DISSERTATION

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

Verfasserin
Mag. Kathrin Prantz

angestrebter akademischer Grad
Doktorin der Naturwissenschaft (Dr.rer.nat.)

Wien, 2009

Studienkennzahl lt. Studienblatt: A 091 419
Dissertationsgebiet lt. Studienblatt: Chemie
Betreuerin / Betreuer: Prof. Dr. Johann Mulzer
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
Peloruside A

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 paclitaxel 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

Publications, Posters and Oral Presentations Resulting from this Thesis

Publications


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**


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 “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).
Table of Contents

1. Introduction ........................................................................................................... 1
   1.1. Background ........................................................................................................ 1
   1.2. Antitumor Agents ............................................................................................ 2
       1.2.1. Introduction ............................................................................................... 2
       1.2.2. Chemotherapy .......................................................................................... 2
       1.2.3. Microtubule Stabilizing Anticancer Agents [4] ........................................... 2
   1.3. Isolation, Structural Elucidation and Biological Activity ......................... 5
       1.3.1. Epothilones [9, 10] .................................................................................. 5
       1.3.2. Discodermolide [12] ............................................................................... 7
       1.3.3. Peloruside A [19] .................................................................................... 8

2. Literature Syntheses .................................................................................. 9
   2.1. Carbonyl Olefination Reactions ...................................................................... 9
       2.1.1. Wittig Reaction ......................................................................................... 9
       2.1.2. Still-Gennari Reaction ............................................................................ 10
   2.2. Cross Coupling reactions ............................................................................... 12
       2.2.1. Suzuki Coupling ....................................................................................... 12
       2.2.2. Negishi Coupling ...................................................................................... 16
   2.3. Ring Closing Metathesis (RCM) .................................................................... 18
       2.3.1. RCM as Macrocyclization ........................................................................ 18
       2.3.2. RCM of Medium-Sized Rings .................................................................. 18
   2.4. Cupration ......................................................................................................... 20
   2.5. Pericyclic Reactions ....................................................................................... 22
       2.5.1. Cycloadditions: Hetero-Diels-Alder Reaction ........................................ 22
       2.5.2. Claisen-type [3,3]-Rearrangement ............................................................ 22
       2.5.3. Allylic Rearrangement ............................................................................. 23
   2.6. Miscellaneous .................................................................................................. 24

3. Grob Fragmentation .................................................................................... 26
   3.1. Introduction ...................................................................................................... 26
   3.2. Some Examples in Literature ......................................................................... 28

4. Results and Discussion – The Concept ..................................................... 31
   4.1. The Hydroxide Induced Decarboxylative Grob-type Fragmentation ......... 31

5. Results and Discussion - Epothilone B ................................................... 32
5.1. General Retrosynthesis .................................................................32
5.2. First Approach: Pig Liver Esterase (PLE) Route .........................33
  5.2.1. Quaternary Center by Desymmetrization ...............................33
  5.2.2. Chain Elongation .................................................................37
  5.2.3. Fragmentation Precursor .......................................................41
  5.2.4. Fragmentation .................................................................48
  5.2.5. Testing the Fragmentation Reaction of Different Diastereomeric Precursors ... 49
  5.2.6. Fragmentation of the Open Chain .......................................53
5.3. Second Approach: Lactate Route ..............................................56
  5.3.1. Building Lactone 262 .........................................................57
  5.3.2. Quaternary Center by Tsuji-Trost Allylation ........................58
  5.3.3. Fragmentation Precursor ...................................................61
  5.3.4. Fragmentation .................................................................63
  5.3.5. Endgame .................................................................64
5.4. Summary – Epothilone B ..........................................................65

6. Results and Discussion - Discodermolide ................................. 66
6.1. General Retrosynthesis .............................................................66
6.2. Enzymatic Hydrolysis ...............................................................67
  6.2.1. Quaternary Center by Desymmetrization ...............................67
  6.2.2. Fragmentation Precursor ...................................................69
  6.2.3. Fragmentation .................................................................71
6.3. Introduction of the Quaternary Center by Regioselective Epoxide Opening ........72
  6.3.1. Epoxide Opening ...............................................................73
6.4. Diastereoselective Carboxalkylation of Enolates ..............................74
  6.4.1. Quaternary Center by Acylation .......................................75
6.5. Wagner-Meerwein Rearrangement of Epoxide for the Generation of the Quaternary Center .................................................................76
  6.5.1. Quaternary Center by Rearrangement ..................................76
  6.5.2. Fragmentation Precursor ...................................................77
  6.5.3. Fragmentation of the Open Chain Precursor ..........................78
  6.5.4. Conversion into δ-Lactone 340 ...........................................79
  6.5.5. Fragmentation .................................................................82
  6.5.6. First Formal Synthesis Goal ..............................................83
  6.5.7. Second Formal Synthesis Goal .........................................84
  6.5.8. Stereoselective Methylation at C16 ....................................84
  6.5.9. Attaching the C18 to C21 Fragment ......................................85
6.6. Summary – Discodermolide ...................................................................................96

7. Results and Discussion - Peloruside A ..................................................... 97
  7.1. Retrosynthetic Analysis ..................................................................................97
  7.2. α-Alkylation of Menthyl Tiglate.................................................................98
  7.3. Enzymatic Desymmetrization with PLE ....................................................99
    7.3.1. Quaternary Center by Desymmetrization .......................................99
    7.3.2. Fragmentation Precursor ....................................................................100
    7.3.3. Fragmentation ...................................................................................102
  7.4. Summary – Peloruside A ............................................................................103

8. Results and Discussion - Nucleophile Additions to an Aldehyde with
   Quaternary α-Center .......................................................................................104
  8.1. Allylation ......................................................................................................104
    8.1.1. Allylation with Chiral Allyl Reagents...............................................104
    8.1.2. Allylation with Achiral Allyl Reagents ...........................................105
  8.2. Aldol Additions ..............................................................................................107
    8.2.1. Boron Enolates[98] ...............................................................................107
    8.2.2. Lithium Enolates ..................................................................................109
    8.2.3. Mukaiyama Aldol reaction .................................................................110
  8.3. Fragmentations ...............................................................................................111
    8.3.1. Fragmentation Precursors ...................................................................111
    8.3.2. Fragmentations ...................................................................................112
  8.4. Aldol Addition of an Ethyl Ketone featuring a Quaternary α-Center ..........114
  8.5. Summary - Nucleophile Additions...............................................................115

9. Conclusion and Outlook ............................................................................... 116

10. Experimental Section ................................................................................ 118
  10.1. General Experimental ...............................................................................118
  10.2. Experimental Procedures ........................................................................121
    10.2.1. Epothilone B: Pig Liver Esterase Route ...........................................121
    10.2.2. Epothilone B: Lactate Route ..............................................................171
    10.2.3. Discodermolide .................................................................................195
    10.2.4. Peloruside A .......................................................................................245
    10.2.5. Nucleophile Additions .......................................................................255

11. Appendices ........................................................................................................287
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).

![Chemical structures of Epothilone B (1), Discodermolide (3), and Peloruside A (2).]

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 β-tubule dimerize to form α/β-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.\[6\]

\[4\]

\[5\]

\[6\]

\[7\]

\[8\]

**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).
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.\cite{5} Ojima has proposed a common pharmacophore uniting these structure diverse molecules.\cite{8}

On the other hand, vinblastine (11), colchicine (12) and combretastatin A-7 (13) (Scheme 3) cause apoptosis by depolymerization of microtubules.\cite{5}
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).

The epothilones are 16-membered macrolides, named after their fundamental structural features (epoxide, thiazole and ketone). 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.
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).\(^{[16]}\)

![](https://example.com/scheme5.png)

**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\(^{\text{®}}\) (4). Additionally the anti-proliferation activity remains in cell lines already resistant to taxol\(^{\text{®}}\) (4). Competition studies to probe the binding site showed the ability of discodermolide (3) to replace taxol\(^{\text{®}}\) (4) which indicates the same or overlapping binding sites on β-tubule. However, the presence of taxol\(^{\text{®}}\) (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\textsuperscript{[19]}

Peloruside A (2) was isolated in 2000 from the marine sponge \textit{Mycale hentscheli} by Northcote and co-workers collected from the Pelorus Sound on the north coast of the South Island of New Zealand.\textsuperscript{[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 \textit{ent-}peloruside A (\textit{ent-}2) by De Brabander in 2003 established the absolute configuration.\textsuperscript{[21]}

\begin{center}
\textbf{Scheme 6:} Peloruside A (2).
\end{center}

Soon after the isolation its paclitaxel-like microtubule stabilizing activity was reported.\textsuperscript{[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\textsuperscript{[5]} binding site on the β-tubule. Synergistic effects have been observed with taxoid site drugs like taxol\textsuperscript{[5]} (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]

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.
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).](image)

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).](image)

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. 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.

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). 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 12: Danishefsky’s Suzuki coupling.
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.

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). 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 alkene 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). 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). 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. 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).\textsuperscript{[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.](image)

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).\textsuperscript{[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.](image)

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).\textsuperscript{[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.

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.
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.](image-url)
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).\cite{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).\textsuperscript{[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.

\begin{center}
\textbf{Scheme 27:} Myles’ hetero-Diels-Alder for the discodermolide (3) synthesis.
\end{center}

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).\textsuperscript{[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. 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.

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.\cite{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.\cite{51, 52} Substrates contain a certain carbon and heteroatom combination and are typically 1,3-dihetero-functionalized compounds featuring a nucleophilic atom with a negative charge or lone electron pair and a leaving group in a 1,3 relationship.

![Figure 4: Schematic Grob Fragmentation.](image)

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.](image)

Stereoelectronic and stereochemical factors influence the outcome of the reaction, which can proceed via a concerted or a stepwise mechanism (Figure 6).\cite{53} In the two step process,
either similar to an E1 or S$_\text{N}1$ 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 electrofugual 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 electrofugual 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 \( \beta \)-mesyloxy ketone 150 which was treated with potassium hydroxide or methyl magnesium iodide to generate fragmentation product 149 and 152, respectively.\(^{[55]}\)

Corey used a fragmentation reaction in his synthesis of \( \beta \)-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 \( \beta \)-caryophyllene (157).

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.
Eschenmoser described a decarboxylative double fragmentation as macrolide synthesis, generating two double bonds in one step (Scheme 36).\textsuperscript{[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 dioxonium ion to give two double bonds - a disubstituted (Z)- and a trisubstituted (E)-olefin (Scheme 37).

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).\textsuperscript{[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]

As fragmentation precursor β-meslyoxy-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 R² 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 β,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 β-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.](image)

**5.2.1. Quaternary Center by Desymmetrization**

**Synthesis of the *meso* substrate**

The synthesis of side chain 185 was accomplished in a straightforward 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 \(\alpha\)-chiral aldehyde was C2 elongated by means of a Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions, giving exclusively \(\alpha,\beta\)-unsaturated \((E)\)-ester 184.\(^{[64]}\) DIBALH reduction to the corresponding allylic alcohol was followed by protection, to give elongated allylic carbonate 185.
Results and Discussion

![Chemical structures and reactions]

**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).\(^\text{[65, 66]}\) 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.\(^\text{[67]}\)

**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.\(^\text{[68, 69]}\)
Results and Discussion

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).
Results and Discussion

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] ¹H-NMR, ¹⁹F-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.
Selective manipulation of the methyl ester group

The great 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).

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.
Results and Discussion

**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.

<table>
<thead>
<tr>
<th>catalyst</th>
<th>solvent</th>
<th>rxn time</th>
<th>197 (eq.)</th>
<th>203 (eq.)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubbs II (5 mol%)</td>
<td>DCM</td>
<td>24 h</td>
<td>1</td>
<td>1</td>
<td>24%</td>
</tr>
<tr>
<td>Grubbs II (5 mol%)</td>
<td>DCM</td>
<td>24 h</td>
<td>1</td>
<td>2</td>
<td>26%</td>
</tr>
<tr>
<td>Grubbs-Hoveyda II (5 mol%)</td>
<td>DCM</td>
<td>48 h</td>
<td>1</td>
<td>2</td>
<td>28%</td>
</tr>
<tr>
<td>Grubbs-Hoveyda II (10 mol%)</td>
<td>DCM</td>
<td>48 h</td>
<td>1</td>
<td>2</td>
<td>38%</td>
</tr>
<tr>
<td>Grubbs-Hoveyda II (10 mol%)</td>
<td>toluene</td>
<td>1 h</td>
<td>1</td>
<td>2</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Table 1*: Cross metathesis conditions.

At the same time, classical olefination methods such as Wittig reaction and Julia-Lythgoe-Kocienski reaction were also probed. 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).
Results and Discussion

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). Thus, alcohol 183 was transformed by Appel reaction into the corresponding iodide. Treatment with PPh₃ 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.](image)

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.](image)
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 \( \alpha \)-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.](image)

![Scheme 57: Aldol addition.](image)

Evans-Carreira \textit{anti}-reduction with triacetoxy boron hydride to generate \textit{anti} diol \( 217 \) was followed by hydrolysis of the methyl ester to the acid and the \( \delta \)-lactone ring was closed to generate fragmentation precursor \( 181 \) (Scheme 58).\[^79\]
Results and Discussion

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). MgBr₂·Et₂O 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: Et₂AlCl, SnCl₄, ZnCl₂, TiCl₄, Ti(OiPr)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 TiCl₄ and trimethyl silyl enol ether 219.
Results and Discussion

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 \( \alpha \)- and \( \beta \)-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, \( \alpha \)-bromo ketone 221 was prepared first\(^{[80]} \) and reacted with aldehyde 212; unfortunately just the use of Sml\(_2\) featured the Cram chelate product alas as the minor diastereoisomer in a 1:4 diastereomeric ratio (Scheme 62).
Results and Discussion

![Chemical Structures]

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.
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).\textsuperscript{[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.

The stereochemical outcome should be controlled by the chiral $\alpha$-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).
Results and Discussion

In literature, high stereocontrol in acetate aldol additions is only observed when the acetated Crimmins’ auxiliary is employed.\textsuperscript{[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 $\beta$-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 $\delta$-position, the later C15, had to be inverted which is possible by simple generating $\text{syn}$ diol 232 instead of $\text{anti}$ 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 $\text{syn}$ diol 231.\textsuperscript{[83]}
Results and Discussion

<table>
<thead>
<tr>
<th>reagent</th>
<th>product syn:anti (231:232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEt₃, MeOH, NaBH₄ (-30 °C)</td>
<td>3:1</td>
</tr>
<tr>
<td>BEt₃, MeOH, NaBH₄ (-78 °C)</td>
<td>4:1</td>
</tr>
<tr>
<td>BBu₃, MeOH, NaBH₄ (0 °C)</td>
<td>borane ester very stable</td>
</tr>
<tr>
<td>DIBALH</td>
<td>ester reduced, TBS deprotected</td>
</tr>
<tr>
<td>Zn(BH₄)₂</td>
<td>1:1, ester reduced</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>1:1, ester reduced</td>
</tr>
<tr>
<td>SmI₂, NEt₃, H₂O</td>
<td>no reaction</td>
</tr>
<tr>
<td>catecholborane</td>
<td>86% only syn (231)</td>
</tr>
</tbody>
</table>

Table 2: Conditions for syn reduction of hydroyx 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 NaBH₄ at low temperatures led exclusively to desired δ-lactone 181.

Scheme 67: Fragmentation precursor 181.
Results and Discussion

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

\[ \text{Scheme 68: NOE signals of fragmentation precursor 181.} \]

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.

\[ \text{Scheme 69: Fragmentation of 181.} \]

To finish the formal synthesis, the free secondary alcohol was protected as silyl ether 33.\(^{[25, 33, 84]} \]
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).

Fragmentations

With all four diastereoisomers in hand, the leaving group in form of a mesylate was introduced under standard conditions, methansulfonyl chloride in Et2O and triethylamine, and used directly in the following fragmentation reaction. Lactones 181 and 218 with a syn
Results and Discussion

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 unstable triflate (Table 3).
**Results and Discussion**

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

![Scheme 74](image)

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

<table>
<thead>
<tr>
<th>LG</th>
<th>T</th>
<th>243</th>
<th>244</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMs</td>
<td>0 °C</td>
<td>34%</td>
<td>36%</td>
</tr>
<tr>
<td>OMs</td>
<td>r.t.</td>
<td>24%</td>
<td>46%</td>
</tr>
<tr>
<td>OTf</td>
<td>0 °C</td>
<td>23%</td>
<td>21%</td>
</tr>
<tr>
<td>OTs</td>
<td>r.t.</td>
<td>35%</td>
<td>36%</td>
</tr>
</tbody>
</table>

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.

![Scheme 75](image)
### Table 4: Variation of the temperature in the fragmentation of 237.

<table>
<thead>
<tr>
<th>base</th>
<th>T</th>
<th>247</th>
<th>248</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOH</td>
<td>r.t.</td>
<td>52%</td>
<td>36%</td>
</tr>
<tr>
<td>LiOH</td>
<td>0 °C</td>
<td>43%</td>
<td>34%</td>
</tr>
</tbody>
</table>

**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-butylidemethylsily ether, here the allylic alcohol in δ-position can be selectively protected with TBSCI 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
Results and Discussion

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). 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 carbonyldimidazole. 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.](image)

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
Results and Discussion

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](image)

**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](image)

**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. 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). 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. 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 bulb-to-bulb 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). 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.
Results and Discussion

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.

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.

<table>
<thead>
<tr>
<th>Pd/Ln*</th>
<th>base</th>
<th>solvent</th>
<th>yield</th>
<th>ax:eq 273a:273b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh3)4</td>
<td>K2CO3</td>
<td>H2O/EtOAc</td>
<td>98%</td>
<td>3:1</td>
</tr>
<tr>
<td>Pd2(dba)3·CHCl3 (R,R)-Trost DACH</td>
<td>LDA</td>
<td>THF</td>
<td>lactone opening</td>
<td>-</td>
</tr>
<tr>
<td>Pd2(dba)3·CHCl3 (R,R)-Trost DACH</td>
<td>LiHMDS</td>
<td>THF</td>
<td>82%</td>
<td>1:2</td>
</tr>
<tr>
<td>Pd2(dba)3·CHCl3 (R,R)-Trost DACH</td>
<td>DBU</td>
<td>toluene</td>
<td>60%</td>
<td>2:3</td>
</tr>
<tr>
<td>Pd2(dba)3·CHCl3 (S,S)-Trost DACH</td>
<td>LiHMDS</td>
<td>THF</td>
<td>75%</td>
<td>3:1</td>
</tr>
<tr>
<td>Pd2(dba)3·CHCl3 (S,S)-Trost DACH</td>
<td>DBU</td>
<td>toluene</td>
<td>92%</td>
<td>7:2</td>
</tr>
</tbody>
</table>

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). 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.

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).

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.
Results and Discussion

<table>
<thead>
<tr>
<th>Pd/Lₜₜ*</th>
<th>OLG</th>
<th>base</th>
<th>solvent</th>
<th>yield</th>
<th>ax: eq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OTroc</td>
<td>K₂CO₃</td>
<td>H₂O/EtOAc</td>
<td>97%</td>
<td>3:1</td>
</tr>
<tr>
<td>Pd₂(dba)₃·CHCl₃ (R,R)-Trost DACH</td>
<td>OTroc</td>
<td>DBU</td>
<td>toluene</td>
<td>60%</td>
<td>2:3</td>
</tr>
<tr>
<td>Pd₂(dba)₃·CHCl₃ (S,S)-Trost DACH</td>
<td>OTroc</td>
<td>DBU</td>
<td>toluene</td>
<td>54%</td>
<td>3:2</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OTroc</td>
<td>DBU</td>
<td>toluene</td>
<td>41%</td>
<td>3:1</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OC(O)CH₂Cl</td>
<td>DBU</td>
<td>toluene</td>
<td>17%</td>
<td>4:1</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OC(O)OEt</td>
<td>DBU</td>
<td>toluene</td>
<td>34%</td>
<td>4:1</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OC(O)OEt</td>
<td>-</td>
<td>H₂O/EtOAc</td>
<td>85%</td>
<td>4:1</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>OC(O)OEt</td>
<td>K₂CO₃</td>
<td>H₂O/EtOAc</td>
<td>97%</td>
<td>4:1</td>
</tr>
</tbody>
</table>

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

Comparison with literature revealed the nucleophiles 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 far 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
Results and Discussion

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.](image)

**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 K₂CO₃ 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.](image)

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.
5.3.4. Fragmentation

Going on with the epimeric mixture of lactone 284, mesylation installed the required leaving group in $\beta$-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 $\alpha$- and $\beta$-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 $\beta$-hydroxyl group and axial side chain in the fragmentation reaction, which produced 264 in 91% yield.
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 nBuLi 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.

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

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).

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.
Results and Discussion

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

\[
\begin{align*}
\text{MeO} & \quad \text{PLE} (95\%) \\
\text{HO} & \quad \text{1,ClCO}_2\text{Me} (68\%) \\
\text{HO} & \quad \text{2,NaBH}_4 \\
\end{align*}
\]

\textit{Scheme 98: Enzymatic desymmetrization and reduction to alcohol 298.}

\[
\text{Determination of the enantiomeric ratio of 298}
\]

Alcohol 298 was converted into Mosher's ester 299 and 300 and HPLC analyses, \textsuperscript{1}H-NMR and \textsuperscript{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.

\[
\begin{align*}
\text{HO} & \quad (R)-\text{MTPACl, DMAP, NEt}_3 \\
\text{HO} & \quad (S)-\text{MTPACl, DMAP, NEt}_3 \\
\end{align*}
\]

\textit{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).
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]

![Diagram of Scheme 101](image1)

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.

![Diagram of Scheme 102](image2)

Scheme 102: Paterson aldol addition.
Results and Discussion

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.

![Scheme 103: Reduction to *anti* diol 304.](image)

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.

![Scheme 104: Generation of δ-lactone 305.](image)
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.\cite{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.](image)

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.](image)
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.](image)

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 bulb-to-bulb 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 acotropic 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.](image)
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).\cite{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 $\alpha$-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 methyl iodide 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 $\beta$-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 nucleophile and its steric repulsion will promote the transfer of the siloxy methyl moiety.

![Scheme 114: Organoaluminium-catalyzed rearrangement of epoxides.](image)

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).](image)

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. This reaction can be performed with catalytic amounts of MABR on multi-gram scale.

![Scheme 116: Yamamoto’s organoaluminium-promoted rearrangement.](image)

### 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. 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, which proceeded very slowly and therefore was stopped after three days and 50% conversion.
Results and Discussion

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.
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
Results and Discussion

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.
<table>
<thead>
<tr>
<th>acid</th>
<th>eq.</th>
<th>rxn time</th>
<th>products</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA</td>
<td>0.2</td>
<td>4 h</td>
<td>36% 356 and 38% 357</td>
</tr>
<tr>
<td>CSA</td>
<td>0.1</td>
<td>2 h</td>
<td>68% 356 and 31% 346</td>
</tr>
<tr>
<td>pTsOH</td>
<td>0.2</td>
<td>2 h</td>
<td>26% 356 and mixture of 346 and 357</td>
</tr>
<tr>
<td>PPTS</td>
<td>0.5</td>
<td>8 h</td>
<td>58% 356 and mixture of 346 and 357</td>
</tr>
</tbody>
</table>

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.](image)

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 CH₂Cl₂: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.](image)

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 mCPBA. 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.](image)

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.](image)
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 methyl iodide 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.
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 (4R)-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.

