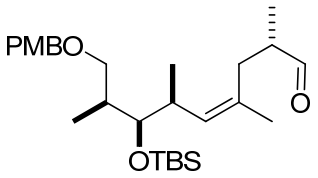
^{13}C-NMR (100 MHz, $CHCl_3$): *δ* = 176.0, 159.0, 132.8, 131.1, 130.2, 129.1, 113.7, 78.5, 72.7, 72.5, 65.2, 55.3, 53.2, 48.3, 47.7, 44.6, 38.6, 38.4, 37.9, 35.5, 34.2, 32.9, 29.5, 26.4, 26.2, 23.0, 20.9, 19.9, 18.4, 17.8, 16.9, 14.7, -3.8, -3.9.

IR (film): 2959, 1696, 1513, 1332, 1248, 1132, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{37}H_{61}O_6SNSiNa$: 698.3887, found: 698.3902.

$[\alpha]_D^{20}$ 55.30 (*c* = 1.00, CH_2Cl_2)

(*Z*)-(2*S*,6*S*,7*R*,8*S*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-2,4,6,8-tetramethyl-non-4-enal (370)



To *N*-acyl sultam **369** (65 mg, 0.092 mmol) in DCM (2 mL) at -100 °C was slowly added DIBALH (62 µL, 1.5 M in toluene, 0.092 mmol) and the mixture was stirred for 1 h. A second equivalent of DIBALH (62 µL, 1.5 M in toluene, 0.092 mmol) was added and stirring was continued for 1 h, at which time the temperature reached -65 °C. The reaction was quenched by the addition of a small amount of methanol and potassium sodium tartrate was added and the mixture was stirred vigorously at r.t. for 2 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 40 mg (94%) of aldehyde **370**.

R_f = 0.50 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.61 (d, *J* = 1.52 Hz, 1H), 7.24 (d, *J* = 8.84 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.12 (d, *J* = 10.64 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.48 (dd, *J* = 9.08, 5.04 Hz, 1H), 3.38 (dd, *J* = 5.82, 4.78 Hz, 1H), 3.19 (dd, *J* = 8.82, 8.10 Hz, 1H), 2.57-2.43 (m, 2H), 2.22 (dd, *J* = 13.90, 5.82 Hz, 1H), 2.16 (dd, *J* = 13.78, 9.46 Hz, 1H), 2.26-2.17 (m, 1H), 2.00-1.88 (m, 1H), 1.63 (d, *J* = 1.24 Hz, 3H), 1.00 (d, *J* = 6.84 Hz, 3H), 0.94 (d, *J* = 6.80 Hz, 3H), 0.90 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

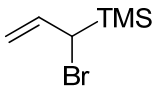
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.5, 158.6, 134.0, 133.0, 130.9, 129.3, 113.8, 78.5, 72.7, 72.4, 57.6, 55.2, 44.5, 38.4, 35.7, 32.6, 26.8, 23.3, 17.1, 14.9, 13.0, -4.1, -4.2.

IR (film): 2958, 2930, 2856, 1727, 1513, 1472, 1462, 1249, 1091, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{27}H_{46}O_4Si$: 462.3165, found: 462.3171.

$[\alpha]_D^{20}$ 3.92 (*c* = 1.30, CH_2Cl_2)

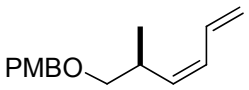
(1-bromoallyl)trimethylsilane (385)



To allyl bromide (8.5 mL, 100 mmol) and freshly distilled chlorotrimethylsilane (9.5 mL, 75 mmol) in THF (25 mL) at -78 °C was added LDA, prepared by the addition of *n*BuLi (20 mL, 2.5 M in hexane, 50 mmol) to diisopropylamine (7 mL, 50 mmol) in THF (25 mL) and hexane (15 mL) at 0 °C and stirring for 15 min, *via* cannula over 20 min. After another 20 min water (50 mL) and 1M HCl (110 mL) was added. The aqueous solution was extracted with pentane and the combined organic solution was dried over $MgSO_4$. After filtration the solvent was distilled off through a Vigreux column. Vacuum distillation at 55 °C (12 mmHg) of the remaining liquid yielded 5.5 g (52%) of the desired product as colorless liquid.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 5.92 (td, *J* = 16.60, 9.86 Hz, 1H), 5.20-5.02 (m, 2H), 3.80 (d, *J* = 9.70 Hz, 1H), 0.14 (s, 9H).

(*Z*)-(*S*)-1-methoxy-4-((2-methylhexa-3,5-dienyloxy)methyl)benzene (386)



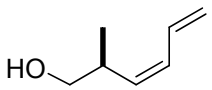
To chromium(III) chloride (793 mg, 5.00 mmol) in THF (10 mL) at r.t. was added lithium aluminium hydride (95 mg, 2.50 mmol) whereupon the violet solution turned black and stirring was continued for 30 min. The mixture was cooled to 0 °C and a solution of aldehyde **279** (350 mg, 1.67 mmol) and (1-bromoallyl)trimethylsilane (**385**) (800 mg, 4.23 mmol) in THF (2 mL) was added. After 2 h the reaction was brought to r.t. and was allowed to age over night. 6N KOH (20 mL) and methanol (10 mL) were added at 0 °C and stirred for 1 h at 0 °C and 2 h at r.t.. The mixture was acidified with 3N HCl and the aqueous solution was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 350 mg (90%) of diene **386**.

R_f = 0.60 (hexane:EtOAc = 10:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.45 Hz, 2H), 6.87 (d, *J* = 8.57 Hz, 2H), 6.64 (td, *J* = 16.73, 10.59 Hz, 1H), 6.02 (t, *J* = 10.97 Hz, 1H), 5.27 (m, 1H), 5.13 (m, 2H), 4.45 (s, 2H),

3.81 (s, 3H), 3.30 (ddd, *J* = 14.83, 9.07, 6.70 Hz, 2H), 2.97 (m, 1H), 1.02 (d, *J* = 6.62 Hz, 3H).

(*Z*)-(*S*)-2-methylhexa-3,5-dien-1-ol (518)

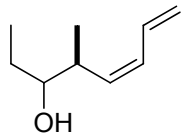


To a stirred solution of diene **386** (200 mg, 0.86 mmol) in wet DCM (6 mL) was added DDQ (215 mg, 0.95 mmol) in small portions and the mixture was stirred vigorously for 1 h. The reaction was quenched with saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane:DCM = 1:1) to yield 90 mg (93%) of volatile **518**.

$\mathbf{R_f}$ = 0.30 (hexane:EtOAc = 10:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 6.64 (td, *J* = 17.26, 10.39 Hz, 1H), 6.14 (t, *J* = 10.97 Hz, 1H), 5.27-5.13 (m, 3H), 3.54 (ddd, *J* = 7.99, 10.45, 5.70 Hz, 1H), 3.38 (ddd, *J* = 10.62, 7.93, 4.04 Hz, 1H), 2.89 (m, 1H), 1.39 (dd, *J* = 7.94, 4.16 Hz, 1H (OH)), 0.99 (d, *J* = 6.62 Hz, 3H).

(*Z*)-(*S*)-4-Methyl-octa-5,7-dien-3-ol (519)



To a stirred suspension of alcohol **518** (90 mg, 0.8 mmol) and $NaHCO_3$ (403 mg, 4.8 mmol) in DCM (8 mL) at r.t. was added Dess-Martin periodinane (679 mg, 1.6 mmol) and the suspension was stirred for 4 h. The reaction was quenched with water, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated to yield crude aldehyde **387**.

To aldehyde **387** (90 mg, 0.8 mmol) in Et_2O (8 mL) at 0 °C was slowly added EtMgBr (0.4 mL, 3M in Et_2O, 1.2 mmol). After 3 h brine was added and acidified with 5% H_2SO_4. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and the solvent was carefully evaporated. Purification

by column chromatography (hexane:DCM = 1:1) yielded 100 mg (89%) of volatile alcohol **519** as 1:1 mixture of diastereoisomers.

R_f = 0.40 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.68 (m, 1H), 6.03 (t, *J* = 10.99 Hz, 1H), 5.38-5.28 (m, 1H), 5.26-5.11 (m, 2H), 3.38-3.30 (m, 1H), 2.77-2.65 (m, 1H), 1.64-1.53 (m, 2H), 1.04 (d, *J* = 6.82 Hz, 3H), 0.97 (t, *J* = 7.45 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.8, 132.3, 129.6, 117.8, 77.3, 38.2, 27.3, 16.4, 10.3.

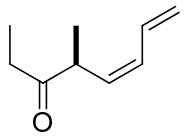
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.68 (m, 1H), 6.13 (t, *J* = 10.99 Hz, 1H), 5.29 (m, 1H), 5.26-5.11 (m, 2H), 3.38-3.30 (m, 1H), 2.77-2.65 (m, 1H), 1.42-1.26 (m, 2H), 1.01 (d, *J* = 6.82 Hz, 3H), 0.96 (t, *J* = 7.45 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.1, 132.2, 130.8, 118.1, 77.3, 38.0, 27.1, 17.2, 9.9.

IR (film): 3585, 3391, 2964, 1651, 1644, 1634 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_9H_{16}O$: 140.1201, found: 140.1211.

(*Z*)-(*S*)-4-Methyl-octa-5,7-dien-3-one (388)



Dess-Martin periodinane (1.14 g, 2.70 mmol) was added portion wise to a suspension of alcohol **519** (190 mg, 1.35 mmol) and $NaHCO_3$ (684 mg, 8.1 mmol) in DCM (14 mL) at r.t. under argon. After 3 h water was added and the layers were separated. The aqueous layer was extracted with DCM and the combined DCM layer was dried over $MgSO_4$ and the solvent was carefully evaporated. Column chromatography (hexane:DCM = 1:1) yielded 190 mg (99%) of ethyl ketone **388**.

R_f = 0.45 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.70-6.60 (m, 1H), 6.10 (t, *J* = 10.86 Hz, 1H), 5.32 (t, *J* = 10.48 Hz, 1H), 5.32-5.20 (m, 2H), 3.65 (dq, *J* = 10.10, 6.82 Hz, 1H), 2.52 (dq, *J* = 17.81, 7.28 Hz, 1H), 2.41 (dq, *J* = 17.81, 7.28Hz, 1H), 1.16 (d, *J* = 6.57 Hz, 3H), 1.02 (t, *J* = 7.20 Hz, 3H).

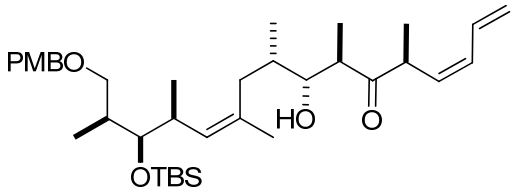
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 211.6, 131.4, 131.0, 130.9, 119.3, 45.9, 33.9, 16.6, 7.7.

IR (film): 2976, 2937, 1716, 1458, 1375 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_9H_{14}O$: 138.1045, found: 138.1057.

$[\alpha]_D^{20}$ 350.12 (*c* = 0.85, CH_2Cl_2)

(3*Z*,11*Z*)-(5*S*,7*R*,8*R*,9*S*,13*S*,14*S*,15*S*)-14-(tert-Butyl-dimethyl-silanyloxy)-8-hydroxy-17-(4-methoxy-phenoxy)-5,7,9,11,13,15-hexamethyl-heptadeca-1,3,11-trien-6-one (520)



To ethyl ketone **388** (12 mg, 0.09 mmol) in DCM (1 mL) at -78 °C was added Bu_2BOTf (110 µL, 1M in DCM, 0.11 mmol) and triethylamine (18 µL, 0.12 mmol). After 10 min at -78 °C the mixture was brought to 0 °C for 30 min and was recooled to -78 °C. Aldehyde **370** (30 mg, 0.06 mmol) in DCM (1 mL) was added and stirring was continued for 3 h at -78 °C, then the mixture was kept at 0 °C for 1 h and quenched by the addition of pH 7 buffer, methanol and H_2O_2. After 1.5 h at r.t. the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 25 mg (69%) of aldol adduct **256** and 6 mg (20%) of aldehyde **520**.

R_f = 0.47 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.86 Hz, 2H), 6.87 (d, *J* = 8.59 Hz, 2H), 6.73-6.61 (m, 1H), 6.14 (t, *J* = 10.86 Hz, 1H), 5.35-5.22 (m, 3H), 5.04 (d, *J* = 10.10 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.79 (m, 1H), 3.57-3.43 (m, 2H), 3.41-3.35 (m, 1H), 3.20 (dd, *J* = 9.09, 8.33 Hz, 1H), 2.98 (t, *J* = 6.95 Hz, 1H), 2.60-2.50 (m, 1H), 2.47-2.41 (m, 1H), 2.20-1.93 (m, 3H), 1.76-1.66 (m, 1H), 1.58 (s, 3H), 1.17 (d, *J* = 6.82 Hz, 3H), 1.16 (d, *J* = 6.57 Hz, 3H), 1.09 (d, *J* = 7.07 Hz, 3H), 1.07 (d, *J* = 7.07 Hz, 3H), 0.95 (d, *J* = 7.07 Hz, 3H), 0.90 (d, *J* = 6.84 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 216.6, 159.0, 131.9, 131.6, 131.3, 131.0, 130.1, 129.0, 119.7, 113.8, 79.1, 78.5, 76.5, 72.7, 72.5, 55.3, 50.1, 47.2, 46.5, 38.6, 35.5, 33.9, 32.6, 26.1, 23.2, 22.7, 17.0, 16.3, 15.0, 14.6, 14.2, -3.8, -4.0.

IR (film): 3503, 2940, 2930, 2856, 1711, 1513, 1458, 1249, 1092, 1037, 1004 cm^{-1}.

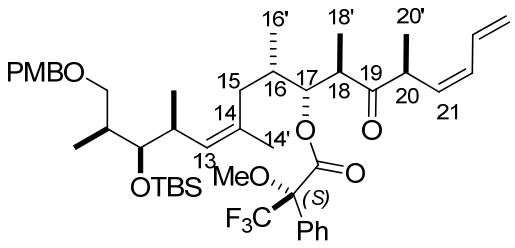
HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{36}H_{60}O_5Si$: 600.4210, found: 600.4219.

$[\alpha]_D^{20}$ 154.00 (*c* = 0.85, CH_2Cl_2)

(*R*)- and (*S*)-MTPA esters of **520** were prepared according to the general procedure (page 123) and comparison of the shift differences between the two side chains from the C17 center of the two diastereoisomers confirmed the absolute configuration to be (17*R*).

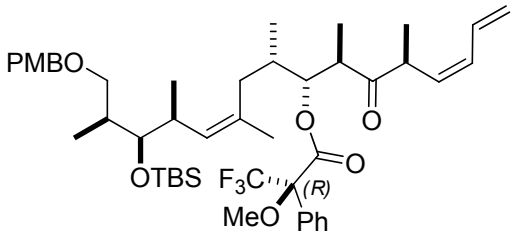
carbon	(*S*)-Mosher ester	(*R*)-Mosher ester	R vs. S
13	6,106	6,114	R>S
14’	1,5415	1,5656	R>S
15a	2,1490	2,2134	R>S
15b	1,7340	1,8184	R>S
16	2,008	2,020	R>S
16’	0,7797	0,8059	R>S
17	5,4256	5,4488	R>S
18	3,1347	3,1653	R>S
18’	1,0170	1,0013	R<S
20	3,4850	3,5350	R>S
20’	0,9549	0,9294	R<S
21	5,2430	5,2480	R~S

(*S*)-MTPA ester of 520:



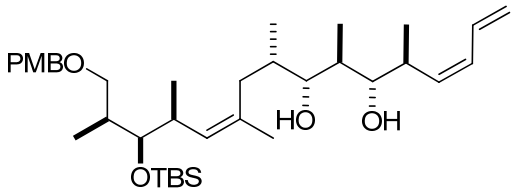
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 2H), 7.40 (m, 3H), 7.24 (d, *J* = 8.69 Hz, 2H), 6.86 (d, *J* = 8.69 Hz, 2H), 6.55 (dt, *J* = 17.18, 10.29 Hz, 1H), 6.11 (t, *J* = 10.57 Hz, 1H), 5.42 (dd, *J* = 9.44, 3.02 Hz, 1H), 5.31-5.19 (m, 3H), 5.04 (d, *J* = 10.20 Hz, 1H), 4.39 (d, *J* = 11.70 Hz, 1H), 4.36 (d, *J* = 11.70 Hz, 1H), 3.80 (s, 3H), 3.48 (m, 1H), 3.45 (m, 1H), 3.44 (s, 3H), 3.36 (dd, *J* = 6.23, 4.72 Hz, 1H), 3.20 (dd, *J* = 9.06, 8.31 Hz, 1H), 3.13 (dd, *J* = 9.44, 7.18 Hz, 1H), 2.43 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.73 (m, 1H), 1.55 (s, 3H), 1.02 (d, *J* = 7.17 Hz, 3H), 0.95 (d, *J* = 6.79 Hz, 3H), 0.92 (d, *J* = 7.17 Hz, 3H), 0.89 (s, 9H), 0.84 (d, *J* = 6.42 Hz, 3H), 0.77 (d, J = 6.80 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

(*R*)-MTPA ester of 520:



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 2H), 7.39 (m, 3H), 7.23 (d, *J* = 8.69 Hz, 2H), 6.86 (d, *J* = 8.69 Hz, 2H), 6.64 (dt, *J* = 16.81, 10.10 Hz, 1H), 6.11 (t, *J* = 10.58 Hz, 1H), 5.45 (dd, *J* = 9.44, 2.64 Hz, 1H), 5.32-5.21 (m, 3H), 5.05 (d, *J* = 10.57 Hz, 1H), 4.39 (d, *J* = 11.71 Hz, 1H), 4.35 (d, *J* = 11.71 Hz, 1H), 3.80 (s, 3H), 3.53 (m, 1H), 3.44 (s, 3H), 3.43 (dd, *J* =9.25, 5.09 Hz, 1H), 3.38 (dd, *J* = 6.42, 4.53 Hz, 1H), 3.20 (dd, J = 9.19, 8.24 Hz, 1H), 3.17 (dd, *J* = 9.63, 6.98 Hz, 1H), 2.46 (m, 1H), 2.21 (t, *J* = 12.46 Hz, 1H), 2.02 (m, 1H), 1.96 (m, 1H), 1.81 (d, *J* = 11.70 Hz, 1H), 1.55 (s, 3H), 1.00 (d, *J* = 7.17 Hz, 3H), 0.93 (d, *J* = 6.42 Hz, 3H), 0.92 (d, *J* = 6.70 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.42 Hz, 3H), 0.80 (d, *J* = 6.80 Hz, 3H), 0.03 (s, 6H).

(3*Z*,11*Z*)-(5*S*,6*S*,7*R*,8*R*,9*S*,13*S*,14*S*,15*S*)-14-(*tert*-Butyl-dimethyl-silanyloxy)-17-(4-methoxy-phenoxy)-5,7,9,11,13,15-hexamethyl-heptadeca-1,3,11-triene-6,8-diol (521)



To a solution of **520** (10 mg, 0.016 mmol) in THF (0.5 mL) at -10 °C under argon was added catecholborane (9 µL, 0.083 mmol) and the mixture was stirred for 2 h. A saturated solution of potassium sodium tartrate was added and stirring was continued for 1 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (Hexane:EtOAc = 5:1) yielded 6.5 mg (65%) of diol **521** as colorless oil.

R_f = 0.35 (hexane:EtOAc = 5:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.65 Hz, 2H), 6.87 (d, *J* = 8.64 Hz, 2H), 6.63-6.57 (m, 1H), 6.02 (t, *J* = 11.31 Hz, 1H), 5.51 (t, *J* = 9.99 Hz, 1H) 5.24-5.12 (m, 2H), 5.04 (d, *J* = 10.20 Hz, 1H), 4.39 (m, 2H), 3.80 (s, 3H), 3.56-3.47 (m, 2H), 3.37 (dd, *J* = 6.03, 4.53 Hz, 1H), 3.20 (dd, *J* = 9.06, 8.28 Hz, 1H), 2.96-2.91 (m, 1H), 2.61-2.53 (m, 1H), 2.25-2.21 (m, 1H), 2.00-1.89 (m, 3H), 1.82-1.77 (m, 1H), 1.62 (d, *J* = 1.14 Hz, 3H), 1.01 (d, *J* = 6.84 Hz, 3H), 0.95 (d, *J* = 6.78 Hz, 3H), 0.88 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H).

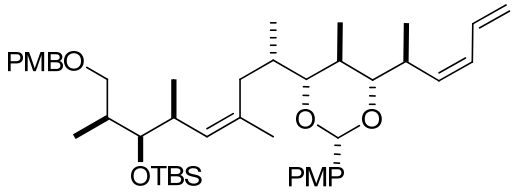
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.7, 135.9, 132.0, 131.8, 131.7, 129.1, 128.8, 117.9, 113.7, 80.7, 78.7, 72.7, 72.6, 55.3, 38.1, 35.6, 34.9, 33.0, 31.8, 29.7, 26.2, 25.4, 23.3, 21.0, 17.0, 16.7, 15.0, 14.2, 13.8, 11.3, -3.8, -3.9.

IR (film): 3398, 2960, 1613, 1513, 1458, 1249, 1038 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{36}H_{62}O_5SiNa$: 625.4264, found: 625.4260.

$[\alpha]_D^{20}$ 33.20 (*c* = 0.25, CH_2Cl_2)

***tert*-Butyl-{(*Z*)-(1*S*,2*S*,6*S*)-1-[(*S*)-3-(4-methoxy-phenoxy)-1-methyl-propyl]-6-[(2*R*,4*R*,5*R*,6*S*)-2-(4-methoxy-phenyl)-5-methyl-6-((*Z*)-(*S*)-1-methyl-penta-2,4-dienyl)-[1,3]dioxan-4-yl]-2,4-dimethyl-hept-3-enyloxy}-dimethyl-silane (397)**



To diol **521** (5 mg, 0.0083 mmol) in DCM (0.5 mL) was added anisaldehyde dimethyl acetal (3 µL, 0.0170 mmol) and CSA (0.5 mg, 0.0020 mmol) at r.t. under argon. The mixture was stirred for 1 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (Hexane:EtOAc = 20:1) yielded 6 mg (99%) of acetal **397** as colorless oil.

R_f = 0.70 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.28 Hz, 2H), 7.19 (d, *J* = 8.64 Hz, 2H), 6.85 (d, *J* = 8.70 Hz, 2H), 6.83 (d, *J* = 8.70 Hz, 2H), 6.63 (m, 1H), 5.98 (t, *J* = 10.77 Hz, 1H), 5.71 (t, *J* = 10.20 Hz, 1H), 5.45 (s, 1H), 5.24-5.12 (m, 2H), 5.07 (d, *J* = 10.14 Hz, 1H), 4.36 (d, *J* = 11.71 Hz, 1H), 4.30 (d, *J* = 11.71 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.49 (dd, *J* = 9.06, 4.14 Hz, 1H), 3.38 (m, 1H), 3.35 (t, *J* = 5.28 Hz, 1H), 3.16 (t, *J* = 8.88 Hz, 1H), 3.01 (m, 1H), 2.58 (m, 1H), 2.48 (dd, *J* = 13.41, 12.27 Hz, 1H), 2.04-1.84 (m, 3H), 1.64 (d, *J* = 0.78 Hz, 3H),1.33-1.22 (m, 2H), 0.95 (d, *J* = 6.78 Hz, 3H), 0.94 (d, *J* = 7.20 Hz, 3H), 0.89 (d, *J* = 6.78 Hz, 3H), 0.88 (d, *J* = 6.42 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J* = 6.78 Hz, 3H), 0.00 (s, 3H), -0.01 (s, 3H).

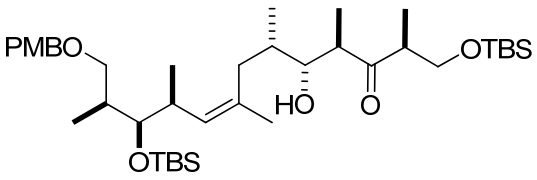
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.4, 158.9, 132.3, 131.9, 131.8, 129.1, 127.3, 113.6, 113.2, 100.2, 86.5, 80.4, 78.7, 72.6, 72.4, 65.1, 55.3, 55.1, 38.1, 36.6, 35.3, 31.8, 31.5, 31.4, 26.2, 25.9, 23.2, 22.7, 18.4, 18.3, 16.8, 16.3, 14.1, 11.3, 9.7, -3.8, -3.9, -5.3, -5.4.

IR (film): 2930, 1615, 1515, 1249, 1083, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{44}H_{68}O_6SiNa$: 743.4683, found: 743.4650.

$[\alpha]_D^{20}$ 43.43 (*c* = 0.175, CH_2Cl_2)

(*Z*)-(2*S*,4*R*,5*R*,6*S*,10*S*,11*S*,12*S*)-1,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-hydroxy-14-(4-methoxy-phenoxy)-2,4,6,8,10,12-hexamethyl-tetradec-8-en-3-one (398)



To ethyl ketone **382** (14 mg, 0.060 mmol) in DCM (1 mL) at -78 °C was added Bu_2BOTf (72 µL, 1M in DCM, 0.072 mmol) and triethylamine (11 µL, 0.080 mmol). After 15 min at -78 °C the mixture was brought to 0 °C for 30 min and was recooled to -78 °C. Aldehyde **370** (20 mg, 0.040 mmol) in DCM (0.5 mL) was added and stirring was continued for 3 h at -78 °C, then the mixture was kept at 0 °C for 1 h and quenched by the addition of pH 7 buffer, methanol and H_2O_2. After 1 h at r.t. the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 15 mg (54%) of aldol adduct **398** and 6 mg (43%) of aldehyde **370**.

R_f = 0.47 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* = 7.25 (d, *J* = 8.65 Hz, 2H), 6.87 (d, *J* = 8.60 Hz, 2H), 5.05 (d, *J* = 10.08 Hz, 1H), 4.39 (m, 2H), 3.81 (dd, *J* = 9.60, 8.34 Hz, 1H), 3.80 (s, 3H), 3.54 (dd, *J* = 9.70, 4.94 Hz, 1H), 3.51-3.48 (m, 2H), 3.39 (dd, *J* = 5.78, 4.86 Hz, 1H), 3.19 (t, *J* = 8.72 Hz, 1H), 2.97-2.87 (m, 2H), 2.74 (d, *J* = 6.80 Hz, 1H (OH)), 2.61-2.52 (m, 1H), 2.15 (dd, *J* = 12.95, 11.76 Hz, 1H), 2.01-1.93 (m, 2H), 1.82-1.77 (m, 1H), 1.60 (s, 3H), 1.14 (d, *J* = 7,32 Hz, 3H), 0.99 (d, *J* = 7.04 Hz, 3H), 0.95 (d, *J* = 6.84 Hz, 3H), 0.89 (d, *J* = 7.20 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.83 (d, *J* = 6.80 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0,02 (s, 3H), 0.01 (s, 3H).

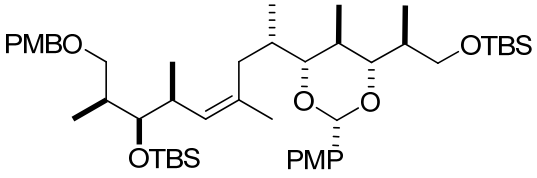
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 218.6, 159.0, 131.8, 131.7, 131.1, 129.1, 113.7, 78.6, 78.1, 72.7, 72.5, 65.2, 55.3, 48.3, 48.2, 38.5, 35.4, 33.5, 32.6, 26.2, 25.9, 23.2, 18.4, 16.9, 16.4, 14.7, 13.6, 13.3, -3.8, -3.9, -5.5, -5.6.

IR (film): 2958, 2930, 2857, 1514, 1463, 1361, 1250, 1097 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{39}H_{72}O_6Si_2Na$: 715.4765, found: 715.4761.

$[\alpha]_D^{20}$ 15.48 (*c* = 0.58, CH_2Cl_2)

(2*R*,4*S*,5*R*,6*R*)-4-[(*Z*)-(1*S*,5*S*,6*S*,7*S*)-6-(tert-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-phenoxy)-1,3,5,7-tetramethyl-non-3-enyl]-6-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (401)



To diol **399** (9 mg, 0.013 mmol) in DCM (0.5 mL) was added anisaldehyde dimethyl acetal (5 µL, 0.026 mmol) and CSA (1 mg, 0.003 mmol) at r.t. and the mixture was stirred for 1 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 20:1) yielded 15 mg (99%) of acetal **401** as colorless oil.

R_f = 0.63 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 9.06 Hz, 2H), 7.19 (d, *J* = 8.70 Hz, 2H), 6.85 (d, *J* = 8.70 Hz, 2H), 6.83 (d, *J* = 8.70 Hz, 2H), 5.45 (s, 1H), 5.07 (d, *J* = 9.84 Hz, 1H), 4.36 (d, *J* = 11.70 Hz, 1H), 4.30 (d, *J* = 11.76 Hz, 1H), 3.79 (s, 6H), 3.67 (t, *J* = 9.06 Hz, 1H), 3.64 (dd, *J* = 9.81, 1.89 Hz, 1H), 3.49 (dd, *J* = 9.03, 4.53 Hz, 1H), 3.47 (dd, *J* = 9.63, 5.49 Hz, 1H), 3.40 (dd, *J* = 9.42, 1.92 Hz, 1H), 3.35 (t, *J* = 5.28 Hz, 1H), 3.15 (t, *J* = 8.67 Hz, 1H), 2.61-2.57 (m, 1H), 2.37 (dd, *J* = 13.38, 11.88 Hz, 1H), 2.05-1.98 (m, 2H), 1.96 (m, 3H), 1.63 (d, *J* = 1.14 Hz, 3H),1.31-1.25 (m, 2H), 0.95 (d, *J* = 6.84 Hz, 3H), 0.93 (d, *J* = 7.20 Hz, 3H), 0.90 (s, 9H), 0.88 (d, *J* = 6.06 Hz, 3H), 0.86 (d, *J* = 7.20 Hz, 3H), 0.87 (s, 9H), 0.79 (d, *J* = 6.42 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H).

