Taxane C-Ring Precursors: Enantioselective Synthesis and Application in Total Synthesis; Enantiodivergent Synthesis of Cyclohepta[b]indoles

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submitted by
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To the brave defenders of Ukraine.

Вічна слава Героям!
Parts of this thesis have been presented at scientific conferences or have been published as scientific articles:

31. Irseer Naturstofftage, Kloster Irsee, 20. – 22.02.2019


Further publications not discussed in this thesis:


Abstract

Part A.

In this part of the thesis, an efficient preparation of a small library of novel enantioenriched taxane C-ring intermediates is described. The respective C-ring building blocks were categorized into three groups (A–C) according to the position of their reactive site (marked with blue). A unified strategy accessing the diversely substituted and densely functionalized taxane C-ring precursors has been established (Scheme A).

Furthermore, the reactive sites were properly incorporated into the precursors’ structure to make the compounds IV–VIII applicable to the convergent synthetic strategies of the total synthesis of taxane natural products.

In fact, compound X demonstrated its common applicability to both of the investigated synthetic strategies. Thus, allowing us to develop a short and efficient synthetic route toward the key strategic precursors IX and XI (Scheme B). Although the construction of the targeted taxane tricyclic core was not achieved, a rapid accessibility of the corresponding key precursors showed potential in using the C-rings IV–VIII as starting point in future synthetic approaches.
In addition, a boron-mediated formal CO insertion was investigated as a novel synthetic tool for the construction of the taxane skeleton. First results towards the formation of the suitable CO insertion precursor have been achieved.
Part B.

In the second part of this work, a synthetic methodology exhibiting a general, enantiodivergent access to cyclohepta[b]indoles is broadly described. Relying on the Pd-catalyzed directing group-mediated cyclopropane C(sp³)–H activation, the valuable synthetic precursors with general structure XII were obtained in yields up to 67%, large quantities and excellent enantioselectivity (92% e.e.). Further transformation of the initial C–H activation product XII by submitting the latter to previously established synthetic routes eventually delivered both enantiomeric forms of the targeted cyclohepta[b]indole XVII.

Scheme C. Synthesis of cyclohepta[b]indoles XVII.

Further diversification of the methodology by varying the olefination reagents eventually led to the synthesis of a small library of diversely substituted cyclohepta[b]indoles XVII–XXII (Figure A).

Figure A. Prepared diversely substituted cyclohepta[b]indoles.

In general, the Pd-catalyzed cyclopropane C(sp³)–H activation as a key step in the enantiodivergent synthesis of cyclohepta[b]indoles with high enantiomeric excess (>91%) was widely investigated. Additionally, defined synthetic limitations of the described methodology were determined and further discussed in this work.
Zusammenfassung

Teil A.


Schema A. Herstellung einer kleinen Bibliothek von enantiomerenangereicherten Taxan-C-Ring-Intermediaten.

Im Zuge dessen wurde die Position der reaktiven Zentren der Intermediate so gewählt, dass die Verbindungen IV–VIII Anwendung in der konvergenten Totalsynthese von Taxan-Naturstoffen finden können.

Darüber hinaus wurde eine Bor-vermittelte formale CO-Insertion als neuartiges Synthesewerkzeug für den Aufbau des Taxangerüsts untersucht. Erste Ergebnisse zur Bildung des geeigneten CO-Insertionsvorräufers wurden erzielt.
Teil B.


Eine weitere Diversifikation der Methodik durch Variation der Olefinierungsreagentien ermöglichte die Synthese einer kleinen Bibliothek der unterschiedlich substituierten Cyclohepta[b]indole XVII–XXII (Abbildung A).

Im Allgemeinen wurde die Pd-katalysierte Cyclopropan-C(sp²)-H-Aktivierung als Schlüsselschritt in der enantiodivergenten Synthese von Cyclohepta[b]indolen mit hohem Enantiomerüberschuss (>91%) umfassend untersucht. Darüber hinaus wurden in dieser Arbeit definierte synthetische Einschränkungen der beschriebenen Methodik aufgezeigt und weiter diskutiert.
List of Abbreviations

[α] specific rotation
2,6-lut. 2,6-lutidine
9-BBN 9-borabicyclo(3.3.1)nonane
Ac acetyl
acac acetylacetonate
A-FABP adipocyte fatty acid-binding protein
AIBN 2,2’-azobis(2-methylpropionitrile)
Ar aryl
ATP adenosine triphosphate
BAX pro-apoptotic protein Bcl-2-associated X
Bcl-2 anti-apoptotic protein B-cell Leukemia 2
BMS Bristol-Myers Squibb
Bn benzyl
Boc tert-butyloxycarbonyl
BOM benzyloxymethyl
Bz benzoyl
CAM ceric ammonium molybdate
Cbz benzyloxycarbonyl
CDP-MEP 4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate
CMS 4-diphosphocytidyl-2-C-methyl-D-erythritol synthase
CoA acetyl-coenzyme A
COSY correlation spectroscopy
Cp cyclopentadienyl anion
CPTS collidinium \textit{para}-toluenesulfonate
CSA camphorsulfonic acid
CuTC copper(I) thiophene-2-carboxylate
d.r. diastereomeric ratio
DA Diels-Alder
DABCO 1,4-diazabicyclo[2.2.2]octane
dba dibenzylideneacetone
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>methylene chloride</td>
</tr>
<tr>
<td>DG</td>
<td>directing group</td>
</tr>
<tr>
<td>DHP</td>
<td>dihydropyran</td>
</tr>
<tr>
<td>DHQD</td>
<td>hydroquinidine 1,4-phthalazinediyldiether</td>
</tr>
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<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
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<td>DIPA</td>
<td>diisopropylamine</td>
</tr>
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<td>DIPEA</td>
<td>diisopropylethylamine</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>DMAPP</td>
<td>dimethylallyl pyrophosphate</td>
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<tr>
<td>DMC</td>
<td>dimethoxycarbene</td>
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<tr>
<td>DMDO</td>
<td>dimethylidioxirane</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
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<tr>
<td>DMPPU</td>
<td>N,N’-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DMTr</td>
<td>dimethoxytrityl</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOXP</td>
<td>1-deoxy-D-xylulose-5-phosphate</td>
</tr>
<tr>
<td>DVCPR</td>
<td>divinylcyclopropane rearrangement</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EA</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<td>et al.</td>
<td>et alii</td>
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<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FPP</td>
<td>farnesyl pyrophosphate</td>
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GGPP  geranylgeranyl pyrophosphate
GPP  geranyl pyrophosphate
HMBC  heteronuclear multiple bond correlation spectroscopy
HMB-PP  (E)-4-hydroxy-3-methylbut-2-enyl pyrophosphate
HMG  hydroxy-3-methylglutaryl
HMPA  hexamethylphosphoramide
HRMS  high resolution mass spectrometry
HSQC  heteronuclear single quantum correlation spectroscopy
IC₅₀  half maximal inhibitory concentration
IMDA  intramolecular Diels-Alder
IPP  isopentenyl pyrophosphate
iPr  isopropyl
IUPAC  International Union of Pure and Applied Chemistry
KHMDK  potassium bis(trimethylsilyl)amide
LA  Lewis acid
LD₅₀  median lethal dose
LDA  lithium N,N-diisopropylamide
m-CPBA  meta-chloroperoxybenzoic acid
MDR  multidrug resistance
Me  methyl
MeOH  methanol
MAPH  monoammonium phosphate
MEP  2C-methyl-D-erythritol-4-phosphate
MMP  mitochondrial membrane potential
MMTr  monomethoxytrityl
MOM  methoxymethyl
MS  molecular sieve
Ms  mesyl
MTAs  microtubule targeting agents
MVA  mevalonate
MVAPP  diphosphorylated mevalonic acid
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<td>myeloid differentiation primary response 88</td>
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<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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<td>n-Bu</td>
<td>n-butyl</td>
</tr>
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<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NF-κB</td>
<td>nuclear factor 'kappa-light-chain-enhancer' of activated B-cells</td>
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<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
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<td>NMR</td>
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<td>NOE</td>
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<td>nuclear Overhauser enhancement spectroscopy</td>
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<td>no reaction</td>
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<td>NSCLC</td>
<td>non-small-cell lung carcinoma</td>
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<td>PAMPs</td>
<td>pathogen-associated molecular patterns</td>
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<td>pyridinium chlorochromate</td>
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<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PE</td>
<td>petroleum ether</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
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<td>phthalazinediyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
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<tr>
<td>PIDA</td>
<td>(diacetoxyiodo)benzene</td>
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<tr>
<td>Pin</td>
<td>pinacolate</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PLE</td>
<td>porcine liver esterase</td>
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<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
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<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
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<tr>
<td>PTSA</td>
<td>para-toluenesulfonic acid</td>
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<td>PTX</td>
<td>paclitaxel</td>
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<td>pyr</td>
<td>pyridine</td>
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<td>quant.</td>
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XVIII
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<td>reducing agent</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>RD</td>
<td>retrosynthetic disconnection</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>s-Bu</td>
<td>sec-butyl</td>
</tr>
<tr>
<td>SEM</td>
<td>trimethylsilylethoxymethyl</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SIRT1</td>
<td>Sirtuin 1</td>
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<tr>
<td>TADDOL</td>
<td>tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol</td>
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<tr>
<td>TBAF</td>
<td>tetra(n-butyl)ammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra(n-butyl)ammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>Thexyl</td>
<td>1,1,2-trimethylpropyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TLR4</td>
<td>toll-like receptor 4</td>
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<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulfonyl</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
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XXI
Part A. Enantioselective Synthesis of Taxane C-Ring Precursors and Their Application to the Total Synthesis
1 Introduction