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.](image)

**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.](image)

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

\[
\begin{align*}
\text{MeO} & \text{OH} \\
\text{ent-182} & \\
\xrightarrow{1. \text{PG}} & \text{MeN} \\
2. \text{MeNHOMe+HCl,} & \text{OPG} \\
\xrightarrow{i\text{PrMgCl}} & \text{EtMgBr} \\
& \text{OPG}
\end{align*}
\]

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, tBuOK 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.

\[
\begin{align*}
\text{PGO} & \text{OH} \\
\text{383} & \\
\xrightarrow{1. \text{IBX}} & \text{PPh3Br} \\
\xrightarrow{2. \text{base},} & \text{PG} = \text{TES, THP, TIPS, TBDPS}
\end{align*}
\]

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). 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.
Results and Discussion

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.\textsuperscript{[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).

<table>
<thead>
<tr>
<th>ketone</th>
<th>LA, base</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>382</td>
<td>(-)-Ipc\textsubscript{2}BOTf, DIPEA</td>
<td>no reaction</td>
</tr>
<tr>
<td>380</td>
<td>(-)-Ipc\textsubscript{2}BOTf, DIPEA</td>
<td>no reaction</td>
</tr>
<tr>
<td>388</td>
<td>(-)-Ipc\textsubscript{2}BOTf, DIPEA</td>
<td>no reaction</td>
</tr>
<tr>
<td>382</td>
<td>LiHMDS</td>
<td>1:1</td>
</tr>
<tr>
<td>388</td>
<td>LiHMDS</td>
<td>3:2</td>
</tr>
<tr>
<td>388</td>
<td>Bu\textsubscript{2}BOTf, TEA</td>
<td>1 diast.</td>
</tr>
<tr>
<td>382</td>
<td>Bu\textsubscript{2}BOTf, TEA</td>
<td>1 diast.</td>
</tr>
</tbody>
</table>

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.\textsuperscript{[111]} With \(\alpha\)-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).

\[ \text{Scheme 136: Aldolization with dibutylboron triflate.} \]

\[ \text{Determination of the configuration at C17 and C18} \]

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]
Results and Discussion

Scheme 137: Determination of the absolute configuration at C17.

To prove the *syn* selectivity of the aldol addition cyclic acetal *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).
To validate this unexpected result, namely the aldol reaction via the (E)-enolate despite 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.
Results and Discussion

**Stepwise elongation**

Thus, the synthetic strategy was changed to a stepwise 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.](image)

Then a second aldol addition should be performed, 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.](image)

**Model substrate**

As model substrate stereotriad 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.](image)

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.](image)
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). 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. 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.

<table>
<thead>
<tr>
<th>LA</th>
<th>eq.</th>
<th>additives</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgCl₂</td>
<td>0.1 (in EtOAc)</td>
<td>TMSCl, NaSbF₆</td>
<td>63% sm</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>0.1 (in THF)</td>
<td>TMSCl, NaSbF₆</td>
<td>50% sm</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>0.2</td>
<td>TMSCl</td>
<td>52% sm</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>2 + 20 eq. NEt₃</td>
<td>TMSCl</td>
<td>60% TMS enol ether of sm</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>2 + 3 eq. NEt₃</td>
<td>TMSCl</td>
<td>35% 1:2 mix</td>
</tr>
<tr>
<td>Cy₂BCl</td>
<td>1.2</td>
<td>-</td>
<td>59% sm</td>
</tr>
</tbody>
</table>

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

**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 (\textit{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]
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.

![Scheme 149: Retrosynthetic analysis of peloruside A (2).](image)

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.

![Scheme 150: Synthetic strategy for peloruside A fragment 420.](image)

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.](image)

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.](image)
7.3. Enzymatic Desymmetrisation with PLE

7.3.1. Quaternary Center by Desymmetrisation

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.\textsuperscript{119}

\[
\text{MesO} \quad \text{O} \quad \text{OMe} \quad \text{OrBu} \quad \xrightarrow{\text{PLE}} \quad \text{HO} \quad \text{O} \quad \text{(R-CO}_2\text{Me)} \quad \text{OrBu} \quad 96\%\text{ ee}
\]

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).\textsuperscript{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.

\[
\text{MOMCl} + \text{tBuOH} \xrightarrow{\text{NaH}} \text{MOMtBu} \xrightarrow{\text{BO}_{3}} \text{tBuOCH}_2\text{Cl} \xrightarrow{\text{hv, NCS, CCl}_4} \text{tBuOMe}
\]

\[
\text{MeO} \quad \text{O} \quad \text{OMe} \xrightarrow{\text{Nal, tBuOCH}_2\text{Cl}} \text{(65\%)} \quad \text{MeO} \quad \text{O} \quad \text{OMe} \xrightarrow{\text{NaH, MeI}} \text{(92\%)} \quad \text{MeO} \quad \text{O} \quad \text{OMe}
\]

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.
<table>
<thead>
<tr>
<th>eq. (LiBH₄)</th>
<th>T</th>
<th>rxn time</th>
<th>solvent</th>
<th>products</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-20 °C</td>
<td>3 h</td>
<td>Et₂O, 0.25% MeOH</td>
<td>21% 432</td>
</tr>
<tr>
<td>1.5</td>
<td>-20 °C</td>
<td>4 h</td>
<td>Et₂O, 0.5% MeOH</td>
<td>28% 432; 29% 434</td>
</tr>
<tr>
<td>1.5</td>
<td>-20 °C</td>
<td>3 h</td>
<td>Et₂O, 0.5% H₂O</td>
<td>decomposition</td>
</tr>
<tr>
<td>1.5</td>
<td>-20 °C</td>
<td>3 h</td>
<td>THF</td>
<td>no rxn</td>
</tr>
<tr>
<td>1.3</td>
<td>-10 °C</td>
<td>0.5 h</td>
<td>Et₂O, 2% MeOH</td>
<td>66% 432</td>
</tr>
<tr>
<td>1</td>
<td>0 °C</td>
<td>0.5 h</td>
<td>Et₂O, 2% MeOH</td>
<td>25% 432, 27% 434</td>
</tr>
<tr>
<td>1</td>
<td>0 °C</td>
<td>0.5 h</td>
<td>Et₂O, 1% MeOH</td>
<td>56% 432, 12% 434</td>
</tr>
<tr>
<td>1</td>
<td>0 °C</td>
<td>0.5 h</td>
<td>Et₂O, 0.5% MeOH</td>
<td>80% 432</td>
</tr>
<tr>
<td>0.75</td>
<td>0 °C</td>
<td>0.5 h</td>
<td>Et₂O, 2% MeOH</td>
<td>26% 432, 27% 434, 25% 431</td>
</tr>
</tbody>
</table>

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).

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.\textsuperscript{123} Catalytic amounts of TFA yielded monoprotected diol 438 an intermediate form Gosh’s synthesis (Scheme 159).\textsuperscript{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 $\alpha$-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 $\alpha$-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).

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.
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.

<table>
<thead>
<tr>
<th>reagent (ligand)</th>
<th>yield</th>
<th>440:441</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-iPc</td>
<td>51%</td>
<td>3:1</td>
</tr>
<tr>
<td>(+)-iPc</td>
<td>quant.</td>
<td>20:1</td>
</tr>
<tr>
<td>L-(+)-DIPT</td>
<td>69%</td>
<td>8:1</td>
</tr>
<tr>
<td>D-(-)-DIPT</td>
<td>60%</td>
<td>20:1</td>
</tr>
</tbody>
</table>

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.](image-url)
Results and Discussion

<table>
<thead>
<tr>
<th>LA</th>
<th>T</th>
<th>X</th>
<th>yield</th>
<th>440:441</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF₃·Et₂O</td>
<td>-78 °C</td>
<td>TMS</td>
<td>84%</td>
<td>440</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>-78 °C</td>
<td>TMS</td>
<td>85%</td>
<td>441</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>-78 °C</td>
<td>SnBu₃</td>
<td>quant.</td>
<td>1:2</td>
</tr>
<tr>
<td>MgBr₂·Et₂O</td>
<td>r.t.</td>
<td>SnBu₃</td>
<td>87%</td>
<td>1:7</td>
</tr>
</tbody>
</table>

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

In the Paterson aldol addition the stereocontrol comes from the methyl center of the ethyl ketone and the enolate geometry. Thus with ethyl ketone \( \text{380} \) 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 \( \text{439} \) (Scheme 164). This was also found in the products, as there was in general a good diastereomeric ratio.

\[
\begin{align*}
\text{BnO} & \quad \text{O} \\
\text{380} \\
\text{BnO} & \quad \text{O} \\
\text{439} & \quad \text{BnO} & \quad \text{O} \\
\text{Cy_2BCl, NEt_3} & \quad \text{(87\%)} & \quad \text{9:1} \\
\text{BnO} & \quad \text{O} \\
\text{444} \\
\text{BnO} & \quad \text{O} \\
\text{439} & \quad \text{Bu_2BOTf, NEt_3} & \quad \text{(15\%)} & \quad \text{4:1} & \quad \text{(98\% b.r.s.m.)} \\
\text{BnO} & \quad \text{O} \\
\text{445} \\
\end{align*}
\]

Scheme 164: Matched boron mediated aldol additions.

When ethyl ketone \( \text{ent-380} \) 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).
Results and Discussion

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.

<table>
<thead>
<tr>
<th>R</th>
<th>LA</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>MgBr$_2$·Et$_2$O</td>
<td>91%</td>
</tr>
<tr>
<td>H</td>
<td>TiCl$_4$</td>
<td>no rxn</td>
</tr>
<tr>
<td>H</td>
<td>-</td>
<td>97%</td>
</tr>
<tr>
<td>OMe</td>
<td>MgBr$_2$·Et$_2$O</td>
<td>71%</td>
</tr>
<tr>
<td>OMe</td>
<td>TiCl$_4$</td>
<td>no rxn</td>
</tr>
<tr>
<td>OMe</td>
<td>-</td>
<td>72%</td>
</tr>
</tbody>
</table>

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.

Scheme 168: Mukaiyama aldol addition.

<table>
<thead>
<tr>
<th>R</th>
<th>LA</th>
<th>SiR'₃</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>MgBr₂·Et₂O</td>
<td>TBS</td>
<td>no rxn</td>
</tr>
<tr>
<td>H</td>
<td>TiCl₄</td>
<td>TBS</td>
<td>35%</td>
</tr>
<tr>
<td>H</td>
<td>SnCl₄</td>
<td>TBS</td>
<td>no rxn</td>
</tr>
<tr>
<td>H</td>
<td>MgBr₂·Et₂O</td>
<td>TMS</td>
<td>no rxn</td>
</tr>
<tr>
<td>H</td>
<td>SnCl₄</td>
<td>TMS</td>
<td>no rxn</td>
</tr>
<tr>
<td>H</td>
<td>TiCl₄</td>
<td>TMS</td>
<td>42% (1 h), 34% (2.5 h)</td>
</tr>
<tr>
<td>OMe</td>
<td>TiCl₄</td>
<td>TMS</td>
<td>59%</td>
</tr>
</tbody>
</table>

Table 14: Mukaiyama aldol addition.
8.3. Fragmentations

8.3.1. Fragmentation Precursors

To prove the relative configuration between $\alpha$- and $\beta$-center of the adducts gained in the aldol additions, the corresponding $\delta$-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 $\delta$-lactones (Scheme 169).

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 $\delta$-lactones (Scheme 170).
Results and Discussion

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).
Results and Discussion

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).

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).

\[
\begin{align*}
\text{439} & \xrightarrow{\text{EtMgBr}} \text{OH} \xrightarrow{\text{IBX}} \text{487} \\
\text{EtMgBr} & \quad (71\%) \quad 4:1 \\
\text{IBX} & \quad (81\%)
\end{align*}
\]

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.

\[
\begin{align*}
\text{488} & \quad R = H \\
\text{490} & \quad R = \text{OMe} \\
\text{487} & \xrightarrow{\text{Bu₂BOTf, NEt₃}} \text{489} \quad R = H \quad (58\%) \quad 1:1 \\
& \quad \text{491} \quad R = \text{OMe} \quad (42\%) \quad 1:1
\end{align*}
\]

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).
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 TiCl₄, SnCl₄ and MgBr₂·Et₂O and the Felkin-Anh product with BF₃·Et₂O. 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 Sn2 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 $\alpha$-substituents, to generate more complex trisubstituted olefins. The introduction of a second $\beta$-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 F₂₅₄ 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. H₂SO₄ (25 mL)], *Ceric(IV) sulfate* [Ce(SO₄)₂ (0.1 g), phosphormolybdic acid (20 g) in H₂SO₄ (10%, 400 mL)], *Vanilline* [vanilline (0.5 g) in ethanol (20 mL) and H₂SO₄ (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 CDCl₃ solutions and referenced to the residual CHCl₃ 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.
Experimental Section

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.

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

**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 NH₄Cl solution, layers were separated and the aqueous solution was extracted with Et₂O. The combined organic layers were dried over MgSO₄ 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.

R_f = 0.64 (hexane:EtOAc = 3:1)

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): δ = 172.3, 132.5, 119.1, 53.6, 52.4, 40.2, 19.8.


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

To malonate 193 (3.00 g, 16 mmol) suspended in 0.05M KH₂PO₄ 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 Et₂O. Upon acidification with 3N HCl to pH 1 mono acid 194
Experimental Section

was extracted with DCM, the organic layers were dried over MgSO₄ 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.

Rₜ = 0.08 (hexane:EtOAc = 1:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ 1.32 (c = 2.8, CHCl₃)

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.

Rₜ = 0.09 (hexane:EtOAc = 1:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): δ = 175.9, 172.2, 53.6, 52.7, 38.2, 20.3, 17.9, 14.2.


[α]D²⁰ -1.92 (c = 2.45, CHCl₃)
(S)-2-Hydroxymethyl-2-methyl-pent-4-enoic acid methyl ester (197)

![Chemical Structure]

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 Et₂O and the combined organic phase was concentrated. The residue was dissolved in methanol (25 mL) and cooled to 0 °C where NaBH₄ (1.88 g, 50.00 mmol) was added portion wise. After 1 h the reaction was carefully quenched with a saturated solution of NH₄Cl and extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) gave 2.95 g (75%) of alcohol 197.

Rᵣ = 0.34 (hexane:EtOAc = 3:1)

**¹H-NMR** (400 MHz, CDCl₃): 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).

**¹³C-NMR** (100 MHz, CDCl₃): 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.


[α]D⁻²⁰ -4.40 (c = 1.5, CH₂Cl₂)

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 NH₄Cl solution was added and the layers were separated. The aqueous layer was extracted with DCM, the combined organic
Experimental Section

Layer was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 20 mg (90%) of the MTPA esters.

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

(R)-MTPA ester (198)

![R-MTPA ester (198)](image)

Major:

¹H-NMR (400 MHz, CDCl₃): 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:

¹H-NMR (400 MHz, CDCl₃): δ = 7.49 (m, 2H), 7.39 (m, 3H), 5.70-5.62 (m, 1H), 5.10-5.02 (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)

![S-MTPA ester (199)](image)

Major:

¹H-NMR (600 MHz, CDCl₃): 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).
Experimental Section

Minor:

\(^1H\)-NMR (600 MHz, CDCl\(_3\)) \(\delta = 7.49 \text{ (m, } 2\text{H}), 7.40 \text{ (m, } 3\text{H}), 5.70-5.62 \text{ (m, } 1\text{H}), 5.10-5.02 \text{ (m, } 2\text{H}), 4.42 \text{ (d, } J = 10.85 \text{ Hz, } 1\text{H}), 4.27 \text{ (d, } J = 10.85 \text{ Hz, } 1\text{H}), 3.62 \text{ (s, } 3\text{H}), 3.52 \text{ (s, } 3\text{H}), 2.35 \text{ (dd, } J = 13.91, 7.55 \text{ Hz, } 1\text{H}), 2.31 \text{ (dd, } J = 14.03, 7.67 \text{ Hz, } 1\text{H}), 1.20 \text{ (s, } 3\text{H}).

\((R)-2\text{-Allyl-2-methyl-malonic acid tert-butyl ester methyl ester (201)}\)

![Image](image.png)

To acid 194 (100 mg, 0.58 mmol) in DCM (2 mL) was added a catalytic amount of H\(_2\)SO\(_4\)\text{conc.} 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.

\(R_f = 0.64 \text{ (hexane:EtOAc = 10:1)}\)

\(^1H\)-NMR (400 MHz, CDCl\(_3\)) \(\delta = 5.75-5.65 \text{ (m, } 1\text{H}), 5.13-5.08 \text{ (m, } 2\text{H}), 3.71 \text{ (s, } 3\text{H}), 2.57 \text{ (d, } J = 7.32 \text{ Hz, } 2\text{H}), 1.43 \text{ (s, } 9\text{H}), 1.35 \text{ (s, } 3\text{H}).

\(^{13}C\)-NMR (100 MHz, CDCl\(_3\)) \(\delta = 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-CH\(_3\)]\(^+\) calcd for C\(_{11}\)H\(_{17}\)O\(_4\): 213.1127, found: 213.1131.  
\([\alpha]_D^{20} = 8.42 \text{ (c } = 1.2, \text{ CH}_2\text{Cl}_2)\)
(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:Et₂O (1:1). The combined organic layers were dried over MgSO₄ 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.

Rf = 0.27 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): δ = 176.1, 133.5, 118.2, 81.1, 67.9, 47.7, 40.2, 28.1, 19.7.


(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 NaHCO₃ was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 75 mg (75%) of aldehyde 202 as colorless oil.
Rf = 0.74 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ 7.11 (c = 0.45, CH₂Cl₂)

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

\[
\text{MeO} \quad \text{OTBS}
\]

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 TBSCI (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 Et₂O. The combined organic solution was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) furnished 3.9 g (quant.) of the TBS ether 493 as colorless oil.

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

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): δ = 175.4, 65.2, 51.5, 42.5, 25.6, 18.2, 13.4, -5.5.

[α]D²⁰ -18.10 (c = 3.03, CHCl₃)
Experimental Section

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

\[
\text{HO} \quad \text{OTBS}
\]

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:Et2O (1:1) and the combined organic solution was dried over MgSO4. 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.

\[ R_f = 0.23 \text{ (hexane:EtOAc = 10:1)} \]

\[ ^{1}H\text{-NMR} \text{ (400 MHz, CDCl}_3\text{): } \delta = 3.72 \text{ (dd, } J = 10.0, \text{ 4.0 Hz, 1H}), 3.61 \text{ (m, 2H), } 3.53 \text{ (dd, } J = 10.0, 8.0 \text{ Hz, 1H}), 2.78 \text{ (dd, Hz, } J = 6.0, 4.5 \text{ Hz, 1H}), 1.93 \text{ (m, 1H), } 0.89 \text{ (s, 9H), } 0.83 \text{ (d, } J = 6.5 \text{ Hz, 3H), } 0.06 \text{ (s, 6H).} \]

\[ ^{13}C\text{-NMR} \text{ (100 MHz, CDCl}_3\text{): } \delta = 68.8, 68.3, 37.0, 25.9, 18.2, 13.1, -5.6. \]

\[ [\alpha]_D^{20} = -20.60 \text{ (c = 0.8, CHCl}_3\text{)} \]

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

\[
\text{O} \quad \text{OTBS}
\]

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 NH4Cl solution, the organic layer separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over MgSO4 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.
**Experimental Section**

1H-NMR (250 MHz, CDCl₃): 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)**

![Structural formula of tert-Butyl-dimethyl-((S)-2-methyl-but-3-enyloxy)-silane]

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)

1H-NMR (400 MHz, CDCl₃): 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).

13C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -6.00 (c = 1.15, CH₂Cl₂)

2-[(R)-3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propylsulfanyl]-benzothiazole (495)

![Structural formula of 2-[(R)-3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-propylsulfanyl]-benzothiazole]

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-mercaptopbenzothiazole (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 NaHCO₃
Experimental Section

was added and the mixture was filtered over celite. The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic layer was dried over MgSO₄, 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.

Rₚ = 0.79 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -6.41 (c = 1.45, CH₂Cl₂)

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 Et₂O. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) gave 780 mg (90%) of sulfone 206 as pale yellow oil.

Rₚ = 0.39 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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
Experimental Section

= 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).

\(^{13}\text{C-NMR}\) (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.

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

\(\text{HRMS}\) (ESI) (m/z): [M-CH\(_3\)]\(^+\) calcd for C\(_{16}\)H\(_{22}\)O\(_3\)NSiS\(_2\): 370.0967, found: 370.0969.

\([\alpha]_D^{20}\) 0.56 (c = 1.25, CH\(_2\)Cl\(_2\))

\textit{tert-Butyl-(3-iodo-2-methyl-propoxy)-dimethyl-silane (496)}

\[
\text{I} \quad \text{OTBS}
\]

To a solution of alcohol 183 (200 mg, 0.98 mmol) in acetonitrile (6 mL) and Et\(_2\)O (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\(_2\)S\(_2\)O\(_3\) solution and the layers were separated. The aqueous layer was extracted with Et\(_2\)O and the combined organic phases were washed with a saturated Na\(_2\)S\(_2\)O\(_3\) 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)

\(^1\text{H-NMR}\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): δ = 66.7, 37.4, 25.9, 17.2, 13.8, -5.4.

\(\text{HRMS}\) (ESI) (m/z): [M-CH\(_3\)]\(^+\) calcd for C\(_9\)H\(_{20}\)OISi: 299.0328, found: 299.0325.
Experimental Section

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

![Chemical Structure](image)

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 Et₂O. The combined ethereal phase was washed with water, dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) gave 3.10 g of silyl ether 208 as colorless oil.

Rₛ = 0.76 (hexane:EtOAc = 10:1)

**¹H-NMR** (400 MHz, CDCl₃): 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).

**¹³C-NMR** (100 MHz, CDCl₃): 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.


[α]₂₀ D -3.00 (c = 1.2, CH₂Cl₂)

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

![Chemical Structure](image)

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.
**Experimental Section**

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

\(^1\)H-NMR \((400 \text{ MHz, CDCl}_3)\): \( \delta = 9.77 \) (dd, \( J = 2.28, 1.76 \text{ Hz, 1H} \)), 3.87 (d, \( J = 9.36 \text{ Hz, 1H} \)), 3.71 (s, 3H), 3.55 (d, \( J = 9.60 \text{ Hz, 1H} \)), 2.75 (dd, \( J = 16.68, 2.28 \text{ Hz, 1H} \)), 2.60 (dd, \( J = 16.64, 1.76 \text{ Hz, 1H} \)), 1.24 (s, 3H), 0.93 (t, \( J = 7.96 \text{ Hz, 9H} \)), 0.57 (q, \( J = 7.92 \text{ Hz, 6H} \)).

\(^{13}\)C-NMR \((100 \text{ MHz, CDCl}_3)\): \( \delta = 201.00, 175.4, 68.2, 52.0, 48.8, 46.7, 20.7, 6.6, 4.2.\)

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

HRMS \((\text{ESI})\) \((m/z)\): [M-C\(_2\)H\(_5\)]\(^+\) calcd for C\(_{11}\)H\(_{21}\)O\(_4\)Si: 245.1209, found: 245.1205.