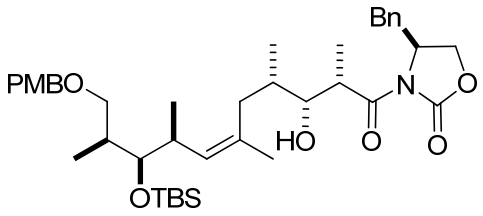
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.4, 158.9, 132.3, 131.9, 131.8, 129.1, 127.3, 113.6, 113.2, 100.2, 86.5, 80.4, 78.7, 72.6, 72.4, 65.1, 55.3, 55.1, 38.1, 36.6, 35.3, 31.8, 31.5, 31.4, 26.2, 25.9, 23.2, 22.7, 18.4, 18.3, 16.8, 16.3, 14.1, 11.3, 9.7, -3.8, -3.9, -5.3, -5.4.

IR (film): 2728, 1722, 1435, 1293, 1233, 1150 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{47}H_{80}O_7Si_2Na$: 835.5340, found: 835.5351.

$[\alpha]_D^{20}$ 7.67 (*c* = 0.3, CH_2Cl_2)

(*S*)-4-Benzyl-3-[(*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*S*)-9-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-11-(4-methoxy-benzyloxy)-2,4,6,8,10-pentamethyl-undec-6-enoyl]-oxazolidin-2-one (402)



To a stirred solution of acyloxazolidinone ***ent*-373** (17 mg, 0.071 mmol) in DCM (0.7 mL) at -78 °C under argon was slowly added dibutylboron triflate (74 µL, 1M in DCM, 0.074 mmol) followed by triethylamine (12 µL, 0.081 mmol) and stirring was continued for 10 min. The reaction mixture was warmed to 0 °C for 1 h and then recooled to -78 °C. Aldehyde **370** (29 mg, 0.062 mmol) in DCM (0.5 mL) was added dropwise. After 1 h the reaction mixture was warmed to 0 °C and stirred for 1.5 h. pH 7 buffer solution (2 mL), methanol (1 mL) and H_2O_2 (0.1 mL, 30% aqueous) were added and the mixture was stirred for 1 h at r.t.. Layers were separated and the aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 5:1 to 3:1) to yield 28 mg (65%) of aldol adduct **402** and 10 mg (34%) of aldehyde **370**.

R_f = 0.33 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 4H), 7.24-7.19 (m, 3H), 6.86 (d, *J* = 8.53 Hz, 2H), 5.05 (d, *J* = 10.04 Hz, 1H), 4.67 (ddt, *J* = 9.45, 6.88, 3.43 Hz, 1H), 4.44 (d, *J* = 11.54 Hz, 1H), 4,38 (d, *J* = 11.79 Hz, 1H), 4.18 (m, 2H), 3,94 (m, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 10.04, 5.02 Hz, 1H), 3.58 (dd, *J* = 9.29, 4.77 Hz, 1H), 3.35 (dd, *J* = 6.65, 3.64 Hz, 1H), 3.24 (dd, *J* = 13.30, 3.26 Hz, 1H), 3.20-3.16 (m, 2H), 2.77 (dd, *J* = 13.30, 9.53 Hz, 1H), 2.64 (dt, *J* = 9.91, 6.71 Hz, 1H), 2.10 (dd, *J* = 13.30, 6.77 Hz, 1H), 1.98-1.86 (m, 2H), 1.77 (m, 1H), 1.63 (d, *J* = 1.00 Hz, 3H), 1.20 (d, *J* = 6.77 Hz, 3H), 0.94 (d, *J* = 7.02 Hz, 3H), 0.89 (d, *J* = 6.22 Hz, 3H), 0.88 (s, 9H), 0.88 (d, *J* = 6.27 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H).

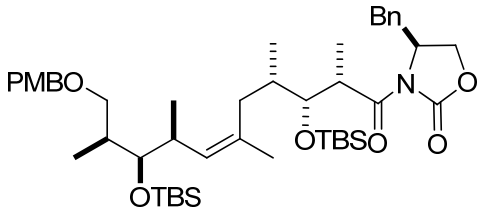
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 159.1, 152.8, 135.1, 132.0, 131.8, 130.7, 129.4, 128.9, 127.4, 113.7, 79.1, 74.0, 72.7, 72.5, 65.9, 55.3, 55.1, 40.5, 38.2, 37.7, 35.9, 35.8, 33.4, 29.2, 26.2, 23.1, 18.4, 17.3, 15.6, 14.4, 12.7, -3.7, -3.8.

IR (film): 2928, 1781, 1701, 1512, 1458, 1388, 1248, 1080 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{40}H_{61}NO_7Si$: 695.4217, found: 695.4225.

$[\alpha]_D^{20}$ 32.22 (*c* = 0.45, CH_2Cl_2)

(*S*)-4-Benzyl-3-[(*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*S*)-3,9-bis-(*tert*-butyl-dimethyl-silanyloxy)-11-(4-methoxy-benzyloxy)-2,4,6,8,10-pentamethyl-undec-6-enoyl]-oxazolidin-2-one (523)



To a stirred solution of alcohol **402** (14 mg, 0.019 mmol) in DCM (1 mL) was added 2,6-lutidine (4 µL, 0.029 mmol) and TBSOTf (5 µL, 0.023 mmol). After 1 h the reaction was quenched with saturated NH_4Cl solution, the layers were separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 5:1) yielded 16 mg (quant.) of **523** as colorless oil.

R_f = 0.73 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.35-7.27 (m, 3H), 7.24-7.19 (m, 4H), 6.86 (d, *J* = 8.53 Hz, 2H), 5.02 (d, *J* = 10.04 Hz, 1H), 4.65-4.59 (m, 1H), 4.41 (d, *J* = 11.54 Hz, 1H), 4.36 (d, *J* = 11.79 Hz, 1H), 4.16 (d, *J* = 5.02 Hz, 2H), 3.98 (m, 2H), 3.80 (s, 3H), 3.49 (dd, *J* = 9.16 Hz, 4.89 Hz, 1H), 3.37 (dd, *J* = 6.02, 4.77 Hz, 1H), 3.26 (dd, *J* = 13.30, 3.26 Hz, 1H), 3.21 (t, *J* = 8.90 Hz, 1H), 2.75 (dd, *J* = 13.30, 9.54 Hz, 1H), 2.51 (m, 1H), 2.21 (t, *J* = 12.42 Hz, 1H), 1.96 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.57 (s, 3H), 1.24 (d, *J* = 6.28 Hz, 3H), 0.95 (d, *J* = 7.02 Hz, 3H), 0.93 (s, 9H), 0.88 (d, *J* = 6.52 Hz, 3H), 0.88 (s, 9H), 0.74 (d, *J* = 6.77 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.01 (s, 6H).

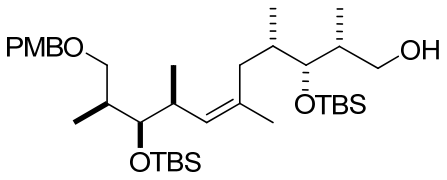
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.0, 159.0, 152.8, 135.3, 131.2, 129.5, 129.1, 128.9, 127.4, 113.7, 78.5, 76.9, 72.7, 72.5, 65.9, 55.6, 55.3, 41.6, 38.7, 37.7, 36.5, 35.5, 26.1, 25.7, 23.1, 18.4, 17.0, 14.5, 14.4, 14.0, -3.5, -3.8, -4.0.

IR (film):2930, 1784, 1698, 1514, 1463, 1385, 1249, 1040 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{46}H_{75}NO_7Si_2Na$: 832.4980, found: 832.4987.

$[\alpha]_D^{20}$ 48.00 (*c* = 0.6, CH_2Cl_2)

(*Z*)-(2*R*,3*R*,4*S*,8*S*,9*R*,10*S*)-3,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-11-(4-methoxy-benzyloxy)-2,4,6,8,10-pentamethyl-undec-6-en-1-ol (403)



To aldol adduct **523** (18 mg, 0.022 mmol) in Et_2O (0.5 mL) with methanol (10 µL) at 0 °C was slowly added $LiBH_4$ (12 µL, 2M in THF, 0.024 mmol). After 1.5 h the reaction was quenched by the addition of brine and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent, purification by column chromatography (hexane:EtOAc = 5:1) yielded 12 mg (86%) of **403**.

R_f = 0.59 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.78 Hz, 2H), 6.86 (d, *J* = 8.78 Hz, 2H), 5.02 (d, *J* = 10.04 Hz, 1H), 4.40 (d, *J* = 11.54 Hz, 1H), 4.36 (d, *J* = 11.54 Hz, 1H), 3.80 (s, 3H), 3.60 (m, 2H), 3.49-3.43 (m, 2H), 3.38 (dd, *J* = 6.15, 4.64 Hz, 1H), 3.21 (t, *J* = 8.78 Hz, 1H), 2.51 (m, 1H), 2.16 (t, *J* = 12.04 Hz, 1H), 1.99-1.88 (m, 2H), 1.83 (m, 1H), 1.77 (m, 1H), 1.59 (s, 3H), 0.94 (d, *J* = 7.02 Hz, 3H), 0.91 (d, *J* = 6.50 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (d, *J* = 8.09 Hz, 3H), 0.79 (d, *J* = 6.77 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 131.9, 131.5, 131.1, 129.1, 113.7, 78.5, 77.8, 72.6, 72.5, 66.4, 55.3, 39.4, 38.5, 36.6, 35.6, 34.5, 26.1, 26.0, 23.1, 18.4, 18.3, 17.0, 15.0, 14.8, 12.3, -3.8, -3.9, -4.1.

IR (film): 2929, 2856, 1613, 1513, 1462, 1250, 1039 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{36}H_{68}O_5Si_2Na$: 636.4605, found: 636.4598.

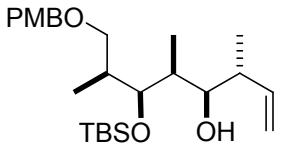
$[\alpha]_D^{20}$ 1.81 (*c* = 0.55, CH_2Cl_2)

Stock solution (*E*)-Crotylboronate (408)

To KOtBu (561 mg, 5.0 mmol) in THF (5 mL) at -78 °C was added *trans*-butene (0.51 mL, 5.5 mmol). *n*BuLi (2 mL, 2.5M in hexane, 5.0 mmol) was added *via* syringe pump over 1 h. The orange mixture was warmed to -50 °C and the mixture was stirred for 15 min. After recooling

to -78 °C, triisopropylborate (1.15 mL, 5.0 mmol) was added *via* syringe pump over 1 h. After addition was completed the mixture was stirred another 10 min and then rapidly poured on a 1N HCl solution (10 mL) saturated with NaCl. DIPT (1.06 mL, 5.0 mmol) in Et_2O (2 mL) was added and vigorously shaken. The layers were separated and the aqueous phase was repeatedly extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ for 2 h and filtered into a Schlenk flask. The solvent was removed and the crude product was taken up in toluene (10 mL) to give a 0.3 M stock solution.

(3*R*,4*R*,5*S*,6*S*,7*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-8-(4-methoxy-benzyloxy)-3,5,7-trimethyl-oct-1-en-4-ol (409)



To (*E*)-(*S*,*S*)-crotyl boronate (**408**) (2.6 mL, 0.3M in toluene, 0.78 mmol) at -78 °C was added aldehyde **76** (100 mg, 0.26 mmol) in toluene (1 mL) very slowly. The mixture was allowed to warm to 0 °C over night and then 1N NaOH was added and the mixture was stirred for 45 min at 0 °C. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 5:1) yielded 110 mg (97%) of olefin **409** as single diastereoisomer.

$\mathbf{R_f}$ = 0.49 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.60 Hz, 2H), 6.87 (d, *J* = 8.56 Hz, 2H), 5.79-5.60 (m, 1H), 5.10-5.06 (m, 2H), 4.43 (d, *J* = 11.60 Hz, 1H), 4.39 (d, *J* = 11.64 Hz, 1H), 3.80 (s, 3H), 3.75 (t, *J* = 4.42 Hz,1H), 3.51 (dd, *J* = 9.22, 6.18 Hz, H), 3.38 (dt, *J* = 7.06, 3.53 Hz, 1H), 3.25 (t, *J* = 9.08, 6.84 Hz, 1H), 2.27 (m, 1H), 2.13 (m, 1H), 1.96 (d, *J* = 3.28 Hz, 1H (OH)), 1.81 (m, 1H), 0.96 (d, *J* = 7.08 Hz, 3H), 0.92 (d, *J* = 7.56 Hz, 3H), 0.89 (s, 9H), 0.89 (d, *J* = 9.12 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

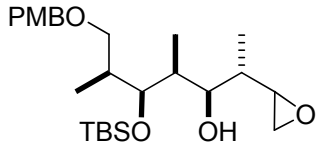
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.1, 141.5, 130.7, 129.2, 115.7, 113.7, 77.0, 75.7, 72.7, 72.5, 55.3, 42.0, 38.0, 37.5, 26.1, 18.4, 16.8, 15.4, 9.2, -3.8, -3.9.

IR (film): 3479, 2957, 2930, 1514, 1463, 1249, 1039 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{25}H_{44}O_4Si$: 436.3009, found: 436.3015.

$[\alpha]_D^{20}$ -2.43 (*c* = 1.15, CH_2Cl_2)

(2*S*,3*S*,4*S*,5*S*,6*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-8-(4-methoxy-phenoxy)-4,6-dimethyl-2-oxiranyl-octan-3-ol (410)



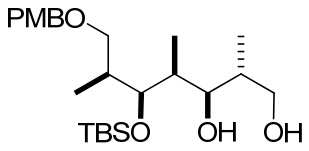
To olefin **409** (18 mg, 0.041 mmol) in DCM (1.5 mL) was added $VO(acac)_2$ (0.6 mg, 5 mol%, 0.002 mmol) at 0 °C followed by *t*BuOOH (16 µL, 5.5M in decane, 0.082 mmol). The reaction mixture was allowed to warm to r.t. over night. A saturated $Na_2S_2O_3$ solution was added and the layers were separated. The aqueous phase was extracted with DCM and the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5 :1) yielded 15 mg (81%) of epoxide **410** as colorless oil.

R_f = 0.45 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.24 (d, *J* = 8.84 Hz, 2H), 6.86 (d, *J* = 8.84 Hz, 2H), 4.43 (d, *J* = 11.60 Hz, 1H), 4.39 (d, *J* = 11.36 Hz, 1H), 3.79 (s, 3H), 3.76 (dd, *J* = 5.42, 3.42 Hz,1H), 3.66 (dt, *J* = 7.92, 2.60 Hz, H), 3.26 (dd, *J* = 9.08, 6.65 Hz, 1H), 2.93 (ddd, *J* = 7.19, 4.17, 2.89 Hz, 1H), 2.70 (m, 1H), 2.45 (dd, *J* = 4.80, 2.76 Hz, 1H), 2.20 (m, 1H), 1.84 (m, 1H), 1.43 (m, 1H), 0.98 (d, *J* = 7.04 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 7.08 Hz, 3H), 0.80 (d, *J* = 7.08 Hz, 3H), 0.06 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.1, 130.7, 129.3, 113.7, 77.3, 76.2, 72.7, 72.2, 55.4, 55.2, 44.8, 39.5, 38.4, 37.2, 26.1, 18.4, 15.7, 12.6, 9.0, -3.7, -3.9.

(2*R*,3*R*,4*S*,5*S*,6*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-8-(4-methoxy-phenoxy)-2,4,6-trimethyl-octane-1,3-diol (524)



To epoxide **410** (15 mg, 0.033 mmol) in Et_2O:THF (1:1, 1 mL) at 0 °C was added $HIO_4 \cdot 2H_2O$ (12 mg, 0.055 mmol) and the mixture was stirred over night at 0 °C. A saturated $NaHCO_3$ solution was added and diluted with DCM, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was taken up in methanol (1 mL) and $NaBH_4$ was added. After 30 min brine was added, the layers were separatd and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 12 mg (82%) of alcohol **524**.

R_f = 0.39 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.56 Hz, 2H), 6.88 (d, *J* = 8.56 Hz, 2H), 4.43 (d, *J* = 11.36 Hz, 1H), 4.39 (d, *J* = 11.36 Hz, 1H), 3.80 (s, 3H), 3.77 (t, *J* = 4.04 Hz, 1H), 3.66 (dd, *J* = 9.46, 1.66 Hz, 1H), 3.55 (m, 2H), 3.52 (t, *J* = 8.84 Hz, 1H), 3.28 (dd, *J* = 9.10, 5.06 Hz, 1H), 2.24 (m, 1H), 1.84-1.75 (m, 2H), 0.92 (d, *J* = 8.08 Hz, 3H), 0.91 (s, 9H), 0.90 (d, *J* = 7.32 Hz, 3H), 0.71 (d, *J* = 7.08 Hz, 3H), 0.08 (s, 6H).

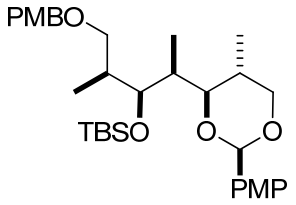
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.4, 129.9, 129.4, 113.8, 79.1, 78.1, 73.0, 72.6, 69.2, 55.3, 38.7, 37.4, 36.5, 26.0, 18.2, 15.9, 13.9, 8.5, -3.9, -4.4.

IR (film): 2929, 1514, 1250, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{24}H_{44}O_5Si$: 440.2958, found: 440.2968.

$[\alpha]_D^{20}$ -2.00 (*c* = 0.2, CH_2Cl_2)

***tert*-Butyl-((1*S*,2*S*)-4-(4-methoxy-phenoxy)-1-{(*S*)-1-[(2*R*,4*R*,5*R*)-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-ethyl}-2-methyl-butoxy)-dimethyl-silane (411)**



To diol **524** (8 mg, 0.018 mmol) in DCM (0.5 mL) was added anisaldehyde dimethyl acetal (7 µL, 0.036 mmol) and CSA (cat.) at r.t. under argon. The mixture was stirred for 1 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (Hexane:EtOAc = 10:1) yielded 10 mg (99%) of acetal **411** as colorless oil

R_f = 0.42 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.37 (d, *J* = 8.84 Hz, 2H), 7.19 (d, *J* = 8.60 Hz, 2H), 6.85 (d, *J* = 8.84 Hz, 2H), 6.84 (d, *J* = 8.60 Hz, 2H), 5.37 (s, 1H), 4.36 (d, *J* = 11.36 Hz, 1H), 4.32 (d, *J* = 11.36 Hz, 1H), 4.06 (dd, *J* = 11.36, 4.80 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 (dd, *J* = 7.08, 2.28 Hz,1H), 3.56 (dd, *J* = 9.22, 5.42 Hz, H), 3.55 (*J* = 9.92, 1.60 Hz, 1H), 3.44 (t, *J* = 11.10 Hz, 1H), 3.25 (dd, *J* = 9.10, 7.82 Hz, 1H), 2.16 (m, 1H), 2.03 (m, 1H), 1.95 (dt, *J* = 7.08, 1.76 Hz, 1H), 1.00 (d, *J* = 6.80 Hz, 3H), 0,99 (d, *J* = 7.08 Hz, 3H), 0.87 (s, 9H), 0.65 (d, *J* = 6.56 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

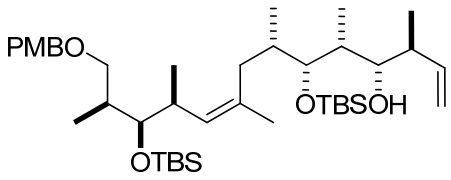
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.7, 159.0, 131.5, 130.9, 129.2, 127.3, 113.7, 113.4, 100.9, 83.0, 77.1, 73.3, 72.6, 71.9, 55.26, 55.24, 37.9, 36.8, 30.8, 26.2, 18.4, 16.3, 12.0, 10.9, -3.9.

IR (film): 2929, 1614, 1514, 1462, 1248, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{32}H_{50}O_6Si$: 558.3377, found: 558.3371.

$[\alpha]_D^{20}$ -32.75 (*c* = 0.4, $CHCl_3$)

(*Z*)-(3*S*,4*S*,5*R*,6*R*,7*S*,11*S*,12*R*,13*S*)-6,12-Bis-(*tert*-butyl-dimethyl-silanyloxy)-14-(4-methoxy-benzyloxy)-3,5,7,9,11,13-hexamethyl-tetradeca-1,9-dien-4-ol (413)



To alcohol **403** (10 mg, 0.015 mmol) in DMSO (0.5 mL) at r.t. under argon was added IBX (9 mg, 0.031 mmol) and the mixture was stirred for 2 h. Water and Et_2O were added and the phases were separated. The aqueous layer was extracted with Et_2O and the combined ethereal layer was dried over $MgSO_4$. After evaporation of the solvent crude aldehyde **412** was used without further purification.

To (*E*)-(*R*,*R*)-crotyl boronate (***ent*-408**) (0.5 mL, 0.3M in toluene, 0.150 mmol) at -78°C was added aldehyde **412** (9 mg, 0.015 mmol) in toluene (0.5 mL) very slowly. The mixture was kept at -78 °C over night and then 1N NaOH was added and the mixture was stirred for 45 min at 0 °C. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 9 mg (87%) of olefin **413** as single diastereoisomer.

R_f = 0.49 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.56 Hz, 2H), 6.86 (d, *J* = 8.84 Hz, 2H), 5.79-5.69 (m, 1H), 5.15-5.09 (m, 2H), 5.02 (d, *J* = 10.12 Hz, 1H), 4.40 (d, *J* = 11.64 Hz, 1H), 4.36 (d, *J* = 11.60 Hz, 1H), 3.80 (s, 3H), 3.64 (dd, *J* = 5.56 Hz, *J* = 3.28 Hz, 1H), 3.48 (dd, *J* = 9.10, 4.54 Hz, 1H), 3.39 (dd, *J* = 5.74, 5.10 Hz, 1H), 3.31 (dt, *J* = 7.32, 3.66 Hz, 1H), 3.21 (t, *J* = 8.84 Hz, 1H), 2.52 (m, 1H), 2.29 (dd, *J* = 14.60, 7.52 Hz, 1H), 2.22 (t, *J* = 12.12 Hz, 1H), 1.99-1.87 (m, 2H), 1.83-1.77 (m, 2H), 1.60 (s, 3H), 0.99 (d, *J* = 6.80 Hz, 3H), 0.95 (d, *J* = 7.32 Hz, 3H), 0.93 (d, *J* = 7.04 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.89 (d, *J* = 8.08 Hz, 3H), 0.75 (d, *J* = 6.84 Hz, 3H), 0.09 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H).

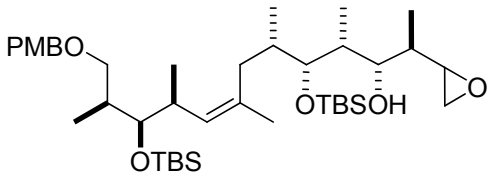
^{13}C-NMR (100MHz, $CDCl_3$): δ = 159.1, 141.3, 132.1, 131.4, 131.0, 129.1, 116.4, 113.7, 78.8, 78.5, 75.8, 72.6, 72.5, 55.3, 42.4, 38.6, 37.9, 36.2, 35.6, 35.1, 26.2, 26.1, 23.2, 18.5, 18.4, 16.9, 16.7, 14.6, 13.5, 9.4, -3.3, -3.7, -3.9.

IR (film): 2958, 2930, 2856, 1514, 1463, 1250, 1079, 1040 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{40}H_{74}O_5Si_2$: 690.5075 , found: 690.5081.

$[\alpha]_D^{20}$ 12.00 (*c* = 0.4, CH_2Cl_2)

(*Z*)-(2*R*,3*S*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(*tert*-butyl-dimethyl-silanyloxy)-13-(4-methoxy-benzyloxy)-4,6,8,10,12-pentamethyl-2-oxIRanyl-tridec-8-en-3-ol (414)



To olefin **413** (9 mg, 0.013 mmol) in DCM (0.5 mL) was added $VO(acac)_2$ (0.2 mg, 5 mol%) at 0 °C followed by *t*BuOOH (5 µL, 5.5M in decane, 0.026 mmol). The reaction mixture was kept over night at 0 °C. A saturated $Na_2S_2O_3$ solution was added and the layers were separated. The aqueous phase was extracted with DCM and the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 8 mg (87%) of epoxide **414** as colorless oil.

R_f = 0.47 (hexane:EtOAc = 10:1)

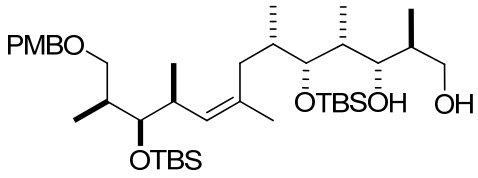
^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.24 (d, *J* = 8.60 Hz, 2H), 6.86 (d, *J* = 8.56 Hz, 2H), 5.03 (d, *J* = 10.36 Hz, 1H), 4.40 (d, *J* = 11.60 Hz, 1H), 4.36 (d, *J* = 11.60 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, *J* = 6.06, 3.02 Hz, 1H), 3.64 (dt, *J* = 8.20, 2.84 Hz, 1H), 3.49 (dd, *J* = 9.12, 4.80 Hz, 1H), 3.40 (t, *J* = 5.56 Hz, 1H), 3.21 (t, *J* = 8.70 Hz, 1H), 2.92 (ddd, *J* = 7.83, 4.05, 2.81 Hz, 1H), 2.75 (t, *J* = 4.42 Hz, 1H), 2.53 (m, 1H), 2.48 (dd, *J* = 4.80, 2.76 Hz, 1H), 2.40 (d, *J* = 3.04 Hz, 1H (OH)), 2.27 (t, *J* = 12.24 Hz, 1H), 2.00-1.93 (m, 2H), 1.84-1.78 (m, 2H), 1.62 (s, 3H), 0.97 (d, *J* = 6.84 Hz, 3H), 0.95 (d, *J* = 6.80 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 12H), 0.86 (d, *J* = 6.32 Hz, 3H), 0.75 (d, *J* = 6.84 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.0, 132.1, 131.3, 131.1, 129.1, 113.7, 78.7, 78.5, 77.1, 72.6, 72.5, 55.8, 55.3, 45.1, 4.0, 38.6, 38.2, 36.2, 35.6, 34.9, 26.2, 26.1, 23.2, 18.5, 18.4, 16.9, 14.6, 14.1, 13.3, 12.9, 9.2, -3.3, -3.7, -3.9.

IR (film): 2929, 1513, 1462, 1250, 1039 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{40}H_{74}O_6Si_2$: 706.5024, found: 706.5029.

(*Z*)-(2*S*,3*S*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(tert-butyl-dimethyl-silanyloxy)-13-(4-methoxy-benzyloxy)-2,4,6,8,10,12-hexamethyl-tridec-8-ene-1,3-diol (525)



To epoxide **414** (7 mg, 0.0099 mmol) in Et_2O:THF (1:1, 1 mL) at 0 °C was added $HIO_4 \cdot 2H_2O$ (3 mg, 0.0140 mmol) and the mixture was stirred 16 h at 0 °C. A saturated $NaHCO_3$ solution was added and DCM, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was taken up in methanol (1 mL) and $NaBH_4$ was added at 0 °C. After 30 min brine was added and DCM, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 2 mg (29%, 51% b.r.s.m.) of alcohol **525** and 3 mg of epoxide **414**.

R_f = 0.41 (hexane:EtOAc = 10:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.64 Hz, 2H), 6.86 (d, *J* = 8.64 Hz, 2H), 5.04 (d, *J* = 10.20 Hz, 1H), 4.39 (d, *J* = 11.70 Hz, 1H), 4.37 (d, *J* = 11.70 Hz, 1H), 3.80 (s, 3H), 3.68 (t, *J* = 3.96 Hz, 1H), 3.66 (m, 2H), 3.54 (dd, *J* = 9.39, 0.09 Hz, 1H), 3.49 (dd, *J* = 9.06, 4.50 Hz, 1H), 3.38 (dd, *J* = 6.03, 4.89 Hz, 1H), 3.21 (t, *J* = 8.67 Hz, 1H), 2.53 (m, 1H), 2.20 (t, *J* = 12.27 Hz, 1H), 1.97 (m, 1H), 1.91 (m, 1H), 1.88-1.83 (m, 2H), 1.60 (s, 3H), 0.95 (d, *J* = 6.78 Hz, 6H), 0.91 (d, *J* = 9.48 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.79 (d, *J* = 6.78 Hz, 3H), 0.76 (d, *J* = 6.78 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

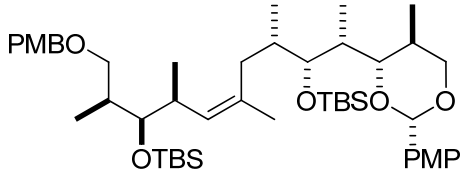
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.8, 131.8, 129.1, 116.1, 113.7, 81.4, 80.4, 78.5, 72.6, 68.8, 55.3, 38.5, 37.6, 37.2, 36.9, 35.7, 35.0, 26.2, 26.1, 23.2, 16.8, 14.8, 14.5, 13.7, 9.8, 8.2, -3.3, -3.8, -4.6.

IR (film): 3325, 2928, 2855, 1513, 1466, 1364, 1248, 1098, 1039 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{39}H_{74}O_6Si_2$: 694.5024 , found: 694.5018.