1.1 Terpenoids (Terpene Natural Products)

Terpenoids, also known as isoprenoids, are a structurally diverse and widely distributed family of natural products containing over 60,000 defined compounds, which makes them the largest group of secondary metabolites derived from natural sources. Although the term “terpenoid” is often interchangeable with “terpene”, terpenoids contain additional functionalities, mostly oxygen-containing functional groups, whereas terpenes are carbocyclic compounds without functional groups. The majority of terpenoids has been isolated from plants where they serve as different functional units such as hormones (gibberellins, abscisic acid), photosynthetic pigments (phytol, carotenoids), electron carriers (ubiquinone, plastoquinone), mediators of polysaccharide assembly (polyprenyl phosphates), structural components of membranes (phytosterols) as well as interspecies communicators (attractants for pollinators and seed dispersers) and defense agents (as competitive phytotoxins, antibiotics, and herbivore repellents).\[1\] Many terpenes are considered of high economic importance, including essential oils, carotenoid pigments, natural rubber, agrochemicals and pharmaceuticals. In addition, they play a significant role in prevention and treatment of various diseases.\[2-3\]

1.1.1 Classification of Terpenoids

Terpenoids are classified according to the number of isoprene units that comprise the parent terpene (the core structure, without functional groups). The construction of the core terpene structure follows a general principle, whereby a repetitive addition of isoprene (2-methyl-1,3-butadiene (1)) units, builds up the carboskeleton. The principle is referred to as “isoprene rule” and was first postulated by Wallach (1914) and Ruzicka (1953). It led to formulation of terpene classification as follows: hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di- (C_{20}), sester- (C_{25}), tri- (C_{30}), tetra- (C_{40}) and polyterpenes (C_5)_n with n > 8 (see Figure 1). In mono-, sesqui-, di- and sesterterpenes the isoprene units are tethered together in head-to-tail fashion, whereas in tri- and tetraterpenes they are linked in tail-to-tail manner.\[4\]
Naturally occurring terpenoids are usually very densely decorated with oxygen-containing functionalities such as alcohols, ethers, aldehydes, ketones, carboxylic acids, esters and glycosides. Despite the wide diversity of the oxygenated terpenes, their general classification relies on the above described “isoprene rule” (also known as “C5 rule”). It is noteworthy that in nature, the isoprenoids not only occur in a linear hydrocarbon chain form but mainly in cyclized and further oxidized forms. The origin of the extremely large number of cyclized terpenes is discussed in the next subchapter.

1.2.2 Biosynthesis of Taxane Terpenoids

The biosynthesis of terpenoids comprises four stages with all terpenes having one common biosynthetic precursor – the acetyl-coenzyme A (CoA, 4). The first stage of the biosynthesis exhibits the conversion of acetyl-CoA into the “active isoprene units” isopentenyl pyrophosphate (IPP, 2) and its isomer dimethylallyl pyrophosphate (DMAPP, 3). Two different pathways are known for the DMAPP/IPP biosynthesis. The first one, more common in eukaryotes, archaea, some eubacteria and plants is known as the mevalonate (MVA) pathway.[5] The second one, called the MEP/DOXP (2C-methyl-D-erythritol-4-phosphate / 1-deoxy-D-xylulose-5-phosphate) pathway occurs mostly in prokaryotic organisms (bacteria) and eukaryotic parasites.[5]
The MVA pathway commences with the reaction of three molecules of acetyl-CoA (4) yielding 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, 5). In the following step, the enzymatic reduction by dihydronicotinamide adenine dinucleotide phosphate (NADPH) in the presence of water affords mevalonic acid (MVA, 6). Subsequent phosphorylation of MVA with two molecules of adenosine triphosphate (ATP) delivers diphosphorylated mevalonic acid (MVAPP). Finally, decarboxylation followed by dehydration provides isopentenyl pyrophosphate (2) which can then undergo isomerization to dimethylallyl pyrophosphate (3) (Scheme 1).[4]

Scheme 1. The MVA pathway.[4]

Until the late 1980s, when the group of researches performed several $^{13}$C labeling experiments on some prokaryotic organisms, the mevalonate pathway of DMAPP/IPP synthesis was the only known one.[6-8] The conducted experiments revealed that the obtained DMAPP/IPP must have been synthesized through an alternative pathway. The knowledge gained from these studies consequently led to the discovery of a novel non-mevalonate pathway for terpenoid biosynthesis – the MEP/DOXP pathway.[6-8] This pathway commences with the DOXP synthase (DXS)-catalyzed condensation of pyruvate (7) and glyceraldehyde-3-phosphate (8) yielding phosphate 9. Subsequently, the obtained phosphate 9 is isomerized and reduced with NADPH resulting in triol 10. In the next step, the 4-diphosphocytidyl-2-C-methyl-D-erythritol synthase (CMS) attaches the cytidyl monophosphate rest to triol 10 forming diphosphocytidyl-erythritol 11. This is further converted to 4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate (CDP-MEP, 12) by CM kinase in the presence of ATP, followed by MCS-catalyzed cyclization. The produced cyclophosphate 13 is further reduced to (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP, 14) by the enzyme HMB-PP synthase. Finally, the biosynthetic intermediate 14 is converted into the building blocks IPP (2) and DMAPP (3) by hydroxymethylbutenyl diphosphate reductase (HDR) (see Scheme 2).[9-10]
Scheme 2. The MEP/DOXP pathway.\textsuperscript{[9–10]}

In the second stage of the terpene biosynthesis, higher order terpenoid building blocks are generated via the combinative assembly of IPP (2) and DMAPP (3) by means of so-called “prenyl coupling”.\textsuperscript{[11]} These newly formed advanced building blocks namely are geranyl pyrophosphate (GPP, C\textsubscript{10}), farnesyl pyrophosphate (FPP, C\textsubscript{15}) and geranylgeranyl pyrophosphate (GGPP, C\textsubscript{20}) which can further serve as monoterpene, sesquiterpene and diterpene precursors (Scheme 3).\textsuperscript{[3]}

Scheme 3. Higher order terpene building blocks.

In the third step of the biosynthetic process, the above mentioned building blocks 15–17 undergo cationic cyclization commonly referred to as “cyclase phase”. In case of taxane natural
products, taxadiene synthase (TXS) promoted cyclization of linear geranylgeranyl diphosphate (GGPP, 17) results in the formation of taxa-4(5),11(12)-diene (18) (Scheme 4).\cite{12-14}

![Scheme 4](image)

Scheme 4. "Cyclase phase" of taxane biosynthesis.\cite{12-14}

In the course of the fourth stage of the biosynthesis, several of mono- and dioxygenases are decorating the final oxidized terpenoid structure. It is noteworthy that alongside functional group installations, various fragmentation and rearrangement events can take place leading to the formation of degraded and rearranged taxanes.\cite{15} The overall process, the so-called “oxidase phase”, is considered to be the most complex event in the whole terpenoid biosynthesis.

In the case of taxanes, the specific enzymatic oxidations are taking place sequentially. In 2004, Jennewein et al.\cite{16} identified the oxygenase involved in the first oxidation step (cytochrome P450 taxoid 5α-hydroxylase) and thereby marked the beginning of mechanistic studies on the “oxidase phase”. Even though further valuable studies were conducted in the last decades,\cite{17-19} some of the processes still need to be verified. Based on the available reports, the summarized sequence from taxadiene (18) to the advanced baccatin III precursor was postulated as follows (see Scheme 5).\cite{15}
Nature’s concept of dividing the terpenoid biosynthesis into “cyclase phase” and “oxidase phase” demonstrates the overall complexity of the process. To obtain a natural terpenoid from the simple building blocks IPP (2) and DMAPP (3), a complex enzyme cascade is required. Despite the wide diversity of the known terpene natural products, for the majority of them, the enzymatic processes behind their biosynthesis remain unclear.
1.2 Taxanes – History, Development and Importance

For over a thousand years, the evergreen trees called yews (Taxus spp., Taxaceae) have been considered as extremely poisonous and hazardous plants. The most commonly appearing varieties are the English yew, which is also known as common or European yew (T. baccata), Pacific or Western yew (T. brevifolia), American yew (T. canadensis), and Japanese yew (T. cuspidata). Species in the genus of Taxus contain a large number of taxanes, a group of diterpenoids with a taxane skeleton as their characteristic constituents. Already in ancient times, yew extracts were used as a strong poison. However, the very first description of yew poisoning was reported not earlier than 1836. Additionally, the bark, needles and branch tips also found use in traditional medicine. For example, the bark of T. brevifolia would be applied as a disinfectant or, in some particular cases, was used as a treatment for skin cancer. With further development of natural sciences, the remarkable toxicity of the yews’ extracts triggered first chemical and biological studies. In 1856, a white amorphous powder was extracted from needles of T. baccata by Lucas. The isolated substance was given a name – taxine, and undoubtedly believed to account for the toxicity of the plant. Although, high instability of the substance and limited technology restricted further investigations, purification or structure elucidation at that time, the accomplishment of isolating an individual taxane derivative marked a new chapter in taxane diterpenes history.

Starting with the first isolation of taxine in 1856, progress in taxane chemistry was rather moderate till the early 1960s. In the early 1950s, the National Cancer Institute (NCI) and the U.S. Department of Agriculture initiated an ultimate screening program in search for novel antitumor agents among the plant kingdom. In 1964, the program proved fruitful and reported the high activity of T. brevifolia’s the stem bark extract which further was confirmed by the KB cytotoxicity assay.