\([\alpha]_D^{20}\) 5.00 \((c = 0.8, \text{CH}_2\text{Cl}_2)\)

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

**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 \((400 \text{ MHz, CDCl}_3)\): \( \delta = 5.41-5.32 \) (m, 2H), 3.64 (s, 3H), 3.65 (d, \( J = 9.36 \text{ Hz, 1H} \)), 3.55 (d, \( J = 9.36 \text{ Hz, 1H} \)), 3.47 (dd, \( J = 9.72, 5.92 \text{ Hz, 1H} \)), 3.35 (d, \( J = 7.32 \text{ Hz, 1H} \)), 2.31 (dd, \( J = 13.01, 5.68 \text{ Hz, 1H} \)), 2.28 (m, 1H), 2.15 (dd, \( J = 13.13, 6.31 \text{ Hz, 1H} \)), 1.12 (s, 3H), 0.96 (d, \( J = 6.57 \text{ Hz, 3H} \)), 0.94 (t, \( J = 7.96 \text{ Hz, 9H} \)), 0.89 (s, 9H), 0.56 (q, \( J = 7.99 \text{ Hz, 6H} \)), 0.03 (s, 6H).
Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta = 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$_3$]$^+$ calc for C$_{22}$H$_{45}$O$_4$Si$_2$: 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$_4$Cl 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$_3$): $\delta = 5.41$-$5.32$ (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$_3$): $\delta = 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$_3$): $\delta = 5.31$-$5.24$ (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$_3$): $\delta = 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$_2$H$_5$]$^+$ calc for C$_{21}$H$_{43}$O$_4$Si$_2$: 415.2700, found: 415.2693.
(2S,6S)-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 MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 920 mg (92%) of alcohol 497 as colorless oil.

Rᵣ = 0.40 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.

Experimental Section

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

Olefin 497 (930 mg, 2.8 mmol) and PtO₂ (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.

Rᶠ = 0.40 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D₂₀⁻²⁺ -2.48 (c = 1.25, CH₂Cl₂)
(2S,6S)-7-(tert-Butyl-dimethyl-silylloxy)-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 NaHCO₃ was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 635 mg (91%) of aldehyde 212 as colorless oil.

Rₛ = 0.78 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]ₜ⁰⁻²⁻¹.55 (c = 0.9, CH₂Cl₂)
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 Et₂O. The aqueous layer was cautiously neutralized with solid NaHCO₃ and extracted with DCM. The combined extracts were dried over MgSO₄ 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.

Rₛ = 0.25 (hexane:EtOAc = 2:1)

¹H-NMR (400 MHz, CDCl₃): 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 MgSO₄ and the solvent was evaporated to yield 2.2 g (97%) of aldehyde 130 as a yellow powder.

Rₛ = 0.20 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃): δ = 10.0 (s, 1H), 8.05 (s, 1H), 2.81 (s, 3H)
Experimental Section

\[ mp = 56 \, ^\circ C \]

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

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

\[ ^1\text{H-NMR (250 MHz, CDCl}_3\text{): } \delta = 3.79 (d, J_{\text{HH}} = 11.18 \text{ Hz, } 6\text{H}), 3.10 (d, J_{\text{PH}} = 22.84 \text{ Hz, } 2\text{H}), 2.33 (s, 3\text{H}) \]

\[ \text{bp} = 97 \, ^\circ C / 5 \text{ mbar} \]

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

\[
\text{Phosphonate 498 (300 mg, 1.8 mmol) in THF (5 mL) was slowly added to a stirred suspension of NaH (64 mg, 1.8 mmol) in THF (5 mL) at 0 \, ^\circ C \text{ and the mixture was stirred at r.t. for } 1.5 \text{ h. MeI (0.1 mL, 2.2 mmol) was added and stirring was continued over night at r.t.}} \]

\[
\text{The reaction was quenched with saturated NH}_4\text{Cl solution and extracted with DCM. The combined extract was dried over MgSO}_4\text{ and the solvent was evaporated to give 280 mg (87\%) of alkylated phosphonate 215 as colorless liquid.}}
\]

\[ ^1\text{H-NMR (250 MHz, CDCl}_3\text{): } \delta = 3.78 (d, J_{\text{HH}} = 10.14 \text{ Hz, } 6\text{H}), 3.23 (dq, J_{\text{HH}} = 6.93 \text{ Hz, } J_{\text{PH}} = 24.90 \text{ Hz, } 1\text{H}), 2.34 (s, 3\text{H}), 1.37 (dd, J_{\text{HH}} = 7.19 \text{ Hz, } J_{\text{PH}} = 17.92 \text{ Hz, } 3\text{H}). \]
Experimental Section

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

A mixture of phosphonate 215 (250 mg, 1.4 mmol) and Ba(OH)$_2$·8H$_2$O (440 mg, 1.4 mmol) 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$_4$Cl 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$_3$): $\delta = 7.53$ (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$_3$): $\delta = 200.2, 161.5, 151.8, 137.7, 131.9, 121.2, 25.8, 19.2, 13.2$.

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


$mp = 69^\circ$C
**Experimental Section**

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

![Chemical structure](image)

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 MgBr₂·Et₂O (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 NH₄Cl solution was added and the aqueous phase was extracted with DCM. The combined organic layer was dried over MgSO₄ 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)

\[\text{IR (film): 3436, 2953, 1722, 1652, 1628, 1250, 1087 cm}^{-1}\]

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

\[\left[\alpha\right]_{D}^{20} = 26.15 (c = 1.3, \text{ CH}_2\text{Cl}_2)\]
Experimental Section

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

\[ \text{LiHMDS (1.22 mL, 1M in THF, 1.22 mmol) was added to methyl ketone 216 (150 mg, 0.82 mmol) in THF (3 mL) at -78 °C. After 1 h TMSCl (0.13 mL, 1.07 mmol), freshly distilled from CaH}_2, \text{ was added and stirring was continued for 30 min. The mixture was warmed to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in hexane and filtered over celite. After evaporation of the solvent, crude enol ether 219 was used directly in the following reaction.} \]

\[ ^1\text{H-NMR (400 MHz, C}_6\text{D}_6): \delta = 7.35 (s, 1H), 6.54 (s, 1H), 4.73 (s, 1H), 4.52 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H), 0.22 (s, 9H). \]

\[ ^13\text{C-NMR (100 MHz, CDCl}_3): \delta = 158.2, 154.4, 120.5, 117.7, 93.6, 18.9, 15.1, 0.08. \]

(E)-(2S,3S)-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\textsubscript{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\textsubscript{3} solution was cautiously added and layers were separated. The aqueous layer was extracted with DCM, the combined DCM solution was dried over MgSO\textsubscript{4} and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 34 mg (13%) of aldol adduct 180 as colorless oil.

\[ R_f = 0.14 \text{ (hexane:EtOAc = 3:1)} \]
1H-NMR (400 MHz, CDCl₃): 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).

13C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -28.88 (c = 0.8, CH₂Cl₂)

(2S,6S)-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 Et₂O, 0.35 mmol). After 1.5 h the reaction was quenched by the addition of a saturated NH₄Cl solution, the layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over MgSO₄ 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.

Rᵣ = 0.66 (hexane:EtOAc = 3:1)

1H-NMR (250 MHz, CDCl₃): 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).
(2S,6S)-2-Acetyl-7-(tert-butyl-dimethyl-silanyloxy)-2,6-dimethyl-heptanoic acid methyl ester (222)

\[
\text{O} \quad \text{OMe} \\
\text{O} \\
\text{OTBS}
\]

Dess-Martin periodinane (294 mg, 0.69 mmol) was added portionwise to alcohol 499 (80 mg, 0.23 mmol) in DCM (3 mL) at 0°C. After 4 h saturated NaHCO₃ solution was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 70 mg (88%) of methyl ketone 222.

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

\[^1\text{H-NMR}\ (400\ MHz,\ \text{CDCl}_3): \delta = 3.72\ (s,\ 3H),\ 3.38\ (ddd,\ J = 15.85,\ 9.78,\ 6.12\ Hz,\ 2H),\ 2.13\ (s,\ 3H),\ 1.89\ (ddd,\ J = 13.65,\ 12.25,\ 4.67\ Hz,\ 1H),\ 1.70\ (ddd,\ J = 13.84,\ 11.92,\ 4.62\ Hz,\ 1H),\ 1.57\ (m,\ 1H),\ 1.40\ (m,\ 1H),\ 1.33\ (s,\ 3H),\ 1.28-1.03\ (m,\ 3H),\ 0.88\ (s,\ 9H),\ 0.84\ (d,\ J = 6.60\ Hz,\ 3H),\ 0.02\ (s,\ 6H)\]

(E)-(2S,3R,5R)-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 NaHCO₃ and solid NaHCO₃ were added very carefully till gas evolution ceased. The aqueous layer
was extracted with DCM, the combined organic layer was dried over MgSO₄ 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)

**1H-NMR** (400 MHz, CDCl₃): 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).

**13C-NMR** (100 MHz, CDCl₃): 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.


$$[\alpha]_{D}^{20} = 14.60 \ (c = 0.5, \ CH₂Cl₂)$$

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

![Chemical Structure](image)

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 MgSO₄ 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)
Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_5$NSSi: 513.2945, found: 513.2936.

$[\alpha]_D^{20}$ -0.40 ($c$ = 0.5, CH$_2$Cl$_2$)

(E)-(2S,3R,5R)-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$_3$): $\delta$ = 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
Experimental Section

1H-NMR (400 MHz, CDCl3): 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).


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 MgSO4 and the solvent was evaporated. Column chromatography (hexane:EtOAc = 2:1) yielded 192 mg (85%) of lactone 218 as colorless oil.
Experimental Section

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

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.00 \) (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\(_3\)): \( \delta = 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\(^{-1}\).


\([\alpha]_D^{20}\) -6.60 (c = 2, CH\(_2\)Cl\(_2\))

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

\[
\text{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\(_3\)): \( \delta = 7.04 \) (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 = 6.84 Hz, 3H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -23.40 (c = 1.0, CH₂Cl₂)

(3S,4S,6R)-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 MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 1:1) yielded 18 mg (90%) of lactone 237 as colorless oil.

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

^{1}H-NMR (400 MHz, CDCl₃): 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, 9H), 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, CDCl₃): 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.
Experimental Section

**HRMS** (ESI) (m/z): [M+Na]$^+$ calcd for C$_{25}$H$_{43}$O$_4$NSiNa: 504.2580, found: 504.2589.

$[\alpha]_D^{20}$ 0.44 ($c = 1.1$, CH$_2$Cl$_2$)

(3S,4R,6S)-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)

![Chemical Structure](image)

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$_4$NSi: 481.2682, found: 481.2669.

$[\alpha]_D^{20}$ -0.54 ($c = 1.4$, CH$_2$Cl$_2$)
(3S,6R)-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 portionwise 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 = 3:1)

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 7.03$ (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$_3$): $\delta = 205.9$, 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$^{-1}$.


$[\alpha]_D^{20}$ 6.89 ($c = 1.2$, CH$_2$Cl$_2$)
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 MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 1:1) yielded 140 mg (93%) of lactone 181 as colorless oil.

Rᵣ = 0.48 (hexane:EtOAc = 1:1)

\[^{1}H\text{-NMR}\] (400 MHz, CDCl₃): 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).

\[^{13}C\text{-NMR}\] (100 MHz, CDCl₃): 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.


[α]_D⁰ = -11.45 (c = 2.0, CH₂Cl₂)

General procedure for the fragmentation reactions:

To a 0.1M solution of β-hydroxy lactone (1 eq.) in Et₂O:Et₃N (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 Et₂O. The combined ethereal layer was dried over MgSO₄ 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
NH₄Cl solution was added, layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated.

(1E,5Z)-(3S,10S)-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 Et₂O:Et₃N (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 Et₂O. The combined ethereal layer was dried over MgSO₄ 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 NH₄Cl solution was added, the layers were separated and the aqueous phase was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 17.5 mg (81%) of di-olefin 235 as colorless oil.

Rᵣ = 0.72 (hexane:EtOAc = 1:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ = -8.20 (c = 0.5, CH₂Cl₂)
Experimental Section

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

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

1H-NMR (400 MHz, CDCl3): 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).

13C-NMR (100 MHz, CDCl3): 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.


[α]D 20 5.10 (c = 1.0, CH2Cl2)

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

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

1H-NMR (400 MHz, CDCl3): 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).
15C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -9.06 (c = 0.85, CH₂Cl₂)

(3S,4S)-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]-4-methyl-oxetan-2-one (244)

1H-NMR (400 MHz, CDCl₃): 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).

13C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -25.90 (c = 1.35, CH₂Cl₂)
(1E,5E)-(3S,10S)-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:Et₂O (1:1). The combined organic layer was dried over MgSO₄ 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<sub>f</sub> = 0.35 (hexane:EtOAc = 3:1)

<sup>1</sup>H-NMR (400 MHz, CDCl₃): 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), 1.46-1.53 (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).

<sup>13</sup>C-NMR (100 MHz, CDCl₃): 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.


[α]₂⁰<sup>⁰</sup> -10.60 (c = 0.15, CH₂Cl₂)

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

R<sub>f</sub> = 0.36 (hexane:EtOAc = 3:1)
**Experimental Section**

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.94\) (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\(_3\)): \(\delta = 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\(^{-1}\).


\([\alpha]_D^{20}\) 1.73 (c = 0.75, CH\(_2\)Cl\(_2\))

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

![Chemical Structure](image)

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

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.96\) (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\(_3\)): \(\delta = 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\(^{-1}\).


\([\alpha]_D^{20}\) 14.40 (c = 0.5, CH\(_2\)Cl\(_2\))
Experimental Section

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

To β-hydroxy lactone 234 (18 mg, 0.035 mmol) in Et₂O:NEt₃ (10:1, 1 mL) at 0 °C under argon was added MsCl (0.05 mL, 1M in Et₂O, 0.053 mmol). After 1.5 h brine was added and the aqueous layer was extracted with Et₂O. The combined ethereal layer was dried over MgSO₄ 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 NH₄Cl solution was added, layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 1:1) furnished 15 mg (72%) of methyl ester 236.

\(\text{R}_{f} = 0.38 \text{ (hexane:EtOAc = 1:1)}\)

\(^1\text{H-NMR} \text{ (400 MHz, CDCl}_3\text{): } \delta = 6.97 \text{ (s, 1H), 6.61 (s, 1H), 5.13 (dd, } J = 7.32, 3.28 \text{ Hz, 1H), 4.38 (dd, } J = 7.32, 5.32 \text{ Hz, 1H), 3.70 (s, 3H), 3.37 (ddd, } J = 14.49, 9.77, 5.97 \text{ Hz, 1H), 3.06 (s, 3H), 2.71 (s, 3H), 2.06 (s, 3H), 2.01 (m, 1H), 1.97-1.92 (m, 1H), 1.72-1.61 (m, 1H), 1.58-1.49 (m, 1H), 1.41-1.32 (m, 2H), 1.30-1.21 (m, 1H), 1.23 (s, 3H), 1.07-0.97 (m, 2H), 0.88 (s, 9H), 0.83 (d, } J = 6.60 \text{ Hz, 3H), 0.02 (s, 6H).}\)

\(^{13}\text{C-NMR} \text{ (100 MHz, CDCl}_3\text{): } \delta = 174.7, 164.8, 152.5, 140.5, 120.1, 116.3, 85.1, 75.8, 68.0, 52.1, 51.6, 39.0, 36.8, 36.0, 35.4, 33.4, 25.9, 21.8, 19.2, 18.3, 16.5, 15.9, 13.8, -5.4.\)

\(\text{HRMS (ESI) (m/z): } [\text{M}]^{+} \text{ calcd for } C_{27}H_{49}O_{7}NS_{2}Si: 591.2720, \text{ found: 591.2732.}\)
Experimental Section

4-[(1E,5Z)-(3S,10S)-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 NH₄Cl solution and extracted with DCM. The combined organic solution was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 16 mg (85%) of protected 33 as colorless oil.

Rₛ = 0.45 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ 3.50 (c = 1.1, CH₂Cl₂)
Experimental Section

Benzoic acid (Z)-(1S,8S)-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 Et₂O:NEt₃ (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 Et₂O. The combined ethereal layer was dried over MgSO₄ 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 NH₄Cl solution was added, layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over MgSO₄ 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.

Rₐ = 0.88 (hexane:EtOAc = 3:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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.


[α]D²⁰ 5.20 (c = 0.25, CH₂Cl₂)
Acetic acid \((Z)\)-(1S,8S)-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 \(\beta\)-hydroxy lactone 234 (18 mg, 0.036 mmol)) in \(\text{Et}_2\text{O}:\text{NEt}_3\) (10:1, 1 mL) at 0 °C under argon was added MsCl (4 \(\mu\)L, 0.052 mmol). After 1 h brine was added and the aqueous layer was extracted with \(\text{Et}_2\text{O}\). The combined ethereal layer was dried over \(\text{MgSO}_4\) and the solvent was removed under reduced pressure. The residue was taken up in \(\text{THF}\) (1 mL) and \(\text{MeLi}\) (36 \(\mu\)L, 1.6 M in \(\text{Et}_2\text{O}\), 0.054 mmol) was added at -78 °C. After 5 h a saturated \(\text{NH}_4\text{Cl}\) solution was added, layers were separated and the aqueous extracted with DCM. The combined organic layer was dried over \(\text{MgSO}_4\) 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.

\[ R_f = 0.70 \text{(hexane:EtOAc = 3:1)} \]

\(^1\text{H-NMR}\) (400 MHz, \(\text{CDCl}_3\)): \(\delta = 6.94\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, \(\text{CDCl}_3\)): \(\delta = 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.

\(\text{IR}\) (film): 2929, 1508, 1458.

\(\text{HRMS}\) (ESI) (m/z): [M]+ calcd for \(\text{C}_{26}\text{H}_{45}\text{O}_3\text{SiNS}\): 479.2889, found: 479.2899.

\([\alpha]_D^{20} = -12.00\) (c = 0.1, \(\text{CH}_2\text{Cl}_2\))
Experimental Section

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

\[
\begin{align*}
\text{TBSO} & \quad \text{OH} & \quad \text{OMe} \\
\text{S} & \quad \text{N} & \quad \text{TBSO}
\end{align*}
\]

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 TBSCI (8 mg, 0.063 mmol) and stirring was continued for 48 h. The reaction mixture was quenched with water and extracted with \( \text{Et}_2\text{O} \). The combined organic solution was dried over \( \text{MgSO}_4 \) 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)

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \( \delta = 6.94 \) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \( \delta = 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.
Experimental Section

\((E)-(2S,3R,5S)-2-[(S)-5-(\text{tert-Butyl-dimethyl-silanyloxy})-4-methyl-pentyl]-3-hydroxy-2,6-dimethyl-7-(2-methyl-thiazol-4-yl)-5-triisopropylsilanyloxy-hept-6-enoic acid methyl ester (257)\)

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 NH4Cl solution and extracted with DCM. The combined organic solution was dried over MgSO4 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)

\(^1H\text{-NMR (400 MHz, CDCl}_3\): } \delta = 6.95 (s, 1H), 6.52 (s, 1H), 4.55 (t, \(J = 6.82 \text{ Hz}, 1H\)), 3.79 (dd, \(J = 9.73, 3.92 \text{ Hz}, 1H\)), 3.65 (s, 3H), 3.39 (dd, \(J = 9.60, 5.81 \text{ Hz}, 1H\)), 3.32 (dd, \(J = 9.73, 6.44 \text{ Hz}, 1H\)), 2.75 (d, \(J = 3.74 \text{ Hz}, 1H\)), 2.71 (s, 3H), 1.99 (d, \(J = 1.01 \text{ Hz}, 3H\)), 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, \(J = 6.57 \text{ Hz}, 3H\)), 0.02 (s, 6H).

\(^{13}C\text{-NMR (100 MHz, CDCl}_3\): } \delta = 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\(^{-1}\).


\([\alpha]_D\)\(^{20}\) -0.22 (c = 0.9, CH\(_2\)Cl\(_2\))
Experimental Section

(E)-(2S,3R,5S)-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)

![Chemical Structure](image)

To alcohol 257 (95 mg, 0.14 mmol) in Et$_2$O: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$_2$O. 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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_7$NS$_2$Si$_2$Na: 770.3952, found: 770.3968.

$[\alpha]_D^{20}$ 14.27 (c = 0.55, CH$_2$Cl$_2$)
(5S,6R)-5-[(S)-5-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-pentyl]-5-methyl-6-[(E)-(S)-3-methyl-4-(2-methyl-thiazol-4-yl)-2-triisopropysilanyloxy-but-3-enyl]-2,2-dioxo-2\(\lambda^6\)-[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\(_4\)Cl 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\(_3\)); \(\delta = 6.95\) (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\(_3\)); \(\delta = 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\(_6\)NS\(_2\)Si\(_2\)Na: 738.3690, found: 738.3695.

\([\alpha]\)_D\(^{20}\) 52.86 (c = 0.35, CH\(_2\)Cl\(_2\))
Experimental Section

**Methanesulfonic acid (1R,2R,6S)-7-(tert-butyl-dimethyl-silyloxy)-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 MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 75 mg (87%) of alcohol 503 as colorless oil.

R<sub>f</sub> = 0.23 (hexane:EtOAc = 3:1)

**<sup>1</sup>H-NMR** (400 MHz, CDCl₃): 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).

**<sup>13</sup>C-NMR** (100 MHz, CDCl₃): 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 C₃₅H₇₉O₆NS₂Si₂: 719.4105, found: 719.4112.

[α]<sub>D</sub> <sup>20</sup> 20.17 (c = 1.2, CH₂Cl₂)
Methanesulfonic acid \((1R,2S,6S)-7-(\text{tert-butyl-dimethyl-silanyloxy})-2\text{-formyl-2,6-dimethyl-1-}\{[(E)-(S)-3\text{-methyl-4-(2-methyl-thiazol-4-yl)}-2\text{-triisopropylsilanyloxy-but-3-enyl}\}-\text{heptyl ester} (254)

\[
\begin{align*}
\text{TIPS} & \quad \text{OMs} \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{OTBS}
\end{align*}
\]

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)

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 9.46\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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.

\(\text{IR}\) (film): 2945, 2865, 1731, 1463, 1339, 1174, 1085, 1064 cm\(^{-1}\).

\(\text{HRMS}\) (ESI) (m/z): [M]\(^+\) calcd for C\(_{35}\)H\(_{67}\)O\(_6\)NS\(_2\)Si\(_2\): 717.3948, found: 717.3943.

\([\alpha]_D^{20}\) 23.58 (c = 0.95, CH\(_2\)Cl\(_2\))
4-[(1E,5E)-(3S,10S)-11-(tert-Butyl-dimethyl-silanyloxy)-2,6,10-trimethyl-3-triisopropylsilyloxy-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 NH₄Cl solution was added, layers were separated and the aqueous was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 17 mg (82%) of olefin 253 as colorless oil.

Rₛ = 0.60 (hexane:EtOAc = 10:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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 C₃₃H₆₃O₂NSSi₂: 593.4118, found: 593.4125.

[α]D²⁰ 8.12 (c = 0.85, CH₂Cl₂)
(3S,4R)-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.

Rf = 0.36 (hexane:EtOAc = 10:1)

1H-NMR (600 MHz, CDCl3): 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).

13C-NMR (150 MHz, CDCl3): 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, 1463, 1091 cm⁻¹.