$[\alpha]_D^{20}$ 4.00 (*c* = 0.1, CH_2Cl_2)

(2*S*,4*S*,5*S*)-4-[(*Z*)-(1*R*,2*R*,3*S*,7*S*,8*R*,9*S*)-2,8-Bis-(*tert*-butyl-dimethyl-silanyloxy)-10-(4-methoxy-benzyloxy)-1,3,5,7,9-pentamethyl-dec-5-enyl]-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (415)



To diol **525** (1 mg, 0.0014 mmol) in DCM (0.5 mL) was added anisaldehyde dimethyl acetal (1 µL, 0.0056 mmol) and CSA (cat.) at r.t. and the mixture was stirred for 1.5 h. Brine was added and the mixture was diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (Hexane:EtOAc = 15:1) yielded 1 mg (86%) of acetal **415** as colorless oil. Data were in every aspect identical with the literature data.

R_f = 0.51 (hexane:EtOAc = 15:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.70 Hz, 2H), 7.23 (d, *J* = 8.70 Hz, 2H), 6.87 (d, *J* = 8.64 Hz, 2H), 6.85 (d, *J* = 8.70 Hz, 2H), 5.38 (s, 1H), 5.01 (d, *J* = 10.20 Hz, 1H), 4.39 (d, *J* = 11.70 Hz, 1H), 4.35 (d, *J* = 11.70 Hz, 1H), 4.10 (dd, *J* = 10.95, 4.53 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.61 (dd, *J* = 7.02, 1.68 Hz, 1H), 3.51 (dd, *J* = 9.81, 1.89 Hz, 1H), 3.48 (t, *J* = 11.13 Hz, 1H), 3.47 (dd, *J* = 9.06, 4.92 Hz, 1H), 3.38 (dd, *J* = 5.85, 4.71 Hz, 1H), 3.19 (t, *J* = 8.88 Hz, 1H), 2.51 (m, 1H), 2.32 (t, *J* = 12.09 Hz, 1H), 2.05 (m, 1H), 1.99-1.94 (m, 2H), 1.88 (m, 1H), 1.67 (d, *J* = 11.70 Hz, 1H), 1.55 (s, 3H), 1.01 (d, *J* = 7.20 Hz, 3H), 0.94 (d, *J* = 6.78 Hz, 3H), 0.91 (s, 9H), 0.89 (d, *J* = 6.96 Hz, 3H), 0.88 (s, 9H), 0.74 (d, *J* = 6.78 Hz, 3H), 0.73 (d, *J* = 6.42 Hz, 3H), 0.03 (s, 3H), 0.018 (s, 3H), 0.014 (s, 3H), 0.012 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.7, 159.0, 131.9, 131.5, 129.0, 127.3, 113.7, 113.4, 101.0, 83.3, 78.42, 78.40, 73.3, 72.6, 72.5, 55.3, 55.2, 38.7, 38.2, 37.6, 35.6, 33.6, 30.8, 26.2, 26.1, 23.1, 18.43, 18.39, 17.0, 14.6, 12.5, 12.1, 10.9, -3.6, -3.7, -3.8, -3.9.

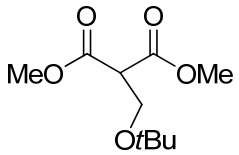
IR (film): 2929, 1514, 1470, 1242, 830 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{47}H_{80}O_7Si_2$: 812.5443, found: 812.5449.

$[\alpha]_D^{20}$ 24.00 (*c* = 0.05, $CHCl_3$)

10.2.4. Peloruside A

Dimethyl 2-(*tert*-butoxymethyl)malonate (429)



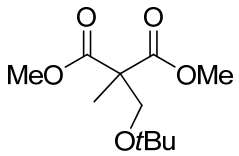
*t*BuOMOM: To a suspension of NaH (8.8 g, 0.22 mol) in THF (150 mL) at r.t. was added *t*BuOH (18.8 mL, 0.20 mol) and the mixture was heated under reflux for 2 h. MOMCl (15.2 mL, 0.20 mol) was added at 0 °C and after 10 min, stirring was continued at r.t. for 3 h. The solids were filtered off over celite and purification by distillation gave 6.5 g of the MOM ether (b.p. 95 °C).

Alkylation: To *t*BuOMOM (1 g, 8.30 mmol) in DCM (5 mL) at 0 °C was added BCl_3 (2.8 mL, 2.77 mmol) and after 15 min the reaction was stirred at r.t. for 2 h to give crude *t*BuOCH_2Cl. To a suspension of NaH (260 mg, 6.50 mmol) in THF (20 mL) at r.t. was added dimethyl malonate (**186**) (0.68 mL, 6.00 mmol) and after 1 h the crude chloride was added. The mixture was stirred over night. The reaction was quenched with saturated NH_4Cl solution, the layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (hexane:EtOAc = 5:1) to yield 850 mg (65%) of **429** as colorless oil.

$\mathbf{R_f}$ = 0.45 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.81 (d, J = 7.60 Hz, 2H), 3.74 (s, 6H), 3.63 (dd, J = 7.84, 7.32 Hz, 1H), 1.17 (s, 9H).

Dimethyl 2-(*tert*-butoxymethyl)-2-methylmalonate (427)



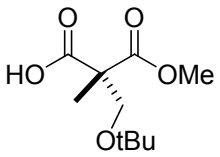
To malonate **429** (4.3 g, 19.72 mmol) in THF (100 mL) was added NaH (868 mg, 60% dispersion in mineral oil, 21.70 mmol) and the mixture was stirred for 1 h. MeI (1.8 mL, 29.58

mmol) was added and stirring was continued for 1 h. The reaction was quenched with saturated NH_4Cl solution, layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (hexane:EtOAc = 10:1) to yield 4.2 g (92%) of **429** as colorless oil.

R_f = 0.46 (hexane:EtOAc = 5:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.71 (s, 6H), 3.69 (s, 2H), 1.48 (s, 3H), 1.13 (s, 9H).

(*R*)-2-*tert*-butoxymethyl-2-methyl-malonic acid (428)

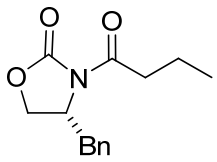


To malonate **427** (4 g, 17 mmol) suspended in 0.05M KH_2PO_4 buffer (180 mL) at pH 7 was added PLE and a pH-stat-controlled burette containing 0.5M NaOH added 34 mL over 24 h. After addition was completed, 1N NaOH was added to the mixture to pH 10 and by-products were removed by extraction with Et_2O. Upon acidification with 3N HCl to pH 1 mono acid **292** was extracted with DCM, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give 3.5 g of crude mono acid **428**.

R_f = 0.05 (hexane:EtOAc = 3:1)

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.82 (d, J = 8.58 Hz, 1H), 3.77 (s, 3H), 3.61 (d, J = 8.45 Hz, 1H), 1.45 (s, 3H), 1.21 (s, 9H).

(*R*)-4-benzyl-3-butyryl-oxazolidin-2-one (37)



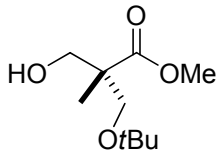
To (*R*)-4-(phenylmethyl)-2-oxazolidinone (**372**) (3 g, 17.0 mmol) in THF (55 mL) at -78 °C was slowly added *n*BuLi (11.7 mL, 1.6M in hexane, 18.7 mmol) followed by butyryl chloride

(1.9 mL, 18.7 mmol). After 30 min the mixture was warmed to r.t. and quenched by the addition of saturated NH_4Cl solution. The organic solvent was removed under reduced pressure and the remaining aqueous solution was extracted with DCM. The combined organic layer was washed with 1N NaOH and brine, dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 3:1) gave 3.9 g (93%) of acylated oxazolidinone **37**.

R_f = 0.38 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 3H), 7.21 (m, 2H), 4.67 (ddt, *J* = 9.66, 7.12, 3.34 Hz, 1H), 4.22-4.13 (m, 2H), 3.30 (dd, *J* = 13.26, 3.42 Hz, 1H), 2.96 (ddd, *J* = 16.93, 7.96, 6.96 Hz, 1H), 2.88 (ddd, *J* = 16.87, 7.63, 7.25 Hz, 1H), 2.77 (dd, *J* = 13.40, 9.60 Hz, 1H), 1.73 (dsext, *J* = 7.40, 1.60 Hz, 2H), 1.01 (t, *J* = 7.44 Hz, 3H).

(*S*)-2-*tert*-Butoxymethyl-3-hydroxy-2-methyl-propionic acid methyl ester (526)



To a solution of mono acid **428** (1.20 g, 5.50 mmol) in THF (15 mL) at 0 °C was added triethylamine (0.84 mL, 6.05 mmol) followed by methyl chloroformate (0.47 mL, 6.05 mmol). After 10 min at 0 °C, the reaction mixture was warmed to r.t. and stirred for 45 min. The white precipitate was filtered off, washed with Et_2O and concentrated. To the residue was added MeOH (15 mL) and the mixture was cooled to 0 °C, then $NaBH_4$ (416 mg, 11.00 mmol) was added portionwise. After 1 h the reaction was quenched with a saturated solution of NH_4Cl, layers were separated and the aqueous layer was extracted with DCM. The combined organic extract was dried over $MgSO_4$ and the organic solvent was emoved under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) gave 934 mg (83%) of alcohol **526**.

R_f = 0.23 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.80 (dd, *J* = 10.98, 5.43 Hz, 1H), 3.74-3.69 (m, 2H), 3.71 (s, 3H), 3.36 (d, *J* = 8.59 Hz, 1H), 2.92 (dd, *J* = 7.58, 5.56 Hz, 1H (OH)), 1.16 (s, 9H), 1.15 (s, 3H).

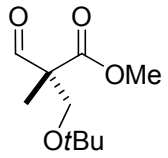
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.8, 73.4, 67.7, 66.4, 51.9, 48.6, 27.5, 18.0, 14.0.

IR (film): 3467, 2975, 1732, 1364, 1234, 1197, 1084, 1049 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_9H_{17}O_4$: 189.1127, found: 189.1129.

$[\alpha]_D^{20}$ 2.00 (*c* = 1.3, CH_2Cl_2)

(*R*)-2-*tert*-Butoxymethyl-2-methyl-3-oxo-propionic acid methyl ester (430)



To a stirred solution of alcohol **526** (3.50 g, 17.13 mmol) in DMSO (50 mL) was added IBX (9.40 g, 34.26 mmol) and stirring was continued for 2.5 h. Water and Et_2O were added and the organic layer was separated. The aqueous layer was extracted with Et_2O and the combined ethereal phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 2.80 g (80%) of aldehyde **430** as colorless oil.

R_f = 0.57 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 3.80 (d, *J* = 8.59 Hz, 1H), 3.75 (s, 3H), 3.52 (d, *J* = 8.34 Hz, 1H), 1.30 (s, 3H), 1.14 (s, 9H).

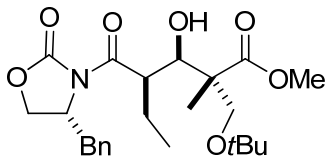
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.8, 171.8, 73.4, 65.0, 58.1, 52.3, 27.2, 15.0.

IR (film): 1724, 1455, 1237, 1195, 1087cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_9H_{15}O_4$: 187.0970, found: 187.0973.

$[\alpha]_D^{20}$ 0.86 (*c* = 1.4, CH_2Cl_2)

(2*R*,3*R*,4*R*)-4-((*R*)-4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-2-*tert*-butoxymethyl-3-hydroxy-2-methyl-hexanoic acid methyl ester (431)



To a stirred solution of oxazolidinone **37** (612 mg, 2.47 mmol) in DCM (3 mL) at -78 °C was slowly added dibutylboron triflate (3.2 mL, 1M in DCM, 3.20 mmol) followed by triethylamine

(0.48 mL, 3.45 mmol) and stirring was continued for 30 min. The reaction mixture was warmed to 0 °C for 1 h and then recooled to -78 °C. Aldehyde **430** (500 mg, 2.47 mmol) in DCM (1 mL) was added dropwise. After 30 min the reaction mixture was warmed to 0 °C and stirred for 3 h. pH 7 buffer solution (10 mL), methanol (3 mL) and H_2O_2 (3 mL, 30% aqueous) were added and the mixture was stirred for 2 h at r.t..The layers were separated and the aqueous layer was extracted with DCM.The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 10:1 to 3:1) to yield 950 mg (85%) of **431** as pale yellow oil.

R_f = 0.36 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.35-7.21 (m, 5H), 4.60-4.54 (m, 1H), 4.23-4.07 (m, 4H), 3.87 (d, *J* = 9.03 Hz, 1H), 3.77 (d, *J* = 10.29 Hz, 1H), 3.64 (s, 3H), 3.43 (d, *J* = 9.03 Hz, 1H), 3.33 (dd, *J* = 13.17, 3.14 Hz, 1H), 2.68 (dd, *J* = 13.30, 10.29 Hz, 1H), 1.97-1.83 (m, 2H), 1.39 (s, 3H), 1.19 (s, 9H), 0.98 (t, *J* = 7.52 Hz, 3H).

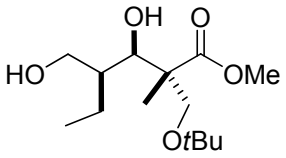
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 175.7, 174.9, 153.3, 135.6, 129.3, 128.9, 127.3, 76.3, 74.0, 65.9, 65.7, 63.8, 55.9, 52.0, 49.5, 46.4, 38.1, 27.2, 23,4, 19.3, 10.7.

IR (film): 2974, 1781, 1718, 1387, 1208, 1072 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{24}H_{35}O_7Na$: 472.2311, found: 472.2323.

$[\alpha]_D^{20}$ -38.47 (*c* = 1.24, CH_2Cl_2)

(2*R*,3*R*,4*S*)-2-*tert*-Butoxymethyl-3-hydroxy-4-hydroxymethyl-2-methyl-hexanoic acid methyl ester (432)



To aldol adduct **431** (440 mg, 0.98 mmol) in Et_2O (10 mL) and methanol (20 µL) at 0 °C was slowly added $LiBH_4$ (21 mg, 0.98 mmol). After 30 min the reaction was quenched by the addition of saturated NH_4Cl solution and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude diol was purified by column chromatography (hexane:EtOAc = 3:1) to yield 215 mg (80%) of **432** as colorless oil.

R_f = 0.22 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.99 (dd, *J* = 8.33, 2.02 Hz, 1H), 3.90 (d, *J* = 8.59 Hz, 1H (OH)), 3.76-3.66 (m, 2H), 3.70 (s, 3H), 3.64 (d, *J* = 8.84 Hz, 1H), 3.54 (d, *J* = 8.59 Hz, 1H), 1.53-1.39 (m, 2H), 1.36-1.27 (m, 1H), 1.23 (s, 3H), 1.14 (s, 9H), 0.94 (t, *J* = 7.20 Hz, 3H).

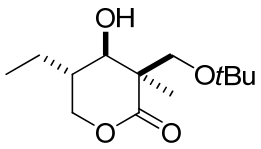
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.9, 77.6, 73.5, 66.6, 64.6, 60.3, 52.0, 49.9, 43.3, 27.2, 18.1, 16.7, 12.1.

IR (film): 3435, 3974, 1728, 1364, 1234, 1197, 1141, 1079, 1046 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{14}H_{28}O_5Na$: 299.1834, found: 299.1832.

$[\alpha]_D^{20}$ 19.90 (*c* = 0.97, CH_2Cl_2)

(3*R*,4*R*,5*S*)-3-*tert*-Butoxymethyl-5-ethyl-4-hydroxy-3-methyl-tetrahydro-pyran-2-one (433)



To a stirred solution of ester **432** (180 mg, 0.65 mmol) in methanol (8 mL) was added K_2CO_3 (180 mg, 1.30 mmol) and stirring was continued for 3 h. The mixture was diluted with water, acidified with 1N HCl and extracted with DCM. After drying the combined organic layer over $MgSO_4$, the solvent was removed to yield 159 mg (quant.) of lactone **433** as white crystals, which was directly used in the following reaction. For analytical purposes a small sample was purified by column chromatography (hexane:EtOAc = 3:1).

R_f = 0.44 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.37 (dd, *J* = 11.49, 4.67 Hz, 1H), 3.88 (t, *J* = 10.99 Hz, 1H), 3.83 (d, *J* = 8.84 Hz, 1H), 3.67 (d, *J* = 7.83 Hz, 1H (OH)), 3.56 (d, *J* = 8.59 Hz, 1H), 3.49 (dd, *J* = 9.22, 8.21 Hz, 1H), 2.07-1.97 (m, 2H), 1.87-1.77 (m, 1H), 1.36 (s, 3H), 1.29-1.20 (m, 1H), 1.19 (s, 9H), 0.97 (t, *J* = 7.45 Hz, 3H).

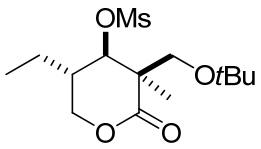
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2, 77.2, 74.5, 69.1, 66.9, 48.2, 41.6, 27.2, 22.0, 21.6, 11.2.

IR (film): 3503, 2973, 1701, 1364, 1237, 1198, 1147, 1089 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{13}H_{24}O_4$: 229.1440, found: 229.1442.

$[\alpha]_D^{20}$ 11.56 (*c* = 1.15, CH_2Cl_2)

Methanesulfonic acid (3*R*,4*R*,5*S*)-3-*tert*-butoxymethyl-5-ethyl-3-methyl-2-oxo-tetrahydro-pyran-4-yl ester (435)



To lactone **433** (160 mg, 0.64 mmol) in DCM (6 mL) and pyridine (0.6 mL) at r.t. was added mesyl chloride (99 µL, 1.28 mmol) and DMAP (cat.). After 1 h brine was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 205 mg (99%) of mesylate **435**.

R_f = 0.45 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.66 (d, *J* = 9.85 Hz, 1H), 4.45 (dd, *J* = 11.62, 5.30 Hz, 1H), 3.88 (t, *J* = 11.24 Hz, 1H), 3.63 (d, *J* = 8.34 Hz, 1H), 3.54 (d, *J* = 8.34 Hz, 1H), 3.11 (s, 3H), 2.88-2.78 (m, 1H), 1.83-1.72 (m, 1H), 1.37 (s, 3H), 1.28-1.18 (m, 1H), 1.16 (s, 9H), 0.96 (t, *J* = 7.58 Hz, 3H).

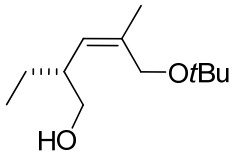
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.0, 85.2, 73.6, 68.6, 66.4, 48.7, 38.8, 38.4, 27.2, 21.9, 21.5, 10.8.

IR (film): 2974, 1732, 1339, 1177, 1093 cm^{-1}.

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{13}H_{23}O_6S$: 307.1215, found: 307.1211.

$[\alpha]_D^{20}$ 44.58 (*c* = 1.2, CH_2Cl_2)

(*Z*)-(*R*)-5-*tert*-Butoxy-2-ethyl-4-methyl-pent-3-en-1-ol (437)



Mesylate **435** (200 mg, 0.6 mmol) was dissolved in dioxane (8 mL) and LiOH (1.8 mL, 1M in water, 1.8 mmol) was added. After 1.5 h the reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 110 mg (83%) of olefin **437**

R_f = 0.40 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.07 (d, *J* = 10.10 Hz, 1H), 3.98 (d, *J* = 9.34 Hz, 1H), 3.63 (d, *J* = 8.34 Hz, 1H), 3.57 (ddd, *J* = 10.23, 6.69, 3.92 Hz, 1H), 3.21 (t, *J* = 9.85 Hz, 1H), 2.87 (dd, *J* = 7.19, 2.64 Hz, 1H (OH)), 2.47-2.38 (m, 1H), 1.82 (s, 3H),1.42-1.33 (m, 1H), 1.27-1.12 (m, 2H), 1.23 (s, 9H), 0.87 (t, *J* = 7.32 Hz, 3H).

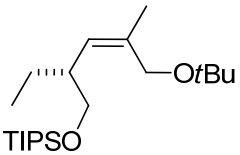
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 136.1, 131.8, 73.6, 65.9, 60.8, 43.0, 27.4, 24.9, 23.2, 11.8.

IR (film): 3629, 2970, 1653, 2559, 1056 cm^{-1}.

HRMS (ESI) (m/z): $[M-H]^+$ calcd for $C_{12}H_{23}O_2$: 199.1698, found: 199.1703.

$[\alpha]_D^{20}$ 32.66 (*c* = 0.65, CH_2Cl_2)

((Z)-(R)-5-*tert*-Butoxy-2-ethyl-4-methyl-pent-3-enyloxy)-triisopropylsilane (527)



To a stirred solution of alcohol **437** (12 mg, 0.06 mmol) in DCM (1 mL) was added 2,6-lutidine (11 µL, 0.09 mmol) and TIPSOTf (18 µL, 0.07 mmol). After 1 h the reaction was quenched by the addition of a saturated NH_4Cl solution, layers were separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 18 mg (85%) of **527** as colorless oil.

R_f = 0.63 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.03 (d, *J* = 9.60 Hz, 1H), 3.91 (d, *J* = 10.36 Hz, 1H), 3.84 (d, *J* = 10.36 Hz, 1H), 3.55 (dd, *J* = 9.60, 5.80 Hz, 1H), 3.48 (dd, *J* = 9.48, 7.20 Hz, 1H), 2.48 (m, 1H), 1.76 (s, 3H),1.70-1.60 (m, 1H), 1.25-1.15 (m, 2H), 1.21 (s, 9H), 1.05 (s, 21H), 0.85 (t, *J* = 7.44 Hz, 3H).

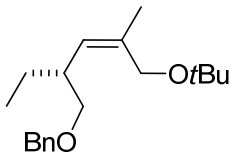
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.9, 129.6, 72.8, 66.9, 61.1, 42.5, 27.6, 24.7, 21.9, 18.1, 12.0, 11.7.

IR (film): 2943, 2866, 1463, 1362, 1197, 1103, 1059, 1014 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{21}H_{44}O_2Si$: 356.3111, found: 356.3105.

$[\alpha]_D^{20}$ -25.56 (*c* = 0.45, CH_2Cl_2)

((*Z*)-(*R*)-5-*tert*-Butoxy-2-ethyl-4-methyl-pent-3-enyloxymethyl)-benzene (528)



To a stirred solution of alcohol **435** (15 mg, 0.070 mmol) in benzylbromide (0.3 mL) was added tetrabutylammonium iodide (2 mg, 0.007 mmol), after 10 min silver(I)oxide (32 mg, 0.140 mmol) was added. After 24 h the mixture was filtered over celite, washed with Et_2O and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 40:1) yielded 21 mg (quant.) of benzyl ether **528** as colorless oil.

R_f = 0.59 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 4H), 7.28 (m, 1H), 5.05 (d, *J* = 9.60 Hz, 1H), 4.49 (s, 2H), 3.88 (s, 2H), 3.36 (dd, *J* = 9,22, 5.93 Hz, 1H), 3.31 (dd, *J* = 9.22, 7.20 Hz, 1H), 2.59 (m, 1H), 1.78 (s, 3H), 1.68-1.60 (m, 1H), 1.26-1.17 (m, 1H), 1.21 (s, 9H), 0.86 (t, *J* = 7.45 Hz, 3H).

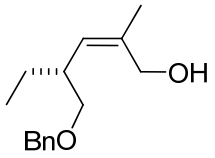
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 138.8, 135.2, 129.2, 128.3, 127.5, 127.4, 74.1, 72.9, 61.0, 39.8, 27.6, 25.2, 21.9, 11.6.

IR (film): 2970, 1454, 1362, 1197, 1058, 1021 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{19}H_{30}O_2$: 290.2246, found: 290.2251.

$[\alpha]_D^{20}$ -37.07 (*c* = 0.75, CH_2Cl_2)

(*Z*)-(*R*)-4-Benzyloxymethyl-2-methyl-hex-2-en-1-ol (437)



To a solution of **528** (21 mg, 0.07 mmol) in DCM (1 mL) at r.t. was added TFA (50 µL) and the mixture was stirred for 16 h. The reaction mixture was diluted with water and the layers were separated. The aqueous layer was extracted with DCM, the combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 40:1) yielded 15 mg (92%) of alcohol **437** as colorless oil.

R_f = 0.43 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 5H), 5.29 (d, *J* = 10.10 Hz, 1H), 4.94 (d, *J* = 11.87 Hz, 1H), 4.80 (d, *J* = 12.38 Hz, 1H), 4.48 (s, 2H), 3.38 (dd, *J* = 9.22, 5.93 Hz, 1H), 3.28 (dd, *J* = 9.22, 6.94 Hz, 1H), 2.57 (m, 1H), 1.81 (d, *J* = 1.51 Hz, 3H), 1.61-1.55 (m, 1H), 1,23-1.16 (m, 1H), 0.84 (t, *J* = 7.45 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.3, 138.5, 134.9, 129.3, 128.3, 127.5, 127.4, 73.5, 73.0, 67.0, 40.4, 24.8, 21.2, 11.5.

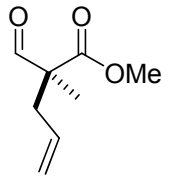
IR (film): 2963, 2895, 1785, 1454, 1364, 1222, 1167 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{15}H_{22}O_2$: 234.1620, found: 234.1917.

$[\alpha]_D^{20}$ -38.80 (*c* = 0.25, CH_2Cl_2)

10.2.5. Nuclephile Additions

(*S*)-2-Formyl-2-methyl-pent-4-enoic acid methyl ester (439)



To a solution of alcohol **197** (2.30 g, 14.45 mmol) in ethyl acetate (45 mL) was added IBX (7.96 g, 28.90 mmol). The mixture was heated under reflux for 2 h, the white precipitate was filtered off and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc =10:1) yielded 1.90 mg (84%) of aldehyde **439** as colorless oil.

R_f = 0.75 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 5.73-5.62 (m, 1H), 5.14-5.09 (m, 2H), 3.75 (s, 3H), 2.62 (dd, *J* = 13.90, 7.34 Hz, 1H), 2.49 (dd, *J* = 13.88, 7.32 Hz, 1H), 1.30 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.0, 172.1, 131.7, 119.5, 119.4, 52.4, 38.5, 16.8.

IR (film): 1722, 1456, 1435, 1235, 1150, 1121 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_8H_{12}O_3$: 156.0786, found: 156.0778.

$[\alpha]_D^{20}$ -4.09 (*c* = 1.6, CH_2Cl_2)

Allylation procedures:

Roush allylation:

Triisopropyl borate (0.92 mL, 4.00 mmol) and allylmagnesium bromide (4.4 mL, 0.9 M in Et_2O, 4.00 mmol) were added simultaneously and very slowly to Et_2O (1 mL) at -78 °C. The mixture was stirred for 30 min at -78 °C, than for 3 h at r.t. and recooled to 0 °C. 1N HCl (4 mL) saturated with NaCl was slowly added and the mixture was stirred for 15 min at r.t.. The organic layer was separated and the aqueous layer was extracted with Et_2O:DCM (5:1) and the combined organic phase was divided in two parts. Each part was treated with either L-(+)- or D-(-)-DIPT (0.42 mL, 2.00 mmol), $MgSO_4$ was added and the mixture was stirred for 2.5 h. Filtration under argon and removal of the solvent under reduced pressure gave a colorless liquid which was taken up in toluene (4 mL) and 4 Å MS (70 mg) was added. The suspension

was cooled to -78 °C and aldehyde **439** (70 mg, 0.45 mmol) was added in toluene (1 mL). The reaction was stirred at -78 °C over night and then quenched by the addition of $NaBH_4$ in ethanol and 1N NaOH. After stirring for 1 h at r.t. the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 15:1 to 5:1) gave with L-(+)-DIPT ester 62 mg (69%) of **440**:**441** in a 8:1 ratio and with D-(-)-DIPT ester 53 mg (60%) of **440**:**441** in a 20:1 ratio always favouring the Felkin-Anh adduct **440**.

Brown allylation:

To methoxydiisopinocampheylborane (632 mg, 2.00 mmol) in Et_2O (1 mL) at 0 °C was slowly added allymagnesium bromide (2.44 mL, 0.9 M in Et_2O, 2.20 mmol). The mixture was stirred at r.t. for 3 h and then the solvent was removed under reduced pressure, whereas the residue was always kept under argon. Pentane (2 mL) was added and the supernatant solution used for the following allylation. To aldehyde **439** (50 mg, 0.32 mmol) in Et_2O (6 mL) at -100 °C was very slowly added the allyldiisopinocampheylborane solution and the mixture was allowed to warm to -85 °C over 2.5 h. The reaction was quenched by the addition of methanol and the solvent was removed under reduced pressure. The residue was taken up in water:THF (1:1, 5 mL), $NaBO_3 \cdot 4H_2O$ was added and the mixture was stirred over night. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 15:1 to 5:1) gave with (+)-*i*Pc 63 mg (quant.) of **440**:**441** as 20:1 mixture and with (-)-*i*Pc 43 mg (51%) of **440**:**441** as 1:1 mixture always favouring the Felkin-Anh adduct **440**.

Allylation with allyltrimethylsilane:

$TiCl_4$ (70 µL, 0.64 mmol) or $BF_3 \cdot Et_2O$ (64 µL, 0.64 mmol) was added to a solution of aldehyde **439** (50 mg, 0.32 mmol) in DCM (3 mL) at -78 °C. After 15 min allyltrimethylsilane (76 µL, 0.48 mmol) was added and the resulting solution was stirred for 2 h. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column

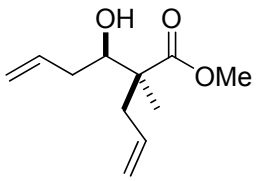
chromatography (hexane:EtOAc = 5:1) gave with $BF_3 \cdot Et_2O$ 53 mg (85%) of **440** and with $TiCl_4$ 52 mg (84%) of **441**.