Through chemical investigation applied to the stem bark extract, an active compound was isolated by Wall and Wani in the yield of 0.014%, and concomitantly named as Taxol (paclitaxel, PTX). The final structure elucidation of paclitaxel (20) using NMR techniques was reported in
1971, alongside the structures of paclitaxel’s methanolsysis products – 10-deacetylbaccatin III (21) and N-benzoyl-3-phenylisoserine methyl ester (22) (Figure 2). At last, the X-ray analysis of both methanolysis products 21 and 22 confirmed the absolute stereochemistry of the isolated paclitaxel.[28] Remarkably, the bioassay data indicated significant loss of biological activity for the tetraol 21 and the methyl ester 22 compared to the parent paclitaxel (20).[28] Furthermore, at the time of its isolation, obtained paclitaxel showed very low antitumor activity when compared to existing drugs. Due to combined problems such as poor solubility, low yield and purification difficulties, clinical trials had to be put on hold for nearly a decade.

This however changed drastically upon the publication of the PTX cytotoxicity mechanism in 1979. It immediately drew high attention to the molecule, since its mode of action was absolutely unique compared to other known cytotoxic agents.[29-31] With the beginning of the clinical trial in 1984, the high demand for paclitaxel at first led to a severe exhaustion of T. brevifolia. Moreover, the manufacturing costs for PTX from T. brevifolia exceeded ten times the clinical trial’s budget. The above mentioned events consequently led to the “race to synthesize Taxol”. [32-35] The unannounced competition between researchers in the total synthesis field eventually resulted in the publication of two total syntheses of paclitaxel by K. C. Nicolaou and R. Holton in 1994.[32-35] Despite the great success of producing paclitaxel in the chemical laboratory, the method was complex and rather expensive. Unable to bear the manufacturing costs of paclitaxel in large scale, the NCI was compelled to hand over the process to a private company – Bristol-Myers Squibb (BMS), which subsequently renamed PTX to the brand name Taxol®. After the approval of Taxol® by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[36], paclitaxel (as Taxol® or other formulations) became one of the most widely used antitumor agents for treating different types of cancers, such as head, breast, ovarian, leucopenia cancers, non-small-cell lung carcinoma (NSCLC) and Kaposi’s sarcoma.[37-38]

The discovery of the antitumoral activity of Taxol® consequently triggered an enormous increase of its demand and price.[39] Due to fast extinction of slow-growing Taxus sp., low efficacy of a non-environmentally friendly extraction process and complexity of the existing chemical synthesis, the discovery of alternative sources of paclitaxel (or its advanced precursor) remained a priority for PTX manufactures. Finally, alternative technologies and production methods for Taxol® have been found, such as extraction from non-Taxus plants, using endophytic fungi cultures,[40] metabolic engineering of natural and heterologous hosts, and novel total syntheses.[37]
Starting from the 1990s, an impressive number of total syntheses has been published, showcasing synthetic elegance and recent advances in synthetic organic chemistry. Along with those, a number of semi-synthetic approaches has been reported which helped to increase the yield of the overall production process.\textsuperscript{[37, 41-43]} However, the complexity and manufacturing costs made the alternative synthetic methods completely unfeasible on an industrial level. Despite the great efforts over the last decades to find cheaper and more sustainable sources of taxanes, extraction from the yew trees remains the main method of PTX manufacturing.\textsuperscript{[37, 44]}

1.2.1 Taxol\textsuperscript{®} – Mechanism of Action

One of the main characteristics of cancer diseases is the unrestrained growth and dividing of cells, with concomitant invading of other parts of the body. According to the World Health Organization (WHO) report in 2018, cancer has become one of the deadliest diseases humanity has ever faced. Based on the statistics, the report stated that one in eight men and one in eleven women will die because of cancer disease. This statistic alone explains the great challenge to find treatments in order to fight different types of cancer.\textsuperscript{[45]}

Since its approval by the FDA in 1993, Taxol\textsuperscript{®} turned into one of the most widely used anticancer drugs. Besides its unique structure (see Figure 2), paclitaxel (20) has a rather uncommon mechanism of action.

![Proposed PTX mechanisms of action](image)

\textit{Figure 3. Proposed PTX mechanisms of action (figure taken from an open access article).}\textsuperscript{[37]}

Whereas most of the known antitumor agents are targeting DNA or RNA, Taxol\textsuperscript{®} promotes cellular death by binding to a specific binding site on the microtubule, and thus inhibiting the depolymerization of microtubules.\textsuperscript{[37, 46-48]} Due to its specific mode of action, Taxol\textsuperscript{®} was assigned
to the group of Microtubule Targeting Agents (MTAs). Microtubules are tubulin heterodimers which are part of numerous cellular processes. The production of tubulin and its polymerization into the microtubules happens during the G2 phase of the cell division cycle. The tumor cells exposed to Taxol® are stalled in the G2/M-phase, which subsequently leads to the non-progression of their cycle and hence mitotic arrest followed by cellular death (see Figure 3). However, it is noteworthy that cells can activate mitotic exit (also known as “mitotic slippage”), the major way of escaping from MTAs and therefore limiting their efficacy.

Although mitotic arrest is believed to be the main mechanism of action of paclitaxel, a second pathway leading to cellular death is known. The so-called metabolic apoptosis is associated with the activation of transcription factor p53, also known as tumor suppressor, which plays a significant role in tumor progression. Furthermore, it has been reported that paclitaxel causes an increase in reactive oxygen species (ROS) and overexpression of proteins responsible for stress of the endoplasmic reticulum (ER) in cancer cells. However, it still has to be proven whether the stress on the ER originates from the specific gene dysregulation induced by p53 activation. Alternatively, the ER damage might cause an uncontrolled release of Ca²⁺, leading to inevitable Ca²⁺ overload, resulting in mitochondrial damage and subsequent increase in ROS production.

Also, another study has reported that in specific canine mammary gland tumor cells, Taxol® inhibits an expression of the anti-apoptotic protein B-cell Leukemia 2 (Bcl-2) and enhances an expression of the pro-apoptotic protein Bcl-2-associated X (BAX). These changes cause the mitochondrial apoptosis via disruption of the mitochondrial membrane potential (MMP), releasing the cytochrome C and destroying the caspase-3-protein (see Figure 3).

On the other hand, paclitaxel was reported to provoke dysregulation of the toll-like receptor 4 (TLR4) signaling pathway. Under normal conditions, the TLR4 pathway has a solid role in cell defense. It is believed that the presence of inflammatory mediators in paclitaxel-treated cells might decrease the antitumor effect of the drug. Moreover, treating the cell with PTX causes a cascade (PTX pathway), which not only leads to its survival, but also develops a further drug resistance.

Despite the efforts made on improving the treatment with Taxol®, the acquisition of drug resistance still remains a major setback.

In terms of this doctoral thesis, drug resistance issues including possible ways of overcoming multidrug resistance (MDR) in taxane chemotherapy are not further discussed.
1.2.1 Nomenclature of Classical Taxanes

About 50 years ago, the classical taxane skeleton was numbered by IUPAC. Due to the lack of technology for the stereochemistry determination at that time, the numbering was assigned according to a flat chemical concept. The core skeleton was numbered in a counterclockwise direction, starting from the bridgehead $sp^3$-carbon (position C1) and ending with the methyl group (position C18). This is followed by numbering in clockwise direction from methyl group (position C18) to methyl/methylene group (position C20). Since the molecule was considered to be flat, the geminal dimethyl moiety was numbered according to the relative orientation to the taxane core plane. Thus, the C16 methyl group was assumed to have $\alpha$-configuration (below the plane), and the C17 methyl group $\beta$-configuration (above the plane). Although the explained nomenclature system is still maintained by IUPAC, the numbering of methyl groups at position 16 and 17 was later switched after the elucidation of the exact cage form of the molecule (see Figure 4).

Importantly, the depicted numbering system in Figure 4 (C1 to C20) is extensively applied to all taxane derivatives, as well as to synthetic intermediates or precursors employed in their chemical synthesis. The common naming approach for the rings in the taxane terpenoid scaffold (rings A, B, C, D), as it is illustrated in Figure 4, is in the same way applicable to all taxane natural products and their synthetic precursors.
1.2.1 Structure-Activity Relationships of Taxol®

Taxol® is one of the most efficient anticancer drugs developed and has been widely utilized during the past three decades. Naturally, the discovery of paclitaxel’s antitumor activity has triggered numerous studies on relationships between its structure and pharmacological activity (structure-activity relationships, SAR). In the past, lots of reports were published highlighting the importance and significance of the unique structural shape and diverse oxidation patterns of the drug (Figure 5).[65-69]

In contrast to the low significance of the oxygenated functional groups, the stereochemistry at position C3 and C8 is essential for the cytostatic activity of paclitaxel.[69] Multiple studies on structure-activity relationships of Taxol® led to the development of the second generation PTX derivatives (Figure 6). Some of them already got approved for clinical use such as docetaxel (Taxotere®, 23) and cabazitaxel (Jevtana®, 24). Currently, several paclitaxel analogs are in clinical trials e.g. ortataxel (25) and tesetaxel (26).[70]

*Figure 5. SAR of paclitaxel.*[69]

*Figure 6. Active PTX derivatives.*
1.3 Synthesis of Taxanes

Ever since the first report of paclitaxel structure elucidation in 1971, its exceptional structural complexity proved highly interesting for synthetic organic chemists all over the world. The total synthesis of an oxygenated taxane with its structural features comprising a densely oxygenated 6/8/6 tricyclic ring system, diverse chirality including quaternary and contiguous chiral centers, advanced arrangement of oxygen containing functional groups and the extremely strained bicyclo[5.3.1]undecene ring system bearing a bridgehead double bond poses one of the greatest challenges known to synthetic chemists. Particularly, the construction of an eight-membered carbocycle is often challenging as the high degree of a ring strain and transannular interactions limit the choice of synthetic methods. Additionally, the flexible conformations are strongly dependent on the nature of the substituents. As a result, prediction and control of the functional groups’ reactivity are only possible through the practical approach. As a consequence, the presence of the eight-membered carbocycle in taxane’s core forces chemists to build their synthetic approach around its formation. However, in the past decades, great progress in the synthesis of eight-membered rings has been made, particularly, in the total synthesis of natural products containing eight-membered carbocycles.