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:Et₂O (1:1). The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 10 mg (73%) of olefin 260.

Rᵣ = 0.60 (hexane:EtOAc = 10:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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.


[α]₀²⁰ 6.28 (c = 0.175, CH₂Cl₂)
10.2.2. Epothilone B: Lactate Route

\textit{p-Methoxybenzyl-trichloroacetimidate (504)}

To a suspension of NaH (35 mg, 1.5 mmol) in Et$_2$O (7 mL) was added a solution of \textit{p}-methoxybenzylalcohol (2 g, 14.5 mmol) in Et$_2$O (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$_2$O 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$_3$): $\delta$ = 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).

\textit{(2S)-2-(4-Methoxy-benzylxoy)-propionic acid ethyl ester (505)}

To a stirred solution of \textit{p}-methoxybenzyl-trichloroacetimidate (504) (3.70 g, 13 mmol) in cyclohexane (14 mL) was added (S)-(−)-ethylactate (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$_2$O (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.

$R_f = 0.47$ (hexane:EtOAc = 3:1)
Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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.

$[\alpha]^0_D$ -64.46 (c = 1.3, CH$_2$Cl$_2$)

(2S)-2-(4-Methoxy-benzyl)oxy-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$_4$Cl solution. The organic layer was separated, the aqueous layer was acidified with 1 N HCl solution to pH 4 and extracted with Et$_2$O. 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$_3$): $\delta$ = 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, 0.10 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$_3$): $\delta$ = 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$^{-1}$.


$[\alpha]^0_D$ 46.22 (c = 1.2, CH$_2$Cl$_2$)
(2S)-2-(4-Methoxy-benzylxylo)-propionaldehyde (223)

\[ \text{OPMB} \]

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 NH₄Cl solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over MgSO₄ 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.

\[ R_f = 0.81 \text{ (hexane:EtOAc = 1:1)} \]

\(^1\text{H-NMR} \) (250 MHz, CDCl₃): \( \delta = 9.63 \text{ (d, } J = 1.8 \text{ Hz, 1H)}, 7.28 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 6.89 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 4.56 \text{ (s, 2H)}, 3.86 \text{ (dq, } J = 6.9, 1.4 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, 1.31 \text{ (d, } J = 6.8 \text{ Hz, 3H}).

2-Methyl-3-oxo-butyric acid tert-butyli ester (506)

\[ \text{O} \]

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 NH₄Cl solution, the organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layer was dried over MgSO₄ 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.

\[ R_f = 0.60 \text{ (hexane:EtOAc = 5:1)} \]

\(^1\text{H-NMR} \) (250 MHz, CDCl₃): \( \delta = 3.40 \text{ (q, } J = 7.12 \text{ Hz, 1H)}, 2.23 \text{ (s, 3H)}, 1.46 \text{ (s, 9H)}, 1.29 \text{ (d, } J = 7.20 \text{ Hz, 3H}).
2-Methyl-3-oxo-butyric acid methyl ester (507)

![Structure](attachment:structure.png)

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 NH₄Cl solution, the organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layer was dried over MgSO₄ 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.

Rₛ = 0.58 (hexane:EtOAc = 3:1)

¹H-NMR (250 MHz, CDCl₃): 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.

Rₛ = 0.57 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.

To aceto acetate 506 (2.4 g, 13.9 mmol) in acetone (8 mL) at -10 °C was added Ac₂O (5.3 mL, 55.7 mmol) and a catalytic amount of conc. H₂SO₄. 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 MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 1.3 g (60%) of 268.

$$R_f = 0.62 \text{ (hexane:EtOAc = 1:1)}$$

$^1$H-NMR (400 MHz, CDCl₃): $\delta = 1.97 \text{ (d, } J = 0.76 \text{ Hz, 3H), 1.81 \text{ (d, } J = 1.00 \text{ Hz, 3H), 1.64 \text{ (s, 6H).}}$

$^{13}$C-NMR (100 MHz, CDCl₃): $\delta = 162.7, 162.6, 104.7, 100.3, 25.1, 17.4, 10.3.$

IR (film): 1728, 1654, 1399, 1348, 1270, 1238, 1207, 1155 cm⁻¹.

HRMS (ESI) (m/z): \([M]^+ \text{ calcd for C}_8\text{H}_{12}\text{O}_3: 156.0786, 156.0793.}\)

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 nBuLi (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 CaH₂, 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 silyl ether 261 as colorless oil.
Experimental Section

$^1$H-NMR (400 MHz, C$_6$D$_6$): $\delta = 4.52$ (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-[[2S,3S]-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$_2$·Et$_2$O (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$_4$Cl 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$_3$): $\delta = 7.25$ (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$_3$): $\delta = 162.9$, 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$^{-1}$.


[$\alpha$]$_D^{20}$ 15.83 ($c = 1.2$, CH$_2$Cl$_2$)
Experimental Section

6-\{[(2S,4S,5S)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxolan-4-yl]methyl\}-2,2,5-trimethyl-4H-1,3-dioxin-4-one (271a)

6-\{[(2R,4S,5S)-2-(4-methoxyphenyl)-5-methyl-[1,3]-dioxolan-4-yl]methyl\}-2,2,5-trimethyl-4H-1,3-dioxin-4-one (271b)

A suspension of monoprotected diol 270 (55 mg, 0.16 mmol) and MS 3 Å (100 mg) in Et₂O (6 mL) under argon at r.t. was stirred for 1 h before a suspension of DDQ (181 mg, 0.8 mmol) in Et₂O (6 mL) also stirred for 1 h was added. After 2 h the reaction was quenched by the addition of a saturated Na₂S₂O₃ solution and the MS was filtered off over celite. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic solvent was dried over MgSO₄ 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: ¹H-NMR (400 MHz, CDCl₃): \( \delta = 7.37 \) (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).

¹³C-NMR (100 MHz, CDCl₃): \( \delta = 161.5, 160.4, 127.7, 113.8, 102.6, 80.3, 78.6, 55.3, 34.6, 25.7, 24.6, 17.8, 10.4. \)

271b: ¹H-NMR (400 MHz, CDCl₃): \( \delta = 7.37 \) (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).

¹³C-NMR (100 MHz, CDCl₃): \( \delta = 161.6, 160.4, 127.8, 113.7, 102.9, 80.3, 79.3, 55.3, 34.2, 25.8, 24.5, 17.7, 10.3. \)
(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$_2$CO$_3$ (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$_2$O 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 $\alpha$-position, and used without further purification.

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

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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 NH₄Cl solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ 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.

Rᵣ = 0.29 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]_D²⁰ -58.73 (c = 0.95, CH₂Cl₂)
Experimental Section

**Tsuji-Trost in biphasic system:**

To Pd(PPh₃)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 K₂CO₃ (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 NH₄Cl solution and phases were separated. The aqueous phase was extracted with DCM, the combined organic layer was dried over MgSO₄ 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:**

Pd₂(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 NH₄Cl solution, layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over MgSO₄ 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:**

Pd₂(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.
(3S,6S)-3-Allyl-6-[(S)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (273a)

$\text{R}_f = 0.21 \ (\text{hexane:EtOAc} = 3:1)$

$^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 7.23 \ (d, J = 8.59 \text{ Hz, } 2H), \ 6.88 \ (d, J = 8.59 \text{ Hz, } 2H), \ 5.74-5.64 \ (m, \ 1H), \ 5.10-5.03 \ (m, \ 2H), \ 4.45 \ (d, J = 11.62 \text{ Hz, } 1H), \ 4.47-4.43 \ (m, \ 1H), \ 4.42 \ (d, J = 11.36 \text{ Hz, } 1H), \ 3.80 \ (s, \ 3H), \ 3.65 \ (\text{ddd}, J = 12.63, 3.79, 3.79 \text{ Hz, } 1H), \ 2.72 \ (\text{dd}, J = 16.16, 3.54 \text{ Hz, } 1H), \ 2.69 \ (\text{dd}, J = 13.33, 6.82 \text{ Hz, } 1H), \ 2.53 \ (\text{dd}, J = 13.64, 8.33 \text{ Hz, } 1H), \ 2.51 \ (\text{dd}, J = 16.16, 10.10 \text{ Hz, } 1H), \ 1.40 \ (s, \ 3H), \ 1.29 \ (d, J = 6.31 \text{ Hz, } 3H).$

$^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta = 205.8, \ 173.2, \ 159.4, \ 132.6, \ 129.7, \ 129.5, \ 119.5, \ 113.9, \ 75.9, \ 73.8, \ 70.9, \ 56.5, \ 55.3, \ 40.9, \ 40.5, \ 23.7, \ 14.6.$

$\text{IR} \ (\text{film}): \ 1749, \ 1713, \ 1513, \ 1246, \ 1031 \text{ cm}^{-1}.$

$\text{HRMS} \ (\text{ESI}) \ (m/z): \ [M]^+ \text{ calcd for C}_{19}\text{H}_{24}\text{O}_5: \ 332.1624, \ \text{found: } 332.1619.$

$[\alpha]_D^{20} -19.41 \ (c = 0.85, \ \text{CH}_2\text{Cl}_2)$

(3R,6S)-3-Allyl-6-[(S)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (273b)

$\text{R}_f = 0.21 \ (\text{Hexane:EtOAc} = 3:1)$

$^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 7.18 \ (d, J = 8.59 \text{ Hz, } 2H), \ 6.86 \ (d, J = 8.59 \text{ Hz, } 2H), \ 5.69-5.59 \ (m, \ 1H), \ 5.12-5.06 \ (m, \ 2H), \ 4.49 \ (d, J = 11.62 \text{ Hz, } 1H), \ 4.47-4.45 \ (m, \ 1H), \ 4.32 \ (d, J = 11.62 \text{ Hz, } 1H), \ 3.80 \ (s, \ 3H), \ 3.49 \ (\text{ddd}, J = 12.69, 6.38, 2.08 \text{ Hz, } 1H), \ 2.79 \ (\text{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$_3$): $\delta = 204.3, 174.1, 159.5, 131.9, 130.2, 128.8, 119.9, 113.8, 76.8, 74.4, 70.6, 57.6, 55.3, 44.5, 40.5, 20.4, 15.2.$

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$_2$Cl$_2$)

(-)-(4S)-(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 triethylphosphonoacetate (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$_2$O. 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$_3$): $\delta = 6.92$ (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$_3$): $\delta = 173.5, 151.4, 120.9, 66.9, 60.1, 39.1, 25.9, 15.5, 14.3, -5.4.$

IR (film): 2956, 2929, 1723, 1258, 1183, 1097 cm$^{-1}$.  

HRMS (ESI) (m/z): [M]$^+$ calcd for C$_{14}$H$_{28}$O$_3$Si: 272.1808, found: 272.1801.  

$[\alpha]_D^{20}$ -11.80 (c = 1.5, CHCl$_3$), $[\alpha]_D^{20}$ -18.72 (c = 1.25, CH$_2$Cl$_2$)
(-)-(4S)-(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:Et₂O (1:1) and the combined organic solution was dried over MgSO₄. 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.

Rₚ = 0.23 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃):  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).

¹³C-NMR (100 MHz, CDCl₃):  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.


[α]D²₀ -7.44 (c = 1.3, CHCl₃), [α]D²₀ -9.91 (c = 1.15, CH₂Cl₂)

Carbonic acid (-)-(4S)-(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 Et₂O, the combined organic solution was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1, 1% NEt₃) yielded 1.4 g (quant.) of carbonate 185 as colorless oil.
Experimental Section

\( R_f = 0.71 \) (hexane:EtOAc = 10:1)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 5.82 \) (dd, \( J = 15.64, 7.08 \) Hz, 1H), 5.64 (dd, \( J = 14.88, 6.82, 1.30 \) 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\(_3\)): \( \delta = 154.97, 140.61, 122.43, 69.96, 67.67, 39.16, 26.06, 26.02, 18.48, 16.21, -5.21.\)

HRMS (ESI) (m/z): [M - tBu\(^+\)] calcd for C\(_{11}\)H\(_{18}\)O\(_4\)SiCl\(_3\): 349.0012, found: 349.0008.

\([\alpha]_D^{20}\) -6.15 (c = 2.1, CHCl\(_3\))

Chloro-acetic acid (E)-(4S)-5-(tert-butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl ester (510)

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{OTBS}
\end{array}
\]

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\(_2\)O, 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\(_3\)): \( \delta = 5.75 \) (d, \( J = 15.41, 7.08 \) Hz, 1H), 5.60 (dt, \( J = 15.47, 6.48, 1.09 \) 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\(_3\)): \( \delta = 167.1, 140.0, 122.6, 118.1, 67.5, 66.9, 40.9, 39.0, 25.9, 18.3, 16.1, -5.4.\)

IR (film): 2956, 2857, 1762, 1257, 1168, 1107 cm\(^{-1}\).

Experimental Section

$[\alpha]_D^{20} -9.80$ (c = 1.5, CH$_2$Cl$_2$)

**Carbonic acid (E)-(S)-5-(tert-butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl ester ethyl ester (511)**

![Chemical Structure](image)

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$_2$O, 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$_3$): $\delta = 5.76$ (d, $J = 15.52$, 6.96 Hz, 1H), 5.61 (dt, $J = 15.58$, 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$_3$): $\delta = 155.0$, 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$_4$SiNa: 325.1811, found: 325.1817.

$[\alpha]_D^{20} -9.20$ (c = 1.25, CH$_2$Cl$_2$)
Experimental Section

(3S,6S)-3-[(E)-(S)-5-(tert-Butyl-dimethyl-silyl oxy)-4-methyl-pent-2-enyl]-6-[(S)-1-(4-methoxy-benzyl ox y)-ethyl]-3-methyl-dihydro-pyran-2,4-dione (277)

To Pd(PPh₃)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 K₂CO₃ (270 mg, 1.950 mmol) in degassed water (2 mL) was added. After stirring for 3 h, the reaction mixture was quenched with saturated NH₄Cl solution and phases were separated. The aqueous phase was extracted with DCM and the combined organic layer was dried over MgSO₄ 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

Rₜ = 0.24 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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 cm⁻¹.


[α]D²⁰ -35.33 (c = 0.3, CH₂Cl₂)
Minor: 277b

\[ R_f = 0.24 \text{ (hexane:EtOAc = 3:1)} \]

$^1$H-NMR (400 MHz, CDCl$_3$): \( \delta = 7.18 \text{ (d, } J = 8.59 \text{ Hz, 2H), 6.86 \text{ (d, } J = 8.59 \text{ Hz, 2H), 5.43 \text{ (dd, } J = 15.54, 6.95 \text{ Hz, 1H), 5.28 \text{ (dt, } J = 15.28, 7.52\text{Hz, 1H), 4.48 \text{ (d, } J = 11.34 \text{ Hz, 1H), 4.44 \text{ (m, } J = 11.62 \text{ Hz, 1H), 3.80 \text{ (s, 3H), 3.48 \text{ (m, 1H), 3.44 \text{ (dd, } J = 9.85, 6.06 \text{ Hz, 1H), 3.35 \text{ (dd, } J = 9.72, 6.95 \text{ Hz, 1H), 2.78 \text{ (dd, } J = 16.01, 6.19 \text{ Hz, 1H), 2.50 \text{ (dd, } J = 16.16, 4.54 \text{ Hz, 1H), 2.49 \text{ (m, 1H), 2.39 \text{ (dd, } J = 13.51, 8.21 \text{ Hz, 1H), 2.26 \text{ (m, 1H), 1.28 \text{ (d, } J = 6.31 \text{ Hz, 3H), 1.26 \text{ (s, 3H), 0.94 \text{ (d, } J = 6.82 \text{ Hz, 3H), 0.87 \text{ (s, 9H), 0.01 (s, 6H).}}\]

$^{13}$C-NMR (100 MHz, CDCl$_3$): \( \delta = 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): \([M-C_4H_9]^+\) calcd for C$_{24}$H$_{35}$O$_6$Si: 447.2203, found: 447.2210.

\([\alpha]_D^{20} 38.31 \text{ (c = 0.95, CH$_2$Cl$_2$)}\]

(3S,4S,6S)-3-[(E)-(S)-5-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-pent-2-enyl]-4-hydroxy-6-[(S)-1-(4-methoxy-benzylloxy)-ethyl]-3-methyl-tetrahydro-pyran-2-one (278)

To $\beta$-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$_4$Cl 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.

\[ R_f = 0.30 \text{ (hexane:EtOAc = 1:1)} \]

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.26 \text{ (d, } J = 8.60 \text{ Hz, 2H)}, 6.87 \text{ (d, } J = 8.84 \text{ Hz, 2H)}, 5.47 \text{ (m, 2H)}, 4.63 \text{ (d, } J = 11.40 \text{ Hz, 1H)}, 4.43 \text{ (d, } J = 11.36 \text{ Hz, 1H)}, 4.42 \text{ (m, 1H)}, 3.82 \text{ (m, 1H)}, 3.80 \text{ (s, 3H)}, 3.56 \text{ (dd, } J = 12.63, 6.31, 3.28 \text{ Hz, 1H)}, 3.46 \text{ (dd, } J = 9.60, 6.31 \text{ Hz, 1H)}, 3.39 \text{ (dd, } J = 9.85, 6.82 \text{ Hz, 1H)}, 2.55 \text{ (dd, } J = 13.64, 5.81 \text{ Hz, 1H)}, 2.40 \text{ (dd, } J = 13.89, 6.06 \text{ Hz, 1H)}, 2.29 \text{ (m, 1H)}, 2.16 \text{ (ddd, } J = 14.21, 7.14, 4.35 \text{ Hz, 1H)}, 1.98 \text{ (dt, } J = 14.14, 7.07 \text{ Hz, 1H)}, 1.20 \text{ (d, } J = 6.56 \text{ Hz, 3H)}, 1.20 \text{ (s, 3H)}, 0.96 \text{ (d, } J = 6.82 \text{ Hz, 3H)}, 0.88 \text{ (s, 9H)}, 0.02 \text{ (s, 6H)}.

\(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta = 175.2, 159.4, 137.4, 129.7, 129.4, 129.1, 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\(^{-1}\).


\([\alpha]\)\(_D\)\(^{20}\) 23.41 (c = 0.85, CH\(_2\)Cl\(_2\) )

\((2R,3R)-3-(4-methoxybenzyloxy)-1-(2,2,5-trimethyl-4-oxo-4H-[1,3]-dioxin-6-yl)butan-2-yl acetate (512)\)

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\(_2\)O. 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.

\[ R_f = 0.53 \text{ (Hexane:EtOAc = 1:1)} \]

\(^1\)H-NMR (250 MHz, CDCl\(_3\)): \(\delta = 7.25 \text{ (d, } J = 8.55 \text{ Hz, 2H)}, 6.88 \text{ (d, } J = 8.67 \text{ Hz, 2H)}, 5.21 \text{ (dt, } J = 9.59, 3.77 \text{ Hz, 1H)}, 4.58 \text{ (d, } J = 11.43 \text{ Hz, 1H)}, 4.42 \text{ (d, } J = 11.53 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, \)
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).

(2R,3R)-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$_3$): $\delta = 5.06$ (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$_3$): $\delta = 170.2, 105.0, 73.8, 68.5, 32.4, 25.6, 24.6, 21.1, 19.4, 10.3.$

(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.
**Experimental Section**

\[ R_f = 0.13 \text{ (hexane:EtOAc = 3:1)} \]

**\(^1\)H-NMR (400 MHz, CDCl\(_3\)):** \( \delta = 5.28 \text{ (t, } J = 6.32 \text{ Hz, 1H)}, 2.82 \text{ (d, } J = 6.32 \text{ Hz, 1H}), 2.22 \text{ (s, 3H)}, 2.14 \text{ (s, 3H)}, 1.85 \text{ (s, 3H)}, 1.64 \text{ (s, 3H)}, 1.60 \text{ (s, 3H)} \).

**\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)):** \( \delta = 203.4, 169.8, 105.3, 40.9, 31.6, 26.1, 25.2, 24.7, 20.5, 10.2 \).

**HRMS (ESI) (m/z):** [M]" calcd for C\(_{13}\)H\(_{18}\)O\(_6\): 270.1103, found: 270.1094.

(3S,4S,6S)-3-[\(\text{S}\)-5-(\(\text{S}\)-\text{5-tert-Butyl-dimethyl-silanyloxy})-4-methyl-pentyl]-4-hydroxy-6-[\(\text{S}\)-1-(4-methoxy-benzyloxy)-ethyl]-3-methyl-tetrahydro-pyran-2-one (284)

\[
\text{TBSO} \quad \begin{array}{c} \text{OH} \\ \text{OPMB} \end{array} 
\]

To \(\beta\)-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.

\[ R_f = 0.30 \text{ (hexane:EtOAc = 1:1)} \]

**\(^1\)H-NMR (400 MHz, CDCl\(_3\)):** \( \delta = 7.26 \text{ (d, } J = 8.84 \text{ Hz, 2H)}, 6.87 \text{ (d, } J = 8.84 \text{ Hz, 2H)}, 4.63 \text{ (d, } J = 11.64 \text{ Hz, 1H)}, 4.42 \text{ (d, } J = 11.60 \text{ Hz, 1H)}, 4.39 \text{ (m, 1H)}, 3.86 \text{ (ddd, } J = 6.95, 6.69, 4.29 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, 3.56 \text{ (ddd, } J = 12.67, 6.39, 3.21 \text{ Hz, 1H)}, 3.42 \text{ (dd, } J = 9.84, 5.80 \text{ Hz, 1H)}, 3.34 \text{ (dd, } J = 9.84, 6.56 \text{ Hz, 1H)}, 2.83 \text{ (d, } J = 6.32 \text{ Hz, 1H)}, 2.14 \text{ (ddd, } J = 14.07, 6.75, 4.23 \text{ Hz, 1H)}, 2.01 \text{ (dt, } J = 14.22, 7.65 \text{ Hz, 1H)}, 1.75-1.67 \text{ (m, 2H)}, 1.59 \text{ (m, 1H)}, 1.33-1.28 \text{ (m, 2H)}, 1.31 \text{ (d, } J = 6.28 \text{ Hz, 3H)}, 1.25 \text{ (s, 3H)}, 1.05 \text{ (m, 1H)}, 0.84 \text{ (d, } J = 6.80 \text{ Hz, 3H)}, 0.88 \text{ (s, 9H)}, 0.03 \text{ (s, 6H)} \).

**\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)):** \( \delta = 175.3, 159.4, 129.7, 129.5, 113.9, 78.1, 74.9, 70.8, 70.7, 68.4, 55.3, 47.0, 35.6, 33.7, 33.1, 28.6, 25.9, 21.1, 18.3, 16.7, 14.6, -5.4 \).

**IR (film):** 2953, 1732, 1514, 1463, 1250, 1092 cm\(^{-1}\).

**HRMS (ESI) (m/z):** [M]" calcd for C\(_{28}\)H\(_{48}\)O\(_6\)Si: 508.3220, found: 508.3224.

\[ [\alpha]_D^{20} 24.75 \text{ (c = 0.4, CH}_2\text{Cl}_2) \]
(Z)-(2S,3S,10S)-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 Et₂O (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 Et₂O. The combined organic layers were dried over MgSO₄ 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 NH₄Cl solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 15:1) yielded 42 mg (91%) of 264 as colorless oil.