Allylation with allyltributylstannane:

$TiCl_4$ (70 µL, 0.64 mmol) was added to a solution of aldehyde **439** (50 mg, 0.32 mmol) in DCM (3 mL) at -78 °C. After 15 min allyltributylstannane (76 µL, 0.48 mmol) was added and the resulting solution was stirred for 2 h. The reaction was quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 5:1) gave 55 mg (87%) of a 7:1 mixture of **441**:**440**.

$MgBr_2 \cdot Et_2O$ (248 mg, 0.96 mmol) was added to a solution of aldehyde **439** (50 mg, 0.32 mmol) in DCM (3 mL) at r.t.. After 25 min allyltributylstannane (76 µL, 0.48 mmol) was added and the resulting solution was stirred for 2 h. The reaction was quenched by the addition of 1N HCl. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 5:1) gave 64 mg (quant.) of a 2:1 mixture of **441**:**440**.

(2*S*,3*R*)-2-Allyl-3-hydroxy-2-methyl-hex-5-enoic acid methyl ester (440)



R_f = 0.71 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90-5.70 (m, 2H), 5.15-5.05 (m, 4H), 3.79 (ddd, *J* = 10.04, 4.86, 2.59 Hz, 1H), 3.69 (s, 3H), 2.59 (dd, *J* = 13.68, 7.07 Hz, 1H), 2.31 (dd, *J* = 13.76, 7.70 Hz, 1H), 2.26-2.19 (m, 1H), 2.14 (d, *J* = 5.05 Hz, 1H), 2.13-2.06 (m, 1H), 1.16 (s, 3H).

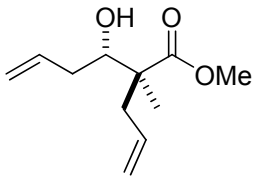
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.2, 135.4, 134.0, 118.1, 117.9, 74.6, 51.7, 50.8, 40.6, 37.2, 16.8.

IR (film): 3502, 1722, 1435, 1219, 1150 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{18}O_3$: 198.1256, found: 198.1253.

$[\alpha]_D^{20}$ -6.50 (*c* = 1.4, CH_2Cl_2)

(2*S*,3*S*)-2-Allyl-3-hydroxy-2-methyl-hex-5-enoic acid methyl ester (441)



R_f = 0.71 (hexane:EtOAc = 10:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.93-5.82 (m, 1H), 5.75-5.65 (m, 1H), 5.15-5.06 (m, 4H), 3.73 (ddd, *J* = 10.16, 6.63, 2.46 Hz, 1H), 3.70 (s, 3H), 2.49 (d, *J* = 6.57 Hz, 1H (OH)), 2.47 (dd, *J* = 14.02, 7.45 Hz, 1H), 2.36-2.30 (m, 1H), 2.29 (dd, *J* = 13.77, 7.45 Hz, 1H), 2.08-1.99 (m, 1H), 1.16 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7, 135.4, 133.2, 118.5, 117.6, 74.9, 51.8, 50.8, 40.9, 36.4, 17.1.

IR (film): 3502, 1726, 1641, 1435, 1220, 1148 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{18}O_3$: 198.1256, found: 198.1249.

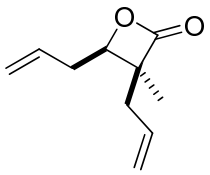
$[\alpha]_D^{20}$ -10.00 (*c* = 1.05, CH_2Cl_2)

General procedure for the conversion of 440 and 441 into the *β*-lactone:

LiOH (3 eq.) was added to the *β*-hydroxy ester (1 eq.) in THF (0.1M) at r.t. and the solution was vigorously stirred for 16 h. Brine was added and the aqueous layer acidified with 1N HCl and extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in DCM (0.1M) and EDC·HCl (1.5 eq.) and DMAP (2 eq.) were added. After 4 h brine was added and the aqueous layer was extracted

with DCM. The combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. The crude *β*-lactone was purified by column chromatography (hexane:EtOAc = 5:1).

(3*S*,4*R*)-3,4-diallyl-3-methyloxetan-2-one (442)



R_f = 0.62 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.87-5.76 (m, 2H), 5.21-5.13 (m, 4H), 4.31 (dd, *J* = 8.59, 5.56 Hz, 1H), 2.63-2.49 (m, 3H), 2.35 (dd, *J* = 14.27, 7.96 Hz, 1H), 1.40 (s, 3H).

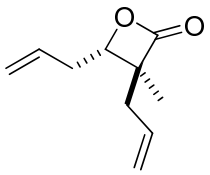
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.0, 132.0, 131.9, 119.5, 118.6, 82.2, 56.4, 34.8, 34.6, 19.9.

IR (film): 2980, 1823, 1701, 1643, 1457, 1384, 1125 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{10}H_{14}O_2$: 166.0992, found: 166.0982.

$[\alpha]_D^{20}$ 17.11 (*c* = 0.9, CH_2Cl_2)

(3*S*,4*S*)-3,4-diallyl-3-methyloxetan-2-one (443)



R_f = 0.61 (hexane:EtOAc = 5:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 5.81-5.70 (m, 2H), 5.21-5.15 (m, 4H), 4.38 (dd, *J* = 7.96, 6.19 Hz, 1H), 2.61-2.37 (m, 4H), 1.29 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.1, 131.7, 131.6, 119.9, 118.6, 79.2, 57.0, 40.1, 34.8, 14.5.

IR (film): 2982, 1824, 1645, 1454, 1125 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{10}H_{14}O_2$: 166.0992, found: 166.0988.

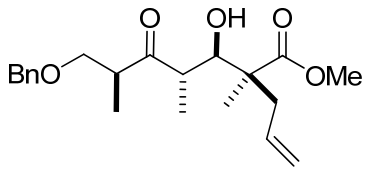
$[\alpha]_D^{20}$ -11.89 (*c* = 0.45, CH_2Cl_2)

Paterson aldol addition:

***Syn*-selective:** To (*R*)-ketone ***ent*-380** or (*S*)-ketone **380** (66 mg, 0.32 mmol) in DCM (1 mL) at -78 °C was added Bu_2BOTf (0.38 mL, 1M in DCM, 0.38 mmol) and triethylamine (60 µL, 0.42 mmol). After 10 min at -78 °C the mixture was warmed to 0 °C for 30 min and afterwards recooled to -78°C. Aldehyde **439** (50 mg, 0.32 mmol) in DCM (1 mL) was added slowly and stirring was continued for 1 h at -78 °C. The mixture was kept at 0 °C for 2 h and quenched by the addition of pH 7 buffer solution (5mL), methanol (1mL) and H_2O_2 (0.5 mL, 30% aqueous). After 1 h at r.t. the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1 to 3:1) yielded the aldol adduct.

***Anti*-selective:** To a solution of chlorodicyclohexylborane (0.38 mL, 1M in hexane, 0.38 mmol) in Et_2O (1 mL) at 0 °C was added triethylamine (60 µL, 0.42 mmol), followed by (*R*)-ketone ***ent*-380** or (*S*)- ketone **380** (66 mg, 0.32 mmol) in Et_2O (0.5 mL) and the mixture was stirred for 20 min. Then the reaction was warmed to r.t. and after 20 min recooled to -78 °C. A solution of aldehyde **439** (50 mg, 0.32 mmol) in Et_2O (1 mL) was added slowly. After the addition was completed, the reaction was kept at -78 °C for 2 h, then it was warmed to 0 °C for 15 min and pH 7 buffer solution (5 mL), methanol (1 mL) and H_2O_2 (0.5 mL, 30% aqueous) were added. After stirring for 1 h at r.t. the mixture was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 10:1 to 5:1).

(2S,3R,4S,6S)-methyl 2-allyl-7-(benzyloxy)-3-hydroxy-2,4,6-trimethyl-5-oxoheptanoate (444)

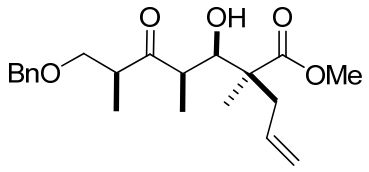


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.26 (m, 5H), 5.74-5.63 (m, 1H), 5.06-5.01 (m, 2H), 4.50 (d, *J* = 11.60 Hz, 1H), 4.45 (d, *J* = 11.88 Hz, 1H), 4.00 (dd, *J* = 7.68, 5.44 Hz, 1H), 4.79 (d, *J* = 7.56 Hz, 1H (OH)), 3.65-3.60 (m, 1H), 3.64 (s, 3H), 3.43 (dd, *J* = 9.08, 4.80 Hz, 1H), 3.08-2.99 (m, 1H), 2.80 (ddd, *J* = 14.35, 7.25, 5.49 Hz, 1H), 2.44 (dd, *J* = 13.64, 7.08 Hz, 1H), 2.33 (dd, *J* = 13.64, 7.80 Hz, 1H), 1.12 (t, *J* = 7.32 Hz, 3H), 1.08 (d, *J* = 5.04 Hz, 3H), 1.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 218.4, 175.8, 137.8, 133.7, 128.4, 127.6, 118.3, 78.1, 73.4, 71.9, 51.6, 51.1, 47.2, 46.2, 42.6, 15.4, 14.9, 13.8.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{21}H_{30}O_5Na$: 385.1991, found: 385.1987.

(2*S*,3*R*,4*R*,6*S*)-methyl 2-allyl-7-(benzyloxy)-3-hydroxy-2,4,6-trimethyl-5-oxoheptanoate (445)

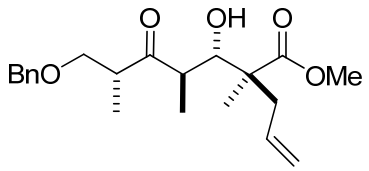


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.25 (m, 5H), 5.74-5.63 (m, 1H), 5.07-5.00 (m, 2H), 4.47 (s, 2H), 4.21 (dd, *J* = 4.54, 2.02 Hz, 1H), 3.64 (m, 1H); 3.62 (s, 3H), 3,43 (dd, *J* = 8.71, 5.43 Hz, 1H), 3.11 (m, 1H), 2.86 (ddd, *J* = 14.15, 7.07, 2.02 Hz, 1H), 2.79 (d, *J* = 4.54 Hz, 1H (OH)), 2.51 (dd, *J* = 13.64, 6.82 Hz, 1H), 2.27 (dd, *J* = 13.64, 8.08 Hz, 1H), 1.19 (s, 3H), 1.11 (d, *J* = 7.07 Hz, 3H), 1.05 (d, *J* = 7.07 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 216.7, 175.8, 137.9, 133.9, 128.5, 127.6, 118.5, 73.5, 72.9, 72.4, 65.5, 51.8, 50.9, 47.8, 44.7, 42.0, 17.4, 13.9, 10.0.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{21}H_{30}O_5Na$: 385.1991, found: 385.1995.

(2*S*,3*S*,4*R*,6*R*)-methyl 2-allyl-7-(benzyloxy)-3-hydroxy-2,4,6-trimethyl-5-oxoheptanoate (446)

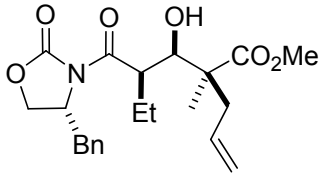


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34-7.27 (m, 5H), 5.72-5.62 (m, 1H), 5.05-5.01 (m, 2H), 4.47 (s, 2H), 3.99 (m, 1H), 3.62 (s, 3H), 3.61 (m, 1H), 3.43 (dd, *J* = 8.96, 4.92 Hz, 1H), 3.03 (m, 1H), 2.92 (ddd, *J* = 14.36, 5.67, 0.17 Hz, 1H), 2.44 (dd, *J* = 13.51, 7.20 Hz, 1H), 2.32 (dd, *J* = 13.64, 7.83 Hz, 1H), 1.11 (d, *J* = 7.32 Hz, 3H), 1.07 (d, *J* = 7.07 Hz, 3H), 1.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 218.9, 175.9, 133.8, 128.5, 127.7, 118.3, 78.6, 73.4, 72.4, 51.5, 51.0, 47.3, 46.5, 42.4, 15.4, 13.9, 13.5.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{21}H_{30}O_5Na$: 385.1991, found: 385.1997.

(2*S*,3*R*,4*R*)-2-Allyl-4-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-3-hydroxy-2-methyl-hexanoic acid methyl ester (449)



To a stirred solution of oxazolidinone **37** (79 mg, 0.32 mmol) in DCM (0.5 mL) at -78 °C was slowly added dibutylboron triflate (0.38 mL, 1M in DCM, 0.38 mmol) followed by triethylamine (60 µL, 0.42 mmol) and stirring was continued for 30 min. The reaction mixture was warmed to 0 °C for 1 h and then recooled to -78 °C. Aldehyde **439** (50 mg, 0.32 mmol) in DCM (0.5 mL) was added dropwise. After 30 min the reaction mixture was warmed to 0 °C and stirred for 2.5 h. pH 7 buffer solution (2 mL), methanol (0.5 mL) and H_2O_2 (0.5 mL, 30% aqueous) were added and the mixture was stirred for 2 h at r.t..The layers were separated and the aqueous layer was extracted with DCM.The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude aldol product was purified by column chromatography (hexane:EtOAc = 10:1 to 3:1) to yield 130 mg (quant.) of **449** as a 10:1 mixture of diastereoisomers.

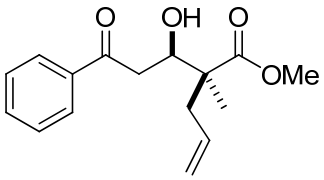
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.31 (m, 2H), 7.29-7.20 (m, 3H), 5.76-5.66 (m, 1H), 5.12-5.06 (m, 2H), 4.63 (m, 1H), 4.27 (d, *J* = 9.34 Hz, 1H (OH)), 4.19-4.11 (m, 2H), 4.01 (m, 2H), 3.69 (s, 3H), 3.47 (dd, *J* = 13.39, 3.28 Hz, 1H), 2.68 (dd, *J* = 13.26, 10.74 Hz, 1H), 2.56 (dd, *J* = 13.77, 6.69 Hz, 1H), 2.35 (dd, *J* = 13.52, 8.21 Hz, 1H), 1.83-1.71 (m, 2H), 1.16 (s, 3H), 0.97 (t, *J* = 7.32 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.8, 175.6, 153.1, 135.5, 133.5, 129.4, 129.0, 127.3, 118.5, 77.6, 66.0, 55.6, 51.9, 51.7, 43.4, 41.9, 37.6, 25.3, 16.5, 11.7.

General procedure for aldol with Li-enolates:

To methyl ketone **450** or **452** (1.1 eq) in THF (0.2M) at -78 °C was added LiHMDS (1.2 eq., 1M in hexane) and the mixture was stirred for 1 h. Aldehyde **439** (1 eq.) was added in THF (1M) and stirring was continued for 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl solution and warmed to r.t.. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

(*S*)-2-((*R*)-1-Hydroxy-3-oxo-3-phenyl-propyl)-2-methyl-pent-4-enoic acid methyl ester (451)



R_f = 0.55 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (m, 2H), 7.59 (m, 1H), 7.50-7.45 (m, 2H), 5.81-5.71 (m, 1H), 5.12-5.07 (m, 2H), 4.48 (ddd, *J* = 6.76, 4.99, 3.72 Hz, 1H), 3.68 (s, 3H), 3.32 (d, *J* = 3.53 Hz, 1H (OH)), 3.10 (m, 2H), 2.61 (dd, *J* = 13.89, 7.07 Hz, 1H), 2.40 (dd, *J* = 13.62, 7.58 Hz, 1H), 1.25 (s, 3H).

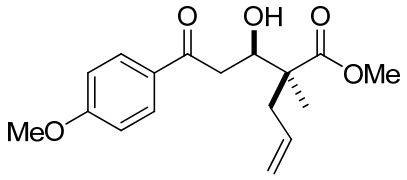
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.0, 176.0, 136.9, 133.5, 133.3, 128.7, 128.1, 118.6, 71.9, 51.9, 50.6, 40.3, 40.2, 17.3.

IR (film): 3525, 2981, 1725, 1684, 1448, 1324, 1215 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{20}O_4Na$: 299.1259, found: 299.1271.

$[\alpha]_D^{20}$ 18.67 (*c* = 0.8, CH_2Cl_2)

(*S*)-2-[(*R*)-1-hydroxy-3-(4-methoxyphenyl)-3-oxopropyl]-2-methyl-pent-4-enoic acid methyl ester (453)



R_f = 0.40 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 9.09 Hz, 2H), 6.94 (d, *J* = 8.84 Hz, 2H), 5.81-5.70 (m, 1H), 5.12-5.06 (m, 2H), 4.41 (dt, *J* = 9.09, 3.16 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.43 (d, *J* = 3.54 Hz, 1H (OH)), 3.03 (m, 2H), 2.60 (dd, *J* = 13.77, 6.95 Hz, 1H), 2.39 (dd, *J* = 13.64, 7.83 Hz, 1H), 1.34 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.1, 175.8, 163.9, 133.8, 130.5, 129.8, 118.3, 113.8, 71.1, 55.5, 51.8, 50.7, 41.0, 40.3, 16.4.

IR (film): 1729, 1671, 1601, 1263, 1225, 1170 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{17}H_{20}O_4$: 288.1362, found: 288.1355.

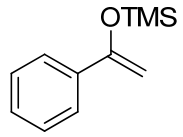
$[\alpha]_D^{20}$ 20.63 (*c* = 0.95, CH_2Cl_2)

General procedure for the preparation of TMS enol ether:

LDA was prepared by the addition of *n*BuLi (1.5 eq., 2.5M in hexane) to diisopropylamine (1.5 eq.) in THF (0.6M) at 0 °C and the solution was stirred for 15 min. Methyl ketone **450** or **452** (1 eq.) was added at -78 °C and stirring was continued for 1 h. Then TMSCl (1.3 eq.), freshly distilled from CaH_2, was added and after 30 min the cooling bath was removed and the mixture was allowed to warm to r.t.. The solvent was removed under reduced pressure and hexane was added. The white precipitate was filtered off and the solvent removed under

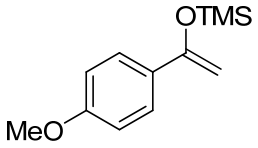
reduced pressure. The crude silyl enol ether was used in the following aldol reaction without further purification.

trimethyl(1-phenylvinyloxy)silane (454)



^{1}H-NMR (400 MHz, C_6D_6): δ = 7.68 (d, J = 7.28 Hz, 2H), 7.15-7.07 (m, 3H), 4.92 (d, J = 1.76 Hz, 1H), 4.46 (d, J = 1.52 Hz, 1H), 0.18 (s, 9H).

1-(4-methoxyphenyl)vinyloxy)trimethylsilane (456)

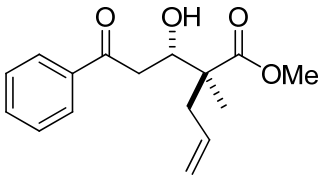


^{1}H-NMR (400 MHz, C_6D_6): δ = 7.64 (d, J = 9.01 Hz, 2H), 6.76 (d, J = 9.05 Hz, 2H), 4.87 (d, J = 1.76 Hz, 1H), 4.44 (d, J = 1.76 Hz, 1H), 3.27 (s, 3H), 0.21 (s, 9H).

General procedure for Mukaiyama aldol with TMS enol ethers:

To aldehyde **439** (1 eq.) in DCM (0.1M) at -78 °C was added $TiCl_4$ (2 eq.) and the mixture was stirred for 15 min. TMS enol ether **454** or **456** (1.5 eq) in DCM (1M) was added and stirring was continued for 1 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and warmed to r.t.. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

(*S*)-2-((*S*)-1-Hydroxy-3-oxo-3-phenyl-propyl)-2-methyl-pent-4-enoic acid methyl ester (455)



R_f = 0.53 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (m, 2H), 7.59 (m, 1H), 7.47 (t, *J* = 7.70 Hz, 2H), 5.81-5.70 (m, 1H), 5.13-5.08 (m, 2H), 4.44 (dd, *J* = 8.08, 4.04 Hz, 1H), 3.74 (s, 3H), 3.11 (m, 2H), 2.52 (dd, *J* = 13.64, 7.32 Hz, 1H), 2.30 (dd, *J* = 13.64, 7.58 Hz, 1H), 1.24 (s, 3H).

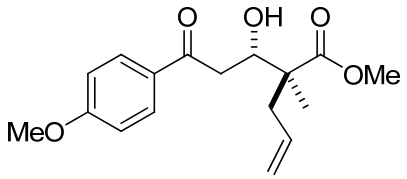
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.6, 175.7, 136.7, 133.7, 133.5, 128.7, 128.2, 118.3, 70.9, 51.8, 50.6, 41.0, 40.8, 16.4.

IR (film): 3503, 29481, 1734, 1684, 1597, 1449, 1221 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.13531.

$[\alpha]_D^{20}$ -20.89 (*c* = 1.12, CH_2Cl_2)

(*S*)-2-[(*S*)-1-hydroxy-3-(4-methoxyphenyl)-3-oxopropyl]-2- methyl-pent-4-enoic acid methyl ester (457)



R_f = 0.41 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.09 Hz, 2H), 6.94 (d, *J* = 8.84 Hz, 2H), 5.81-5.70 (m, 1H), 5.13-5.08 (m, 2H), 4.41 (ddd, *J* = 9.34, 4.55, 2.53 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.35 (d, *J* = 4.80 Hz, 1H (OH)), 3.10 (dd, *J* = 16.92, 2.78 Hz, 1H), 3.02 (dd, *J* = 16.92, 9.35 Hz, 1H), 2.51 (dd, *J* = 13.39, 7.07 Hz, 1H), 2.28 (dd, *J* = 13.64, 7.58 Hz, 1H), 1.23 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.5, 176.0, 163.9, 133.4, 130.5, 130.0, 118.5, 113.8, 72.1, 55.5, 51.9, 50.6, 40.3, 39.6, 17.3.

IR (film): 1734, 1671, 1601, 1512, 1261, 1225, 1172 cm^{-1}.

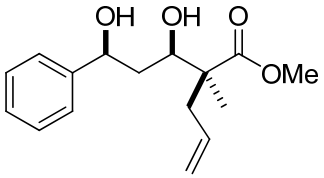
HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{17}H_{22}O_5$: 306.1467, found: 306.1457.

$[\alpha]_D^{20}$ -21.92 (*c* = 1.12, CH_2Cl_2)

General procedure for the *syn*-reduction with catecholborane:

To *β*-hydroxy ketone (1 eq.) in THF (0.1M) at -15 °C was slowly added catecholeborane (5 eq.) and the mixture was stirred for 3 h. The reaction was quenched by the addition of methanol warmed to r.t. and the mixture was stirred with a saturated potassium sodium tartrate solution for 2 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

(*S*)-2-((1*R*,3*S*)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (458)



R_f = 0.18 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 4H), 7.31-7.26 (m, 1H), 5.81-5.71 (m, 1H), 5.08-5.02 (m, 2H), 4.94 (ddd, *J* = 9.74, 2.89, 1.37 Hz, 1H), 4.09 (ddd, *J* = 10.23, 3.54, 1.89 Hz, 1H), 3.67 (s, 3H), 3.61 (d, *J* = 3.79 Hz, 1H (OH)), 3.37 (d, *J* = 1.77 Hz, 1H (OH)), 2.54 (dd, *J* = 13.89, 7.07 Hz, 1H), 2.28 (dd, *J* = 13.89, 7.83 Hz, 1H), 1.85 (dt, *J* = 14.40, 9.98 Hz, 1H), 1.73 (ddd, *J* = 14.40, 2.91, 1.89 Hz,1H), 1.15 (s, 3H).

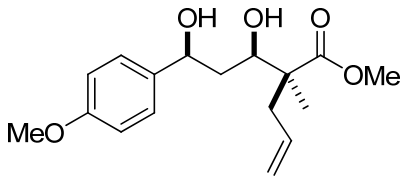
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.4, 144.2, 133.9, 128.5, 127.7, 125.7, 118.2, 76.2, 75.3, 51.9, 50.8, 40.8, 39.9, 17.4.

IR (film): 3435, 2951, 1719, 1455, 1222, 1061 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$: 301.1416, found: 301.1421.

$[\alpha]_D^{20}$ -6.96 (*c* = 1.15, CH_2Cl_2)

(*S*)-2-((1*R*,3*S*)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (460)



R_f = 0.13 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 5.80-5.70 (m, 1H), 5.08-5.02 (m, 2H), 4.87 (dd, *J* = 9.60, 3.03 Hz, 1H), 4.05 (d, *J* = 10.36 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.53 (dd, *J* = 13.89, 6.82 Hz, 1H), 2.27 (dd, *J* = 13.77, 7.96 Hz, 1H), 1.84 (dt, *J* = 14.40, 10.10 Hz, 1H), 1.68 (ddd, *J* = 14.33, 3.09, 1.70 Hz, 1H), 1.15 (s, 3H).

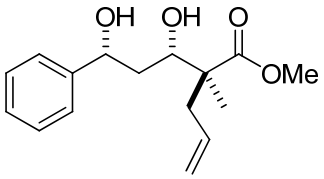
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.4, 159.2, 136.4, 133.9, 127.0, 118.2, 113.9, 76.1, 74.9, 55.3, 51.8, 50.8, 40.6, 40.0, 17.2.

IR (film): 3435, 1722, 1612, 1514, 1247, 1034 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$: 331.1521, found: 331.1526.

$[\alpha]_D^{20}$ -8.00 (*c* = 0.65, CH_2Cl_2)

(*S*)-2-((1*S*,3*R*)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (462)



R_f = 0.15 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.33 (m, 4H), 7.28 (m, 1H), 5.70-5.60 (m, 1H), 5.09-5.03 (m, 2H), 4.94 (dd, *J* = 9.34, 2.27 Hz, 1H), 4.07 (ddd, *J* = 10.42, 5.24, 2.21 Hz, 1H), 3.79 (d, *J* = 1.26 Hz, 1H (OH)), 3.72 (s, 3H), 3.62 (d, *J* = 5.30 Hz, 1H (OH)), 2.36 (dd, *J* = 13.96, 7.65 Hz, 1H), 2.30 (dd, *J* = 13.89, 7.33 Hz, 1H), 1.85-1.70 (m, 2H), 1.15 (s, 3H).

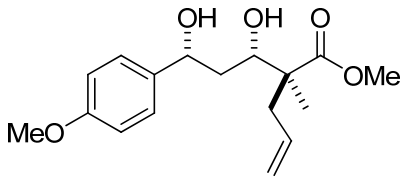
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 144.3, 132.9, 128.5, 127.6, 125.8, 118.6, 76.0, 75.1, 52.0, 50.8, 40.8, 39.8, 17.2.

IR (film):1725, 1455, 1435, 1277, 1222, 1150, 1061 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$: 301.1416, found: 301.1424.

$[\alpha]_D^{20}$ 3.56 (*c* = 0.9, CH_2Cl_2)

(*S*)-2-((1*S*,3*R*)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (464)



R_f = 0.06 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.59 Hz, 2H), 6.89 (d, *J* = 8.84 Hz, 2H), 5.70-5.60 (m, 1H), 5.08-5.02 (m, 2H), 4.89 (dd, *J* = 8.71, 3.91 Hz, 1H), 4.02 (ddd, *J* = 9.73, 5.05, 2.90 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.62 (d, *J* = 1.26 Hz, 1H (OH)), 3.60 (d, *J* = 5.05 Hz, 1H (OH)), 2.36 (dd, *J* = 13.76, 7.45 Hz, 1H), 2.28 (dd, *J* = 13.76, 7.20 Hz, 1H), 1.81-1.69 (m, 2H), 1.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 159.0, 136.6, 133.0, 127.0, 118.6, 113.9, 75.9, 74.6, 55.3, 52.0, 50.8, 40.7, 39.8, 17.2.

IR (film): 3435, 1719, 1513, 1302, 1247, 1175 cm^{-1}.

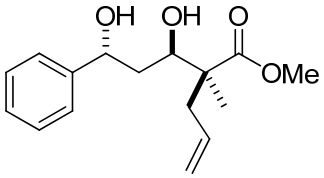
HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$: 331.1521, found: 331.1526.

$[\alpha]_D^{20}$ 3.12 (*c* = 0.8, CH_2Cl_2)

General procedure for *anti*-selective Evans-Carreira reduction:

To a solution of tetramethylammonium triacetoxyboron hydride (8 eq.) in acetonitrile:acetic acid (1:1, 1M) at -30 °C was slowly added a solution of *β*-hydroxy ketone (1 eq.) in acetonitrile (0.15M). After stirring for 9 h a saturated solution of $NaHCO_3$ and solid $NaHCO_3$ was added very carefully till gas evolution ceased. The aqueous layer was extracted with DCM, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Crude dihydroxy ester was purified by column chromatography.

(*S*)-2-((1*R*,3*R*)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (466)



R_f = 0.14 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.35 (m, 4H), 7.29-7.25 (m, 1H), 5.77-5.67 (m, 1H), 5.07-5.01 (m, 3H), 3.99 (d, *J* = 9.85 Hz, 1H), 3.63 (s, 3H), 2.49 (dd, *J* = 13.77, 7.20 Hz, 1H), 2.23 (dd, *J* = 13.89, 7.58 Hz, 1H), 1.87 (ddd, *J* = 14.18, 3.48, 0.08 Hz, 1H), 1.79 (ddd, *J* = 14.34, 7.78, 2.21 Hz, 1H), 1.14 (s, 3H).

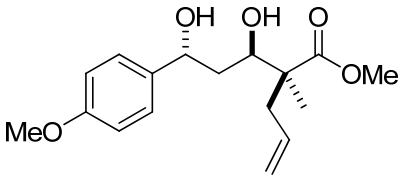
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.6, 144.4, 133.8, 128.4, 127.3, 125.5, 118.2, 72.4, 71.4, 51.8, 50.6, 40.3, 39.8, 17.6.