Despite the extraordinary complexity of taxane natural products, an impressive number of syntheses have been reported in the past decades. To the best of our knowledge, there are eight completed total syntheses and three elegant formal syntheses of Taxol®. Furthermore, numerous methodologies approaching the synthesis of the lower oxidation state taxanes (e.g. taxadiene, taxusin and 1-hydroxytaxinine) or their synthetic precursors were published in the last years.

In terms of this chapter, the main emphasis is on the discussion of the synthetic strategies most relevant to our research. Other unique approaches or examples of published total syntheses are briefly introduced. In addition, earlier reported syntheses of taxane C-ring precursors are broadly discussed.

1.3.1 Advances in the Total Synthesis of Taxol®

Since its discovery, Taxol® has been nominated to be one of the most significant achievements in cancer research therapy. Potent anticancer activity and high clinical demand combined with constant supply crisis have strongly pushed advancing of the chemical synthesis of paclitaxel. From the first published total syntheses in 1994 till nowadays, novel strategies and methods...
towards highly oxidized taxanes have been reported, comprising the most elegant and recent advances in synthetic organic chemistry.

In this subchapter, selected synthetic strategies are discussed with strong focus on the way of constructing taxane’s bicyclo[5.3.1]undecene system.

**Nicolaou 1994**

The total synthesis of Taxol® published by Nicolaou et al. excellently demonstrates a convergent strategy of chemical synthesis. As far as a convergent strategy is concerned, the target molecule is to be assembled from several preassembled building blocks. In Nicolaou’s synthesis, the core structure of paclitaxel is built via connection of the two precursors 27 and 28 (resembling rings A and C) which leads to the formation of the desired inner eight-membered carbocycle (ring B). Subsequent introduction of the oxetane fragment (ring D) is carried out by attachment of Ojima lactam 29 (resembling peptide moiety) to the PTX core affording the target molecule (Figure 7).[^33, 89-92]

![Figure 6. Nicolaou’s preassembled building blocks.](image)

In the course of Nicolaou’s synthetic sequence, two subsequent connectivity steps – the Shapiro reaction (C1–C2 bond) and the pinacol coupling reaction (C9–C10 bond) – are serving as the key steps leading to the assembly of the ABC paclitaxel ring skeleton (compound 32) (see Scheme 6). The suitable C-ring precursor (aldehyde 28) was coupled with the corresponding A-ring precursor (hydrazone 27) via Shapiro reaction delivering the AC coupled product 30 in a yield of 82%. Subsequently, the protected tetraol 30 was converted into the dialdehyde 31 which in turn was subjected to the Ti(III)-mediated intramolecular pinacol coupling reaction affording the desired tricycle 32 in 23-25% yield. Along with diol 32, several other byproducts were delivered in significant amounts resulting in a relatively low overall yield of the corresponding coupling product. It is worth mentioning that until this point the synthesis was racemic. In the following step, an enantiomeric resolution was performed, resulting in the halving of the synthesis scale.
The whole synthetic sequence consists of 51 chemical steps. The discussion of the final stages of Nicolaou’s total synthesis of Taxol® is intentionally omitted.

Holton 1994

In contrast to the previously discussed total synthesis, Holton’s synthesis of Taxol® is a great example of a linear strategy of chemical synthesis.\(^ {34-35}\) Compared to the convergent strategy, the linear process is longer, and therefore the overall yielding is lower due to loss of compounds throughout the synthetic route. The whole synthesis is enantioselective. In Holton’s approach towards Taxol®, the strained bicyclo[5.3.1]undecene system (present in compound 34) was introduced at an early stage of the synthesis. It was accomplished by means of tandem epoxidation and Lewis acid-catalyzed Grob fragmentation of the corresponding precursor 33 (Scheme 7).

In Holton’s case, the key chemical transformations occurred later in the synthetic sequence. The first key step – Chan rearrangement – set the final carbon–carbon bond between the B and C rings. The second one – sulfonyloxaziridine enolate oxidation – provided the regioselective C–H oxidation at C2 and C1 position subsequently.\(^ {34-35}\)
Holton’s total synthesis of Taxol® exhibits an elegant linear enantioselective approach, which comprises 41 single chemical steps.

**Danishefsky 1996**

Shortly after publishing the first two paclitaxel’s total syntheses, another elegant method was reported by Danishefsky *et al.*[74] Despite some notable similarities to Nicolaou’s strategy – assembling ring B via sequential coupling of the A- and C-ring precursors – Danishefsky’s approach comprises significant differences. Firstly, the enantioselectivity of the synthesis does not rely on resolution, instead the asymmetric induction arises from (S)-Wieland Miescher ketone 37, which is further converted to C-ring precursor 36. Secondly, the C-ring precursor 36 was fully functionalized at an early stage, including introduction of the oxetane moiety (ring D). The employment of the fully functionalized CD-ring system prior closing the eight-membered ring enhanced the convergency of Danishefsky’s synthetic sequence. At last, the functionalization of the A ring precursor 35 was accomplished in accordance with the planned strategy (*Figure 7*).

In contrast to the previously reported syntheses, Danishefsky’s key reaction sequence implies C1–C2 bond formation followed by C10–C11 bond construction. The connecting of the suitably functionalized A and CD fragments (35 and 36 respectively) was achieved via lithiation of the corresponding dienyl iodide 35 followed by its concomitant coupling with aldehyde 36 (introduction of C1–C2 bond) and intramolecular Heck reaction of olefin 39 (introduction of C10–11 bond) (*Scheme 8*). The possibility of the ACB-ring system construction by late stage closure at position C10–C11 has been investigated earlier by Kishi *et al.*[93]
The two key intermediates 38 and 40 were obtained in reasonably good yields (93% and 49% respectively) which in turn enabled a relatively high yield of 0.2% for the overall synthetic sequence comprising 47 chemical steps (starting from (S)-Wieland-Miescher ketone 37).

**Wender 1997**

Wender’s total synthesis of Taxol® strongly resembles Holton’s strategy as its way of introducing the bicyclo[5.3.1]undecene system relies on the epoxide-opening ring expansion (Scheme 9).

The enantiopure fragmentation precursor 41 was subsequently treated with m-CPBA and base, setting the desired B ring in place and constructing the strained AB ring system in compound 42 independently of the C-ring.

**Scheme 9.** Wender’s approach towards the establishment of Taxol’s AB-ring system.

Wender’s total synthesis of Taxol® involves 37 steps, providing an overall yield of 0.4% from commercially available (−)-verbenone.
Kuwajima’s total synthesis of Taxol® is another example of a convergent strategy of chemical synthesis in which two pre-assembled parts (ring-A and ring-C precursors) were sequentially coupled, leading to the formation of the ABC taxane ring system. In general, the convergent strategy towards the ABC ring system used in this total synthesis resembles Nicolaou’s and Danishefsky’s approaches. However, Kuwajima employs a densely functionalized A-ring precursor 43 while leaving ring C to be decorated at a later stage in the synthesis (Figure 8).

Kuwajima used a very simple ring C precursor – bromobenzaldehyde derivative 44a/44b. By simplifying one of the pre-assembled building blocks (ring C), the coupling step could easily be scaled up. The construction sequence of the ABC-ring consisted of the following consecutive steps: stereoselective addition of lithiated compound 44 to corresponding aldehyde 43, followed by protection of the resulting diol (45) and subsequent TiCl2(OiPr)2 promoted cyclization (Scheme 10).

An employment of the corresponding A-ring precursor 43, bearing an asymmetric center at C1, allowed the control of all the other asymmetric steps. Particularly, both above mentioned crucial
steps of the ABC ring construction led to the formation of key intermediates 45 and 47 with an excellent stereoselectivity.

Although the strategy towards the ABC taxane ring system reported by Kuwajima is robust and stereoselective, the obtained intermediated 47 lacked stereocenters at the C3- and C8-position, as well as functional groups at the C-ring. The latter problem presented the major drawback of Kuwajima’s total synthesis of Taxol®. The whole synthetic sequence involves 47 chemical steps.

Mukaiyama 1998

Mukaiyama’s total synthesis of Taxol® is considered to be a hallmark in linear organic synthesis. Contrary to the previously published syntheses, where the AB ring system was accessed via epoxy-alcohol fragmentation or convergent strategy including a B-ring closure reaction of connected A–C ring systems, this synthesis starts with the formation of the densely functionalized B ring 49 (eight-membered ring) from its chiral linear precursor 48 (Scheme 11).[78]

\[\text{Scheme 11. Mukaiyama’s approach towards the densely functionalized B-ring.}^{[78]}\]

In the course of the SmI₂-mediated Reformatsky-type cyclization, the chiral linear precursor 48 was converted into the eight-membered ring compound 49 in a good yield of 70%.

In the following steps, the consecutive construction of the BC and ABC ring system was achieved by means of intramolecular aldol cyclization and intramolecular pinacol coupling reaction. Firstly, compound 49 was converted into ketoaldehyde 50 which was then subjected to the base-promoted intramolecular aldol reaction affording the BC ring system of Taxol® (compound 51) in nearly quantitative yields with good diastereoselectivity. Subsequently, compound 51 was transformed into dicarbonyl 52, which was subjected to a low-valent Ti-mediated intramolecular pinacol coupling reaction. The desired pinacol 53 was obtained in up to 71% yield.[78]
Following his pioneering work in the field of aldol chemistry, T. Mukaiyama efficiently employed the aldol reaction no less than five times in his Taxol® synthesis. An elegant application of the intramolecular aldol reaction (C7–C8 connection, Scheme 11) together with other key reactions (Scheme 12) such as the pinacol coupling (C11–C12 connection) and Reformatsky-type cyclization (C8–C3 connection) exhibits one of the most remarkable total syntheses ever published. The linear synthetic sequence consists of 61 chemical steps.\(^{[78]}\)

**Baran 2020**

Following the two-phase terpene synthesis logic (“cyclase phase” followed by “oxidase phase”), Baran’s approach exhibits one of the most efficient total syntheses of Taxol\(^\circledR\).\(^{[82]}\) In 2012, Baran’s group completed a scalable synthesis of (1)-taxa-4(5),11(12)-dien-2-one 57 through a concise “cyclase phase” via consecutive coupling of three components (diene 54, enone 55, cyclohexanone 56) with subsequent intramolecular cyclization, simultaneously creating the C13–C14 and C1–C15 bonds. Serving as a minimally oxidized taxane precursor, taxadienone 57 was further converted into baccatin III (19) through numerous C–O bond-forming events (“oxidase phase”).