Rᵣ = 0.20 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D^20 20.00 (c = 1.9, CH₂Cl₂)
Experimental Section

1-[(Z)-(1S,2S,9S)-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 NH₄Cl solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over MgSO₄ 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)

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): 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, 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, 1093 cm⁻¹.


[α]_D^20 = -2.66 (c = 1.2, CH₂Cl₂)
(Z)-(2S,3S,10S)-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 NaHCO₃ solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over MgSO₄, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 20:1) to yield 63 mg (98%) of 283.

R<sub>f</sub> = 0.45 (hexane:EtOAc = 10:1)

<sup>1</sup>H-NMR (400 MHz, CDCl₃): 6 = 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).

<sup>13</sup>C-NMR (100 MHz, CDCl₃): 6 = 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.


[α]<sub>D</sub><sup>20</sup> 11.81 (c = 1.05, CH₂Cl₂)
Experimental Section

(Z)-(3S,10S)-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 NaHCO₃ solution, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over MgSO₄, the solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 20:1) to yield 39 mg (quant.) of ketone 284.

Rᵣ = 0.57 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


4-[(1E,5Z)-(3S,10S)-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 nBuLi (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 NH₄Cl solution, the organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic solution was dried over MgSO₄ 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.

Rₐ = 0.36 (hexane:EtOAc = 15:1)

¹H-NMR (400 MHz, CDCl₃): 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 = 6.66 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): 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.


[^20]D D 0.66 (c = 0.3, CH₂Cl₂)

10.2.3. Discodermolide

(S)-MTPA ester (299)

![Discodermolide S-MTPA ester](image)

Major:

¹H-NMR (400 MHz, CDCl₃): 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).
Experimental Section

Minor:

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_3$): $\delta$ = 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).

(2S,3R,4S,6S)-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$_2$O (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$_2$O (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$_2$O (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 H₂O₂ (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 MgSO₄ 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.

Rᵣ = 0.48 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.

(2S,3R,4R,5S,6S)-3,5-Dihydroxy-7-(4-methoxy-benzyl)-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 NaHCO₃ and solid NaHCO₃ was added very carefully till gas evolution ceased. The aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ 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.

Rᵣ = 0.31 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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 =
Experimental Section

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}\text{C-NMR} (100 \text{ MHz, CDCl}_3): \delta = 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.

\((3S,4R,5S,6S)-4\text{-hydroxy-6-}(\text{S})-1-(4\text{-methoxybenzyloxy})\text{propan-2-yl})\text{-3,5-dimethyl-3-(2-methylallyl)}\text{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 phase was 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\text{H-NMR} (400 \text{ MHz, CDCl}_3): \delta = 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}\text{C-NMR} (100 \text{ MHz, CDCl}_3): \delta = 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)-(2S,3R,4S)- 1-(4-methoxybenzyloxy)-2,4,6,8-tetramethylnona-5,8-dien-3-ol (307)

To lactone 305 (80 mg, 0.21 mmol) in Et₂O:triethylamine (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 Et₂O. The combined organic phase was dried over MgSO₄ 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 NH₄Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 25 mg (36%) of fragmentation product 307.

Rₜ = 0.83 (hexane:EtOAc = 1:1)

1H-NMR (400 MHz, CDCl₃): 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).

13C-NMR (100 MHz, CDCl₃): 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 P₂O₅, at 0 °C was added L-(+)-DET (0.41 mL, 2.4 mmol) followed by freshly distilled Ti(OiPr)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
Experimental Section

MS was filtered off over celite and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by bulb-to-bulb distillation yielded at 100 °C 5.90 g (quant.) of epoxide 514.

\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 5.08 \ (tt, J = 7.08, 1.26 \text{ Hz, 1H}), \ 3.81 \ (ddd, J = 11.87, 7.07, 4.54 \text{ Hz, 1H}), \ 3.67 \ (ddd, J = 11.83, 6.98, 4.51 \text{ Hz, 1H}), \ 2.97 \ (dd, J = 6.82, 4.29 \text{ Hz, 1H}), \ 2.08 \ (q, J = 7.66 \text{ Hz, 2H}), \ 1.72-1.64 \ (m, 1H), \ 1.68 \ (s, 3H), \ 1.60 \ (s, 3H), \ 1.47 \ (ddd, J = 13.70, 8.65, 7.76 \text{ Hz, 1H}), \ 1.29 \ (s, 3H). \]

\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta = 132.1, 123.3, 62.9, 61.5, 38.5, 25.7, 23.7, 17.6, 16.7. \]

tert-butyldimethyl][(2S,3S)-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:Et₂O (1:1). The combined organic solution was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 50:1) furnished 9.1 g (quant.) of TBS ether 342 as colorless oil.

Rₚ = 0.78 (hexane:EtOAc = 10:1)

\[ ^1\text{H-NMR} \ (250 \text{ MHz, CDCl}_3): \delta = 5.09 \ (bt, J = 7.01 \text{ Hz, 1H}), \ 3.73 \ (d, J = 5.25 \text{ Hz, 2H}), \ 2.90 \ (t, J = 5.49 \text{ Hz, 1H}), \ 2.13-2.03 \ (m, 2H), \ 1.68 \ (s, 3H), \ 1.64 \ (m, 1H), \ 1.60 \ (s, 3H), \ 1.52-1.41 \ (m, 1H), \ 1.26 \ (s, 3H), \ 0.91 \ (s, 9H), \ 0.09 \ (s, 3H), \ 0.08 \ (s, 3H). \]

(S)-2-[(tert-butyldimethylsilyloxy)methyl]-2,6-dimethylhept-5-enal (339)

To 4-bromo-2,6-diter-2,6-butyldiphenol (3.18 g, 11.2 mmol) in degassed DCM (130 mL), distilled from P₂O₅, at r.t. was added AlMe₃ (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.

\[ R_f = 0.88 \] (hexane:EtOAc = 20:1)

\[ ^1H\text{-NMR} \] (400 MHz, CDCl₃): \( \delta = 9.55 \) (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).


\[(2S,4S,5R,6S)-6-(\text{tert-Butyl-dimethyl-silanyloxymethyl})-5-hydroxy-1-(4-methoxy-benzyl)oxy)-2,4,6,10-tetramethyl-undec-9-en-3-one (345)\]

To a solution of chlorodicyclohexylborane (55 mL, 1M in hexane, 54.6 mmol) in Et₂O (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 Et₂O (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 Et₂O (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 H₂O₂ (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 MgSO₄ 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.

\[ R_f = 0.35 \] (hexane:EtOAc = 10:1)
Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_5$SiNa: 543.3482, found: 543.3476.

$[\alpha]_D^{20}$ 16.23 (c = 1.4, CH$_2$Cl$_2$).

(2S,3S,4R,5R,6S)-6-(tert-Butyl-dimethyl-silyloxymethyl)-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$_3$): $\delta$ = 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
Experimental Section

(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$_3$): $\delta$ = 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$_5$SiNa: 545.3638, found: 545.3632.

[$\alpha$]$_{D}^{20}$ -2.98 (c = 1.5, CH$_2$Cl$_2$).

tert-butyl{((S)-2-[(2R,4R,5R,6S)-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$_3$): $\delta$ = 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).
Experimental Section

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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.

\((2S,3R,4S)-4-[(\text{tert-butyl}d\text{imethylsilyloxy})\text{methyl}]-2-[(2S,4S,5S)-2-(4\text{-methoxyphenyl})\text{-5-methyl-}[1,3]-dioxan-4-yl]-4,8\text{-dimethylnon-7-en-3-ol}\) (349)

\[
\begin{align*}
\text{PMP} & \quad \text{OTBS} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{OTBS}
\end{align*}
\]

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\(_2\)S\(_2\)O\(_3\) solution and the MS was filtered off over celite. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer 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)

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.36\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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.
(2S,3R,4R,5S,6S)-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 NaHCO₃ solution and DCM was added. The aqueous layer was extracted with DCM, the combined organic layer was dried over MgSO₄ 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)

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): 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.

[α]_D^20 43.50 (c = 0.6, CH₂Cl₂)
Experimental Section

\((2S,3S,4R)-1-(4\text{-methoxybenzyloxy})-4-[(2S,4R,5S)-2-(4\text{-methoxyphenyl})-5\text{-methyl}-5\text{-}(4\text{-methylpent}-3\text{-enyl})\text{-}[1,3\text{-dioxan-4-yl}]\text{-}2\text{-methylpentan-3-ol}\) (347)

![Chemical Structure](image)

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 MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 10:1) yielded 23 mg (84%) of acetal 347 as colorless oil.

\[ R_f = 0.71 \text{ (hexane:EtOAc = 3:1)} \]

\(^1\text{H-NMR}\) (400 MHz, CDCl₃): \(\delta = 7.38 \text{ (d, } J = 8.84 \text{ Hz, 2H)}, 7.25 \text{ (d, } J = 8.60 \text{ Hz, 2H)}, 6.88 \text{ (d, } J = 8.60 \text{ Hz, 2H)}, 6.85 \text{ (d, } J = 8.60 \text{ Hz, 2H)}, 5.41 \text{ (s, 1H)}, 5.06 \text{ (bt, } J = 6.94 \text{ Hz, 1H)}, 4.44 \text{ (q, } J = 12.04 \text{ Hz, 2H)}, 3.90 \text{ (d, } J = 10.12 \text{ Hz, 1H)}, 3.83 \text{ (d, } J = 11.12 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, 3.79 \text{ (s, 3H)}, 3.71 \text{ (d, } J = 11.08 \text{ Hz, 1H)}, 3.68-3.64 \text{ (m, 2H)}, 3.36 \text{ (dd, } J = 8.96, 7.20 \text{ Hz, 1H}), 2.99 \text{ (d, } J = 1.76 \text{ Hz, 1H (OH)}), 2.05-1.96 \text{ (m, 2H)}, 1.94-1.84 \text{ (m, 2H)}, 1.69 \text{ (s, 3H)}, 1.61 \text{ (s, 3H)}, 1.34-1.18 \text{ (m, 2H)}, 1.24 \text{ (s, 3H)}, 1.05 \text{ (d, } J = 7.08 \text{ Hz, 3H)}, 0.92 \text{ (d, } J = 6.80 \text{ Hz, 3H}).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl₃): \(\delta = 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.

\(\text{IR (film)}: 2963, 1614, 1515, 1249, 1171, 1093, 1036 \text{ cm}^{-1}\).

\(\text{HRMS (ESI) (m/z): } [M]^+ \text{ calcd for C}_{32}\text{H}_{46}\text{O}_{6}: 526.3294, \text{ found: 526.3289}.

\([\alpha]_D^{20} 6.22 \text{ (c = 0.45, CH}_2\text{Cl}_2)\)
(4R,5R,6S)-4-[(S)-1-(tert-butyldimethylsilyloxy)-2,6-dimethylhept-5-en-2-yl]-6-[(S)-1-(4-methoxybenzyl)oxy]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 NH₄Cl solution was added and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 5:1) yielded 31 mg (quant.) of carbonate 350.

Rᵣ = 0.35 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃): 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, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): 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.
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 MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) yielded 50 mg (83%) of 515.

Rᵣ = 0.38 (hexane:EtOAc = 1:1)

$^1$H-NMR (400 MHz, CDCl₃): $δ = 7.23$ (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).

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 NaHCO₃ solution was added, the layers were separated and the aqueous layer was
extracted with DCM. The combined DCM phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 27 mg (68%) of aldehyde 351 as colorless oil.

Rᵥ = 0.45 (hexane:EtOAc = 1:1)

^1H-NMR (400 MHz, CDCl₃): 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).

^13C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ -19.67 (c = 0.3, CH₂Cl₂)

(2S,4S,5R,6S)-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 NaHCO₃ solution was added, the layers were separated and the aqueous layer was extracted with DCM. The combined DCM phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 9 mg (60%) of ketone 354 as colorless oil.

Rᵥ = 0.28 (hexane:EtOAc = 3:1)

^1H-NMR (400 MHz, CDCl₃): 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
Experimental Section

(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$_3$): $\delta$ = 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, cm$^{-1}$.

HRMS (ESI) (m/z): [M+Na]$^+$ calcd for C$_{24}$H$_{38}$O$_5$Na: 429.2617, found: 429.2621.

$[\alpha]_D^{20}$ -28.00 (c = 0.45, CH$_2$Cl$_2$)

$\text{tert-Butyl-}((S)-2-\{((4R,5R,6S)-6-\{(S)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl\}-2,2,5$-
trimethyl-[1,3]dioxan-4-yl\}-2,6-dimethyl-hept-5-enyloxy)-dimethyl-silane (356)}$

\[\begin{array}{c}
\text{PMBO} \\
\text{OTBS}
\end{array}\]

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$_3$): $\delta$ = 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 (d, J = 8.32, 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).
Experimental Section

\[ ^{13}C\text{-NMR} \] (100 MHz, CDCl\(_3\)): \( \delta = 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. \\

\[ \text{IR} \] (film): 2932, 1614, 1513, 1458, 1376, 1248, 1098 cm\(^{-1}\). \\

\[ \text{HRMS} \] (ESI) (m/z): [M]\(^{+}\) calcd for C\(_{33}\)H\(_{58}\)O\(_5\)Si: 562.4054, found: 562.4049. \\

\[ [\alpha]_D^{20} \text{ 6.90  (c = 0.86, CH}_2\text{Cl}_2). \]

\((S)-2-\{(4R,5R,6S)-6-[(S)-2-(4-Methoxy-benzyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl]-2,6-dimethyl-hept-5-en-1-ol \) (357)

![Chemical Structure]

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)

\[ ^1H\text{-NMR} \] (400 MHz, CDCl\(_3\)): \( \delta = 7.25 \) (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).

\[ ^{13}C\text{-NMR} \] (100 MHz, CDCl\(_3\)): \( \delta = 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. \\

\[ \text{IR} \] (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$_2$Cl$_2$).

(R)-2-((4R,5R,6S)-6-[(S)-2-(4-Methoxy-benzyl-oxo)-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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_2$Cl$_2$).
Experimental Section

(R)-2-{(4R,5R,6S)-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 NaClO₂ (4.95 g, 55.00 mmol) and NaH₂PO₄ (4.95 g) in water (15 mL). After 3 h 0.01N NaOH was added and the aqueous layer was extracted with Et₂O, 1N HCl was added until pH 2 was reached and the aqueous layer was extracted with DCM. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 1:1) yielded 1.71 g (quant.) of acid 358.

Rᵣ = 0.25 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ 14.26 (c = 1.36, CH₂Cl₂).
Experimental Section

\((3R,4R,5S,6S)-4\text{-Hydroxy-6-[(S)-2-(4-methoxy-benzyloxy)-1-methyl-ethyl]-3,5-dimethyl-3-(4-methyl-pent-3-enyl)-tetrahydro-pyran-2-one (340)}\)

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)

\(^1\text{H-NMR}\) (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).

\(^{13}\text{C-NMR}\) (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.

\(\text{IR}\) (film): 3435, 2968, 1706, 1513, 1248, 1102 cm\(^{-1}\).

\(\text{HRMS (ESI)}\) (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\(_2\)Cl\(_2\)).
(Z)-(2S,3R,4S)-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 MgSO₄ 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 NH₄Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 333 mg (88%) of olefin 341.

Rᵣ = 0.60 (hexane:EtOAc = 3:1)

₁H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[a]₂⁰D 18.42 (c = 1.14, CH₂Cl₂).
Experimental Section

**tert-Butyl-\((Z)-(1R,2S)-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 NH₄Cl solution and the layers were separated. The aqueous layer was extracted with DCM. The combined organic solution was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 320 mg (quant.) of protected diol 517 as colorless oil.

Rₚ = 0.55 (hexane:EtOAc = 10:1)

**¹H-NMR** (400 MHz, CDCl₃): 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).

**¹³C-NMR** (100 MHz, CDCl₃): 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.


**[α]D⁰** 6.64 (c = 1.28, CH₂Cl₂).
**tert-Butyl-**(Z)-(1R,2S)-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 mCPBA (168 mg, 80% of weight, 0.68 mmol) was added. The mixture was warmed to 0 °C over 2 h and saturated NaHCO₃ solution was added. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 293 mg (92%) of epoxide 360 as 1:1 mixture of diastereoisomers.

Rₐ = 0.25 (hexane:EtOAc = 10:1)

**¹H-NMR** (400 MHz, CDCl₃): 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).

**¹³C-NMR** (100 MHz, CDCl₃): 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, 1037 cm⁻¹.

(Z)-(6S,7R,8S)-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 Et₂O (3 mL) at 0 °C was added dropwise a solution of HIO₄·2H₂O (97 mg, 0.42 mmol) in THF (2 mL). The mixture was stirred for 2.5 h and then a saturated NaHCO₃ solution was added. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 10:1) yielded 155 mg (90%) of aldehyde 365 as colorless oil.

Rᵣ = 0.24 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D° 2.20 (c = 1.00, CH₂Cl₂).
(Z)-(6S,7R,8S)-7-(tert-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzylxy)-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 NaClO₂ (465 mg, 5.2 mmol) and NaH₂PO₄ (465 mg) in water (2 mL). After 3 h 0.01N NaOH was added and the aqueous layer was extracted with Et₂O. 1N HCl was added until pH 2 was reached and the aqueous layer was extracted with DCM. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give 160 mg of crude acid 361 which was directly used for the following reaction.

\[ ^1H-NMR \, (400 \, MHz, \, C₆D₆): \delta = 7.27 \, (d, \, J = 8.56 \, Hz, \, 2H), \, 6.82 \, (d, \, J = 8.59 \, Hz, \, 2H), \, 5.11 \, (d, \, J = 10.10 \, Hz, \, 1H), \, 4.40 \, (d, \, J = 2.00 \, Hz, \, 2H), \, 3.60 \, (dd, \, J = 9.09, \, 5.30 \, Hz, \, 1H), \, 3.53 \, (dd, \, J = 6.30, \, 4.30 \, Hz, \, 1H), \, 3.33 \, (s, \, 3H), \, 3.32 \, (m, \, 1H), \, 2.81-2.72 \, (m, \, 1H), \, 2.37-2.20 \, (m, \, 4H), \, 2.18-2.11 \, (m, \, 1H), \, 1.53 \, (d, \, J = 1.26 \, Hz, \, 3H), \, 1.08 \, (d, \, J = 7.07 \, Hz, \, 3H), \, 1.04 \, (d, \, J = 6.57 \, Hz, \, 3H), \, 1.01 \, (s, \, 9H), \, 0.10 \, (s, \, 6H). \]

\[ ^13C-NMR \, (100 \, MHz, \, C₆D₆): \delta = 179.1, \, 159.7, \, 132.1, \, 131.8, \, 131.2, \, 129.6, \, 114.1, \, 79.1, \, 73.0, \, 72.6, \, 54.8, \, 39.0, \, 36.0, \, 32.7, \, 27.6, \, 26.4, \, 22.9, \, 18.7, \, 17.5, \, 15.4, \, -3.6, \, -3.7. \]

(Z)-(6S,7R,8S)-7-(tert-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4,6,8-trimethyl-non-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 Et₂O) 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.
Experimental Section

$R_f = 0.40$ (hexane:EtOAc = 10:1)

$^1$H-NMR (400 MHz, CHCl$_3$): $\delta = 7.24$ (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$_3$): $\delta = 173.7$, 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$_5$Si: 478.3115, found: 478.3107.

$[^{[\alpha]}]_D^{20}$ 2.20 (c = 0.5, CH$_2$Cl$_2$)

(Z)-(6S,7R,8S)-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 $\mu$L, 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$_3$): $\delta = 7.23$ (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).

220
Experimental Section

\(^{13}\text{C-NMR}\) (100 MHz, CHCl\(_3\)): \(\delta = 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.

\(\text{IR}\) (film): 2928, 1757, 1249 cm\(^{-1}\).

\(\text{HRMS}\) (ESI) (m/z): [M-C\(_4\)H\(_9\)]\(^+\) calcd for C\(_{30}\)H\(_{43}\)O\(_5\)Si: 511.2880, found: 511.2875.

\([\alpha]_D^{20}\) 10.40 (c = 0.25, CH\(_2\)Cl\(_2\))

\((Z)-(6S,7R,8S)-N-[7-(\text{tert-Butyl-dimethyl-silanyloxy})-9-(4\text{-methoxy-benzyloxy})-4,6,8\text{-trimethyl-non-4-enoyl}]-(1'R)-\text{bornan-2',10'-sultam} (368)\)

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 \(\mu\)L, 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.

\(R_t = 0.28\) (hexane:EtOAc = 3:1)

\(^1\text{H-NMR}\) (400 MHz, CHCl\(_3\)): \(\delta = 7.25\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CHCl\(_3\)): \(\delta = 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.

221
Experimental Section

IR (film): 2958, 2855, 1698, 1513, 1461, 1332, 1248, 1212, 1171, 1133, 1085 cm\(^{-1}\).


\([\alpha]_D^{\text{20}}\) 34.95 (c = 1.58, CH\(_2\)Cl\(_2\))

(Z)-(2S,6S,7R,8S)-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 \(\mu\)L, 1M in THF, 0.055 mmol) and the solution was stirred for 1 h. MeI (9 \(\mu\)L, 0.100 mmol) was added and stirring was continued for 1.5 h. The reaction was quenched by the addition of a saturated NH\(_4\)Cl 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 \(\alpha\)-methylated \(N\)-acyl sultam 369.

\(R_f\) = 0.29 (hexane:EtOAc = 3:1)

\(^1\)H-NMR (400 MHz, CHCl\(_3\)): \(\delta = 7.25\) (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\(_3\)): \(\delta = 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_{6}SNSiNa: 698.3887, found: 698.3902.

[α]_D^{20} 55.30 (c = 1.00, CH_{2}Cl_{2})

(Z)-(2S,6S,7R,8S)-7-(tert-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzylhloxy)-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)

^1H-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).

^13C-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_{4}Si: 462.3165, found: 462.3171.

[α]_D^{20} 3.92 (c = 1.30, CH_{2}Cl_{2})
**Experimental Section**

**(1-bromoallyl)trimethylsilane (385)**

![Chemical Structure](image)

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 nBuLi (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 MgSO₄. 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.

**H-NMR** (250 MHz, CDCl₃): \( \delta = 5.92 \) (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 MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 20:1) yielded 350 mg (90%) of diene 386.

**Rf = 0.60 (hexane:EtOAc = 10:1)**

**H-NMR** (250 MHz, CDCl₃): \( \delta = 7.25 \) (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),
Experimental Section

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)

\[
\text{HO} \quad \text{\begin{tikzpicture} [scale=0.5]
\draw (0,0) -- (1,0) -- (1.5,0.5) -- (0.5,0.5) -- cycle;
\end{tikzpicture}\}}
\]

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 NaHCO₃ solution, the organic layer was separated and the aqueous solution was extracted with DCM. The combined organic solution was dried over MgSO₄, the solvent was evaporated and the residue was purified by column chromatography (hexane:DCM = 1:1) to yield 90 mg (93%) of volatile 518.

Rₛ = 0.30 (hexane:EtOAc = 10:1)

\(^1\)H-NMR (250 MHz, CDCl₃): \( \delta = 6.64 \) (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)

\[
\text{OH} \quad \text{\begin{tikzpicture} [scale=0.5]
\draw (0,0) -- (1,0) -- (2,0.5) -- (1.5,0.5) -- cycle;
\end{tikzpicture}\}}
\]

To a stirred suspension of alcohol 518 (90 mg, 0.8 mmol) and NaHCO₃ (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 MgSO₄ and the solvent was evaporated to yield crude aldehyde 387.