IR (film): 3435, 1718, 1701, 1222, 1056 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$: 301.1416, found: 301.1414.

$[\alpha]_D^{20}$ 14.06 (*c* = 1.55, CH_2Cl_2)

(*S*)-2-((1*R*,3*R*)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (468)



R_f = 0.09 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.84 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.79-5.68 (m, 1H), 5.08-4.99 (m, 2H), 4.87 (dd, *J* = 9.46, 5.44 Hz, 1H), 4.05 (d, *J* = 3.17 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 2.87 (d, *J* = 5.30 Hz, 1H (OH)), 2.60 (d, *J* = 5.05 Hz, 1H (OH)), 2.49 (dd, *J* = 14.02, 6.94 Hz, 1H), 2.24 (dd, *J* = 13.89, 7.83 Hz, 1H), 1.84-1.78 (m, 2H), 1.15 (s, 3H).

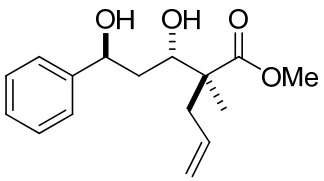
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.6, 158.9, 136.6, 133.9, 126.7, 118.2, 113.8, 72.5, 71.1, 55.3, 51.9, 50.6, 40.3, 39.8, 17.7.

IR (film): 3435, 2952, 1724, 1513, 1302, 1248, 1176, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$: 331.1521, found: 331.1517.

$[\alpha]_D^{20}$ 8.33 (*c* = 0.9, CH_2Cl_2)

(*S*)-2-((1*S*,3*S*)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (470)



R_f = 0.13 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.33 (m, 4H), 7.28-7.24 (m, 1H), 5.67-5.56 (m, 1H), 5.09 (dd, *J* = 8.21, 2.90 Hz, 1H), 5.06-5.00 (m, 2H), 3.98 (d, *J* = 10.86 Hz, 1H), 3.68 (s, 3H), 2.40 (dd, *J* = 13.64, 7.33 Hz, 1H), 2.29 (dd, *J* = 13.89, 7.58 Hz, 1H), 1.89 (ddd, *J* = 14.14, 8.08, 2.02 Hz, 1H), 1.73 (ddd, *J* = 14.08, 10.92, 3.09 Hz,1H), 1.13 (s, 3H).

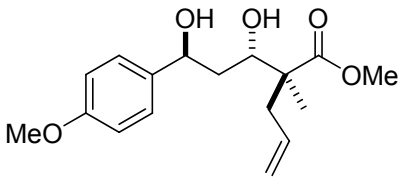
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.2, 144.6, 132.9, 128.4, 127.3, 125.5, 118.6, 72.0, 71.3, 51.9, 50.7, 40.9, 39.8, 17.4.

IR (film): 3435, 1722, 1455, 1222, 1056 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$: 301.1416, found: 301.1425.

$[\alpha]_D^{20}$ -23.20 (*c* = 0.75, CH_2Cl_2)

(*S*)-2-((1*S*,3*S*)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (472)



R_f = 0.06 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.84 Hz, 2H), 5.69-5.59 (m, 1H), 5.07-5.01 (m, 3H), 3.98 (dd, *J* = 9.47, 6.95 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.01 (d, *J* = 6.72 Hz, 1H (OH)), 2.67 (d, *J* = 3.78 Hz, 1H (OH)), 2.41 (dd, *J* = 13.64, 7.33 Hz, 1H), 2.28 (dd, *J* = 13.64, 7.58 Hz, 1H), 1.87 (ddd, *J* = 14.15, 8.21, 1.89 Hz, 1H), 1.69 (ddd, *J* = 14.15, 11.11, 3.03 Hz, 1H), 1.13 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.1, 159.2, 136.8, 133.0, 126.7, 118.6, 113.9, 72.2, 70.8, 55.3, 51.9, 50.7, 40.9, 39.9, 17.4.

IR (film): 3435, 1718, 1513, 1302, 1248, 1176, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$: 331.1521, found: 331.1526.

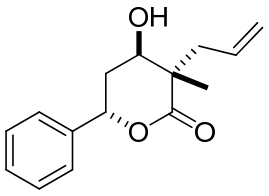
$[\alpha]_D^{20}$ -18.53 (*c* = 0.95, CH_2Cl_2)

General procedure for saponification followed by lactonisation:

LiOH (3 eq.) was added to the dihydroxy ester (1 eq.) in THF (0.1M) at 0 °C and vigorously stirred for 3 h. Brine was added and the layers were separated. The aqueous layer was acidified with 1N HCl and extracted with DCM. The combined organic layer was dried over

$MgSO_4$ and the solvent was evaporated. The residue was dissolved in DCM (0.1M) and EDC·HCl (1.5 eq.) and DMAP (2 eq.) were added. After 2 h, brine was added and the aqueous layer was extracted with DCM, the combined DCM phase was dried over $MgSO_4$ and the solvent was evaporated. The crude lactone was purified by column chromatography.

(3*S*,4*R*,6*S*)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (459)



R_f = 0.58 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.30 (m, 5H), 5.85-5.76 (m, 1H), 5.75 (dd, *J* = 10.19, 4.38 Hz, 1H), 5.16-5.09 (m, 2H), 4.01 (dd, *J* = 5.05, 2.52 Hz, 1H), 2.47 (d, *J* = 7.32 Hz, 2H), 2.32 (ddd, *J* = 14.40, 10.10, 2.52 Hz, 1H), 2.22 (dd, *J* = 14.40, 4.80 Hz, 1H), 1.39 (s, 3H).

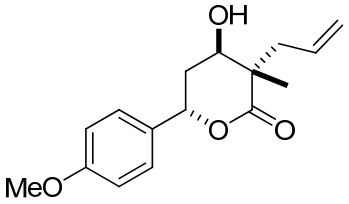
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.9, 140.0, 132.4, 128.6, 128.2, 125.6, 119.4, 77.4, 69.4, 47.1, 42.9, 34.9, 19.3.

IR (film): 3435, 2980, 1707, 1142 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1154.

$[\alpha]_D^{20}$ -2.00 (*c* = 0.6, CH_2Cl_2)

(3*S*,4*R*,6*S*)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (461)



R_f = 0.46 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.34 Hz, 2H), 6.91 (d, *J* = 8.84 Hz, 2H), 5.85-5.75 (m, 1H), 5.77 (dd, *J* = 10.36, 4.04 Hz, 2H), 5.17-5.10 (m, 2H), 4.02 (m, 1H), 3.81 (s, 3H), 2.47 (d, *J* = 7.33 Hz, 2H), 2.33 (ddd, *J* = 14.03, 2.62, 0.10 Hz, 1H), 2.18 (ddd, *J* = 14.40, 4.29, 0.01 Hz, 1H), 1.39 (s, 3H).

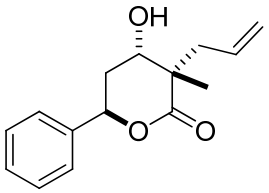
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.9, 159.5, 134.1, 132.4, 127.1, 119.4, 114.0, 77.2, 69.6, 55.3, 46.9, 43.0, 34.8, 19.3.

IR (film): 3435, 1706, 1517, 1253, 1176, 1141 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1368.

$[\alpha]_D$ -1.50 (*c* = 1.2, CH_2Cl_2)

(3*S*,4*S*,6*R*)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (463)



R_f = 0.32 (hexane:EtOAc = 2:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.39-7.31 (m, 5H), 6.03-5.96 (m, 1H), 5.76 (dd, *J* = 11.89, 3.96 Hz, 1H), 5.32-5.22 (m, 2H), 4.01 (m, 1H), 2.76 (dd, *J* = 14.54, 8.12 Hz, 1H), 2.60 (dd, *J* = 14.54, 6.99 Hz, 1H), 2.35 (dd, *J* = 3.21, 1.32 Hz, 1H (OH)), 2.25 (m, 1H), 2.18 (dt, *J* = 14.54, 4.06 Hz, 1H), 1.37 (s, 3H).

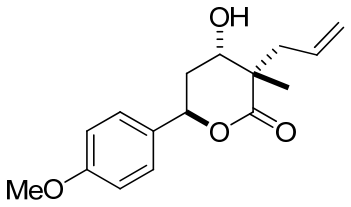
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 175.9, 140.2, 134.0, 128.7, 128.3, 125.7, 119.3, 77.4, 70.6, 45.9, 39.5, 34.9, 24.0.

IR (film): 3435, 1701, 1233, 1182, 1091 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1145.

$[\alpha]_D^{20}$ 16.92 (*c* = 0.65, CH_2Cl_2)

(3*S*,4*S*,6*R*)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (465)



R_f = 0.35 (hexane:EtOAc = 2:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.31 Hz, 2H), 6.90 (d, *J* = 9.06 Hz, 2H), 6.03-5.96 (m, 1H), 5.71 (dd, *J* = 11.89, 3.59 Hz, 1H), 5.32-5.21 (m, 2H), 4.01 (m, 1H), 3.81 (s, 3H), 2.75 (dd, *J* = 14.54, 8.12 Hz, 1H), 2.65 (dd, *J* = 14.35, 6.80 Hz, 1H), 2.33 (dd, *J* = 3.21, 1.32 Hz, 1H (OH)), 2.26 (m, 1H), 2.14 (dt, *J* = 14.54, 3.87 Hz, 1H), 1.37 (s, 3H)

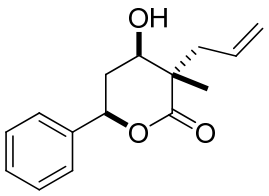
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 176.1, 158.1, 134.1, 130.8, 127.4, 119.2, 114.1, 77.2, 70.6, 55.3, 45.8, 39.4, 34.8, 24.0.

IR (film): 3435, 1705, 1613, 1516, 1250, 1175, 1112, 1085, 1033 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1350.

$[\alpha]_D^{20}$ 10.86 (*c* = 1.4, CH_2Cl_2)

(3*S*,4*R*,6*R*)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (467)



R_f = 0.35 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.32 (m, 5H), 5.91-5.85 (m, 2H), 5.24-5.19 (m, 2H), 4.29 (dd, *J* = 11.49, 4.48 Hz, 1H), 2.75 (dd, *J* = 13.89, 6.06 Hz, 2H), 2.47 (dd, *J* = 13.77, 8.71 Hz, 1H), 2.26 (dt, *J* = 13.64, 4.04 Hz, 1H), 2.17 (dt, *J* = 13.63, 11.62 Hz, 1H), 1.39 (s, 3H).

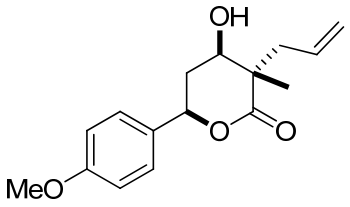
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.6, 139.2, 134.0, 128.7, 128.5, 125.7, 119.4, 77.9, 67.6, 48.7, 40.8, 36.4, 19.6.

IR (film): 3435, 1707, 1235, 1146, 1084, 1051 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1151.

$[\alpha]_D^{20}$ 18.42 (*c* = 1.2, CH_2Cl_2)

(3*S*,4*R*,6*R*)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (469)



R_f = 0.45 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.26 (d, *J* = 7.83 Hz, 2H), 6.90 (d, *J* = 8.59 Hz, 2H), 5.91-5.79 (m, 1H), 5.70 (dd, *J* = 10.48, 4.17 Hz, 1H), 5.24-5.15 (m, 2H), 4.28 (dt, *J* = 10.48, 5.24 Hz, 1H), 3.81 (s, 3H), 2.75 (dd, *J* = 13.77, 5.94 Hz, 1H), 2.47 (dd, *J* = 14.40, 8.08 Hz, 1H), 2.22 (d, *J* = 9.34 Hz, 2H), 1.37 (s, 3H).

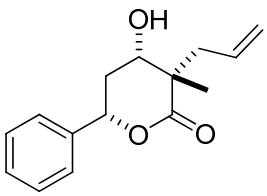
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 176.7, 159.6, 134.2, 131.2, 127.3, 119.4, 114.1, 77.7, 68.0, 55.4, 48.6, 40.8, 36.2, 19.6.

IR (film): 3435, 1707, 1613, 1516, 1238, 1176, 1145, 1081, 1033 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1358.

$[\alpha]_D^{20}$ 10.61 (*c* = 1.65, CH_2Cl_2)

(3*S*,4*S*,6*S*)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (471)



R_f = 0.29 (hexane:EtOAc = 2:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.40-7.32 (m, 5H), 5.97-5.89 (m, 1H), 5.30 (dd, *J* = 9.82, 5.66 Hz, 1H), 5.20-5.15 (m, 2H), 4.12 (ddd, *J* = 9.35, 5.76, 5.19 Hz, 1H), 2.60-2.54 (m, 2H), 2.33 (m, 2H), 1.93 (d, *J* = 5.29 Hz, 1H (OH)), 1.42 (s, 3H).

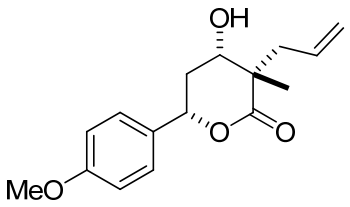
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 174.9, 139.6, 134.0, 128.7, 128.5, 125.7, 118.7, 77.9, 72.7, 38.2, 36.8, 21.7.

IR (film): 3435, 1734, 1718, 1701, 1227, 1124, 1069 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.11435.

$[\alpha]_D^{20}$ -3.28 (*c* = 1.25, CH_2Cl_2)

(3*S*,4*S*,6*S*)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (473)



R_f = 0.37 (hexane:EtOAc = 2:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 9.06 Hz, 2H), 6.90 (d, *J* = 8.69 Hz, 2H), 5.96-5.89 (m, 1H), 5.25 (dd, *J* = 10.95, 4.53 Hz, 1H), 5.20-5.15 (m, 2H), 4.10 (dt, *J* = 10.20, 5.09 Hz, 1H), 3.81 (s, 3H), 2.58-2.54 (m, 2H), 2.33 (dd, *J* = 13.97, 10.76 Hz, 1H), 2.28 (dd, *J* = 13.97, 4.72 Hz, 1H), 1.93 (d, *J* = 5.29 Hz, 1H), 1.41 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 175.1, 159.7, 134.1, 131.5, 127.4, 118.6, 114.0, 77.7, 72.7, 55.4, 48.0, 38.3, 36.6, 21.7.

IR (film): 3435, 2935, 1718, 1613, 1517, 1250, 1125, 1072 cm^{-1}.

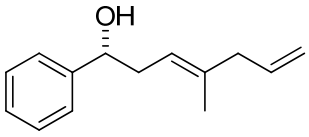
HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1351.

$[\alpha]_D^{20}$ 2.59 (*c* = 0.85, CH_2Cl_2)

General procedure for the fragmentation:

To *β*-hydroxy lactone (1 eq.) in Et_2O:triethylamine (10:1, 0.1M) at 0 °C under argon was added MsCl (1.5 eq.). After 1.5 h brine was added and the aqueous layer was extracted with Et_2O. The combined ethereal layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was taken up in THF (0.1M) and LiOH (3 eq., 1M in water) was added at 0 °C. After TLC showed complete consumption of the starting material, normally 1 to 2 h, a saturated NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography furnished the olefin and the *β*-lactone, respectively.

(*R*,*E*)-4-methyl-1-phenylhepta-3,6-dien-1-ol (474)



R_f = 0.68 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.34 (m, 4H), 7.28 (m, 1H), 5.80-5.73 (m, 1H), 5.23 (t, *J* = 6.70 Hz, 1H), 5.02 (m, 2H), 4.70 (t, *J* = 5.81 Hz, 1H), 2.74 (d, *J* = 6.80 Hz, 2H), 2.52 (dd, *J* = 14.52, 7.70 Hz, 1H), 2.45 (dt, *J* = 14.15, 7.07 Hz, 1H), 1.97 (s, 1H (OH)), 1.56 (s, 3H).

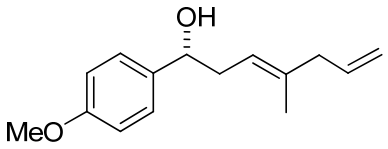
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 144.3, 137.7, 136.6, 128.4, 127.4, 125.8, 120.6, 115.9, 74.1, 44.2, 38.2, 16.3.

IR (film): 3391, 2913, 1635, 1453, 1045 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{14}H_{16}$: 184.1252, found: 184.1246.

$[\alpha]_D^{20}$ 11.00 (*c* = 0.7, CH_2Cl_2)

(*R*,*E*)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (475)



R_f = 0.59 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.81-5.71 (m, 1H), 5.21 (t, *J* = 7.45 Hz, 1H), 5.04-4.99 (m, 2H), 4.65 (ddd, *J* = 7.80, 5.20, 2.50 Hz, 1H), 3.81 (s, 3H), 2.73 (d, *J* = 6.57 Hz, 2H), 2.51 (dt, *J* = 15.03, 7.15 Hz, 1H), 2.41 (dt, *J* = 13.26, 6.03 Hz, 1H), 1.59 (s, 3H).

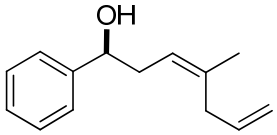
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 136.6, 136.4, 127.0, 120.8, 115.8, 113.8, 73.7, 55.3, 44.2, 38.1, 16.3.

IR (film): 2913, 1611, 1512, 1246, 1174, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{18}O$: 214.1358, found: 214.1360.

$[\alpha]_D^{20}$ 5.20 (*c* = 0.5, CH_2Cl_2)

(*S*,*Z*)-4-methyl-1-phenylhepta-3,6-dien-1-ol (476)



R_f = 0.55 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.33 (m, 4H), 7.28 (m, 1H), 5.75-5.65 (m, 1H), 5.27 (t, *J* = 6.82 Hz, 1H), 5.06-4.98 (m, 2H), 4.69 (ddd, *J* = 7.96, 5,05, 2.90 Hz, 1H), 2.82-2.73 (m, 2H), 2.55-2.40 (m, 2H), 1.97 (d, *J* = 3.03 Hz, 1H (OH)), 1.72 (s, 3H).

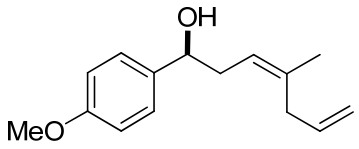
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.2, 137.1, 135.7, 128.4, 127.4, 125.8, 121.2, 115.4, 74.1, 38.1, 36.6, 23.6.

IR (film): 3391, 2914, 1636, 1453, 1048 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{14}H_{16}$: 184.1252, found: 184.1249.

$[\alpha]_D^{20}$ -19.64 (*c* = 1.1, CH_2Cl_2)

(*S*,*Z*)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (477)



R_f = 0.40 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.28 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.76-5.66 (m, 1H), 5.24 (t, *J* = 7.32 Hz, 1H), 5.06-4.98 (m, 2H), 4.64 (t, *J* = 5.94 Hz, 1H), 3.81 (s, 3H), 2.82-2.72 (m, 2H), 2.55-2.47 (m, 1H), 2.44-2.37 (m, 1H), 1.91 (d, *J* = 2.27 Hz, 1H (OH)), 1.71 (s, 3H).

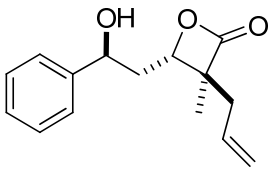
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.0, 136.8, 136.4, 135.7, 127.0, 121.3, 115.4, 113.8, 73.7, 55.3, 37.9, 36.5, 23.6.

IR (film): 2913, 1612, 1513, 1247, 1174, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{18}O$: 214.1358, found: 214.1351.

$[\alpha]_D$ -16.67 (*c* = 1.05, CH_2Cl_2)

(3*S*,4*S*)-3-allyl-4-((S)-2-hydroxy-2-phenylethyl)-3-methyloxetan-2-one (478)



R_f = 0.43 (hexane:EtOAc = 2:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.37 (m, 4H), 7.32 (m, 1H), 5.85-5.75 (m, 1H), 5.23-5.17 (m, 2H), 4.91 (dt, *J* = 8.21, 4.10 Hz, 1H), 4.77 (dd, *J* = 7.20, 5.94 Hz, 1H), 2,51 (dd, *J* = 14.02, 6.94 Hz, 1H), 2.42 (dd, *J* = 14.02, 7.71 Hz, 1H), 2.04 (m, 2H + 1H (OH)), 1.24 (s, 3H).

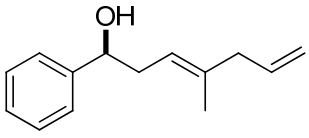
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.3, 144.0, 131.6, 128.8, 128.0, 125.5, 120.0, 77.5, 70.5, 56.9, 40.0, 39.9, 14.8.

IR (film): 3432, 1818, 1457 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{15}H_{18}O_3$: 246.1256, found: 246.1251.

$[\alpha]_D^{20}$ -28.00 (*c* = 0.45, CH_2Cl_2)

(*S*,*E*)-4-methyl-1-phenylhepta-3,6-dien-1-ol (479)



R_f = 0.67 (hexane:EtOAc = 2:1)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.34 (m, 4H), 7.28 (m, 1H), 5.80-5.73 (m, 1H), 5.23 (tdd, *J* = 7.36, 0.38, 1.38 Hz, 1H), 5.02 (m, 2H), 4.70 (ddd, *J* = 8.12, 5.09, 3.02 Hz, 1H), 2.74 (d, *J* = 6.80 Hz, 2H), 2.52 (dt, *J* = 15.11, 7.55 Hz, 1H), 2.45 (dt, *J* = 13.22, 6.61 Hz, 1H), 1.97 (d, *J* = 3.02 Hz, 1H (OH)), 1.56 (s, 3H).

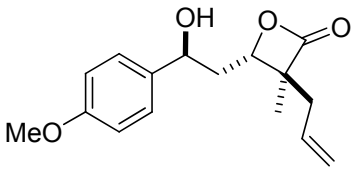
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 144.3, 137.7, 136.6, 128.4, 127.4, 125.8, 120.6, 115.9, 74.1, 44.2, 38.2, 16.3.

IR (film): 3400, 1634, 1454 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{14}H_{16}$: 184.1252, found: 184.1254.

$[\alpha]_D^{20}$ -7.33 (*c* = 0.15, CH_2Cl_2)

(3*S*,4*S*)-3-allyl-4-((*S*)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methyloxetan-2-one (480)



R_f = 0.65 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.59 Hz, 2H), 6.90 (d, *J* = 8.59 Hz, 2H), 5.85-5.75 (m, 1H), 5.22-5.17 (m, 2H), 4.86 (td, *J* = 9.09, 3.41 Hz, 1H), 4.74 (dd, *J* = 9.09, 4.04 Hz,

1H), 3.81 (s, 3H), 2.51 (dd, *J* = 14.02, 6.95 Hz, 1H), 2.42 (dd, *J* = 14.04, 7.70 Hz, 1H), 2.04-1.98 (m, 2H), 1.59 (s, 3H).

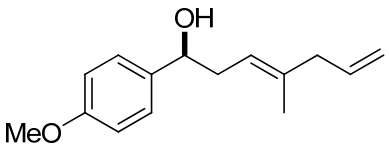
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.4, 159.5, 136.0, 131.7, 126.7, 119.9, 114.2, 77.6, 70.1, 56.9, 55.3, 40.0, 14.9.

IR (film): 3436, 2929, 1814, 1611, 1512, 1246, 1173 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1371.

$[\alpha]_D^{20}$ -28.55 (*c* = 0.55, CH_2Cl_2)

(*S*,*E*)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (481)



R_f = 0.73 (hexane:EtOAc = 1:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.28 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.81-5.71 (m, 1H), 5.21 (ddd, *J* = 7,31, 2.18, 1.35 Hz, 1H), 5.04-4.99 (m, 2H), 4.65 (ddd, *J* = 7.80, 5.20, 2.50 Hz, 1H), 3.81 (s, 3H), 2.73 (d, *J* = 6.57 Hz, 2H), 2.51 (dt, *J* = 14.90, 7.45 Hz, 1H), 2.41 (dt, *J* = 13.51, 6.12 Hz, 1H), 1.59 (s, 3H).

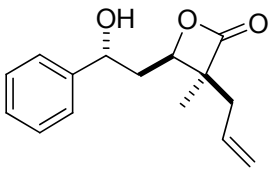
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 159.0, 136.6, 136.4, 127.0, 120.8, 115.8, 113.8, 73.7, 55.3, 44.2, 38.1, 16.3.

IR (film): 2918, 1611, 1512, 1246, 1036 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{18}O$: 214.1358, found: 214.1355.

$[\alpha]_D^{20}$ -7.00 (*c* = 0.3, CH_2Cl_2)

(3*S*,4*R*)-3-allyl-4-((*R*)-2-hydroxy-2-phenylethyl)-3-methyloxetan-2-one (482)



R_f = 0.31 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.41-7.36 (m, 4H), 7.32 (m, 1H), 5.83-5.73 (m, 1H), 5.17-5.09 (m, 2H), 4.94 (td, *J* = 9.85, 3.03 Hz, 1H), 4.69 (dd, *J* = 9.98, 3.12 Hz, 1H), 2.50 (tdd, *J* = 14.36, 6.61, 1.37 Hz, 1H), 2.32 (dd, *J* = 14.27, 7.71 Hz, 1H), 2.15 (ddd, *J* = 14.59, 9.91, 3.35 Hz, 1H), 2.10-2.03 (m, 1H + 1H (OH)), 1.42 (s, 3H).

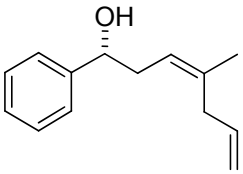
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.3, 144.0, 131.9, 128.8, 128.1, 125.5, 119.4, 80.3, 70.5, 56.1, 39.7, 34.9, 19.8.

IR (film): 3435, 1815, 1454, 1111 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1145.

$[\alpha]_D^{20}$ 48.00 (*c* = 0.25, CH_2Cl_2)

(*R*,*Z*)-4-methyl-1-phenylhepta-3,6-dien-1-ol (483)



R_f = 0.60 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.38-7.33 (m, 4H), 7.28 (m, 1H), 5.75-5.65 (m, 1H), 5.27 (t, *J* = 7.70 Hz, 1H), 5.06-4.98 (m, 2H), 4.69 (dd, *J* = 8.08, 5.30 Hz, 1H), 2.82-2.73 (m, 2H), 2.55-2.40 (m, 2H), 1.72 (s, 3H).

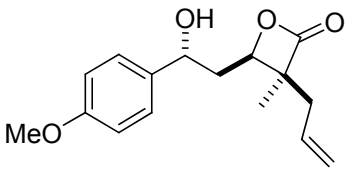
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 144.2, 137.1, 135.7, 128.4, 127.4, 125.8, 121.2, 115.4, 74.1, 38.1, 36.6, 23.6.

IR (film): 3390, 1634, 1449, 1045 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{14}H_{16}$: 184.1252, found: 184.1250.

$[\alpha]_D^{20}$ 20.00 (*c* = 0.45, CH_2Cl_2)

(3*S*,4*R*)-3-allyl-4-((*R*)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methyloxetan-2-one (484)



R_f = 0.24 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* = 7.29 (d, *J* = 8.34 Hz, 2H), 6.91 (d, *J* = 8.84 Hz, 2H), 5.84-5.73 (m, 1H), 5.17-5.10 (m, 2H), 4.87 (dd, *J* = 10.10, 2.02 Hz, 1H), 4.67 (dd, *J* = 10.10, 3.03 Hz, 1H), 3.81 (s, 3H), 2.50 (tdd, *J* = 14.40, 6.40, 1.39 Hz, 1H), 2.32 (dd, *J* = 14.40, 7.83 Hz, 1H), 2.14 (ddd, *J* = 14.53, 10.10, 3.16 Hz, 1H), 2.03 (ddd, *J* = 14.74, 9.89, 3.19 Hz, 1H), 1.42 (s, 3H).

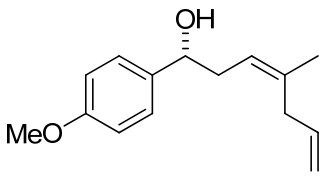
^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 174.3, 159.4, 136.1, 131.9, 126.8, 119.4, 114.1, 80.4, 70.1, 56.1, 55.3, 39.7, 34.9, 19.8.

IR (film): 2917, 1811, 1610, 1510, 1244, 1172, 1031 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362, found: 276.1358.

$[\alpha]_D^{20}$ 35.50 (*c* = 0.2, CH_2Cl_2)

(*R*,*Z*)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (485)



R_f = 0.50 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 5.76-5.66 (m, 1H), 5.24 (t, *J* = 7.20 Hz, 1H), 5.06-4.98 (m, 2H), 4.64 (t, *J* = 6.56 Hz, 1H), 3.81 (s, 3H), 2.82-2.72 (m, 2H), 2.55-2.47 (m, 1H), 2.44-2.37 (m, 1H), 1.71 (s, 3H).

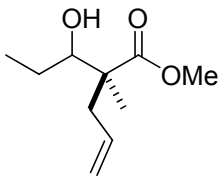
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 136.8, 136.4, 135.7, 127.0, 121.3, 115.4, 113.8, 73.7, 55.3, 37.9, 36.5, 23.6.

IR (film): 3392, 2929, 1612, 1512, 1247, 1173, 1037 cm^{-1}.

HRMS (ESI) (m/z): $[M-H_2O]^+$ calcd for $C_{15}H_{18}O$: 214.1358, found: 214.1352.