**Scheme 12.** Mukaiyama’s approach towards ABC ring system.\(^{[78]}\)

**Scheme 13.** Baran’s two-phase approach towards oxygenated taxanes.\(^{[82]}\)
Being of most relevance to this thesis, the “cyclase phase” of Baran’s total synthesis is discussed in more details in the next chapter.

![Taxanes synthesized via two-phase strategy.](image)

**Figure 9.** Taxanes synthesized via two-phase strategy.

Baran’s Taxol® synthesis represents the shortest chemical route towards oxygenated taxanes ever reported. Furthermore, the above discussed two-phase strategy proved to be divergent, allowing an access to other highly oxidized taxanes such as taxuyunnanine D\(^{[94]}\) (58), decinnamoyltaxinine E (59) and taxabaccatin III (60)\(^{[95]}\) (Figure 9).

Li 2021

Recently, a remarkably concise asymmetric total synthesis of Taxol® was published by Li et al.\(^{[83]}\) The synthetically challenging ABC taxane ring system was assembled by a diastereoselective intramolecular SmI\(_2\)-mediated pinacol coupling reaction to form the C1–C2 bond. The strategy towards completing the ABC ring system was earlier reported by Inoue in 2019 and successfully applied to the synthesis of 1-hydroxytaxinine.\(^{[96]}\)

Being inspired by Inoue’s work, Li and co-workers used the same strategy in their synthetic sequence towards Taxol®. Following the planned synthetic route, intermediate 61 was submitted to the SmI\(_2\)-mediated pinacol coupling reaction affording pinacol 62 (C1–C2 connection) as a single desired trans diastereomer in 64% yield (Scheme 14).

![Scheme 14. Li’s synthesis of the ABC taxane ring system.](image)

This convergent approach proceeds though 19 isolated intermediates and allows the diverse creation of Taxol derivatives via modification of the key intermediate 62. The key transformation in Li’s sequence, the SmI\(_2\)-mediated pinacol coupling, is further discussed in more detail.
1.3.2 The “Diels-Alder Approach” in the Synthesis of Taxanes

In general, an intramolecular Diels-Alder reaction (IMDA) can be divided into two types depending on the joining manner between diene and dienophile moieties and the type of the bicyclic adduct formed in the cycloaddition reaction (Scheme 15).

When diene and dienophile are joined at position 1 of the diene and cycloaddition affords a fused bicyclic adduct. This type of intramolecular Diels-Alder reaction is referred to as type I. In contrast, when diene and dienophile are connected at position 2 of the diene, cycloaddition results in the formation of a bridged bicyclic ring system, the cycloaddition is then considered to be a type II IMDA. The product of the type II IMDA cycloaddition contains a bridgehead double bond. Thus, the reaction provides a direct entry into this class of highly strained molecules.

When considering the core structure of taxane natural products (exemplary shown for taxadiene 18), the AB ring fragment is represented by the strained bicyclo[5.3.1]undecene ring system bearing a bridgehead double bond. Retrosynthetically, the corresponding bicyclic fragment can be considered as an adduct of a type II IMDA reaction (Scheme 16) hinting its diene/dienophile precursor 63.

In the case of taxanes, employment of a type II IMDA reaction would simultaneously lead to two carbon–carbon bond forming events (C14–C13 and C1–C15) alongside the introduction of a newly formed stereocenter at C1 (Scheme 16).

Being considered as a versatile synthetic tool for synthesis of both strained and unstrained bridgehead alkenes, the type II IMDA reaction has been broadly investigated and applied in the synthesis of taxanes.
In 1983, Shea and co-workers were the first to report formation of the AB taxane ring system *via* a thermal intramolecular Diels-Alder reaction (*Scheme 17*).\(^{[97]}\) It was also shown that DA product 65 preferred to exist in an “endo conformation” (exo/endo = 11:89) revealing the barrier between the exo and endo to be 16.5 kcal mol\(^{-1}\).

![Scheme 17. Shea’s IMDA approach towards taxanes.\(^{[97]}\)](image)

Subsequently, Shea reported the Lewis acid (LA) catalyzed variant of the investigated IMDA reaction achieving better yields under milder reaction conditions (−70 °C, Et\(_2\)AlCl).\(^{[98]}\) Later on, Jenkins and Bonnert published their approach towards the assembly of taxane core 70 bearing a methyl substituent at C19 as well as the natural stereochemistry at C1 and C3 in addition to a saturated C-ring (*Scheme 18*).\(^{[99]}\)

![Scheme 18. Jenkins’ IMDA approach towards taxanes.\(^{[99]}\)](image)

In Jenkins’ approach, the corresponding DA precursor 69 was obtained from enone 66 in four steps. The synthetic sequence features a new method for the synthesis of substituted dienes *via* treatment of enone 66 with selenium-containing organolithium compound affording hydroxy selenide 67, which is further converted into diene 68 in moderate yield. The construction of the ABC taxane ring system was performed *via* LA-catalyzed IMDA resulting in formation of the desired tricycle 70 in 55% yield over three steps.\(^{[99]}\)

In 1988, Shea *et al.* published another related approach involving an internally activated dienophile and partially saturated C-ring (*Scheme 19*).\(^{[100]}\) The disguised enone fragment in the C-ring was designed to serve as a handle for the incorporation of the C19 methyl group.
Cycloaddition precursor 75 was prepared in a short six-step sequence from 1,3-cyclohexadione 71. The compound 75 was submitted to the Et₂AlCl-catalyzed DA delivering the desired compound 76 in 30% yield.

Yadav et al. smartly used a combination of the type II IMDA reaction with a Wittig rearrangement in order to assemble the taxane core (Scheme 20).[101]

In Yadav’s model study, the desired ABC ring fragment (compound 79) was derived from cyclic ether 78 via Wittig rearrangement. Compound 78 in turn was obtained by type II IMDA from cycloaddition precursor 77. The reported study marked the first precedent of the synthesis of the taxane ABC core having an oxygen-containing functional group at C10.[101] Later on, the methodology was extended resulting in a publication of the first stereocontrolled entry to the functionalized taxane core bearing a C7 and C10 hydroxy group.[102]

Since the selective C–H oxidation of the taxane core creates a similarly great challenge as its construction, several groups have been working on incorporation of oxygen-containing functionalities to the most problematic positions (e.g. C7, C9 and C10) prior to the intramolecular DA. For example, in 1994, Shea and co-workers reported an IMDA-based method towards the C1-epi-taxinine intermediate 85 bearing functional groups at C2, C9 and C10 along with the pivotal C19 angular methyl group (Scheme 21).[103] Highly functionalized type II intramolecular Diels-Alder precursor 84, suitable for this synthesis, has been prepared in a stereoselective fashion.
The addition of the organocerium reagent, which in turn was in situ generated from bromodiene 81, to aldehyde 80 delivered a 4:1 mixture of diene alcohol 83 and allenyl alcohol 82. Metal-halogen exchange followed by treatment with acrolein afforded a mixture of secondary alcohols, which was subsequently oxidized to enone 84. The latter was submitted to the thermally induced type II IMDA giving tricycle 85 in moderate yield. It was speculated, that the reversal in π-facial selectivity of the corresponding DA reaction was induced by unsaturation at C3–C4 in the precursor 84.

Based on earlier studies on the type II IMDA reaction, Shea and co-workers developed a method for the synthesis of the advanced taxusin intermediate 90 in 2003 (Scheme 22).[104]
accompanied by catalytical amount of Proton Sponge®, resulted in formation of the desired taxusin intermediate 90 in 77% yield. To the best of our knowledge, Shea’s synthesis of the advanced taxusin intermediate remains the only successful example of an employment of the C9, C10-functionalized precursor in an “Diels-Alder approach” towards the taxane scaffold.[104]

Park and co-workers were exploring the effects of the substitution pattern at C9 and C10 position on the π-facial selectivity of the IMDA reaction using a steroid-platform.[105] After surveying a plethora of experimental conditions, the first successful IMDA reaction leading to the ABC ring construct with an oxygen functionality at C10 was reported in 1995 (Scheme 23).[106] In this process, precursor 91 was heated at 180 °C for 66 h constructing the desired ABC ring moiety (compound 92) in 62% yield.

![Scheme 23. Park’s IMDA reaction leading to the ABC ring system on a steroid-platform.][106]

The main side reactions occurring during the IMDA reaction were documented and their mechanisms were broadly investigated. Additionally, the importance of the stereochemistry at C10 position for the feasibility of the IMDA reaction was demonstrated.[105] Interesting results were observed when the C10 β-OBn 93 isomer was subjected to the IMDA reaction. Heating of 93 in a sealed tube at 195 °C or 230 °C gave three major products (95, 98 and 100). Possible intermediates (94 and 97) and the reaction pathways leading to those products have been proposed (see Scheme 24). However, the desired product 99 was not observed in any of the performed experiments. It was thought that intermediate 94 was formed via a thermally induced 1,4-elimination of the benzyl alcohol. In the following step, the thermal type I IMDA reaction took place leading to the formation of compound 95. Dihydropyran 98 could be derived from intermediate 97 via hetero IMDA reaction. In turn, intermediate 97 arose from starting compound 93 through a competing retro-ene reaction. The origin of compound 100 remained unclear. It could presumably be derived from 97 or 98 (path II and path I respectively).