To aldehyde 387 (90 mg, 0.8 mmol) in Et₂O (8 mL) at 0 °C was slowly added EtMgBr (0.4 mL, 3M in Et₂O, 1.2 mmol). After 3 h brine was added and acidified with 5% H₂SO₄. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic phase was dried over MgSO₄ and the solvent was carefully evaporated. Purification
Experimental Section

by column chromatography (hexane:DCM = 1:1) yielded 100 mg (89%) of volatile alcohol 519 as 1:1 mixture of diastereoisomers.

Rf = 0.40 (hexane:EtOAc = 10:1)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.68\) (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\(_3\)): \(\delta = 134.8, 132.3, 129.6, 117.8, 77.3, 38.2, 27.3, 16.4, 10.3\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.68\) (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\(_3\)): \(\delta = 134.1, 132.2, 130.8, 118.1, 77.3, 38.0, 27.1, 17.2, 9.9\).

IR (film): 3585, 3391, 2964, 1651, 1644, 1634 cm\(^{-1}\).

HRMS (ESI) (m/z): [M]\(^+\) calcd for C\(_9\)H\(_{16}\)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.

Rf = 0.45 (hexane:EtOAc = 10:1)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.70-6.60\) (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, \(J = 17.81, 7.28\)Hz, 1H), 1.16 (d, \(J = 6.57\) Hz, 3H), 1.02 (t, \(J = 7.20\) Hz, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta = 211.6, 131.4, 131.0, 130.9, 119.3, 45.9, 33.9, 16.6, 7.7\).
IR (film): 2976, 2937, 1716, 1458, 1375 cm⁻¹.


[α]D²⁰ 350.12 (c = 0.85, CH₂Cl₂)

(3Z,11Z)-(5S,7R,8R,9S,13S,14S,15S)-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 Bu₂BOTf (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 H₂O₂. 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 MgSO₄ 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.

Rf = 0.47 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.
Experimental Section

**HRMS** (ESI) (m/z): [M]+ calcd for C_{36}H_{60}O_{5}Si: 600.4210, found: 600.4219.

[\alpha]_D^{20} 154.00 (c = 0.85, CH_{2}Cl_{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 (17R).

<table>
<thead>
<tr>
<th>carbon</th>
<th>(S)-Mosher ester</th>
<th>(R)-Mosher ester</th>
<th>R vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>6,106</td>
<td>6,114</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>14’</td>
<td>1,5415</td>
<td>1,5656</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>15a</td>
<td>2,1490</td>
<td>2,2134</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>15b</td>
<td>1,7340</td>
<td>1,8184</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>16</td>
<td>2,008</td>
<td>2,020</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>16’</td>
<td>0,7797</td>
<td>0,8059</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>17</td>
<td>5,4256</td>
<td>5,4488</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>18</td>
<td>3,1347</td>
<td>3,1653</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>18’</td>
<td>1,0170</td>
<td>1,0013</td>
<td>R&lt;S</td>
</tr>
<tr>
<td>20</td>
<td>3,4850</td>
<td>3,5350</td>
<td>R&gt;S</td>
</tr>
<tr>
<td>20’</td>
<td>0,9549</td>
<td>0,9294</td>
<td>R&lt;S</td>
</tr>
<tr>
<td>21</td>
<td>5,2430</td>
<td>5,2480</td>
<td>R~S</td>
</tr>
</tbody>
</table>
(S)-MTPA ester of 520:

\[
\begin{array}{c}
\text{PMBO} \\
\text{OTBS} \\
\end{array}
\]

\[\begin{array}{c}
\text{F}_3\text{C} \\
\text{MeO} \\
\text{Ph} \\
\end{array}\]

\(1^H\text{-NMR} (400 \text{ MHz, CDCl}_3): \delta = 7.47 \text{ (m, 2H)}, 7.40 \text{ (m, 3H)}, 7.24 \text{ (d, } J = 8.69 \text{ Hz, 2H)}, 6.86 \text{ (d, } J = 8.69 \text{ Hz, 2H)}, 6.55 \text{ (dt, } J = 17.18, 10.29 \text{ Hz, 1H)}, 6.11 \text{ (t, } J = 10.57 \text{ Hz, 1H)}, 5.42 \text{ (dd, } J = 9.44, 3.02 \text{ Hz, 1H)}, 5.31-5.19 \text{ (m, 3H)}, 5.04 \text{ (d, } J = 10.20 \text{ Hz, 1H)}, 4.39 \text{ (d, } J = 11.70 \text{ Hz, 1H)}, 4.36 \text{ (d, } J = 11.70 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, 3.48 \text{ (m, 1H)}, 3.45 \text{ (m, 1H)}, 3.44 \text{ (s, 3H)}, 3.36 \text{ (dd, } J = 6.23, 4.72 \text{ Hz, 1H)}, 3.20 \text{ (dd, } J = 9.06, 8.31 \text{ Hz, 1H)}, 3.13 \text{ (dd, } J = 9.44, 7.18 \text{ Hz, 1H)}, 2.43 \text{ (m, 1H)}, 2.01 \text{ (m, 1H)}, 1.94 \text{ (m, 1H), 1.73 \text{ (m, 1H), 1.55 \text{ (s, 3H), 1.02 \text{ (d, } J = 7.17 \text{ Hz, 3H), 0.95 \text{ (d, } J = 6.79 \text{ Hz, 3H), 0.92 \text{ (d, } J = 7.17 \text{ Hz, 3H), 0.89 \text{ (s, 9H), 0.84 \text{ (d, } J = 6.42 \text{ Hz, 3H), 0.77 \text{ (d, } J = 6.80 \text{ Hz, 3H), 0.03 \text{ (s, 3H), 0.02 \text{ (s, 3H).}})}
\]

(R)-MTPA ester of 520:

\[
\begin{array}{c}
\text{PMBO} \\
\text{OTBS} \\
\end{array}
\]

\[\begin{array}{c}
\text{F}_3\text{C} \\
\text{MeO} \\
\text{Ph} \\
\end{array}\]

\(1^H\text{-NMR} (400 \text{ MHz, CDCl}_3): \delta = 7.52 \text{ (m, 2H)}, 7.39 \text{ (m, 3H)}, 7.23 \text{ (d, } J = 8.69 \text{ Hz, 2H)}, 6.86 \text{ (d, } J = 8.69 \text{ Hz, 2H)}, 6.64 \text{ (dt, } J = 16.81, 10.10 \text{ Hz, 1H)}, 6.11 \text{ (t, } J = 10.58 \text{ Hz, 1H)}, 5.45 \text{ (dd, } J = 9.44, 2.64 \text{ Hz, 1H)}, 5.32-5.21 \text{ (m, 3H)}, 5.05 \text{ (d, } J = 10.57 \text{ Hz, 1H)}, 4.39 \text{ (d, } J = 11.71 \text{ Hz, 1H)}, 4.35 \text{ (d, } J = 11.71 \text{ Hz, 1H)}, 3.80 \text{ (s, 3H)}, 3.53 \text{ (m, 1H)}, 3.44 \text{ (s, 3H)}, 3.43 \text{ (dd, } J = 9.25, 5.09 \text{ Hz, 1H)}, 3.38 \text{ (dd, } J = 6.42, 4.53 \text{ Hz, 1H)}, 3.20 \text{ (dd, } J = 9.19, 8.24 \text{ Hz, 1H)}, 3.17 \text{ (dd, } J = 9.63, 6.98 \text{ Hz, 1H)}, 2.46 \text{ (m, 1H)}, 2.21 \text{ (t, } J = 12.46 \text{ Hz, 1H)}, 2.02 \text{ (m, 1H)}, 1.96 \text{ (m, 1H)}, 1.81 \text{ (d, } J = 11.70 \text{ Hz, 1H)}, 1.55 \text{ (s, 3H), 1.00 \text{ (d, } J = 7.17 \text{ Hz, 3H), 0.93 \text{ (d, } J = 6.42 \text{ Hz, 3H), 0.92 \text{ (d, } J = 6.70 \text{ Hz, 3H), 0.89 \text{ (s, 9H), 0.86 \text{ (d, } J = 6.42 \text{ Hz, 3H), 0.80 \text{ (d, } J = 6.80 \text{ Hz, 3H), 0.03 \text{ (s, 6H).}})}
\]
Experimental Section

(3Z,11Z)-(5S,6S,7R,8R,9S,13S,14S,15S)-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 MgSO4 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.

Rf = 0.35 (hexane:EtOAc = 5:1)

1H-NMR (600 MHz, CDCl3): 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 = 11.3 Hz, 1H), 5.51 (t, J = 9.99 Hz, 1H) 5.24-5.12 (m, 2H), 5.04 (d, J = 10.2 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).

13C-NMR (150 MHz, CDCl3): 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.


[α]D 20 33.20 (c = 0.25, CH2Cl2)
**Experimental Section**

**tert-Butyl-((Z)-(1S,2S,6S)-1-[(S)-3-(4-methoxy-phenoxy)-1-methyl-propyl]-6-[[2R,4R,5R,6S]-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 MgSO₄ 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)

**1H-NMR (600 MHz, CDCl₃):**

\[ \delta = 7.40 \text{ (d, } J = 8.28 \text{ Hz, 2H)}, \ 7.19 \text{ (d, } J = 8.64 \text{ Hz, 2H)}, \ 6.85 \text{ (d, } J = 8.70 \text{ Hz, 2H)}, \ 6.83 \text{ (d, } J = 8.70 \text{ Hz, 2H)}, \ 6.63 \text{ (m, 1H)}, \ 5.98 \text{ (t, } J = 10.77 \text{ Hz, 1H)}, \ 5.71 \text{ (t, } J = 10.20 \text{ Hz, 1H)}, \ 5.45 \text{ (s, 1H)}, \ 5.24-5.12 \text{ (m, 2H)}, \ 5.07 \text{ (d, } J = 10.14 \text{ Hz, 1H)}, \ 4.36 \text{ (d, } J = 11.71 \text{ Hz, 1H)}, \ 4.30 \text{ (d, } J = 11.71 \text{ Hz, 1H)}, \ 3.79 \text{ (s, 3H)}, \ 3.78 \text{ (s, 3H)}, \ 3.49 \text{ (dd, } J = 9.06, 4.14 \text{ Hz, 1H)}, \ 3.38 \text{ (m, 1H)}, \ 3.35 \text{ (t, } J = 5.28 \text{ Hz, 1H)}, \ 3.16 \text{ (t, } J = 8.88 \text{ Hz, 1H)}, \ 3.01 \text{ (m, 1H)}, \ 2.58 \text{ (m, 1H)}, \ 2.48 \text{ (dd, } J = 13.41, 12.27 \text{ Hz, 1H)}, \ 2.04-1.84 \text{ (m, 3H)}, \ 1.64 \text{ (d, } J = 0.78 \text{ Hz, 3H)}, \ 1.33-1.22 \text{ (m, 2H)}, \ 0.95 \text{ (d, } J = 6.78 \text{ Hz, 3H)}, \ 0.94 \text{ (d, } J = 7.20 \text{ Hz, 3H)}, \ 0.89 \text{ (d, } J = 6.78 \text{ Hz, 3H)}, \ 0.88 \text{ (d, } J = 6.42 \text{ Hz, 3H)}, \ 0.87 \text{ (s, 9H)}, \ 0.85 \text{ (d, } J = 6.78 \text{ Hz, 3H)}, \ 0.00 \text{ (s, 3H)}, \ -0.01 \text{ (s, 3H)}.\]

**13C-NMR (150 MHz, CDCl₃):**

\[ \delta = 159.4, \ 158.9, \ 132.3, \ 131.9, \ 131.8, \ 129.1, \ 127.3, \ 113.6, \ 113.2, \ 100.2, \ 86.5, \ 80.4, \ 78.7, \ 72.6, \ 72.4, \ 65.1, \ 55.3, \ 55.1, \ 38.1, \ 36.6, \ 35.3, \ 31.8, \ 31.5, \ 31.4, \ 26.2, \ 25.9, \ 23.2, \ 22.7, \ 18.4, \ 18.3, \ 16.8, \ 16.3, \ 14.1, \ 11.3, \ 9.7, \ -3.8, \ -3.9, \ -5.3, \ -5.4.\]

**IR (film):**

2930, 1615, 1515, 1249, 1083, 1037 cm⁻¹.


\[ [\alpha]_D^{20} = 43.43 \] (c = 0.175, CH₂Cl₂)
(Z)-(2S,4R,5R,6S,10S,11S,12S)-1,11-Bis-(tert-butyl-dimethyl-silyloxy)-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 Bu₂BOTf (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 H₂O₂. 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 MgSO₄ 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.

Rᵣ = 0.47 (hexane:EtOAc = 10:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]₀₂₀° 15.48 (c = 0.58, CH₂Cl₂)
(2R,4S,5R,6R)-4-[(Z)-(1S,5S,6S,7S)-6-(tert-Butyl-dimethyl-silanyloxy)-9-(4-methoxy-phenoxy)-1,3,5,7-tetramethyl-non-3-enyl]-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 MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (hexane:EtOAc = 20:1) yielded 15 mg (99%) of acetal 401 as colorless oil.

Rf = 0.63 (hexane:EtOAc = 10:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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.


[α]D²⁰ = 7.67 (c = 0.3, CH₂Cl₂)
Experimental Section

(S)-4-Benzyl-3-[{(Z)-(2S,3R,4S,8S,9R,10S)-9-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-11-(4-methoxy-benzyloxy)-2,4,6,8,10-pentamethyl-undec-6-enoyl]-oxazolidin-2-one (402)

![Chemical Structure]

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 H₂O₂ (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 MgSO₄ 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.

Rᵣ = 0.33 (hexane:EtOAc = 3:1)

**¹H-NMR** (400 MHz, CDCl₃): 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 = 11.79 Hz, 1H), 3.54 (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).

**¹³C-NMR** (100 MHz, CDCl₃): 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 C₄₀H₆₁NO₇Si: 695.4217, found: 695.4225.
Experimental Section

\([\alpha]_D^{20} 32.22 \ (c = 0.45, \ \text{CH}_2\text{Cl}_2)\)

(S)-4-Benzyl-3-\{(Z)-(2S,3R,4S,8S,9R,10S)-3,9-bis-(tert-butyl-dimethyl-silanyloxy)-11-(4-methoxy-benzylxyloxy)-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$_4$Cl 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$_3$): \(\delta = 7.35-7.27 \) (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$_3$): \(\delta = 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$_7$Si$_2$Na: 832.4980, found: 832.4987.

\([\alpha]_D^{20} 48.00 \ (c = 0.6, \ \text{CH}_2\text{Cl}_2)\)
(Z)-(2R,3R,4S,8S,9R,10S)-3,9-Bis-(tert-butyl-dimethyl-silyloxy)-11-(4-methoxy-benzylxyloxy)-2,4,6,8,10-pentamethyl-undec-6-en-1-ol (403)

To aldol adduct 523 (18 mg, 0.022 mmol) in Et₂O (0.5 mL) with methanol (10 μL) at 0 °C was slowly added LiBH₄ (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 MgSO₄. After evaporation of the solvent, purification by column chromatography (hexane:EtOAc = 5:1) yielded 12 mg (86%) of 403.

Rᵢ = 0.59 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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 (d, 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).

¹³C-NMR (100 MHz, CDCl₃): 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, 1039 cm⁻¹.


[α]D²⁰ 1.81 (c = 0.55, CH₂Cl₂)

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). nBuLi (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 recouling
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 Et2O (2 mL) was added and vigorously shaken. The layers were separated and the aqueous phase was repeatedly extracted with Et2O. The combined ethereal layer was dried over MgSO4 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.

(3R,4R,5S,6S,7S)-6-(tert-Butyl-dimethyl-silanyloxy)-8-(4-methoxy-benzyl oxy)-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 MgSO4 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.

Rf = 0.49 (hexane:EtOAc = 5:1)

$^1$H-NMR (400 MHz, CDCl₃): 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, CDCl₃): 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, 1039 cm⁻¹.

Experimental Section

$[\alpha]_D^{20} = -2.43 \ (c = 1.15, \ CH_2Cl_2)$

$(2S,3S,4S,5S,6S)-5$(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 tBuOOH (16 μL, 5.5M in decane, 0.082 mmol). The reaction mixture was allowed to warm to r.t. over night. A saturated Na$_2$S$_2$O$_3$ 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$_3$): $\delta$ = 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, 1H), 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$_3$): $\delta$ = 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.
To epoxide 410 (15 mg, 0.033 mmol) in Et₂O:THF (1:1, 1 mL) at 0 °C was added HIO₄·2H₂O (12 mg, 0.055 mmol) and the mixture was stirred overnight at 0 °C. A saturated NaHCO₃ 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 MgSO₄ and the solvent was evaporated. The residue was taken up in methanol (1 mL) and NaBH₄ was added. After 30 min brine was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 3:1) yielded 12 mg (82%) of alcohol 524.

Rf = 0.39 (hexane:EtOAc = 5:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]₀²⁰ = -2.00 (c = 0.2, CH₂Cl₂)
Experimental Section

**tert-Butyl-((1S,2S)-4-(4-methoxy-phenoxy)-1-{(S)-1-[[2R,4R,5R]-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxan-4-yl]-ethyl}-2-methyl-butoxy)-dimethyl-silane (411)**

![Chemical Structure](image)

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 MgSO₄ and the solvent was removed under reduced pressure. Column chromatography (Hexane:EtOAc = 10:1) yielded 10 mg (99%) of acetal 411 as colorless oil

\[ R_f = 0.42 \text{ (hexane:EtOAc = 10:1)} \]

**^1H-NMR** (400 MHz, CDCl₃): 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).

**^13C-NMR** (100 MHz, CDCl₃): 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.


\[ [\alpha]_D^{20} = -32.75 \text{ (c = 0.4, CHCl}_3) \]
Experimental Section

(Z)-(3S,4S,5R,6R,7S,11S,12R,13S)-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 Et₂O were added and the phases were separated. The aqueous layer was extracted with Et₂O and the combined ethereal layer was dried over MgSO₄. 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 MgSO₄ 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.

Rf = 0.49 (hexane:EtOAc = 10:1)

¹H-NMR (400 MHz, CDCl₃): 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, 3H), 0.89 (s, 3H), 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).

¹³C-NMR (100MHz, CDCl₃): 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.

Experimental Section

\[ \alpha \]_D^{20} 12.00 (c = 0.4, CH₂Cl₂)

\((Z)-(2R,3S,4R,5R,6S,10S,11R,12S)-5,11\)-Bis-(tert-butyl-dimethyl-silyloxy)-13-(4-methoxy-benzyl oxy)-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 tBuOOH (5 μL, 5.5M in decane, 0.026 mmol). The reaction mixture was kept over night at 0 °C. A saturated Na₂S₂O₃ solution was added and the layers were separated. The aqueous phase was extracted with DCM and the combined organic layer was dried over MgSO₄ 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, CDCl₃): 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, CDCl₃): 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.

(Z)-(2S,3S,4R,5R,6S,10S,11R,12S)-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 Et₂O:THF (1:1, 1 mL) at 0 °C was added HIO₄·2H₂O (3 mg, 0.0140 mmol) and the mixture was stirred 16 h at 0 °C. A saturated NaHCO₃ solution was added and DCM, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. The residue was taken up in methanol (1 mL) and NaBH₄ 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 MgSO₄ 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.

Rᵣ = 0.41 (hexane:EtOAc = 10:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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.


[α]ᵈ₂⁰ 4.00 (c = 0.1, CH₂Cl₂)
Experimental Section

(2S,4S,5S)-4-[(Z)-(1R,2R,3S,7S,8R,9S)-2,8-Bis-(tert-butyl-dimethyl-silylloxy)-10-(4-methoxy-benzylxyloxy)-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 MgSO₄ 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.

Rᵣ = 0.51 (hexane:EtOAc = 15:1)

¹H-NMR (600 MHz, CDCl₃): 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).

¹³C-NMR (150 MHz, CDCl₃): 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.


[α]D²⁰ 24.00 (c = 0.05, CHCl₃)
10.2.4. Peloruside A

Dimethyl 2-(tert-butoxymethyl)malonate (429)

\[
\text{MeO} \quad \text{O} \quad \text{OMe} \\
\text{OrBu}
\]

\text{tBuOMOM:} To a suspension of NaH (8.8 g, 0.22 mol) in THF (150 mL) at r.t. was added \text{tBuOH} (18.8 mL, 0.20 mol) and the mixture was heated under reflux for 2 h. \text{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).

\text{Alkylation:} To \text{tBuOMOM} (1 g, 8.30 mmol) in DCM (5 mL) at 0 °C was added \text{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 \text{tBuOCH}_2\text{Cl}.

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 \text{NH}_4\text{Cl} solution, the layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over \text{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.

\( R_f = 0.45 \) (hexane:EtOAc = 5:1)

\text{1H-NMR} (400 MHz, CDCl\textsubscript{3}): \( \delta = 3.81 \) (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)

\[
\text{MeO} \quad \text{O} \quad \text{OMe} \\
\text{OrBu}
\]

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 NH₄Cl solution, layers were separated and the aqueous solution was extracted with DCM. The combined organic layer was dried over MgSO₄ 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.

Rᵣ = 0.46 (hexane:EtOAc = 5:1)

¹H-NMR (250 MHz, CDCl₃): 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)

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{O} & \quad \text{Me} \\
\text{OtBu} & 
\end{align*}
\]

To malonate 427 (4 g, 17 mmol) suspended in 0.05M KH₂PO₄ 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 Et₂O. Upon acidification with 3N HCl to pH 1 mono acid 292 was extracted with DCM, the combined organic layers were dried over MgSO₄ and the solvent was evaporated to give 3.5 g of crude mono acid 428.

Rᵣ = 0.05 (hexane:EtOAc = 3:1)

¹H-NMR (250 MHz, CDCl₃): 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 nBuLi (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 NH₄Cl 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 MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 3:1) gave 3.9 g (93%) of acylated oxazolidinone 37.

Rₐ = 0.38 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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 Et₂O and concentrated. To the residue was added MeOH (15 mL) and the mixture was cooled to 0 °C, then NaBH₄ (416 mg, 11.00 mmol) was added portionwise. After 1 h the reaction was quenched with a saturated solution of NH₄Cl, layers were separated and the aqueous layer was extracted with DCM. The combined organic extract was dried over MgSO₄ and the organic solvent was evaporated under reduced pressure. Column chromatography (hexane:EtOAc = 3:1) gave 934 mg (83%) of alcohol 526.

Rₐ = 0.23 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.
Experimental Section


[α]_D^20 2.00 (c = 1.3, CH₂Cl₂)

(R)-2-tert-Butoxymethyl-2-methyl-3-oxo-propionic acid methyl ester (430)

![Structure](image)

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 Et₂O were added and the organic layer was separated. The aqueous layer was extracted with Et₂O and the combined ethereal phase was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 2.80 g (80%) of aldehyde 430 as colorless oil.