$[\alpha]_D^{20}$ 16.66 (*c* = 0.3, CH_2Cl_2)

(2*S*)-2-(1-Hydroxy-propyl)-2-methyl-pent-4-enoic acid methyl ester (487)



To aldehyde **439** (425 mg, 2.70 mmol) in Et_2O (30 mL) at 0 °C was slowly added EtMgBr (0.95 mL, 3M in Et_2O, 2.83 mmol). After 1 h brine was added and the mixture was acidified with 5% H_2SO_4. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and the solvent was carefully evaporated. Purification by column chromatography (hexane:EtOAc = 10:1 to 3:1) yielded 355 mg (71%) of alcohol **487** as 4:1 mixture of diastereoisomers.

R_f = 0.65 (hexane:EtOAc = 3:1)

Major: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.75-5.65 (m, 1H), 5.09-5.04 (m, 2H), 3.70 (s, 3H), 3.51 (ddd, *J* = 10.48, 8.08, 2.28 Hz, 1H), 2.46 (dd, *J* = 13.64, 7.32 Hz, 1H), 2.40 (d, *J* = 7.84 Hz, 1H (OH)), 2.29 (dd, *J* = 13.62, 7.58 Hz, 1H), 1.63-1.53 (m, 1H), 1.27-1.20 (m, 1H), 1.13 (s, 3H), 1.02 (t, *J* = 7.34 Hz, 3H).

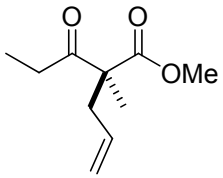
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 133.5, 118.4, 77.3, 51.8, 51.2, 41.1, 24.6, 17.5, 11.1.

Minor: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.82-5.72 (m, 1H), 5.09-5.04 (m, 2H), 3.68 (s, 3H), 3.59 (ddd, *J* = 10.29, 6.63, 2.21 Hz, 1H), 2.50 (dd, *J* = 14.90, 7.34 Hz, 1H), 2.28 (dd, *J* = 13.90, 7.50 Hz, 1H), 2.08 (d, *J* = 6.56 Hz, 1H (OH)),1.49-1.41 (m, 1H), 1.37-1.27 (m, 1H), 1.15 (s, 3H), 1.00 (t, *J* = 6.94 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.6, 134.2, 118.0, 77.7, 51.7, 48.4, 40.4, 25.4, 17.2, 11.2.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{10}H_{18}O_3$: 186.1256, found: 186.1263.

(*S*)-2-Methyl-2-propionyl-pent-4-enoic acid methyl ester (488)



To a solution of alcohol **365** (320 mg, 1.72 mmol) in DMSO (15 mL) was added IBX (962 mg, 3.44 mmol). The mixture was stirred at r.t. for 2 h, water was added and the aqueous layer was extracted with Et_2O. The combined ethereal phase was dried over $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) gave 260 mg (81%) of keto ester **366**.

R_f = 0.67 (hexane:EtOAc = 3:1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.69-5.58 (m, 1H), 5.11-5.06 (m, 2H), 3.71 (s, 3H), 2.63 (dd, *J* = 14.02, 7.18 Hz, 1H), 2.51 (dd, *J* = 13.88, 7.56 Hz, 1H), 2.44 (dq, *J* = 7.28, 2.64 Hz, 2H), 1.33 (s, 3H), 1.05 (t, *J* = 7.20 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.9, 173.2, 132.7, 118.9, 59.2, 52.3, 39.5, 31.7, 19.1, 8.0.

IR (film): 2982, 1744, 1715, 1641, 1458, 1378, 1232, 1145 cm^{-1}.

HRMS (ESI) (m/z): $[M]^+$ calcd for $C_{10}H_{16}O_3$: 184.1099, found: 184.1108.

$[\alpha]_D^{20}$ -9.28 (*c* =1.25, CH_2Cl_2)

11. Appenices

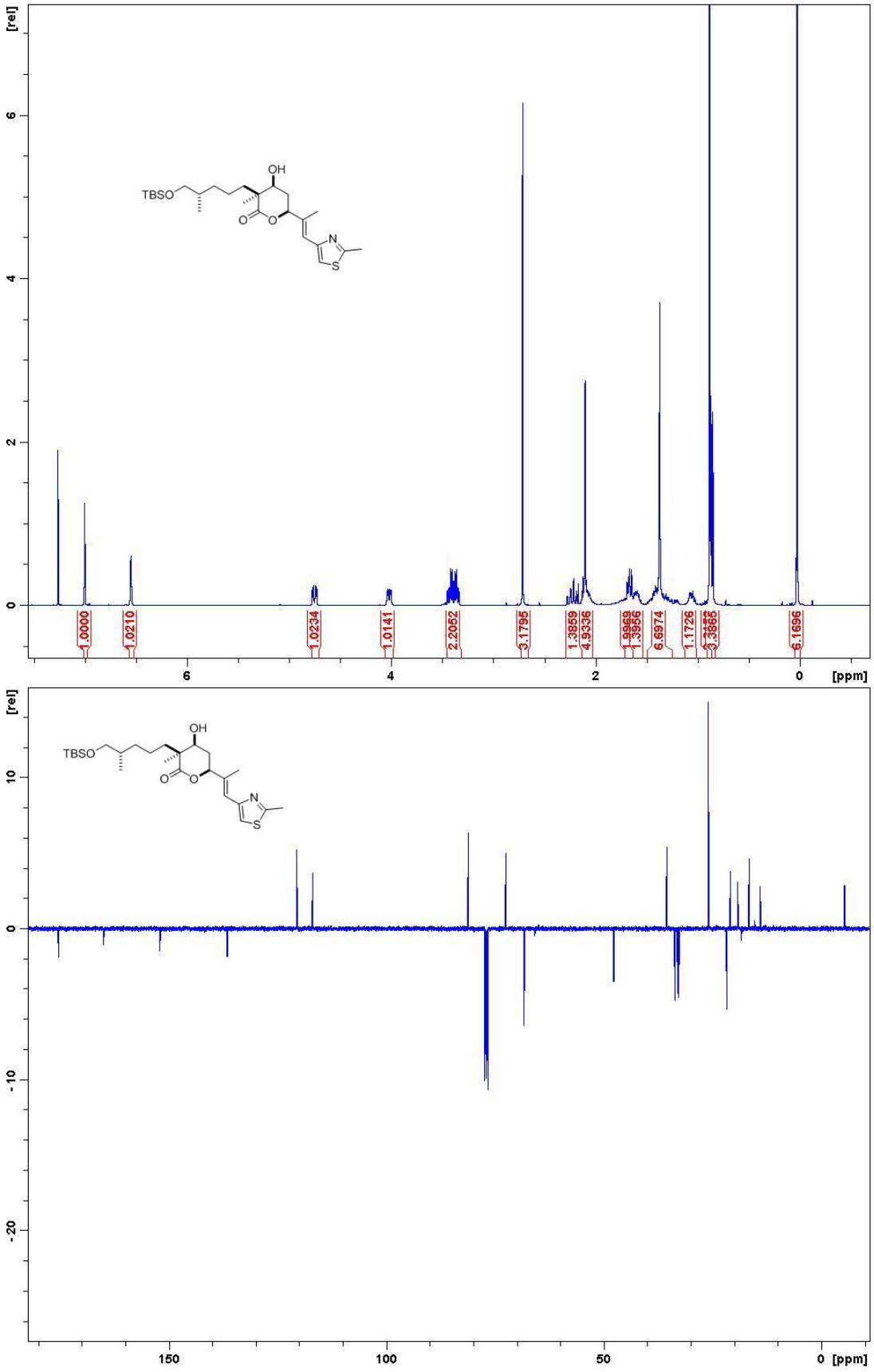
11.1. Abbrevations

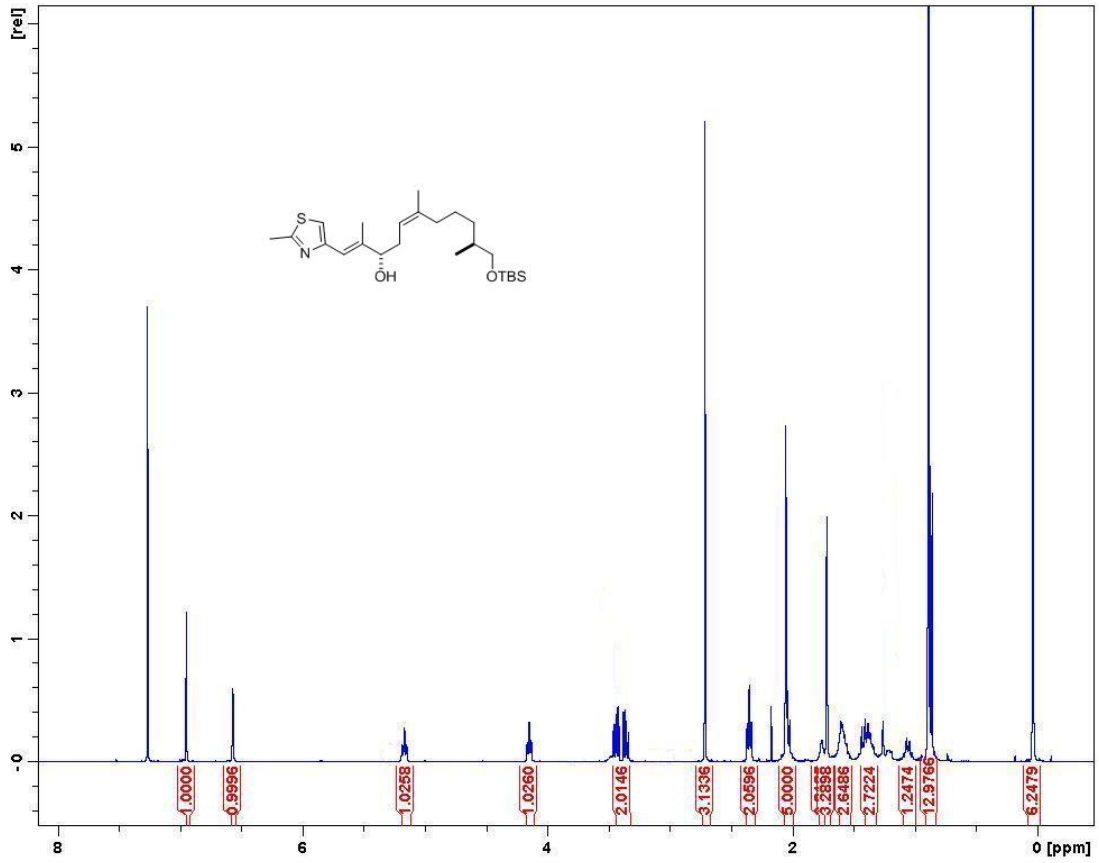
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BOM	benzyloxymethyl
Bu	butyl
c	concentration
cat.	catalyst
CM	cross metathesis
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DIC	*N,N'*-diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane

DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
eq.	equivalent
et al.	latin: “et alii”, meaning “and others”
HMPA	hexamethylsilylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IBX	*o*-iodoxybenzoic acid
J	coupling constant
KHMDS	potassium hexamethylsilylazide
LA	Lewis acid
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium hexamethylsilylazide
*m*CPBA	*meta*-chloroperbenzoic acid
MMPP	magnesium monoperoxyphthalate
mp	melting point
MTPA	*α*-Methoxy-*α*-trifluoromethylphenylacetyl
MOM	methoxymethyl
Ms	methansulfonyl
MS	mass spectroscopy
MVK	methyl vinyl ketone
NaHMDS	sodium hexamethylsilylazide
NBS	*N*-bromosuccinimide
NCS	*N*-iodosuccinimide
NEt_3	triethylamine

NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
py	pyridine
$R_{(1,2\ldots n)}$	any substituent
RCM	ring closing metathesis
R_f	ratio of fronts (TLC)
r.t.	room temperature
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofurane
THP	tetrahydropyran
Tf	trifluoromethanesulfonate
TLC	thin layer chromatography
TMEDA	tetramethylethylendiamin
TMS	trimethylsilyl
Troc	2,2,2-trichloroethyl carbonate
*p*TsOH	*para*-toluene-4-sulfonic acid