The LA catalysis of the IMDA reaction was also investigated. In the same manner, a complex mixture of products was observed in which no desired compound 99 was detected.[105]
The studies on the thermally induced IMDA reaction of C10 α-OBn precursor 91 revealed a strong and predictable correlation between the temperature protocol of the reaction and its outcome. Thus, when thermolysis of 91 was conducted at 180 °C for 66 h, the desired adduct 92 was formed. In contrast, applying the higher temperature protocol (210–220 °C) delivered the undesired product 95 in a moderate yield of 53%, presumably through the already proposed triene intermediate 94.

In 1995, Winkler and co-workers reported a highly stereoselective two-step synthesis of the taxane core (Scheme 25). Extrusion of sulfur dioxide from the easily available diene 101, followed by ZnCl2-catalysed intermolecular DA with dienophile 102 gave the cyclic product 103. Due to the great difference in the reactivity of the mono- and tetra-substituted diene units, the explicit regioselectivity of the DA reaction was observed. In addition, the IMDA reaction took place via BF₃·Et₂O catalysis giving the desired tricycle 104 as a single diastereomer in 82% yield.
The first total synthesis of (+)-taxadiene 18 using the “Diels-Alder approach” was reported by Williams in 1995 (Scheme 26). The synthetic sequence comprises 26 chemical steps. The key goal, formation of the ABC taxane ring system, was accomplished by means of the type II IMDA reaction (LA-catalyzed variant). The DA precursor 105 was treated with BF$_3$·Et$_2$O at –23 °C giving the desired tricycle 106 in a rather low yield of 23%. The latter was further converted into (+)-taxadiene 18 in seven steps.

![Scheme 26. Williams’s approach towards (+)-taxadiene 18.][108]

In 2012, Baran and co-workers reported an enantioselective gram-scale total synthesis of (+)-taxa-4(5),11(12)-dien-2-one (57) and (+)-taxadiene 18 comprising only seven and ten chemical steps respectively (Scheme 27).[109]

![Scheme 27. Baran’s enantioselective total synthesis of (+)-taxadienone 57 and (+)-taxadiene 18.][109]

The synthetic sequence commences with literature known compound 107 and 1,6-addition of an organocopper reagent generated in situ from 81 delivering the corresponding diene 108 in 86% yield. In the following step, an asymmetric introduction of the C19 methyl group was accomplished via stereoselective 1,4-addition of the corresponding organocopper reagent accompanied by chiral phosphoramidite ligand 112. The obtained enantiopure TMS-enol...
ether 109 was submitted to Mukaiyama aldol reaction with acrolein using Kobayashi conditions (Gd(OTf)₃ in 1:10:4 H₂O:EtOH:PhMe). The aldol reaction proceeded smoothly delivering the aldol product as a 2:1 mixture of diastereomers (at C3). The corresponding aldol products were subsequently oxidized with Jones’ reagent giving the desired ketoaldehyde 110 as an inseparable mixture of diastereomers at C3 with 85% yield over two steps. As expected, the BF₃-catalyzed IMDA reaction yielded the desire tricycle 111 in 47% yield. The synthesis of (+)-taxadienone 57 was completed via enol triflate formation followed by Negishi coupling affording ketone 57 in 84% over two steps. Finally, to complete the synthesis of (+)-taxadiene 18, a literature known three-step sequence was performed in 52% yield overall on gram scale.

The “Diels-Alder approach” in the synthesis of taxane derivatives has been broadly investigated in the past two decades resulting in the publication of several elegant syntheses. Although the general feasibility of this strategy can be questioned due its apparent limitations, some useful taxane-like intermediates were produced via the before mentioned methodology.

Relying on the reported studies, the following limitations of the “Diels-Alder approach” could be postulated: a) π-facial selectivity of the IMDA strongly depends on the saturation level of the C-ring; b) prediction of the IMDA reaction outcome is complicated and can only be based on the previous reports of reactions on closely related systems; c) attempts to employ the DA precursors with incorporated functional groups may lead to the formation of unexpected products; d) temperature protocol of the thermal variant of the IMDA reaction plays a crucial role in its successful outcome; e) numerous unpredicted side reactions such as elimination and proton shift can occur in the course of the IMDA reaction; f) intolerance of some functional groups towards acids in the LA-catalyzed IMDA reaction can lead to a complex mixture formation.

Despite the conspicuous limitations of the “Diels-Alder approach”, its utilization for the total synthesis of Taxol® has been reported by Baran exhibiting the shortest synthetic route towards the valuable drug.
1.3.3 The “Pinacol Approach” in the Synthesis of Taxanes

Radical reactions have been proven to be a versatile synthetic tool for the formation of sterically hindered C–C bonds and closing medium-size rings. At the same time, the majority of the known radical reactions are compatible with diverse oxygen functionalities, thereby serving as methods for the synthesis of highly oxygenated natural products.[112-116]

In general, the pinacol coupling reaction is an organic reaction in which a C–C bond is formed between the carbonyl groups in presence of an electron donor (SET donor).[117] Representing one of the known free radical reactions, the intramolecular pinacol coupling reaction has been widely applied in the total synthesis of various natural products such as (−)-actinophylic acid[118], aquayamycin[119], (−)-canataxpropellane[120] and many others.

When considering the synthesis of classical taxanes, the intramolecular pinacol coupling reaction has been successfully employed in several reported total syntheses (Scheme 28).

Nicolaou used the pinacol coupling in his total synthesis of Taxol® to construct the taxane skeleton by closing the B-ring (C9–C10 bond).[33] In turn, Mukaiyama employed a pinacol coupling reaction in his synthesis of Taxol® for completing the ABC taxane ring system by closing of the A-ring (C11–C12 bond). In the most recently published total syntheses of taxanes, the
possibility of the B-ring closure at C1–C2 via intramolecular pinacol coupling reaction was reported (Inoue’s synthesis of 1-hydroxytaxinine and Li’s asymmetric synthesis of Taxol). In this chapter, the most relevant approach to our research strategy, namely the closing of the B-taxane-ring at C1–C2 via intramolecular pinacol coupling as well as its advances and scope are discussed.

Swindell and co-workers were the first to report a synthesis of a taxane-like compound through intramolecular pinacol coupling at C1–C2 positions in 1996. The published synthetic sequence comprises ten chemical steps towards taxane diene 119 from the commercially available compound 120 (Scheme 29).

The suitably preassembled building blocks 114 and 121 were connected via Pd-catalyzed Sonogashira coupling reaction yielding product 115 in 81%. In the following steps, compound 115 was converted into the pinacol coupling precursor 118 in four steps. Then, an intramolecular pinacol coupling was carried out on ketoaldehyde 118 closing the B-ring and concomitantly forming tricycle 119 with an appropriate relative stereochemistry at positions C1 and C2 (trans relation).

In their following study, Swindell and co-workers managed to apply the “pinacol approach” to the synthesis of highly oxygenated C-aromatic taxanes. For this purpose, the approach towards
constructing the pinacol precursor was significantly changed allowing an early stage incorporation of oxygen functionalities at C9 and C10 positions (Scheme 30).  

Styrene 122 was synthesized from iodide 121 via Pd-induced Sonogashira coupling with the acetylene equivalent 1,1-dimethylpropargyl alcohol followed by silylation, base-catalyzed ejection of acetone, and partial hydrogenation of the terminal acetylene group. The resulting alkene was subjected to Sharpless hydroxylation affording vicinal diol 123, which was further converted into α-hydroxy aldehyde 124. The lithiated ring A precursor 126 was then added to aldehyde 124 yielding the predominantly chelation-controlled product (trans-diol) 125, which was converted to acetonide 128 in the following. The corresponding ketoaldehyde 128 was then cyclized via Ti(III)- or Sm(II)-mediated pinacol coupling reaction delivering the desired tricycle 129 in acceptable yield. The major setback of the described method is the presence of the aromatic C-ring in the advanced intermediate 129 lacking crucial stereocenters at C3 and C8 present in natural taxanes, which in turn disabled rapid functionalization of the C-ring fragment.

Later in 1996, Swindell and co-workers reported a method for the construction of the highly oxidized taxane intermediate 136 with partially saturated (non-aromatic) C-ring fragment relying on an intramolecular pinacol coupling at C1–C2 positions (Scheme 31).
Scheme 31. Construction of the highly oxidized intermediate 136 with partially saturated C-ring fragment.

The cyclohexene 132 bearing a C19 methyl group was accessed through Claisen rearrangement of the corresponding ortho-ester derivative of alcohol 131. Following α-hydroxylation of the ester 132 produced alcohol 133 with the desired diastereoselectivity. The obtained hydroxy ester 133 was further protected, reduced and oxidized to aldehyde 134. In the following step, the lithiated precursor 126 was added to aldehyde 134 unexpectedly affording the chelation-controlled product 135. With a subsequent protection/oxidation/deprotection sequence the stage for the key pinacol coupling was set. Subjection of dicarbonyl 136 to SmI₂-treatment delivered the desired tricycle 137 in 74% yield.

The above discussed strategy of the C1–C2 ABC ring system closure via pinacol coupling has laid a solid foundation for the further studies on the total synthesis of taxane natural products.

In 2019, the first total synthesis of 1-hydroxytaxinine relying on the low-valent titanium promoted intramolecular pinacol coupling as a key step was published by Inoue et al. The authors managed to develop an efficient enantioselective route to Swindell’s intermediate 137. The conditions for the key pinacol step have been slightly changed and with this allowing a gram-scale synthesis of the enantipure intermediate 137.