Rₐ = 0.57 (hexane:EtOAc = 3:1)

**¹H-NMR** (400 MHz, CDCl₃): 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).

**¹³C-NMR** (100 MHz, CDCl₃): δ = 199.8, 171.8, 73.4, 65.0, 58.1, 52.3, 27.2, 15.0.

**IR** (film): 1724, 1455, 1237, 1195, 1087 cm⁻¹.


[α]_D^20 0.86 (c = 1.4, CH₂Cl₂)

(2R,3R,4R)-4-((R)-4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-2-tert-butoxymethyl-3-hydroxy-2-methyl-hexanoic acid methyl ester (431)

![Structure](image)

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
Experimental Section

(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 H₂O₂ (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 MgSO₄ 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.

Rᵣ = 0.36 (hexane:EtOAc = 3:1)

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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, 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.


[α]D²⁰⁻₃₈.₄⁷ (c = 1.24, CH₂Cl₂)

(2R,3R,4S)-2-tert-Butoxymethyl-3-hydroxy-4-hydroxymethyl-2-methyl-hexanoic acid methyl ester (432)

To aldol adduct 431 (440 mg, 0.98 mmol) in Et₂O (10 mL) and methanol (20 μL) at 0 °C was slowly added LiBH₄ (21 mg, 0.98 mmol). After 30 min the reaction was quenched by the addition of saturated NH₄Cl solution and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over MgSO₄. 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.
Experimental Section

$R_f = 0.22$ (hexane:EtOAc = 2:1)

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 3.99$ (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$_3$): $\delta = 176.9$, 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$_5$Na: 299.1834, found: 299.1832.

$[\alpha]_D^{20} = 19.90$ (c = 0.97, CH$_2$Cl$_2$)

(3R,4R,5S)-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$_2$CO$_3$ (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$_3$): $\delta = 4.37$ (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$_3$): $\delta = 175.2$, 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_{2}Cl_{2})

Methanesulfonic acid (3R,4R,5S)-3-tert-butoxymethyl-5-ethyl-3-methyl-2-oxotetrahydro-pyran-4-yI 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 \mu L, 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)

^1H-NMR (400 MHz, CDCl_3): \(\delta = 4.66 (d, J = 9.85 \text{ Hz}, 1H), 4.45 (dd, J = 11.62, 5.30 \text{ Hz}, 1H), 3.88 (t, J = 11.24 \text{ Hz}, 1H), 3.63 (d, J = 8.34 \text{ Hz}, 1H), 3.54 (d, J = 8.34 \text{ 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 \text{ Hz}, 3H).

^13C-NMR (100 MHz, CDCl_3): \(\delta = 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\(^{-1}\).


\[\alpha\]_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 NH₄Cl solution and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was evaporated. Column chromatography (hexane:EtOAc = 5:1) yielded 110 mg (83%) of olefin 437

\[ R_f = 0.40 \ (\text{hexane:EtOAc} = 5:1) \]

\(^1\text{H-NMR}\) (400 MHz, CDCl₃): \( \delta = 5.07 \ (d, \ J = 10.10 \text{ Hz}, 1\mathrm{H}), 3.98 \ (d, \ J = 9.34 \text{ Hz}, 1\mathrm{H}), 3.63 \ (d, \ J = 8.34 \text{ Hz}, 1\mathrm{H}), 3.57 \ (ddd, \ J = 10.23, 6.69, 3.92 \text{ Hz}, 1\mathrm{H}), 3.21 \ (t, \ J = 9.85 \text{ Hz}, 1\mathrm{H}), 2.87 \ (dd, \ J = 7.19, 2.64 \text{ Hz}, 1\mathrm{H} \ (\text{OH})), 2.47-2.38 \ (m, 1\mathrm{H}), 1.82 \ (s, 3\mathrm{H}), 1.42-1.33 \ (m, 1\mathrm{H}), 1.27-1.12 \ (m, 2\mathrm{H}), 1.23 \ (s, 9\mathrm{H}), 0.87 \ (t, \ J = 7.32 \text{ Hz}, 3\mathrm{H}).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl₃): \( \delta = 136.1, 131.8, 73.6, 65.9, 60.8, 43.0, 27.4, 24.9, 23.2, 11.8.

\(\text{IR}\) (film): 3629, 2970, 1653, 2559, 1056 cm⁻¹.

\(\text{HRMS}\) (ESI) (m/z): \([\text{M-H}]^+\) calcd for C₁₂H₂₃O₂: 199.1698, found: 199.1703.

\([\alpha]_{D}^{20}\) 32.66 (c = 0.65, CH₂Cl₂)

((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 NH₄Cl solution, layers were separated and the aqueous layer was extracted with DCM. The combined organic solution was dried over MgSO₄ and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 10:1) yielded 18 mg (85%) of 527 as colorless oil.
**Experimental Section**

\( \text{R}_f = 0.63 \) (hexane:EtOAc = 10:1)

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 5.03 \) (d, \( J = 9.60 \text{ Hz}, 1H \)), 3.91 (d, \( J = 10.36 \text{ Hz}, 1H \)), 3.84 (d, \( J = 10.36 \text{ Hz}, 1H \)), 3.55 (dd, \( J = 9.60, 5.80 \text{ Hz}, 1H \)), 3.48 (dd, \( J = 9.48, 7.20 \text{ Hz}, 1H \)), 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, \( J = 7.44 \text{ Hz}, 3H \)).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 134.9, 129.6, 72.8, 66.9, 61.1, 42.5, 27.6, 24.7, 21.9, 18.1, 12.0, 11.7 \).

**IR** (film): 2943, 2866, 1463, 1362, 1197, 1103, 1059, 1014 cm⁻¹.

**HRMS** (ESI) (m/z): [M⁺] calcd for C₂₁H₄₄O₂Si: 356.3111, found: 356.3105.

\( [\alpha]_{D}^{20} = -25.56 \) (c = 0.45, CH₂Cl₂)

**((Z)-(R)-5-tert-Butoxy-2-ethyl-4-methyl-pent-3-enyloxymethyl)-benzene (528)**

![Chemical Structure](image)

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 Et₂O and the solvent was evaporated. Purification by column chromatography (hexane:EtOAc = 40:1) yielded 21 mg (quant.) of benzyl ether 528 as colorless oil.

\( \text{R}_f = 0.59 \) (hexane:EtOAc = 10:1)

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 7.33 \) (m, 4H), 7.28 (m, 1H), 5.05 (d, \( J = 9.60 \text{ Hz}, 1H \)), 4.49 (s, 2H), 3.88 (s, 2H), 3.36 (dd, \( J = 9.22, 5.93 \text{ Hz}, 1H \)), 3.31 (dd, \( J = 9.22, 7.20 \text{ Hz}, 1H \)), 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, \( J = 7.45 \text{ Hz}, 3H \)).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 138.8, 135.2, 129.2, 128.3, 127.5, 127.4, 74.1, 72.9, 61.0, 39.8, 27.6, 25.2, 21.9, 11.6 \).

**IR** (film): 2970, 1454, 1362, 1197, 1058, 1021 cm⁻¹.
Experimental Section

**HRMS (ESI) (m/z): [M]^+ calcd for C_{19}H_{30}O_{2}: 290.2246, found: 290.2251.**

\[
[a]^\circ_{20} = -37.07 \quad (c = 0.75, \text{CH}_2\text{Cl}_2)
\]

**(Z)-(R)-4-Benzylxymethyl-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 MgSO₄ 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.

\[
R_f = 0.43 \quad \text{(hexane:EtOAc = 3:1)}
\]

**\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)):** \(\delta = 7.36-7.27\) (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).

**\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)):** \(\delta = 158.3, 138.5, 134.9, 129.3, 128.3, 127.5, 127.4, 73.5, 73.0, 67.0, 40.4, 24.8, 21.2, 11.5.\)

**\(\text{IR}\) (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.**

\[
[a]^\circ_{20} = -38.80 \quad (c = 0.25, \text{CH}_2\text{Cl}_2)
\]
Experimental Section

10.2.5. Nucleophile Additions

(S)-2-Formyl-2-methyl-pent-4-enoic acid methyl ester (439)

\[
\text{CH}_3\text{CO} = \text{CH} = \text{CH} = \text{CH}-\text{CO}_2\text{CH}_3
\]

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.

\[ R_f = 0.75 \text{ (hexane:EtOAc = 10:1)} \]

\(^1H\)-NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 9.69 \text{ (s, 1H)}, 5.73-5.62 \text{ (m, 1H)}, 5.14-5.09 \text{ (m, 2H)}, 3.75 \text{ (s, 3H)}, 2.62 \text{ (dd, } J = 13.90, 7.34 \text{ Hz, 1H)}, 2.49 \text{ (dd, } J = 13.88, 7.32 \text{ Hz, 1H)}, 1.30 \text{ (s, 3H)}.\)

\(^13C\)-NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 199.0, 172.1, 131.7, 119.5, 119.4, 52.4, 38.5, 16.8.\)

IR (film): 1722, 1456, 1435, 1235, 1150, 1121 cm\(^{-1}\).

HRMS (ESI) (m/z): [M]+ calcd for C\textsubscript{8}H\textsubscript{12}O\textsubscript{3}: 156.0786, found: 156.0778.

\([\alpha]_{D}^{20} -4.09 \text{ (c = 1.6, CH}_2\text{Cl}_2)\)

Allylation procedures:

Roush allylation:

Triisopropyl borate (0.92 mL, 4.00 mmol) and allylmagnesium bromide (4.4 mL, 0.9 M in Et\textsubscript{2}O, 4.00 mmol) were added simultaneously and very slowly to Et\textsubscript{2}O (1 mL) at -78 \textdegree C. The mixture was stirred for 30 min at -78 \textdegree C, then for 3 h at r.t. and recooled to 0 \textdegree 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\textsubscript{2}O: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\textsubscript{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
Experimental Section

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 NaBH₄ in ethanol and 1N NaOH. After stirring for 1 h at r.t. the layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layer was dried over MgSO₄ 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 Et₂O (1 mL) at 0 °C was slowly added allylmagnesium bromide (2.44 mL, 0.9 M in Et₂O, 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 Et₂O (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), NaBO₃·4H₂O was added and the mixture was stirred over night. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by column chromatography (hexane:EtOAc = 15:1 to 5:1) gave with (+)-ιPc 63 mg (quant.) of 440:441 as 20:1 mixture and with (-)-ιPc 43 mg (51%) of 440:441 as 1:1 mixture always favouring the Felkin-Anh adduct 440.

Allylation with allyltrimethylsilane:

TiCl₄ (70 μL, 0.64 mmol) or BF₃·Et₂O (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 NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by column
chromatography (hexane:EtOAc = 5:1) gave with BF₃·Et₂O 53 mg (85%) of 440 and with TiCl₄ 52 mg (84%) of 441.

**Allylation with allyltributylstannane:**

TiCl₄ (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 MgSO₄ 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.

MgBr₂·Et₂O (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 MgSO₄ 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.

(2S,3R)-2-Allyl-3-hydroxy-2-methyl-hex-5-enoic acid methyl ester (440)

\[
\begin{align*}
\text{R}^\gamma &= 0.71 (\text{hexane:EtOAc} = 10:1) \\
^1\text{H-NMR} (400 \text{ MHz, CDCl}_3): &\delta = 5.90-5.70 (m, 2H), 5.15-5.05 (m, 4H), 3.79 (ddd, J = 10.04, 4.86, 2.59 Hz, 1H), 3.69 (s, 3H), 2.59 (dd, J = 13.68, 7.07 Hz, 1H), 2.31 (dd, J = 13.76, 7.70 Hz, 1H), 2.26-2.19 (m, 1H), 2.14 (d, J = 5.05 Hz, 1H), 2.13-2.06 (m, 1H), 1.16 (s, 3H). 
\end{align*}
\]
Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta = 176.2, 135.4, 134.0, 118.1, 117.9, 74.6, 51.7, 50.8, 40.6, 37.2, 16.8.$

IR (film): 3502, 1722, 1435, 1219, 1150 cm$^{-1}$.


$[\alpha]_D^{20}$ -6.50 ($c = 1.4, \text{CH}_2\text{Cl}_2$)

$(2S,3S)$-2- Allyl-3-hydroxy-2-methyl-hex-5-enoic acid methyl ester (441)

$\text{IR}$ (film): 3502, 1726, 1641, 1435, 1220, 1148 cm$^{-1}$.


$[\alpha]_D^{20}$ -10.00 ($c = 1.05, \text{CH}_2\text{Cl}_2$)

General procedure for the conversion of 440 and 441 into the $\beta$-lactone:

LiOH (3 eq.) was added to the $\beta$-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 MgSO₄ and the solvent was evaporated. The crude β-lactone was purified by column chromatography (hexane:EtOAc = 5:1).

(3S,4R)-3,4-diallyl-3-methyloxetan-2-one (442)

\[
\text{R}_{f} = 0.62 \text{ (hexane:EtOAc = 5:1)}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 5.87-5.76 \text{ (m, 2H)}, 5.21-5.13 \text{ (m, 4H)}, 4.31 \text{ (dd, } J = 8.59, 5.56 \text{ Hz, 1H)}, 2.63-2.49 \text{ (m, 3H)}, 2.35 \text{ (dd, } J = 14.27, 7.96 \text{ Hz, 1H)}, 1.40 \text{ (s, 3H)}.

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 174.0, 132.0, 131.9, 119.5, 118.6, 82.2, 56.4, 34.8, 34.6, 19.9.

\(^\text{IR}\) (film): 2980, 1823, 1701, 1643, 1457, 1384, 1125 cm\(^{-1}\).

\(^\text{HRMS}\) (ESI) (m/z): [M\(^+\)] calcd for C\(_{10}\)H\(_{14}\)O\(_2\): 166.0992, found: 166.0982.

\([\alpha]_D^{20} = 17.11 \text{ (c = 0.9, CH}_2\text{Cl}_2\)

(3S,4S)-3,4-diallyl-3-methyloxetan-2-one (443)

\[
\text{R}_{f} = 0.61 \text{ (hexane:EtOAc = 5:1)}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 5.81-5.70 \text{ (m, 2H)}, 5.21-5.15 \text{ (m, 4H)}, 4.38 \text{ (dd, } J = 7.96, 6.19 \text{ Hz, 1H)}, 2.61-2.37 \text{ (m, 4H)}, 1.29 \text{ (s, 3H)}.

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 174.1, 131.7, 131.6, 119.9, 118.6, 79.2, 57.0, 40.1, 34.8, 14.5.\)
Experimental Section

IR (film): 2982, 1824, 1645, 1454, 1125 cm⁻¹.

HRMS (ESI) (m/z): [M]⁺ calcd for C₁₀H_{14}O₂: 166.0992, found: 166.0988.

[α]_{D}{^20} -11.89 (c = 0.45, CH₂Cl₂)

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 Bu₂BOTf (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 H₂O₂ (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 MgSO₄ 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 Et₂O (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 Et₂O (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 Et₂O (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 H₂O₂ (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 MgSO₄ 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)

\[
\begin{align*}
\text{BnO} & \quad \text{O} \quad \text{OH} \quad \text{O} \\
& \quad \text{OMe}
\end{align*}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.35-7.26\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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.


(2S,3R,4R,6S)-methyl 2-allyl-7-(benzyloxy)-3-hydroxy-2,4,6-trimethyl-5-oxoheptanoate (445)

\[
\begin{align*}
\text{BnO} & \quad \text{O} \quad \text{OH} \quad \text{O} \\
& \quad \text{OMe}
\end{align*}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.37-7.25\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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.

Experimental Section

(2S,3S,4R,6R)-methyl 2-allyl-7-(benzyloxy)-3-hydroxy-2,4,6-trimethyl-5-oxoheptanoate (446)

\[
\text{BnO} \quad \text{O} \quad \text{OH} \quad \text{OMe}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.34-7.27\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\textsubscript{3}): \(\delta = 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.

\text{HRMS}\) (ESI) (m/z): [M+Na]\(^+\) calcd for C\textsubscript{21}H\textsubscript{30}O\textsubscript{5}Na: 385.1991, found: 385.1997.

(2S,3R,4R)-2-Allyl-4-((R)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-3-hydroxy-2-methyl-hexanoic acid methyl ester (449)

\[
\text{CO}_2\text{Me}
\]

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 \(\mu\)L, 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\textsubscript{2}O\textsubscript{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\textsubscript{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.
Experimental Section

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 7.36-7.31$ (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$_3$): $\delta = 177.8$, 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$_4$Cl 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)

![Chemical structure of compound 451]

$R_f = 0.55$ (hexane:EtOAc = 3:1)

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 7.95$ (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$_3$): $\delta = 200.0$, 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.
Experimental Section

IR (film): 3525, 2981, 1725, 1684, 1448, 1324, 1215 cm⁻¹.


[α]D²⁰ 18.67 (c = 0.8, CH₂Cl₂)

(S)-2-[(R)-1-hydroxy-3-(4-methoxyphenyl)-3-oxopropyl]-2-methyl-pent-4-enoic acid methyl ester (453)

\[
\text{MeO} \quad \text{O} \quad \text{OH} \quad \text{O} \quad \text{Me}
\]

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

¹H-NMR (400 MHz, CDCl₃): 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).

¹³C-NMR (100 MHz, CDCl₃): 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.


[α]D²⁰ 20.63 (c = 0.95, CH₂Cl₂)

General procedure for the preparation of TMS enol ether:

LDA was prepared by the addition of nBuLi (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 CaH₂, 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)**

OTMS

\[
\begin{align*}
&\text{1H-NMR (400 MHz, C}_6\text{D}_6): \delta = 7.68 (d, J = 7.28 \text{ Hz}, 2H), 7.15-7.07 (m, 3H), 4.92 (d, J = 1.76 \text{ Hz}, 1H), 4.46 (d, J = 1.52 \text{ Hz}, 1H), 0.18 (s, 9H).
\end{align*}
\]

**1-(4-methoxyphenyl)vinylloxy)trimethylsilane (456)**

OTMS

\[
\begin{align*}
&\text{MeO} \\
&\text{1H-NMR (400 MHz, C}_6\text{D}_6): \delta = 7.64 (d, J = 9.01 \text{ Hz}, 2H), 6.76 (d, J = 9.05 \text{ Hz}, 2H), 4.87 (d, J = 1.76 \text{ Hz}, 1H), 4.44 (d, J = 1.76 \text{ Hz}, 1H), 3.27 (s, 3H), 0.21 (s, 9H).
\end{align*}
\]

**General procedure for Mukaiyama aldol with TMS enol ethers:**

To aldehyde 439 (1 eq.) in DCM (0.1M) at -78 °C was added TiCl₄ (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 NaHCO₃ 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 MgSO₄ 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)

\[
\begin{align*}
\text{R}_f &= 0.53 \text{ (hexane:EtOAc = 3:1)} \\
{^1}H\text{-NMR} \ (400 \text{ MHz, CDCl}_3): \delta &= 7.96 \text{ (m, 2H), 7.59 \text{ (m, 1H), 7.47} \text{ (t, } J = 7.70 \text{ Hz, 2H), 5.81-5.70} \text{ (m, 1H), 5.13-5.08} \text{ (m, 2H), 4.44} \text{ (dd, } J = 8.08, 4.04 \text{ Hz, 1H), 3.74 \text{ (s, 3H), 3.11} \text{ (m, 2H), 2.52} \text{ (dd, } J = 13.64, 7.32 \text{ Hz, 1H), 2.30} \text{ (dd, } J = 13.64, 7.58 \text{ Hz, 1H), 1.24} \text{ (s, 3H).}
\end{align*}
\]

{\text{IR} \ (\text{film})}: 3503, 29481, 1734, 1684, 1597, 1449, 1221 cm\textsuperscript{-1}.

\text{HRMS} \ (\text{ESI}) \ (m/z): [M]^+ \text{ calcd for } C_16H_{20}O_4: 276.1362, \text{ found: 276.13531.}

[\alpha]_D^{20} = -20.89 \ (c = 1.12, \text{ CH}_2\text{Cl}_2)

(S)-2-[(S)-1-hydroxy-3-(4-methoxyphenyl)-3-oxopropyl]-2-methyl-pent-4-enoic acid methyl ester (457)

\[
\begin{align*}
\text{R}_f &= 0.41 \text{ (hexane:EtOAc = 3:1)} \\
{^1}H\text{-NMR} \ (400 \text{ MHz, CDCl}_3): \delta &= 7.94 \text{ (d, } J = 9.09 \text{ Hz, 2H), 6.94} \text{ (d, } J = 8.84 \text{ Hz, 2H), 5.81-5.70} \text{ (m, 1H), 5.13-5.08} \text{ (m, 2H), 4.41} \text{ (ddd, } J = 9.34, 4.55, 2.53 \text{ Hz, 1H), 3.88} \text{ (s, 3H), 3.73} \text{ (s, 3H), 3.35} \text{ (d, } J = 4.80 \text{ Hz, 1H (OH)), 3.10} \text{ (dd, } J = 16.92, 2.78 \text{ Hz, 1H), 3.02} \text{ (dd, } J = 16.92, 9.35 \text{ Hz, 1H), 2.51} \text{ (dd, } J = 13.39, 7.07 \text{ Hz, 1H), 2.28} \text{ (dd, } J = 13.64, 7.58 \text{ Hz, 1H), 1.23} \text{ (s, 3H).}
\end{align*}
\]
Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 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$_2$Cl$_2$)

General procedure for the syn-reduction with catecholborane:

To $\beta$-hydroxy ketone (1 eq.) in THF (0.1M) at -15 °C was slowly added catecholborane (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-((1R,3S)-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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$^{-1}$. 
Experimental Section

**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_{2}Cl_{2})

**(S)**-2-((1R,3S)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (460)

![Chemical Structure](image)

R_f = 0.13 (hexane:EtOAc = 3:1)

**1H-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).

**13C-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_{2}Cl_{2})

**(S)**-2-((1S,3R)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (462)

![Chemical Structure](image)

R_f = 0.15 (hexane:EtOAc = 3:1)
**Experimental Section**

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 7.39-7.33 \) (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).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 177.0, 144.3, 132.9, 128.5, 127.6, 125.8, 118.6, 76.0, 75.1, 52.0, 50.8, 40.8, 39.8, 17.2. \)

**IR** (film): 1725, 1455, 1435, 1277, 1222, 1150, 1061 cm\(^{-1}\).

**HRMS** (ESI) (m/z): [M+Na]\(^+\) calcd for C\(_{16}\)H\(_{22}\)O\(_4\)Na: 301.1416, found: 301.1424.

\([\alpha]_{D}^{20}\) 3.56 (c = 0.9, CH\(_2\)Cl\(_2\))

\((S)-2-((1S,3R)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (464)\)

\[R_f = 0.06 \text{ (hexane:EtOAc = 3:1)}\]

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 7.29 \) (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).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 177.0, 159.0, 136.6, 133.0, 127.0, 118.6, 113.9, 75.9, 74.6, 55.3, 52.0, 50.8, 40.7, 39.8, 17.2. \)

**IR** (film): 3435, 1719, 1513, 1302, 1247, 1175 cm\(^{-1}\).

**HRMS** (ESI) (m/z): [M+Na]\(^+\) calcd for C\(_{17}\)H\(_{24}\)O\(_5\)Na: 331.1521, found: 331.1526.

\([\alpha]_{D}^{20}\) 3.12 (c = 0.8, CH\(_2\)Cl\(_2\))
Experimental Section

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 NaHCO₃ and solid NaHCO₃ was added very carefully till gas evolution ceased. The aqueous layer was extracted with DCM, the combined organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. Crude dihydroxy ester was purified by column chromatography.