11.2. Selected Spectra

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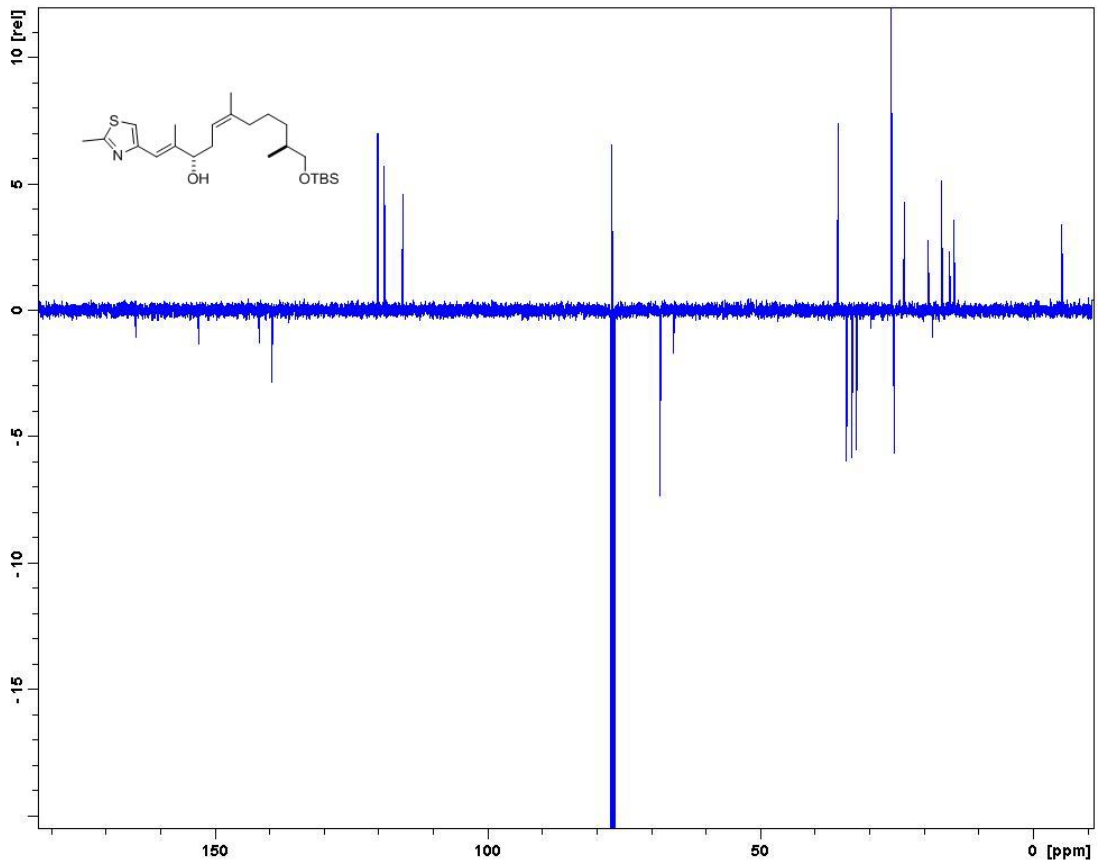
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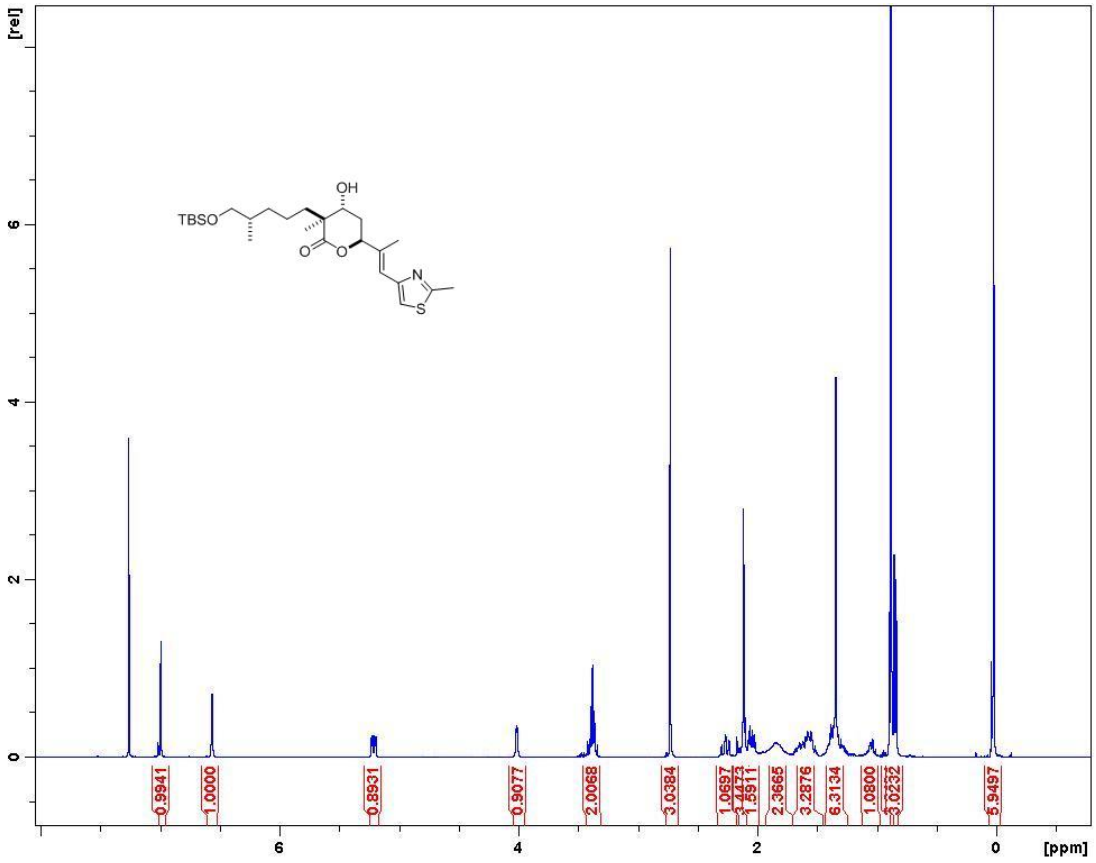
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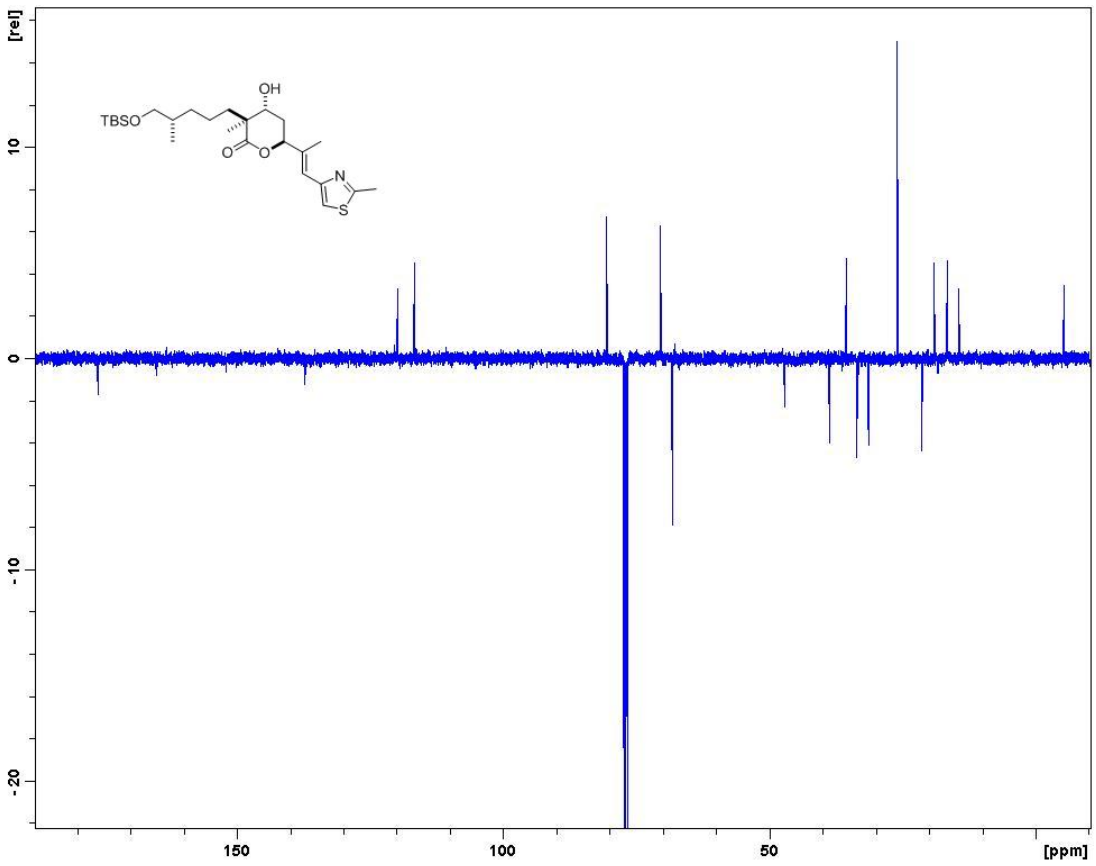
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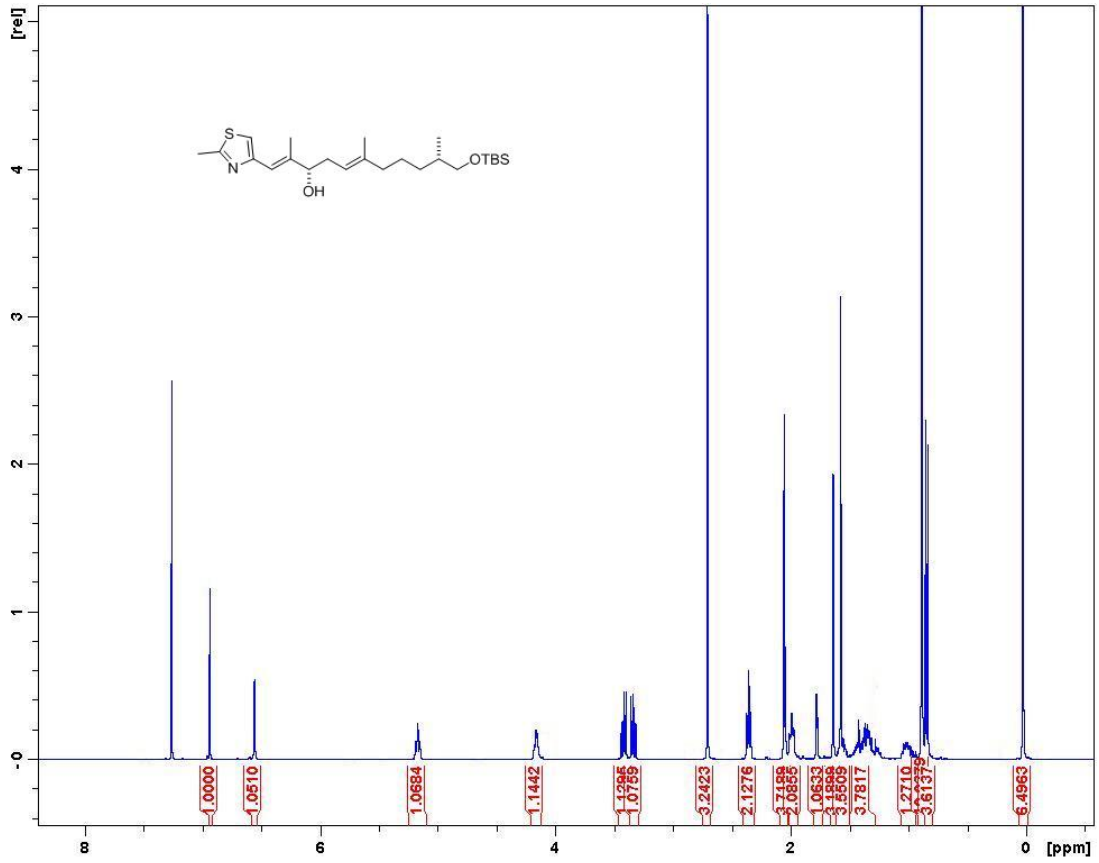
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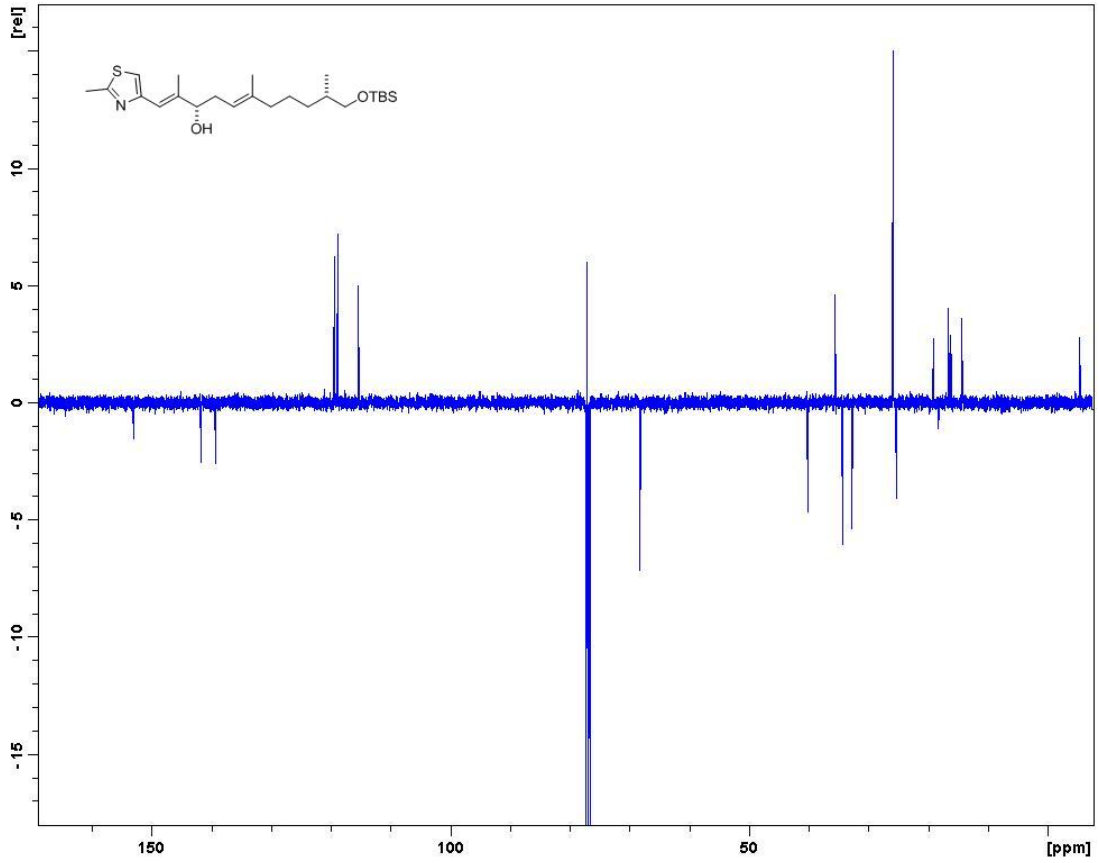
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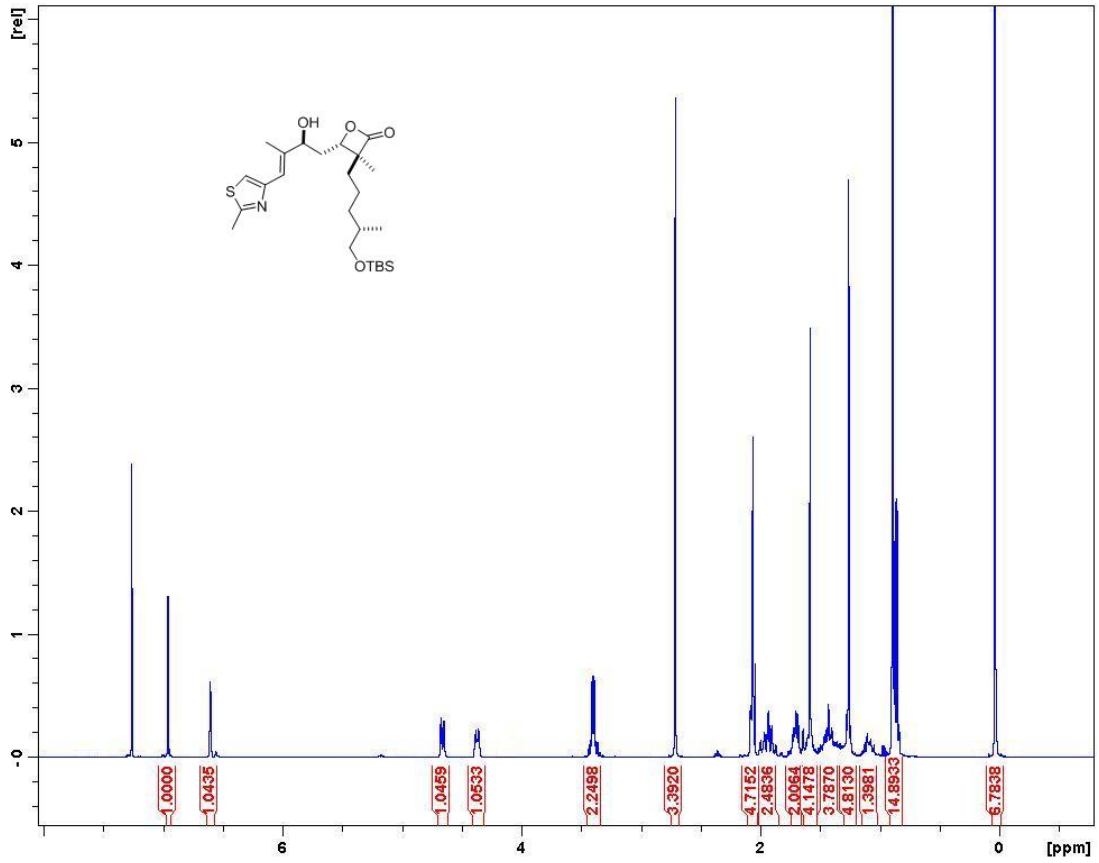
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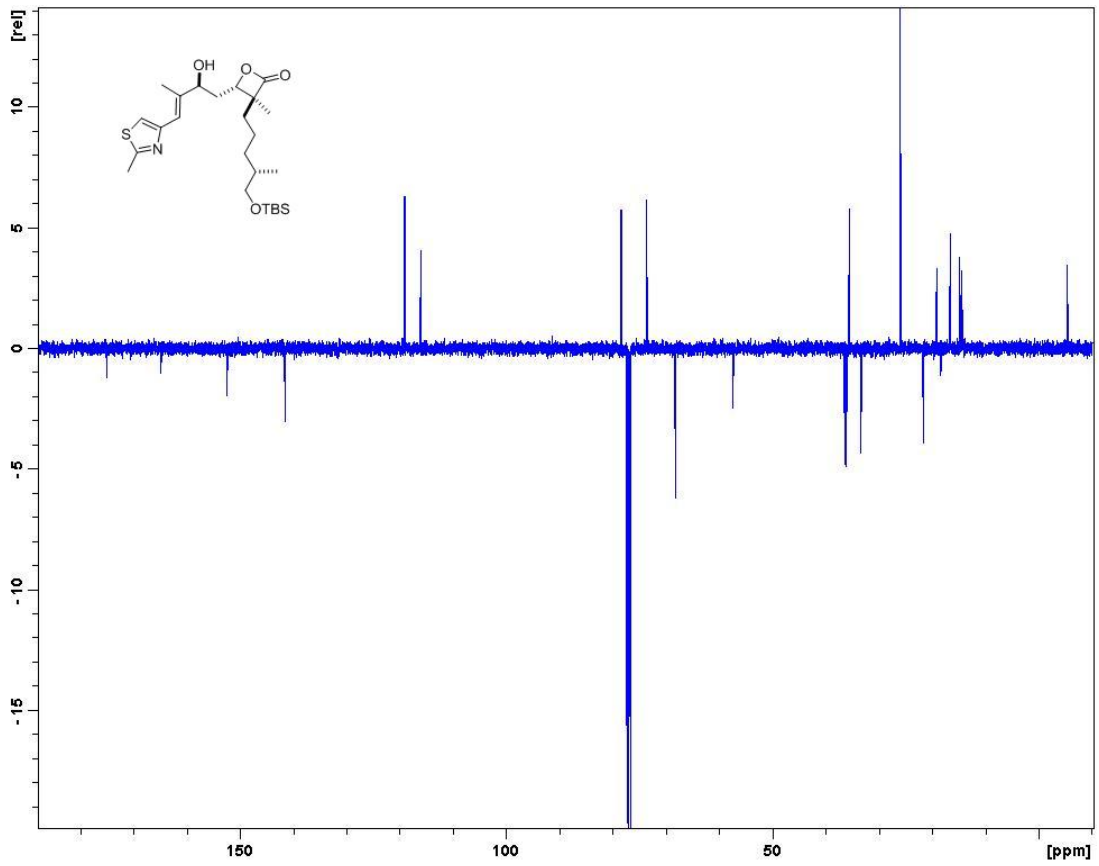
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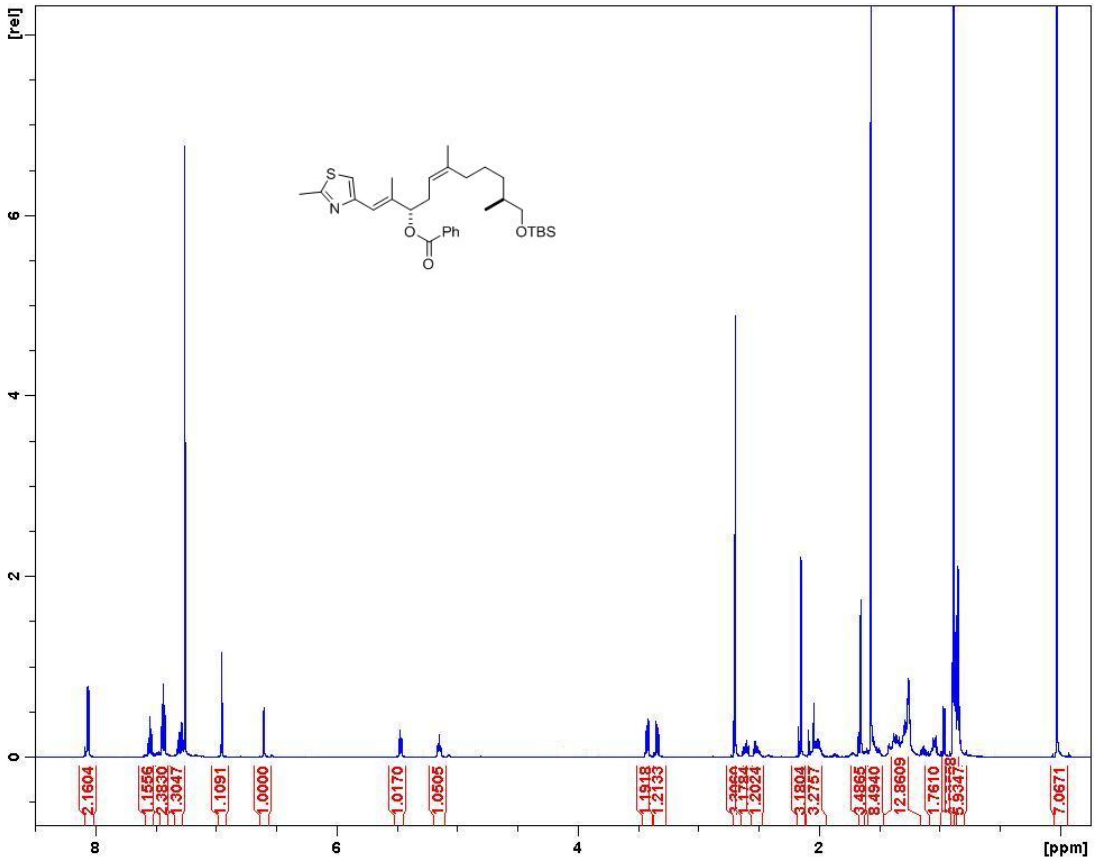
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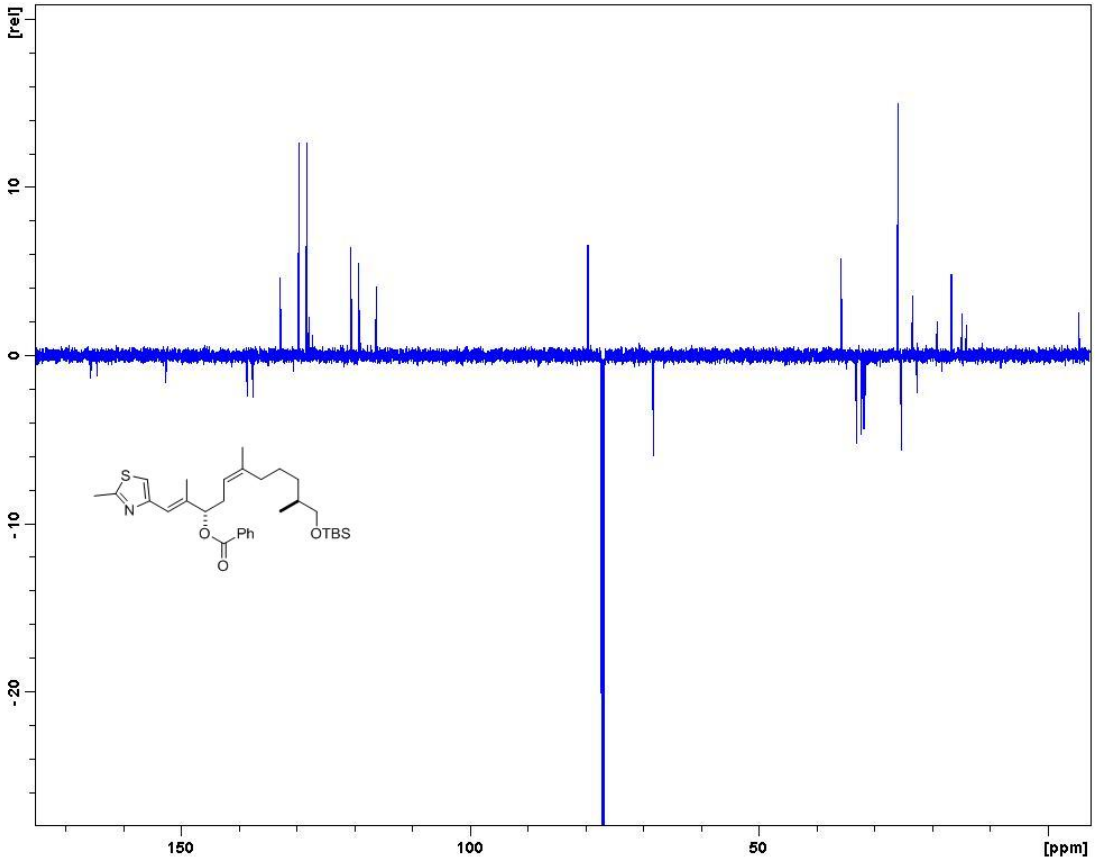
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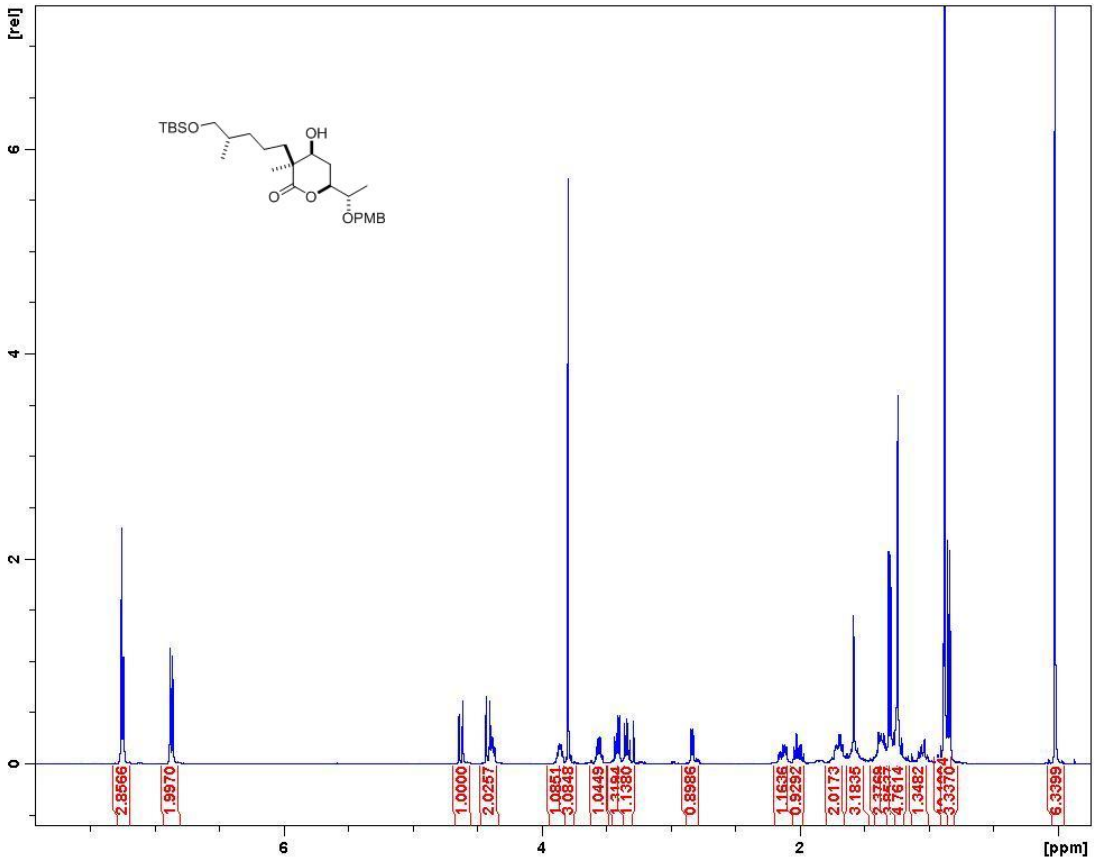
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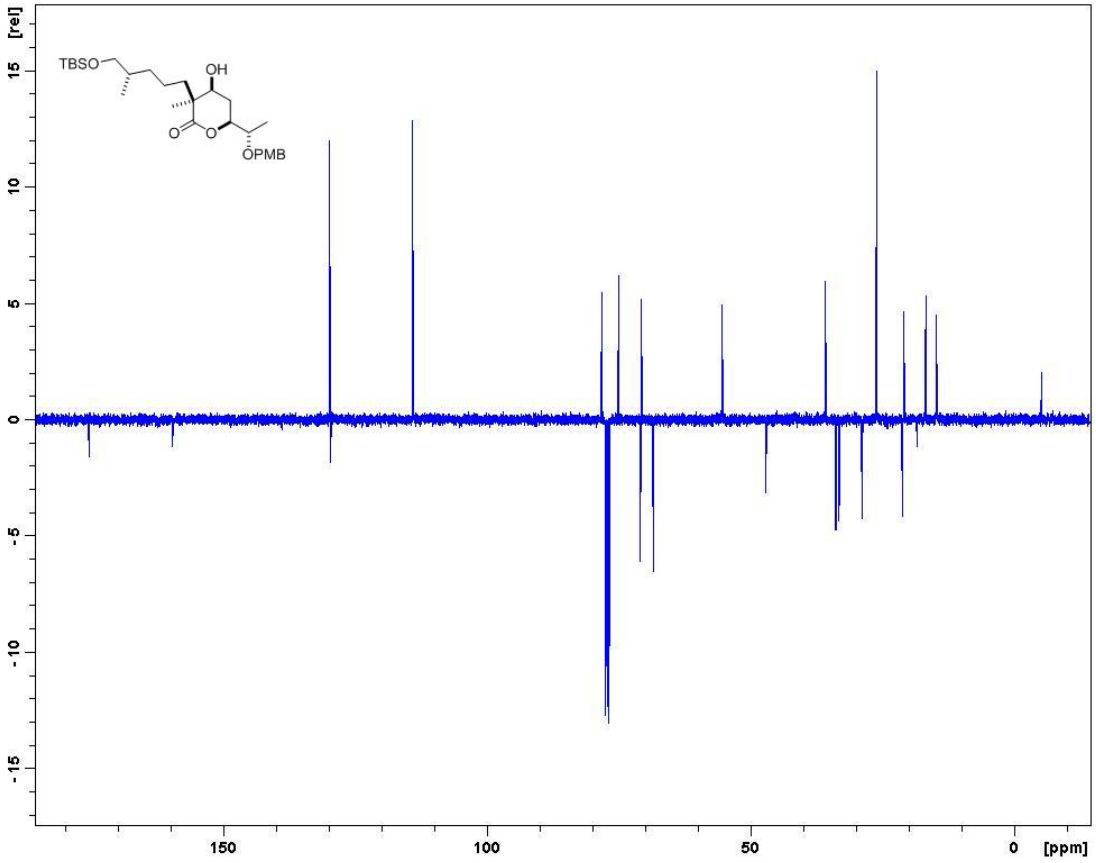
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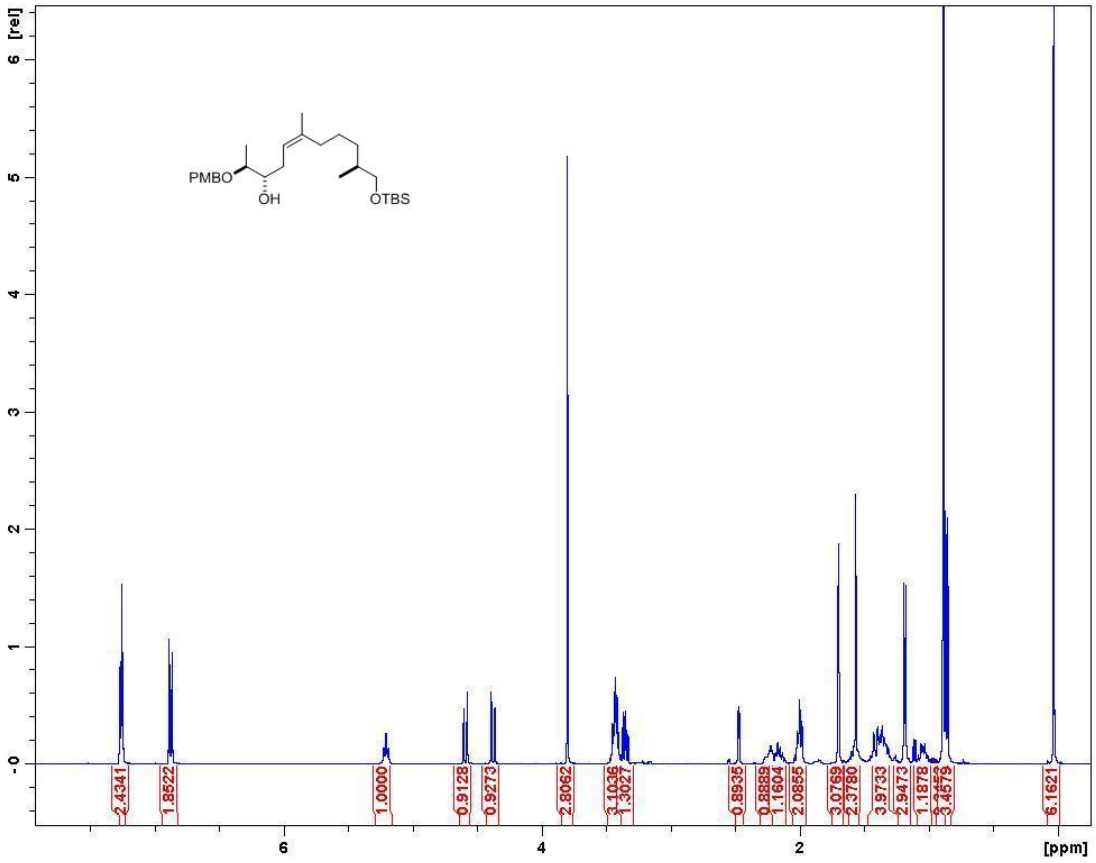
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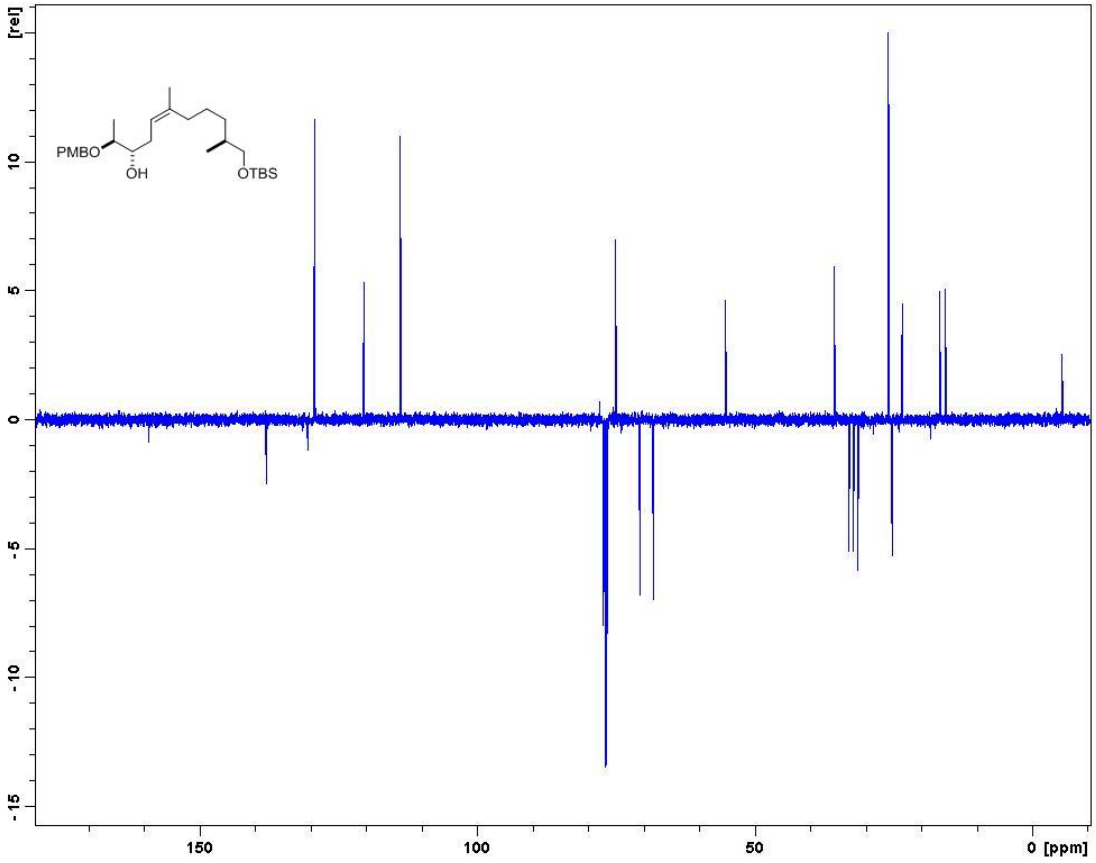
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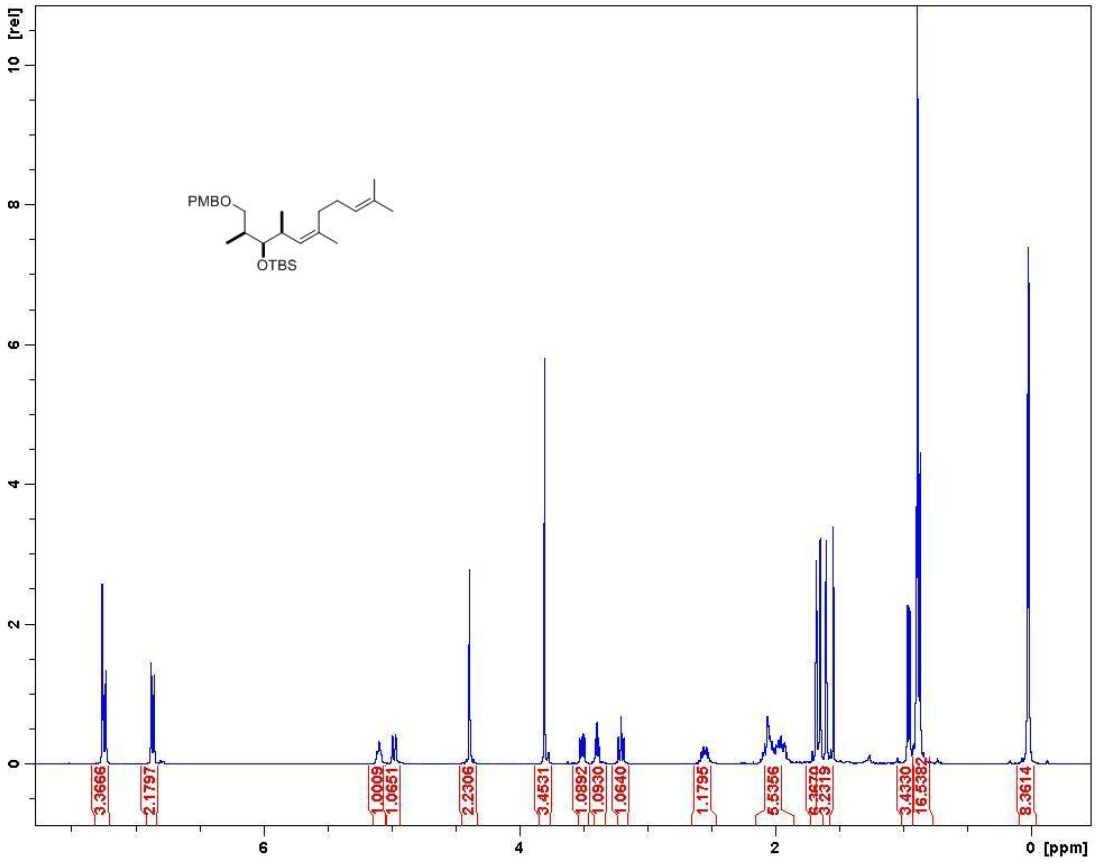
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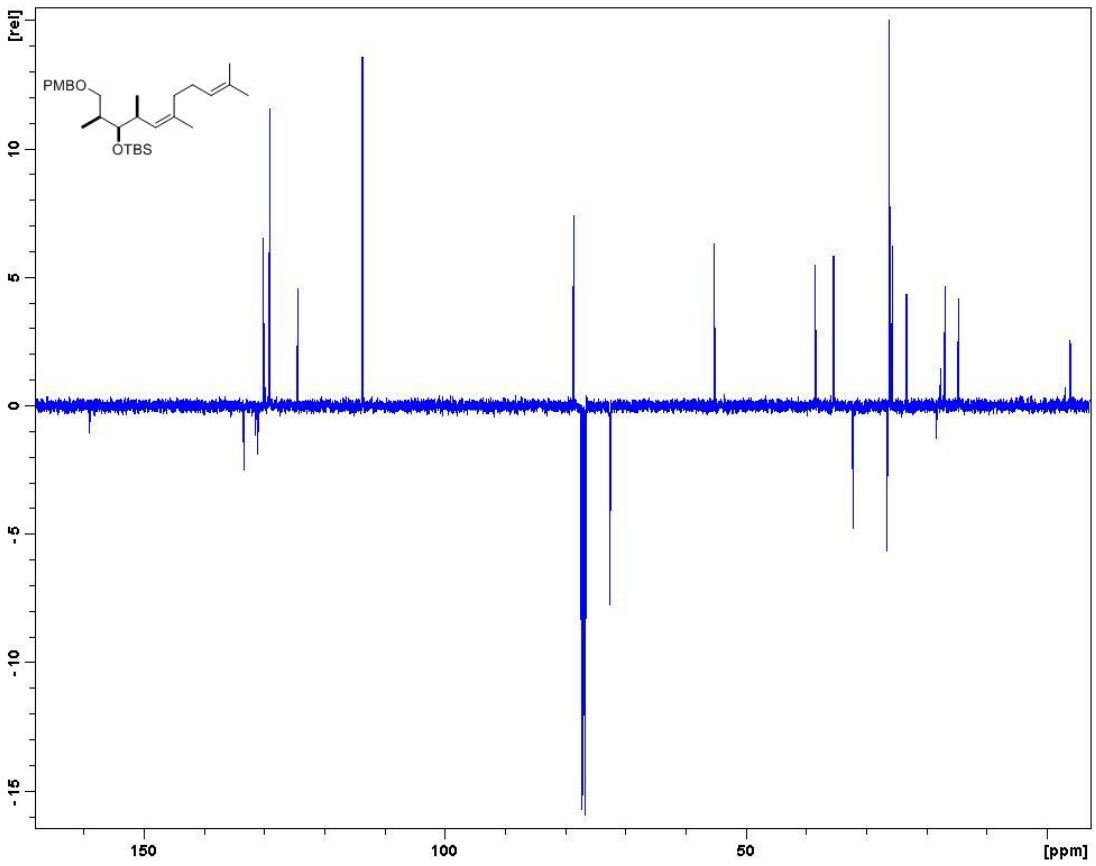
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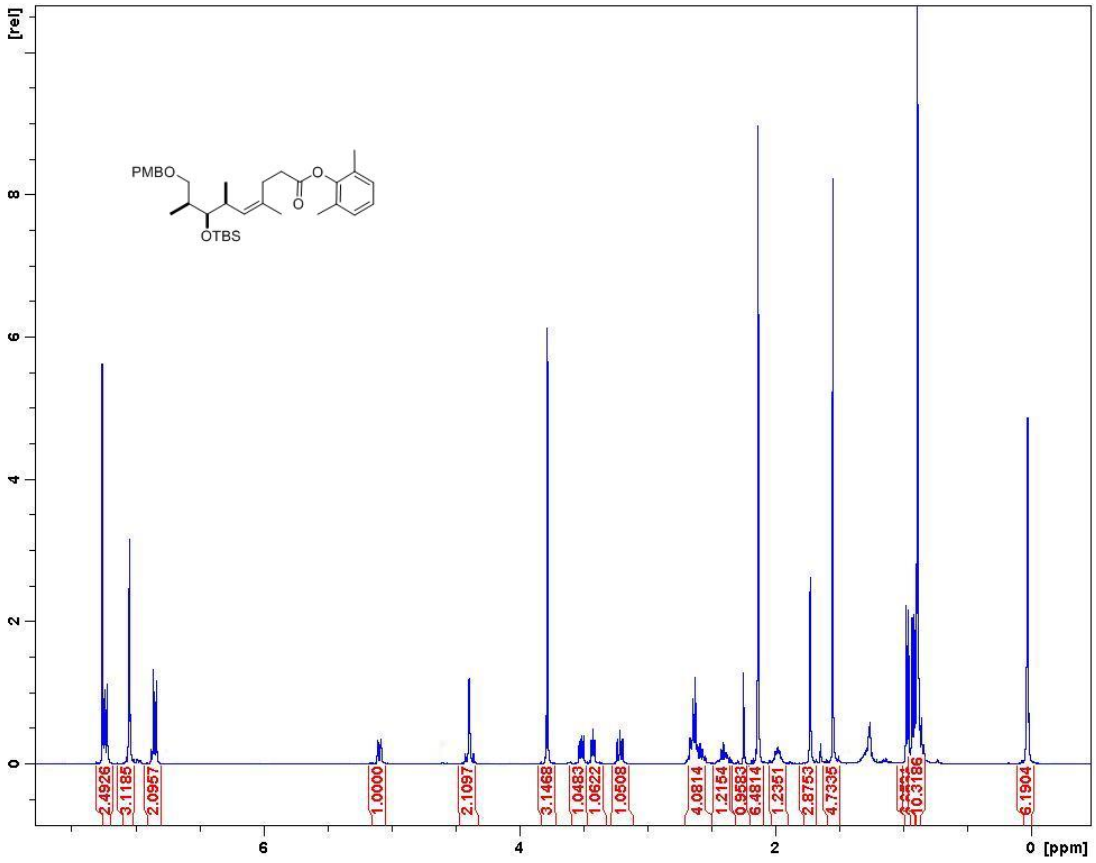
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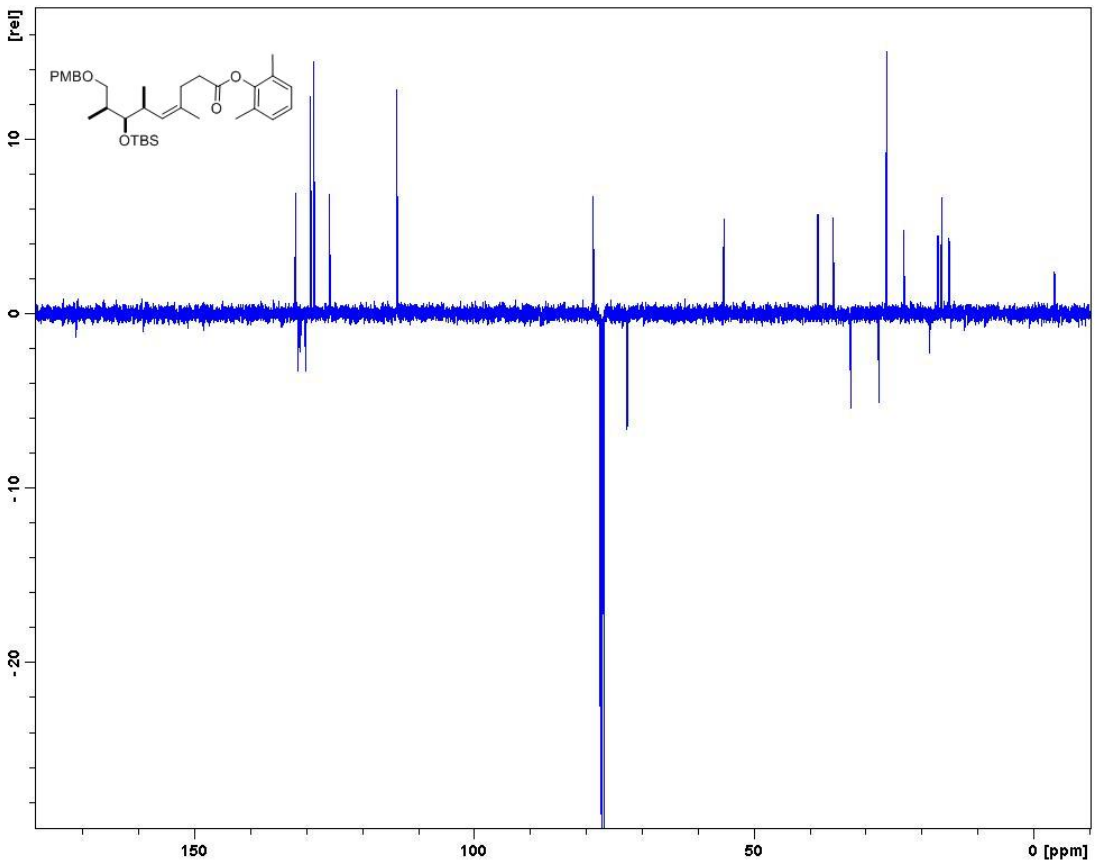
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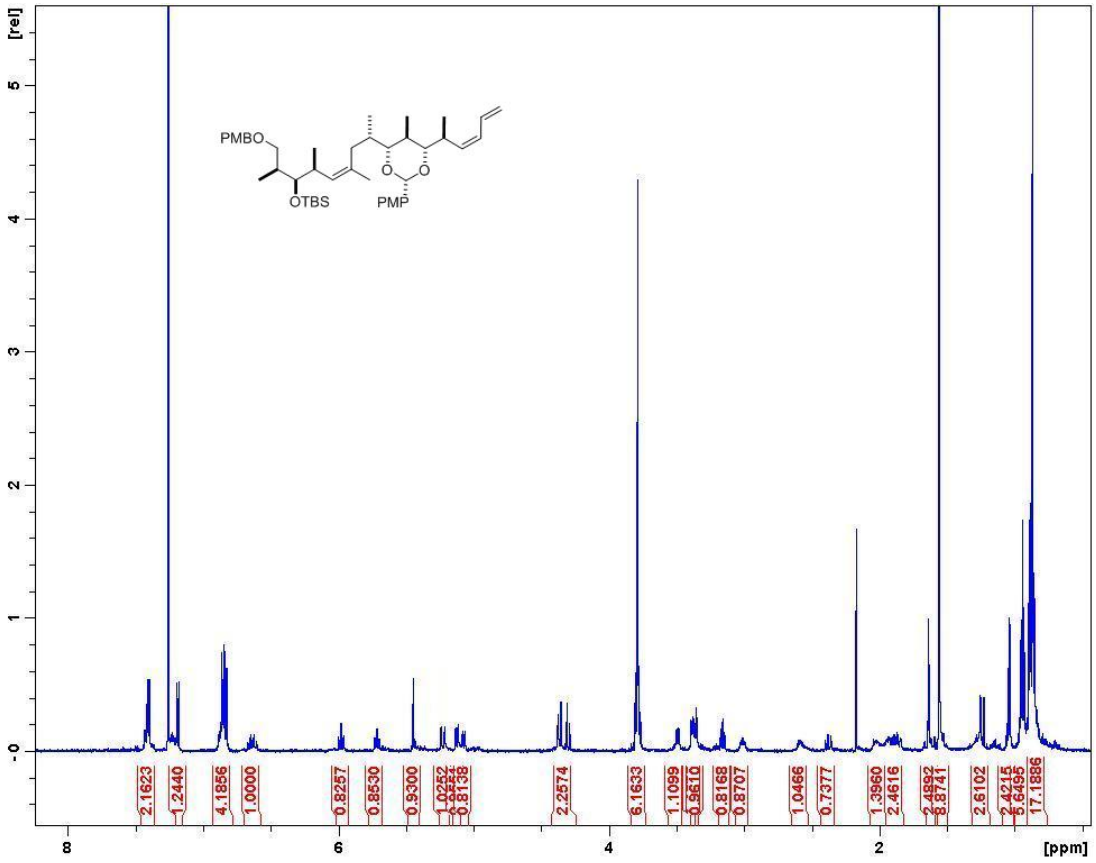
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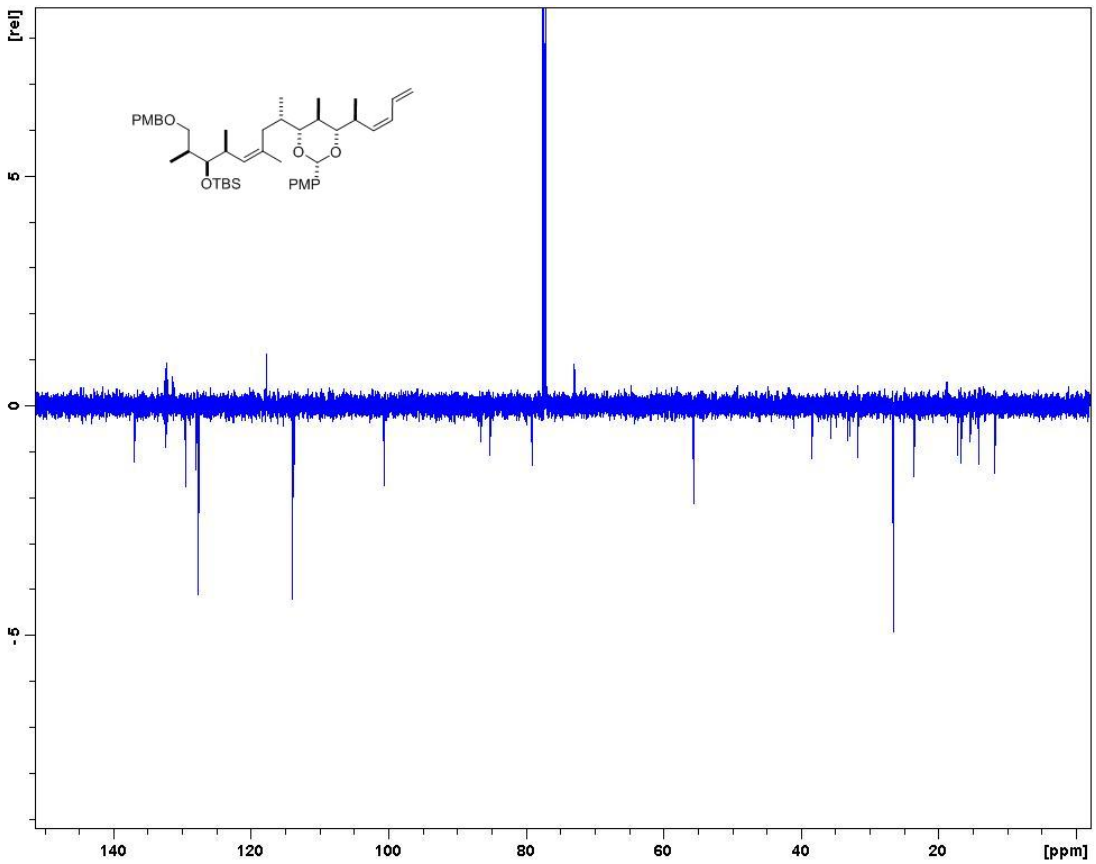
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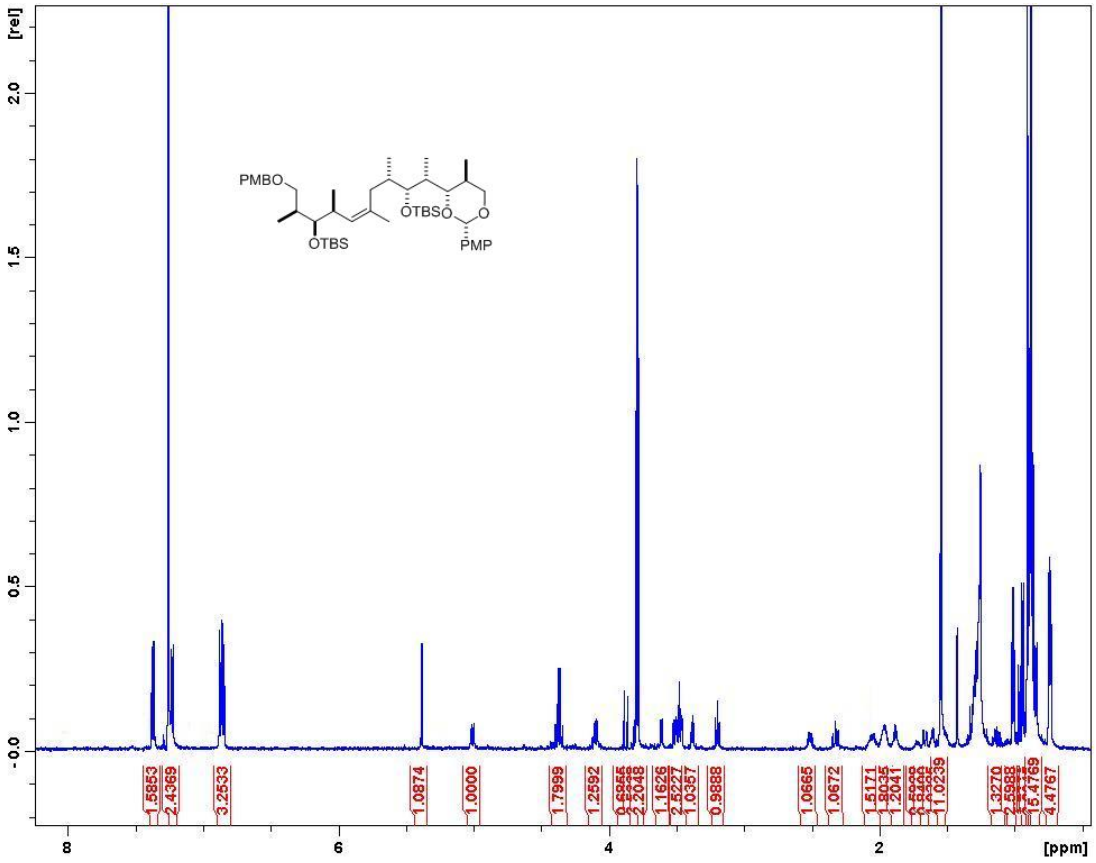
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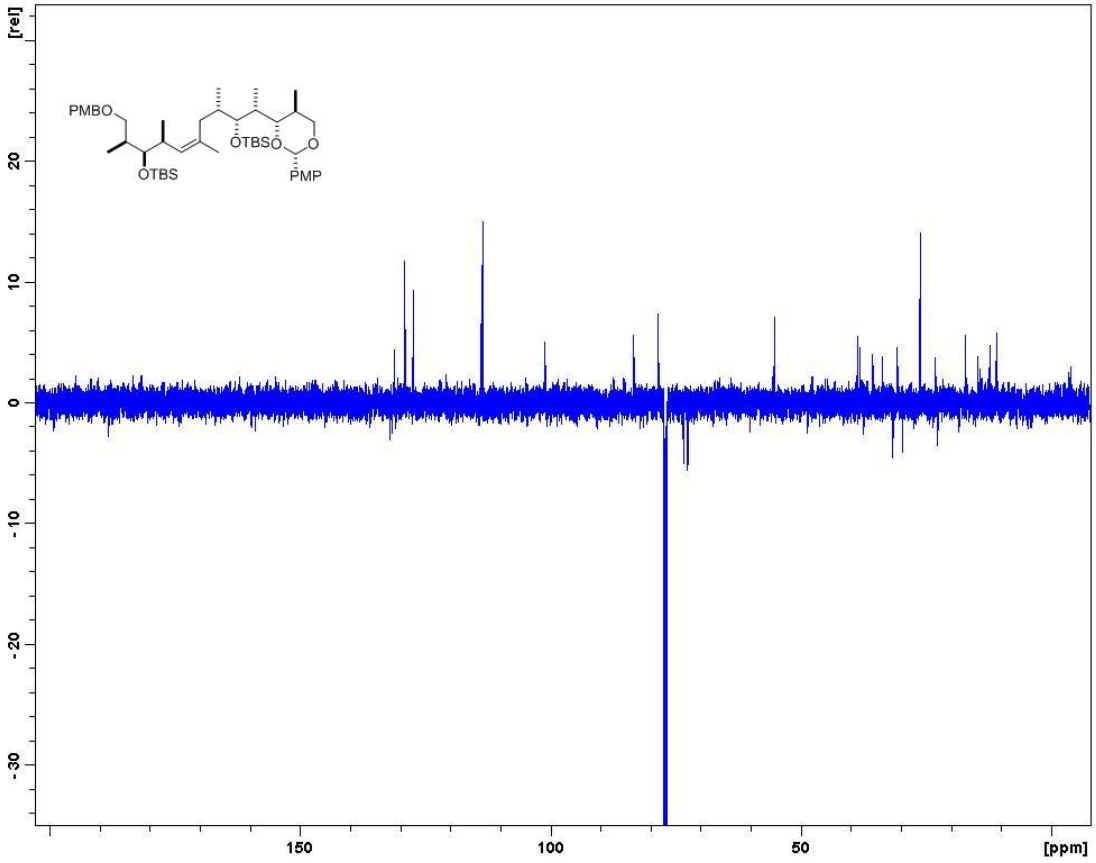
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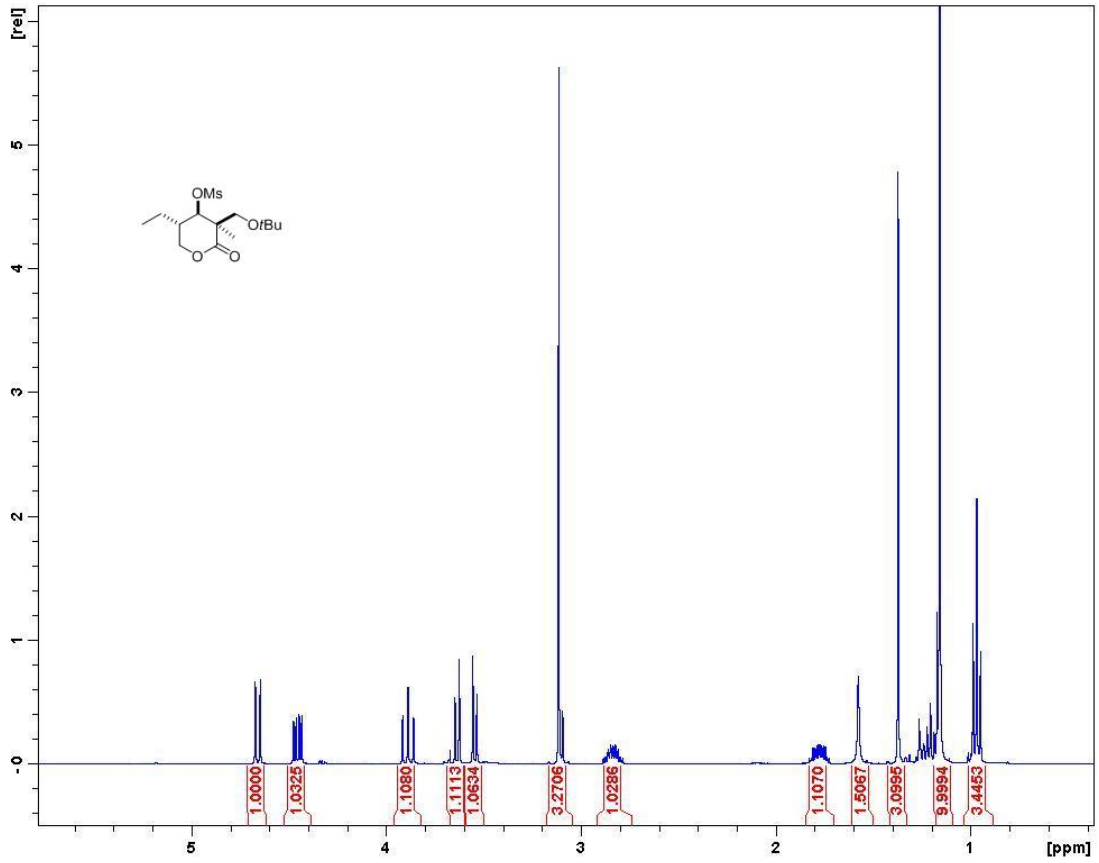
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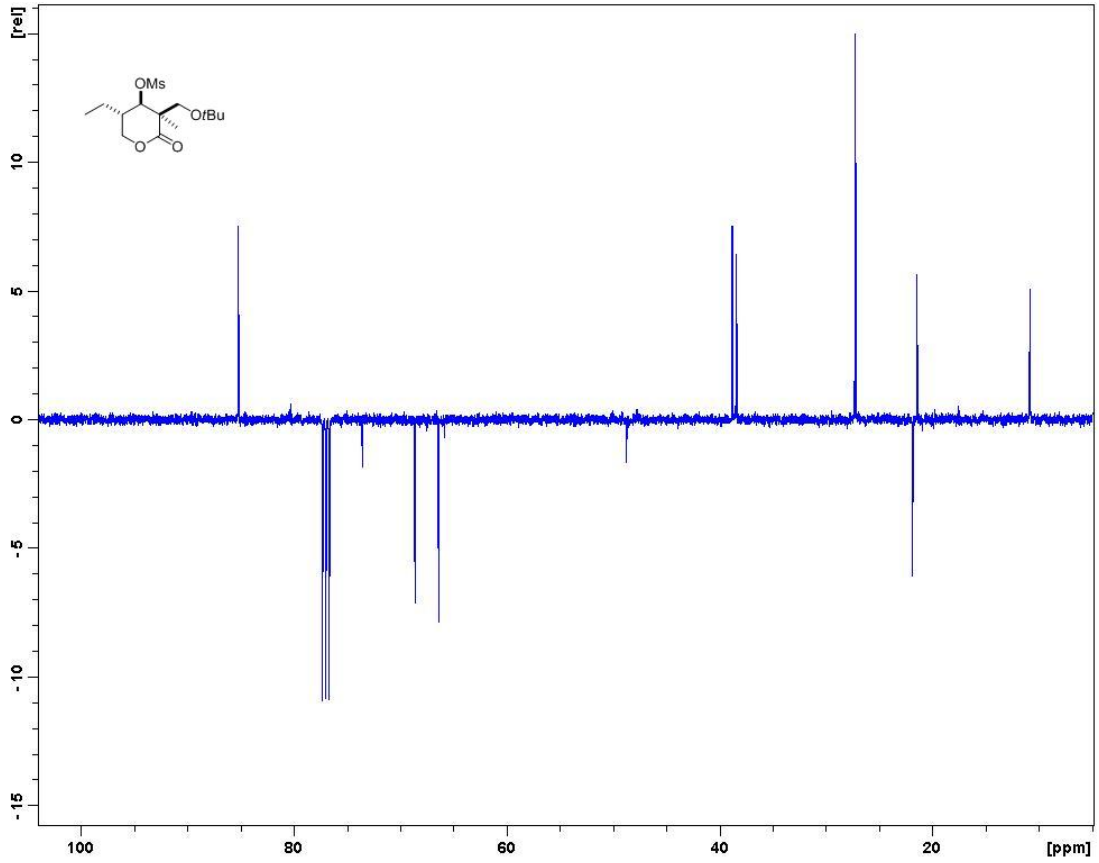
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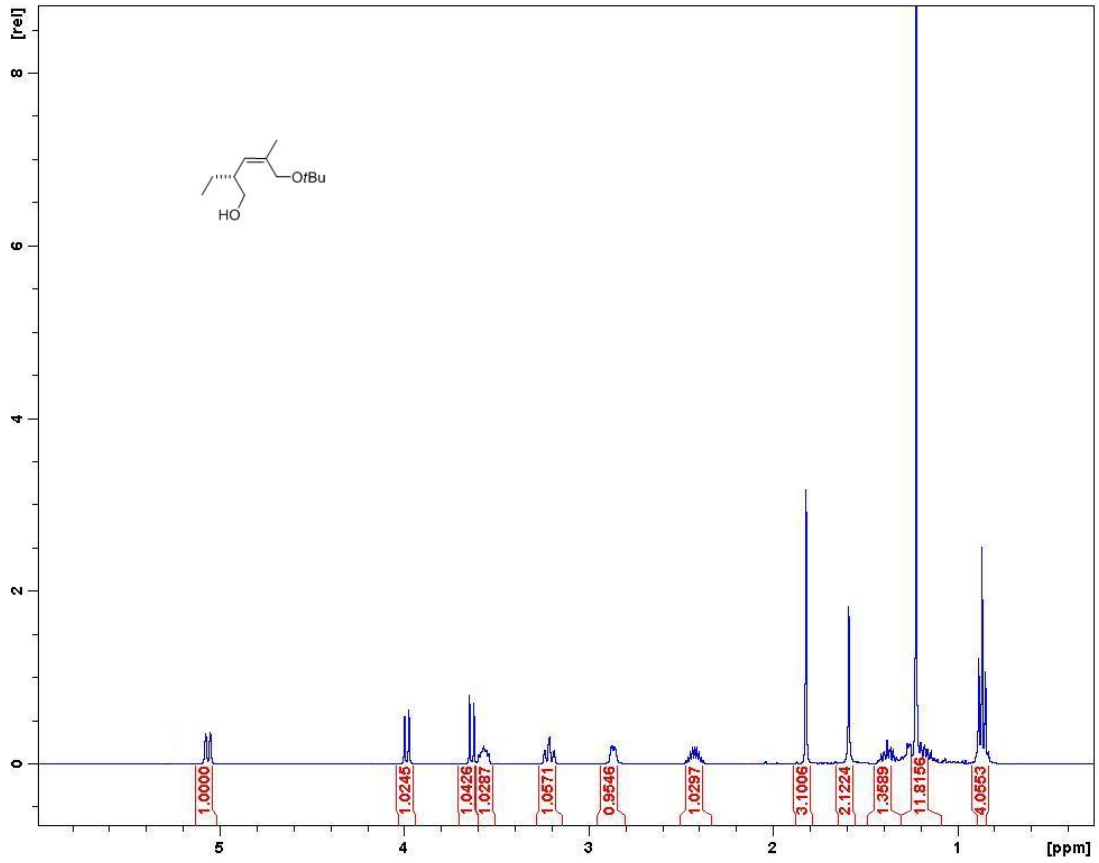
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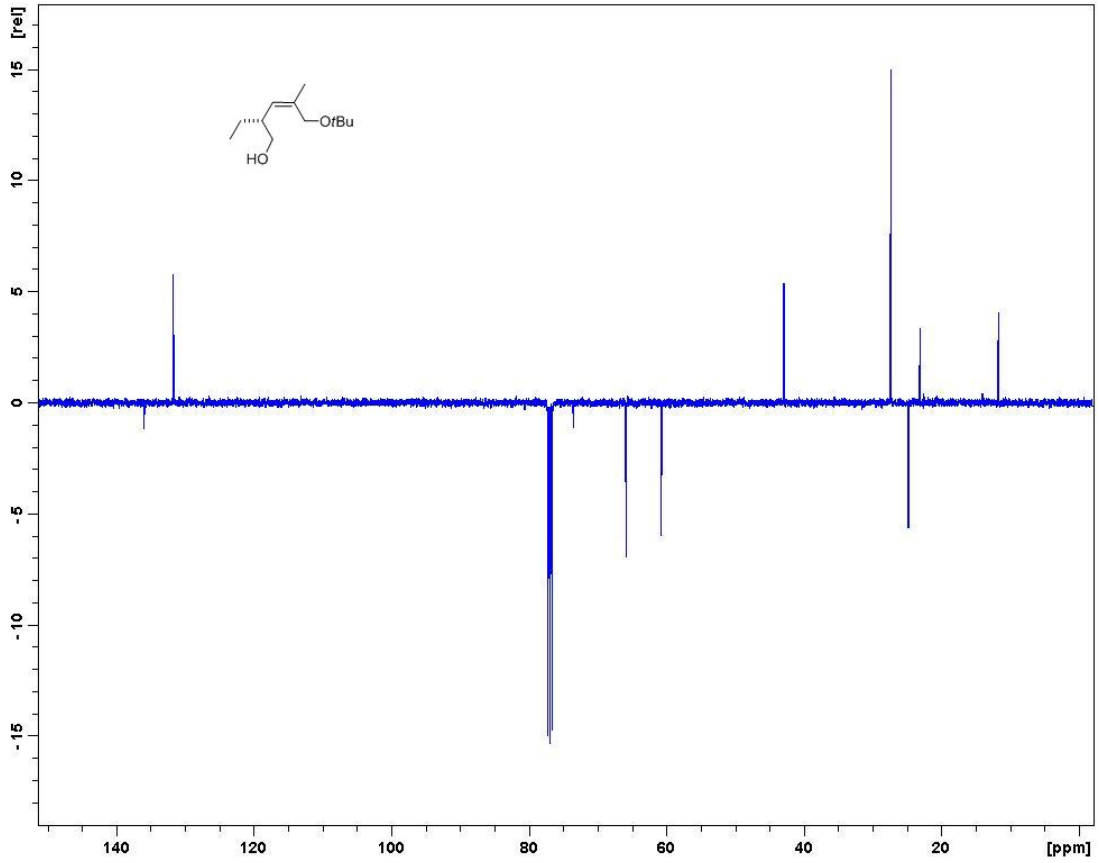
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13. Curriculum Vitae