Inspired by Inoue’s and Swindell’s studies, Li and co-workers completed their asymmetric total synthesis of Taxol® utilizing the intramolecular SmI₂-mediated pinacol coupling as a key reaction for the construction of the taxane core.
1.3.4 Synthesis of Taxane C-Ring Precursors

The majority of the published synthetic routes towards taxane natural products adopted the convergent strategy of the multi-step synthesis where at the complex ABC taxane ring system is being assembled via the connection of two preassembled building blocks (A- and C-ring precursors). The corresponding approach is often referred to as “A and C → ABC” approach.

Another less popular approach leading to the simultaneous formation of the A- and B-ring and therefore completing the ABC taxane ring system commences with the suitably preassembled C-ring precursor. The latter is referred to as “C → ABC” approach.

Several total syntheses of taxane natural products were published in the past complying with one of the aforementioned approaches. Although other effective approaches towards taxanes are known (see chapter 1.3.3), in the course of this thesis, the main focus is put on the approaches which are based on the initial synthesis of the suitable C-ring precursor (“A and C → ABC” and “C → ABC” approaches).

In contrast to the achiral A-ring system, the C-ring of the advanced taxanes contains a number of stereocenters accompanied by diverse oxidation patterns. Generally, a scalable, reproducible and stereoselective synthesis of the C-ring precursors with suitably decorated functional group patterns often creates additional serious synthetic challenges. In the following chapter, the literature known advances in the synthesis of the C-ring precursor are broadly discussed.

In 1994, a pioneering work in the synthesis of the advanced taxane C-ring precursor was reported by Nicolaou as a part of his total synthesis of Taxol®.[90]

![Scheme 32. Nicolaou's synthesis of the C-ring core][90]

The core six-membered structure of the C-ring precursor was assembled via intermolecular Diels-Alder reaction employing 3-hydroxy-2 pyrone 139 as diene and dienophile 138 in the presence of phenylboronic acid. Applying Narasaka’s principle of tethering two reaction partners
in order to direct the regiochemistry of the DA reaction, an explicit regioselectivity of the corresponding DA reaction was achieved yielding the initial DA adduct 141. The bicycle 141 concomitantly rearranged to the desired compound 142. The completion of the C-ring building block 28 was achieved in the following nine chemical steps (Scheme 33).

![Scheme 33. Nicolaou’s synthesis of the C-ring precursor 28.](image)

After protecting group manipulations, ester 143 was subsequently reduced affording diol 144 in 92% overall yield. A treatment of the latter with TBDPSCI resulted in selective silylation of the primary alcohol at C9. The secondary alcohol at C7 was then benzylated affording the fully protected triol 145 in 79% yield over two steps. In the next step, the lactone moiety was reduced, and the resulting 1,2-diol was protected as acetonide (compound 146). Finally, TPAP/NMO oxidation of the primary alcohol in 146 gave the targeted aldehyde 28 in 97% yield.

In summary, Nicolaou’s racemic synthesis of the C-ring precursor 28 represents an elegant approach towards the diastereoselective synthesis of densely functionalized building blocks which involves only ten chemical steps with an overall yield of 33% starting from the DA precursor 138.

In contrast to Nicolaou’s synthesis, Danishefsky targeted the C-ring precursor 36 with an already fused oxetane ring (D-ring) in place. The synthetic sequence (Scheme 34) commenced with the selective reduction of the Wieland-Miescher ketone 37 with NaBH₄ followed by acetylation of the resulting secondary alcohol affording ketone 147.
The obtained ketone 147 was converted to the deconjugated ketal 148, followed by a hydroboration/oxidation sequence resulting in ketone 149 with the right stereochemistry at C8 and C3 in place. The compound 149 was then transformed into epoxide 150 applying Corey’s sulfonium ylide methodology. The desired allylic alcohol 151 was further obtained through a LA-catalyzed epoxide opening reaction. In the following steps, the D-ring (oxetane moiety) was successfully installed via literature known four-step sequence yielding the tricycle 153. After protection of the tertiary alcohol and deprotection of the ketal, ketone 154 was produced. Followed by α-hydroxylation, concomitant α-hydroxyketone cleavage by Pb(IV) and acetal protection, tricycle 154 was converted into the bicyclic compound 156. Finally, the ester functionality was reduced and following elimination/ozonolysis sequence gave rise to the desired C-ring precursor 36.

In overall, Danishefsky’s enantioselective synthesis of the C-ring precursor 36 involves 23 chemical steps from the commercially available Wieland-Miescher ketone 37 and delivers the
desired product in overall yield of 7.6%. Although the early-stage functionalization of the C-ring with emplacement of the oxetane fragment allowed to enhance the convergence of the overall synthetic sequence, the multi-step route towards the desired building block compromises its rapid availability. Moreover, the long synthetic sequence to the C-ring building block restricts variability in further synthetic methods towards taxane natural products and their analogs.

In contrast to the others, Kuwajima used a maximally simplified C-ring fragment in his total synthesis of Taxol®.[79] The relatively short synthetic sequence enabled rapid access to the valuable building block 44a (Scheme 35).

The overall synthetic route to building block 44a, which is still lacking chirality and the proper functionalization pattern, comprises only seven chemical steps. Starting from the commercially available ketone 157, the α-hydroxylated product 158 was derived. The latter was further converted to diol 159 with subsequent formation of thiocarbonate 160. Finally, the thiocarbonate moiety was removed yielding the desired bromodiene 44a in a yield of 27% over the whole sequence.

Being a landmark in the “C → ABC” approach, Baran’s total synthesis of Taxol® commences with the readily available building block 107 which is converted into the desired C-ring precursor (type II IMDA precursor) 110 in only three chemical steps with an overall yield of 65% (see Scheme 27). Although the latter has the right stereochemistry at C3 and C8, it significantly lacks functionalization.[109]

Besides the above discussed methods published in the corresponding total syntheses of Taxol®, plenty of the other syntheses of the C-ring precursors were reported either as a part of total syntheses or as a methodology report.
For example, Takahshi’s synthesis of the C-ring precursor started with geraniol 161. After subsequent acetylation, allylic oxidation and epoxidation, Ti(III)-catalyzed cyclization took place yielding the six-membered ring compound 164 in a yield of 61% (Scheme 36).[[84]

From the cyclic intermediate 164, the racemic C-ring precursor 166 was obtained in three steps. The overall sequence towards precursor 166 comprises only nine chemical steps starting from commercially available geraniol 161.

Sato and Chida have developed two enantioselective routes towards the C-ring precursor, which they successfully employed in the formal synthesis of paclitaxel.[86-87] In the first route, the privileged chiral intermediate 172 was prepared in a literature known ten-step procedure from tri-O-acetyl-D-glucal 167 (Scheme 37).[125-126] The methyl glycoside 168 was prepared via literature known two-step procedure,[125-126] and further converted into iodide 169. The latter was then treated with sodium hydride and benzyl bromide, and subjected to Hg(II)-catalyzed Ferrier’s carbocyclization followed by β-elimination
generating the cyclohexanone 171. Finally, treatment of compound 171 with methyllithium and concomitant oxidation of the addition adduct resulted in the desired chiral cyclohexanone derivative 172.

In 2016, a more practical synthesis of compound 172 was reported. Following the reported method, a multi-gram scale synthesis of intermediate 172 was accomplished in a linear sequence starting from 3-methoxytoluene 173 (Scheme 38).

![Scheme 38. Sato-Chida’s second route towards intermediate 172.]

The SET reduction of 3-methoxytoluene 173, followed by treatment with ethylene glycol delivered ketal 174. In turns, compound 174 was further dihydroxylated with OsO₄/NMO affording a racemic mixture of diols, from which the desired enantiomer 175 was isolated by means of enzymatic resolution. In the next step, the secondary alcohol 175 was benzylated and the resulting tertiary alcohol 176 was treated with p-toluenesulfonic acid simultaneously triggering the elimination/ketal deprotection sequence to give 172 in 90% yield. With having building block 172 in hand, the synthesis of the C-ring precursor 181 was accomplished in the following nine-step sequence (Scheme 39).

![Scheme 39. Completion of the C-ring precursor synthesis by Sato-Chida.]

1) Li, liq. NH₃, EtOH, -78 °C
2) HCO₂H, (CH₂OH)₂

1) OsO₄/NMO tBuOH, H₂O, 83%
2) enzymatic res. 54%

NaH, BnBr TBAI, THF 88%

Scheme 38. Sato-Chida’s second route towards intermediate 172.

Scheme 39. Completion of the C-ring precursor synthesis by Sato-Chida.
To the chiral enone 172, vinylmagnesium bromide was added in the presence of copper(I) iodide in 1,4-fashion. The resulting adduct was trapped as a TMS enol ether, which was subsequently treated with formalin and Sc(OTf)$_3$ giving rise to alcohol 177. The compound 177, bearing the right stereochemistry at C8 and C3 and prerequisite functional groups in place, was further protected and reduced (ketone moiety) to yield compound 179, which was then transformed into tetraol 180. Finally, protecting group manipulations followed by an oxidation of the primary alcohol to the aldehyde with TPAP/NMO led to the desired C-ring precursor 181.

In overall, the reported synthetic routes by Sato and Chida deliver the corresponding compound 181 as a single enantiomer in a yield of 8.7% (1$^{st}$ route, 19 chemical steps) and 7.1% (2$^{nd}$ route, 14 chemical steps), respectively.