(S)-2-((1R,3R)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (466)

\[
\begin{align*}
\text{Rf} & = 0.14 \text{ (hexane:EtOAc = 3:1)} \\
^1\text{H-NMR} \text{ (400 MHz, CDCl}_3\text{): } \delta = 7.35 \text{ (m, 4H), 7.29-7.25 (m, 1H), 5.77-5.67 (m, 1H), 5.07-5.01 (m, 3H), 3.99 (d, J = 9.85 Hz, 1H), 3.63 (s, 3H), 2.49 (dd, J = 13.77, 7.20 Hz, 1H), 2.23 (dd, J = 13.89, 7.58 Hz, 1H), 1.87 (ddd, J = 14.18, 3.48, 0.08 Hz, 1H), 1.79 (ddd, J = 14.34, 7.78, 2.21 Hz, 1H), 1.14 (s, 3H). \\
^13\text{C-NMR} \text{ (100 MHz, CDCl}_3\text{): } \delta = 176.6, 144.4, 133.8, 128.4, 127.3, 125.5, 118.2, 72.4, 71.4, 51.8, 50.6, 40.3, 39.8, 17.6. \\
\text{IR} \text{ (film): } 3435, 1718, 1701, 1222, 1056 \text{ cm}^{-1}. \\
\text{HRMS (ESI)} \text{ (m/z): } [\text{M+Na}]^+ \text{ calcd for C}_{16}\text{H}_{22}\text{O}_4\text{Na: 301.1416, found: 301.1414.} \\
[\alpha]_D^{20} & = 14.06 \text{ (c = 1.55, CH}_2\text{Cl}_2\text{).}
\end{align*}
\]
**Experimental Section**

(S)-2-((1R,3R)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (468)

R<sub>f</sub> = 0.09 (hexane:EtOAc = 3:1)

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): 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).

**<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>): 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<sup>-1</sup>.

**HRMS** (ESI) (m/z): [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub>Na: 331.1521, found: 331.1517.

[α]<sub>D</sub> = 8.33 (c = 0.9, CH<sub>2</sub>Cl<sub>2</sub>)

(S)-2-((1S,3S)-1,3-dihydroxy-3-phenylpropyl)-2-methylpent-4-enoic acid methyl ester (470)

R<sub>f</sub> = 0.13 (hexane:EtOAc = 3:1)

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): 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).
**Experimental Section**

\[^{13}\text{C-NMR}\] (100 MHz, CDCl\textsubscript{3}): \(\delta = 177.2, 144.6, 132.9, 128.4, 127.3, 125.5, 118.6, 72.0, 71.3, 51.9, 50.7, 40.9, 39.8, 17.4\).

**IR** (film): 3435, 1722, 1455, 1222, 1056 cm\(^{-1}\).

**HRMS** (ESI) (m/z): [M+Na]\(^+\) calcd for C\textsubscript{16}H\textsubscript{22}O\textsubscript{4}Na: 301.1416, found: 301.1425.

\([\alpha]_D^{20} -23.20\) (c = 0.75, CH\textsubscript{2}Cl\textsubscript{2})

\((S)-2-((1S,3S)-1,3-dihydroxy-3-(4-methoxyphenyl)propyl)-2-methylpent-4-enoic acid methyl ester (472)\)

![Chemical Structure](image)

\(R_f = 0.06\) (hexane:EtOAc = 3:1)

\[^{1}\text{H-NMR}\] (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.29\) (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).

\[^{13}\text{C-NMR}\] (100 MHz, CDCl\textsubscript{3}): \(\delta = 177.1, 159.2, 136.8, 133.0, 126.7, 118.6, 113.9, 72.2, 70.8, 55.3, 51.9, 50.7, 40.9, 39.9, 17.4\).

**IR** (film): 3435, 1718, 1513, 1302, 1248, 1176, 1036 cm\(^{-1}\).

**HRMS** (ESI) (m/z): [M+Na]\(^+\) calcd for C\textsubscript{17}H\textsubscript{24}O\textsubscript{5}Na: 331.1521, found: 331.1526.

\([\alpha]_D^{20} -18.53\) (c = 0.95, CH\textsubscript{2}Cl\textsubscript{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
MgSO₄ 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 MgSO₄ and the solvent was evaporated. The crude lactone was purified by column chromatography.

(3S,4R,6S)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (459)

\[ \text{IR (film): } 3435, 2980, 1707, 1142 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI) (m/z): } [\text{M-H}_2\text{O}]^+ \text{ calcd for C}_{15}\text{H}_{16}\text{O}_2: 228.1150, \text{ found: 228.1154.} \]

\[ [\alpha]_{D}^{20} = -2.00 \text{ (c = 0.6, CH}_2\text{Cl}_2) \]

(3S,4R,6S)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (461)

\[ \text{IR (film): } 3435, 2980, 1707, 1142 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI) (m/z): } [\text{M-H}_2\text{O}]^+ \text{ calcd for C}_{17}\text{H}_{17}\text{O}_3: 262.0969, \text{ found: 262.0964.} \]

\[ [\alpha]_{D}^{20} = -1.91 \text{ (c = 0.5, CH}_2\text{Cl}_2) \]
Experimental Section

$^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 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, $J$ = 14.40, 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$_3$): $\delta$ = 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$^{-1}$.


$[\alpha]_D^2$ -1.50 (c = 1.2, CH$_2$Cl$_2$)

(3S,4S,6R)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (463)

![Chemical Structure Image]

$R_f$ = 0.32 (hexane:EtOAc = 2:1)

$^{1}$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_2$O]$^+$ calcd for C$_{15}$H$_{16}$O$_2$: 228.1150, found: 228.1145.

$[\alpha]_D^{20}$ 16.92 (c = 0.65, CH$_2$Cl$_2$)
Experimental Section

(3S,4S,6R)-3-allyl-4-hydroxy-6-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one (465)

\[
\text{R}_f = 0.35 \text{ (hexane:EtOAc = 2:1)}
\]

\(^1\text{H-NMR}\) (600 MHz, CDCl\(_3\)): \(\delta = 7.29\) (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)

\(^{13}\text{C-NMR}\) (150 MHz, CDCl\(_3\)): \(\delta = 176.1, 158.1, 134.1, 130.8, 127.4, 119.2, 114.1, 77.2, 70.6, 55.3, 45.8, 39.4, 34.8, 24.0\).

\(\text{IR}\) (film): 3435, 1705, 1613, 1516, 1250, 1175, 1112, 1085, 1033 cm\(^{-1}\).

\(\text{HRMS (ESI)}\) (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\(_2\)Cl\(_2\))

(3S,4R,6R)-3-allyl-4-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (467)

\[
\text{R}_f = 0.35 \text{ (hexane:EtOAc = 2:1)}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.40-7.32\) (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).

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 175.6, 139.2, 134.0, 128.7, 128.5, 125.7, 119.4, 77.9, 67.6, 48.7, 40.8, 36.4, 19.6\).
Experimental Section

IR (film): 3435, 1707, 1235, 1146, 1084, 1051 cm\(^{-1}\).

HRMS (ESI) (m/z): [M-H\(_2\)O]\(^+\) calcd for C\(_{15}\)H\(_{16}\)O\(_2\): 228.1150, found: 228.1151.

[\(\alpha\)]\(_D\)\(^{20}\) 18.42 (c = 1.2, CH\(_2\)Cl\(_2\))

\((3S,4R,6R)-3\text{-allyl}-4\text{-hydroxy}-6\text{-}(4\text{-methoxyphenyl})\text{-}3\text{-methyltetrahydro-2H-pyran-2-one (469)}\)

\[\text{R}_f = 0.45 \text{ (hexane:EtOAc = 1:1)}\]

\(\text{\(^1H-NMR\) (400 MHz, CDCl}_3\)): \(\delta = 7.26\) (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).

\(\text{\(^{13}C-NMR\) (100 MHz, CDCl}_3\)): \(\delta = 176.7, 159.6, 134.2, 131.2, 127.3, 119.4, 114.1, 77.7, 68.0, 55.4, 48.6, 40.8, 36.2, 19.6\).

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\(_2\)Cl\(_2\))

\((3S,4S,6S)-3\text{-allyl}-4\text{-hydroxy-3-methyl-6-phenyltetrahydro-2H-pyran-2-one (471)}\)

\[\text{R}_f = 0.29 \text{ (hexane:EtOAc = 2:1)}\]
Experimental Section

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_2$O]$^+$ calcd for C$_{15}$H$_{16}$O$_2$: 228.1150, found: 228.11435.

$[\alpha]_D^{20}$ -3.28 (c = 1.25, CH$_2$Cl$_2$)

(3S,4S,6S)-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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$^{-1}$.


$[\alpha]_D^{20}$ 2.59 (c = 0.85, CH$_2$Cl$_2$)
General procedure for the fragmentation:

To β-hydroxy lactone (1 eq.) in Et₂O: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 Et₂O. The combined ethereal layer was dried over MgSO₄ 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 NH₄Cl solution was added. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO₄ 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)

_1H-NMR_ (400 MHz, CDCl₃): 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).

_13C-NMR_ (100 MHz, CDCl₃): 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.


[a]_D²⁰_ 11.00 (c = 0.7, CH₂Cl₂)
Experimental Section

(R,E)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (475)

\[ \text{Rf} = 0.59 \text{ (hexane:EtOAc = 2:1)} \]

\[^1\text{H-NMR} \text{ (400 MHz, CDCl}_3\text{)}: \delta = 7.28 \text{ (d, } J = 8.59 \text{ Hz, 2H), 6.88 \text{ (d, } J = 8.59 \text{ Hz, 2H), 5.81-5.71} \text{ (m, 1H), 5.21} \text{ (t, } J = 7.45 \text{ Hz, 1H), 5.04-4.99} \text{ (m, 2H), 4.65} \text{ (ddd, } J = 7.80, 5.20, 2.50 \text{ Hz, 1H), 3.81} \text{ (s, 3H), 2.73} \text{ (d, } J = 6.57 \text{ Hz, 2H), 2.51} \text{ (dt, } J = 15.03, 7.15 \text{ Hz, 1H), 2.41} \text{ (dt, } J = 13.26, 6.03 \text{ Hz, 1H), 1.59} \text{ (s, 3H).} \]

\[^{13}\text{C-NMR} \text{ (100 MHz, CDCl}_3\text{)}: \delta = 159.0, 136.6, 136.4, 127.0, 120.8, 115.8, 113.8, 73.7, 55.3, 44.2, 38.1, 16.3. \]

\[^{\text{IR}} \text{ (film): 2913, 1611, 1512, 1246, 1174, 1036 cm}^{-1}. \]

\[^{\text{HRMS} \text{ (ESI) (m/z): } [\text{M-H}_2\text{O}]^+ \text{ calcd for } C_{15}H_{18}O: 214.1358, \text{ found: 214.1360.} \]

\[^{\alpha_\text{D}} 5.20 \text{ (c = 0.5, CH}_2\text{Cl}_2\text{)} \]

(S,Z)-4-methyl-1-phenylhepta-3,6-dien-1-ol (476)

\[ \text{Rf} = 0.55 \text{ (hexane:EtOAc = 3:1)} \]

\[^1\text{H-NMR} \text{ (400 MHz, CDCl}_3\text{): } \delta = 7.38-7.33 \text{ (m, 4H), 7.28} \text{ (m, 1H), 5.75-5.65} \text{ (m, 1H), 5.27} \text{ (t, } J = 6.82 \text{ Hz, 1H), 5.06-4.98} \text{ (m, 2H), 4.69} \text{ (ddd, } J = 7.96, 5.05, 2.90 \text{ Hz, 1H), 2.82-2.73} \text{ (m, 2H), 2.55-2.40} \text{ (m, 2H), 1.97} \text{ (d, } J = 3.03 \text{ Hz, 1H (OH)), 1.72} \text{ (s, 3H).} \]

\[^{13}\text{C-NMR} \text{ (100 MHz, CDCl}_3\text{): } \delta = 144.2, 137.1, 135.7, 128.4, 127.4, 125.8, 121.2, 115.4, 74.1, 38.1, 36.6, 23.6. \]

\[^{\text{IR}} \text{ (film): 3391, 2914, 1636, 1453, 1048 cm}^{-1}. \]

\[^{\text{HRMS} \text{ (ESI) (m/z): } [\text{M-H}_2\text{O}]^+ \text{ calcd for } C_{14}H_{16}: 184.1252, \text{ found: 184.1249.} \]
(S,Z)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (477)

\[ \alpha_D^{20} -19.64 \ (c = 1.1, \text{CH}_2\text{Cl}_2) \]

\[
\begin{align*}
\text{R}_f &= 0.40 \ (\text{hexane:EtOAc} = 3:1) \\
^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): &\delta = 7.28 \ (d, \ J = 8.59 \text{ Hz}, 2\text{H}), 6.88 \ (d, \ J = 8.59 \text{ Hz}, 2\text{H}), 5.76-5.66 \ (m, \ 1\text{H}), 5.24 \ (t, \ J = 7.32 \text{ Hz}, 1\text{H}), 5.06-4.98 \ (m, 2\text{H}), 4.64 \ (t, \ J = 5.94 \text{ Hz}, 1\text{H}), 3.81 \ (s, 3\text{H}), 2.82-2.72 \ (m, 2\text{H}), 2.55-2.47 \ (m, 1\text{H}), 2.44-2.37 \ (m, 1\text{H}), 1.91 \ (d, \ J = 2.27 \text{ Hz}, 1\text{H (OH)}), 1.71 \ (s, 3\text{H}).
\end{align*}
\]

\[
^13\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta = 159.0, 136.8, 136.4, 135.7, 127.0, 121.3, 115.4, 113.8, 73.7, 55.3, 37.9, 36.5, 23.6.
\]

IR (film): 2913, 1612, 1513, 1247, 1174, 1037 cm\(^{-1}\).


\[ \alpha_D^{20} -16.67 \ (c = 1.05, \text{CH}_2\text{Cl}_2) \]

(3S,4S)-3-allyl-4-((S)-2-hydroxy-2-phenylethyl)-3-methyloxetan-2-one (478)

\[ \alpha_D^{20} -16.67 \ (c = 1.05, \text{CH}_2\text{Cl}_2) \]

\[
\begin{align*}
\text{R}_f &= 0.43 \ (\text{hexane:EtOAc} = 2:1) \\
^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): &\delta = 7.37 \ (m, 4\text{H}), 7.32 \ (m, 1\text{H}), 5.85-5.75 \ (m, 1\text{H}), 5.23-5.17 \ (m, 2\text{H}), 4.91 \ (dt, \ J = 8.21, 4.10 \text{ Hz}, 1\text{H}), 4.77 \ (dd, \ J = 7.20, 5.94 \text{ Hz}, 1\text{H}), 2.51 \ (dd, \ J = 14.02, 6.94 \text{ Hz}, 1\text{H}), 2.42 \ (dd, \ J = 14.02, 7.71 \text{ Hz}, 1\text{H}), 2.04 \ (m, 2\text{H + 1H (OH)}), 1.24 \ (s, 3\text{H}).
\end{align*}
\]

\[
^13\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta = 174.3, 144.0, 131.6, 128.8, 128.0, 125.5, 120.0, 77.5, 70.5, 56.9, 40.0, 39.9, 14.8.
\]
**Experimental Section**

**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\(_2\)Cl\(_2\))

\((S,E)-4\)-methyl-1-phenylhepta-3,6-dien-1-ol (479)

![Structure of (S,E)-4-methyl-1-phenylhepta-3,6-dien-1-ol (479)](image)

\(R_f = 0.67\) (hexane:EtOAc = 2:1)

\(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.34\) (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\(_3\)): \(\delta = 144.3, 137.7, 136.6, 128.4, 127.4, 125.8, 120.6, 115.9, 74.1, 44.2, 38.2, 16.3\).

**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\(_2\)Cl\(_2\))

\((3S,4S)-3\)-allyl-4-((S)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methylxetan-2-one (480)

![Structure of (3S,4S)-3-allyl-4-((S)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methylxetan-2-one (480)](image)

\(R_f = 0.65\) (hexane:EtOAc = 1:1)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.29\) (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,
Experimental Section

$^1$H-NMR (400 MHz, CDCl₃): $\delta = 7.28$ (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, CDCl₃): $\delta = 159.0$, 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$^{-1}$.


$[\alpha]_D^{20} = -7.00$ (c = 0.3, CH$_2$Cl$_2$)

(S,E)-1-(4-methoxyphenyl)-4-methylhepta-3,6-dien-1-ol (481)

$\alpha_D^{20} = -28.55$ (c = 0.55, CH$_2$Cl$_2$)

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

$^1$H-NMR (400 MHz, CDCl₃): $\delta = 7.28$ (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, CDCl₃): $\delta = 159.0$, 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$^{-1}$.


$[\alpha]_D^{20} = -7.00$ (c = 0.3, CH$_2$Cl$_2$)
(3S,4R)-3-allyl-4-((R)-2-hydroxy-2-phenylethyl)-3-methyloxetan-2-one (482)

\[
\text{R}_{f} = 0.31 \text{ (hexane:EtOAc = 3:1)}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.41-7.36 \text{ (m, 4H)}, 7.32 \text{ (m, 1H)}, 5.83-5.73 \text{ (m, 1H)}, 5.17-5.09 \text{ (m, 2H)}, 4.94 \text{ (td, } J = 9.85, 3.03 \text{ Hz, 1H)}, 4.69 \text{ (dd, } J = 9.98, 3.12 \text{ Hz, 1H)}, 2.50 \text{ (tdd, } J = 14.36, 6.61, 1.37 \text{ Hz, 1H)}, 2.32 \text{ (dd, } J = 14.27, 7.71 \text{ Hz, 1H)}, 2.15 \text{ (ddd, } J = 14.59, 9.91, 3.35 \text{ Hz, 1H)}, 2.10-2.03 \text{ (m, 1H + 1H (OH))}, 1.42 \text{ (s, 3H)}.

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 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).

\(\text{IR}\) (film): 3435, 1815, 1454, 1111 cm\(^{-1}\).

\(\text{HRMS}\) (ESI) (m/z): \([\text{M-H}_2\text{O}]^+\) calcd for C\(_{15}\)H\(_{16}\)O\(_2\): 228.1150, found: 228.1145.

\([\alpha]_D^{20}\) 48.00 (c = 0.25, CH\(_2\)Cl\(_2\))

\((R,Z)-4\)-methyl-1-phenylhepta-3,6-dien-1-ol (483)

\[
\text{R}_{f} = 0.60 \text{ (hexane:EtOAc = 3:1)}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.38-7.33 \text{ (m, 4H)}, 7.28 \text{ (m, 1H)}, 5.75-5.65 \text{ (m, 1H)}, 5.27 \text{ (t, } J = 7.70 \text{ Hz, 1H)}, 5.06-4.98 \text{ (m, 2H)}, 4.69 \text{ (dd, } J = 8.08, 5.30 \text{ Hz, 1H)}, 2.82-2.73 \text{ (m, 2H)}, 2.55-2.40 \text{ (m, 2H)}, 1.72 \text{ (s, 3H)}.

\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 144.2, 137.1, 135.7, 128.4, 127.4, 125.8, 121.2, 115.4, 74.1, 38.1, 36.6, 23.6.

\(\text{IR}\) (film): 3390, 1634, 1449, 1045 cm\(^{-1}\).
HRMS (ESI) (m/z): [M-H$_2$O]$^+$ calcd for C$_{14}$H$_{16}$: 184.1252, found: 184.1250.

$[\alpha]_D^{20}$ 20.00 (c = 0.45, CH$_2$Cl$_2$)

(3S,4R)-3-allyl-4-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methyloxetan-2-one (484)

$\alpha_D^{20}$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$

$\alpha_D$
**Experimental Section**

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 7.27 \) (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).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 159.0, 136.8, 136.4, 135.7, 127.0, 121.3, 115.4, 113.8, 73.7, 55.3, 37.9, 36.5, 23.6 \).

**IR** (film): 3392, 2929, 1612, 1512, 1247, 1173, 1037 cm\(^{-1}\).


\([\alpha]_D^{20}\) 16.66 \( (c = 0.3, \text{CH}_2\text{Cl}_2)\)

**285**

### (2S)-2-(1-Hydroxy-propyl)-2-methyl-pent-4-enoic acid methyl ester (487)

![Structure of (2S)-2-(1-Hydroxy-propyl)-2-methyl-pent-4-enoic acid methyl ester](image)

To aldehyde 439 (425 mg, 2.70 mmol) in Et₂O (30 mL) at 0 °C was slowly added EtMgBr (0.95 mL, 3M in Et₂O, 2.83 mmol). After 1 h brine was added and the mixture was acidified with 5% H₂SO₄. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic phase was dried over MgSO₄ 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:**

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 5.75-5.65 \) (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).

**13C-NMR** (100 MHz, CDCl₃): \( \delta = 177.0, 133.5, 118.4, 77.3, 51.8, 51.2, 41.1, 24.6, 17.5, 11.1 \).

**Minor:**

**1H-NMR** (400 MHz, CDCl₃): \( \delta = 5.82-5.72 \) (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).
Experimental Section

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta =$ 176.6, 134.2, 118.0, 77.7, 51.7, 48.4, 40.4, 25.4, 17.2, 11.2.


(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$_2$O. 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$_3$): $\delta =$ 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$_3$): $\delta =$ 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$^{-1}$.


[$\alpha$]$_D^{20}$ -9.28 (c =1.25, CH$_2$Cl$_2$)
11. Appenices

11.1. Abbrevations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOM</td>
<td>benzyloxymethyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>CM</td>
<td>cross metathesis</td>
</tr>
<tr>
<td>COSY</td>
<td>correlated spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBALH</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N'-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EDC</td>
<td>$N$-(3-Dimethylaminopropyl)-$N'$-ethylcarbodiimide</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent</td>
</tr>
<tr>
<td>et al.</td>
<td>Latin: “et alii”, meaning “and others”</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylsilylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IBX</td>
<td>o-iodoxybenzoic acid</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethylsilylazide</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethylsilylazide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>MMPP</td>
<td>magnesium monoperoxyphthalate</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MTPA</td>
<td>$\alpha$-Methoxy-$\alpha$-trifluoromethylphenylacetyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>Ms</td>
<td>methansulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MVK</td>
<td>methyl vinyl ketone</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethylsilylazide</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>$N$-iodosuccinimide</td>
</tr>
<tr>
<td>NEt$_3$</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>R(1,2,…n)</td>
<td>any substituent</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>Rf</td>
<td>ratio of fronts (TLC)</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>SEM</td>
<td>(trimethylsilyl)ethoxymethyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra-n-butylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofurane</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylendiamin</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-trichloroethyl carbonate</td>
</tr>
<tr>
<td>pTsOH</td>
<td>para-toluene-4-sulfonic acid</td>
</tr>
</tbody>
</table>
11.2. Selected Spectra
12. References


References


[60] K. Prantz, diplomathesis, University of Vienna **2005**.


References


13. Curriculum Vitae

Personal Data:

Name: Kathrin Prantz
Address: Canisiusgasse 27/4
         A-1090 Vienna
Date of Birth: 6.Mai 1981
Birth Place: Vienna, Austria
Nationality: Austrian
Family status: single
Degree: Mag.rer.nat.
Telephone: +43 (0)699 10631474
E-mail: kathrin.prantz@univie.ac.at

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).

Awards:


ERASMUS scholarship of mobility to participate in an exchange program (2003).