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University studies:

July 2007:	Award of the doctoral fellowship of the Ernst Schering Foundation.
Since February 2006:	Ph.D. research at the University of Vienna under the supervision of Prof. Dr. Johann Mulzer.
7. October 2005:	Completion of undergraduate studies (passed with distinction). Subjects of diploma examination: ■ Organic Chemistry (Prof. Dr. Johann Mulzer) ■ Food chemistry (Prof. Dr. Gerhard Sontag)
September 2004 to September 2005:	Development of diploma thesis at the University of Vienna under the supervision of Prof. Dr. Johann Mulzer.
01. September 2003 to 16. December 2003:	Exchange program at the University of Warwick, research project in bioinorganic chemistry under the supervision of Prof. Dr. Michael J. Hannon.
30. September 2002:	Finished the general part of undergraduate chemistry degree after only six terms (passed with distinction) and specialized in organic

chemistry, inorganic chemistry and food chemistry.

October 1999: Registered for chemistry at the University of Vienna.

Education:

23.06.1999: Matura (summa cum laude).

1995-1999: Grammar school at the „ORG der Englischen Fräulein“ (Krems, Austria), with main focus on natural science and mathematic.

1991-1995: Grammar school at the Piaristengymnasium (Krems, Austria), with main focus on Latin and geometry.

Working experience:

Since February 2006: Assistant position at the University of Vienna (Vienna, Austria) Teaching assistant, supervision, tutoring and grading students in the field of synthetic organic chemistry.

September 2004 to September 2005: University of Vienna (Vienna, Austria) Research assistant, Synthesis of natural products.

September 2002: Kronospan Lamperdswalde (Dresden, Germany), analytic laboratory.

August 2002: Internship at Biochemie GmbH (Kundl, Austria), R&D laboratory.

July 2001: Internship at Dynea ASA (Lillestrøm, Norway), R&D laboratory.

Language skills:

German (first language), English (fluently), Spanish (communication skills).

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