In 1997, Nagaoka et al. reported an efficient stereoselective synthesis of the taxane C-ring by fragmentation of bicyclo[2.2.2]octane derivative 184 (Scheme 40).[129]

**Scheme 40.** Synthesis of the taxane C-ring by fragmentation of a bicyclo[2.2.2]octane derivative 184.[129]

Bicycle 183 was accessed via intermolecular DA reaction between dienophile 182 and in situ generated diene 189. The obtained compound 183 was then converted into fragmentation precursor 184. Following reduction of the ketone moiety with sodium borohydride in the presence of strong base (potassium tert-butoxide) triggered the fragmentation which led to the formation of compound 185. From the latter, in a five-step reaction sequence, the desired intermediate 188 was obtained. The whole synthetic route comprises 15 chemical steps starting
from the readily available compound 182. The enantiopure intermediate 188 with the right stereochemistry in place was synthesized in an overall yield of 24%, representing one of the most efficient syntheses of taxane C-ring precursors.

Another concise synthesis of an enantioenriched taxane C-ring precursor 195 employing a [2,3]-Wittig rearrangement was reported by Kishi and co-workers in 1993 (Scheme 41).\(^{[130]}\)

\[\text{Scheme 41. Synthesis of enantiomerically pure taxane C-ring precursor 195 by Kishi.}\]

At first, racemic 3-methyl-2-cyclohexen-1-ol (190) was kinetically resolved according to Noyori’s procedure providing an access to (S)-3-methyl-2-cyclohexen-1-ol, which was subsequently converted into compound 191. The latter was submitted to the [2,3]-Wittig rearrangement and concomitantly transformed into the TBS-protected diol 192. In the next steps, an allylic oxidation afforded an enone, to which an organocopper reagent was added yielding compound 193. The completion of the synthesis of intermediate 195 was then performed in a four-step sequence where formaldehyde was added to the TMS enol ether 193 followed by subsequent reduction of the ketone and protection of the resulting 1,3-diol. The enantioenriched C-ring precursor 195 was synthesized in 14 steps from 3-methyl-2-cyclohexen-1-ol 190 in a yield of 14% providing an excellent enantiomeric excess (90% e.e.).

In 1997, Magnus et al. reported the synthesis of C-ring precursor 203 relying on the Schultz asymmetric Birch reduction methodology (Scheme 42).\(^{[133]}\) Reduction of the readily available benzoic acid derivative 196 under Birch conditions followed by α-methylation gave the desired product 197 as a single diastereomer. In the following steps, an acidic hydrolysis of the enol ether was carried out to give the corresponding ketone. In the next steps, its reduction to the secondary alcohol followed by benzylation afforded compound 198. With this compound in hand, an iodolactonization reaction was done affording bicyclic compound 199. Next, the
epoxialdehyde 199 was obtained via subsequent treatment of the lactone with DIBAL-H and DBU. Reduction of ketone 199 with concomitant treatment of the product with diethylaluminum 2,2,6,6-tetramethylpiperidide 200 gave rise to the desired allylic alcohol 201 in an excellent yield of 89%. In the next step, diol 201 was mono-protected with TBSCI and subsequently converted into compound 202.

Scheme 42. Synthesis of the C-ring precursor 203 relying on the Schultz asymmetric Birch reduction methodology.[131]

At last, the desired C-ring precursor 203 was derived from compound 202 in the course of a four-step reaction sequence. The whole synthetic route involves 16 steps and delivers aldehyde 203 in an overall yield of 36% (Scheme 42).

In one of the more recent total syntheses of taxanes, Li and co-workers reported a synthetic route towards C-ring precursor 208 starting from (2R,3S)-3-hydroxy-2-methyl-2-(2-propen-1-yl)cyclohexanone 204 (Scheme 43).[83] In the paper, the authors claimed starting material 204 to be commercially available. However, due to its high price (1567 USD/g), availability of the latter could be questioned. In industry, the corresponding compound 204 is produced via asymmetric microbial reduction of its prochiral cyclohexanedione and therefore its quantity is limited.[132]

Nevertheless, in the reported sequence, compound 204 was benzylated, brominated and formylated followed by reduction of the resulting bromoaldehyde to give the allylic alcohol 205. In the next step, free alcohol functionality was removed, and the exo-methylene moiety was subsequentially oxidatively cleaved yielding aldehyde 206. The obtained compound 206 was
then transformed into silyl enol ether 207 and treatment with m-CPBA followed by *in situ* protection of the resulting free alcohol delivering the targeted building block 208.

**Scheme 43.** Li’s synthesis of the C-ring precursor 208.\(^{[83]}\)

Li’s synthesis of the C-ring precursor 208 involves only 6 chemical steps from \((2R,3S)-3\text{-hydroxy-2-methyl-2-(2-propen-1-yl)cyclohexanone} \) 204 and delivers the targeted substance in 18% overall yield.

In summary, a number of efficient stereoselective syntheses of taxane C-ring precursors were published in the past three decades. Some of the published approaches were successfully employed in the total synthesis of taxane natural products. Even though numerous methodologies have been developed, rapid availability of the enantiomerically pure C-ring precursor with suitably arranged oxidation/functionalization patterns along with the native stereochemistry through an economically reasonable synthetic sequence remains an unsolved problem.
1.4 Boron-Mediated Reactions in Preparative Organic Synthesis

Organoborons are widely used as highly efficient and versatile reagents in many reactions, such as cross-coupling, hydroboration, homologation (including carbonylation and cyanidation) and asymmetric crotyleboration (allylboration).[133] In the following chapter, reactions most relevant to this thesis are broadly discussed. Some recent advances in their application to the total synthesis of natural products are shown.

1.4.1 Homologation of Organoboranes

In the 1980s, a reaction sequence of an enantioselective C1 homologation of chiral boronic esters was developed by Matteson.[134] In the following years, this type of reaction became known as “Matteson’s boronic ester homologation” and found its application in plenty of published total syntheses. In its essence, the readily available chiral boronic ester 209 reacts with the dichloromethylithium to form a boronate complex (ate-complex) that undergoes a 1,2-metalate shift providing chiral α-alkyl organoboron/α-haloboronic ester 210. In the second step, an organometallic nucleophile attacks the boronate to form another ate-complex that undergoes a 1,2-metalate shift in the same manner, causing an inversion of the stereochemistry at the α-position and resulting in the boronic ester 211. The compound 211 can either be subjected to an oxidative work-up to give a secondary alcohol[135-136] or submitted to further homologation. (Scheme 44).

![Scheme 44. The essence of Matteson’s boronic ester homologation.[134]](image)

Due to the substrate-controlled manner of establishing the desired stereochemistry in the second homologation step, the opposite configuration is only accessible via introducing a different chiral diol to form the organoboron precursor.

The direct approach using lithiated carbamates in reaction with boranes and boronic esters for homologation was developed by Aggarwal and co-workers.[137] Nowadays, this type of homologation reaction is known as Aggarwal lithiation-borylation sequence. It can be divided into three steps: 1) α-lithiation of a carbamate or a benzoate 212 generates a chiral
Li-carbenoid 213, 2) trapping of the Li-carbenoid with boranes or boronic esters to form a boronate complex 214, 3) migration of the substituent at the boron atom to the chiral α-carbon atom and expulsion of the leaving group in a 1,2-metallate rearrangement. This delivers the desired chiral homologated boronate 215 (Scheme 45).[^138]

![Scheme 45](image)

Employing the boronic ester homologation methodology, Aggarwal and co-workers reported the total synthesis of (+)-faranal (221) (Scheme 46).[^140]

![Scheme 46](image)

(+)-Faranal (221) is an insect pheromone isolated from *Monomorium pharaonic*,[^141] of which previously published total syntheses required 10 to 29 steps.[^140] In contrast, following the above depicted pathway comprising a one-pot sequence of four consecutive homologations, the desired product (+)-faranal was accessed in only six steps with an overall yield of 13%.[^140] Lithiation of iodide 216 and its reaction with chloromethyl pinacol boronic ester 222 resulted in homologated boronic ester 217, which was then attacked by chiral lithiated carbamate 223 at low temperatures. The resulting complex rearranged to homologated boronic ester 218 upon warming up to 40 °C. The second analogous homologation afforded boronic ester 219, which was then treated with vinyllithium in the fourth homologation step and subsequently reacted with iodine and sodium methanolate, providing the terminal olefin 220. Conversion of the latter
to an alcohol via common hydroboration/oxidation reaction sequence, followed by oxidation with PDC delivered the final aldehyde (+)-faranal (221).

1.4.2 Carbyloration of Organoboranes

Due to its specific electrophilic nature, organoboron compounds can take part in carbyloration reactions (CO insertion into carbon-boron bonds). The reaction of carbon monoxide with organoboranes normally allows three possible rearrangements. Strongly depending on the reaction conditions, different types of group migration can occur leading to a variety of carbonyls as well as primary, secondary and tertiary alcohols.\[142\]

During the carbyloration reaction, addition of CO to the corresponding trialkylborane 224 leads to the formation of an ate-complex 225 with subsequent migration of a R group to the CO moiety in the same manner as previously demonstrated for the C1 homologation reactions (see Scheme 44). After migration of the suitable rest, the stable intermediate 226 was formed, which in turns can then be converted into the mono-migration product 227 in the presence of a mild reducing agent (e.g. potassium triisopropoxyborohydride) (Scheme 47).

Scheme 47. Addition of CO to trialkylboranes.

The oxidative reaction work-up then affords the corresponding aldehyde. Alternatively, treatment of the mono-migration product 227 with lithium aluminium hydride followed by oxidative work-up delivers the primary alcohol. In preparative synthesis, conversion of the alkene, hydroborated with 9-BBN, to the corresponding aldehydes via carbyloration/oxidation sequence provides an access to a variety of aldehydes with valuable and unique alkyl rests. For example, applying this sequence to 2-methylcyclopentene 228 delivers trans-2-methylcyclopentane carboxaldehyde 230, the practically unavailable compound through other synthetic methods (Scheme 48).\[143\]

Scheme 48. Synthesis of trans-2-methylcyclopentane carboxaldehyde 230.\[143\]
When the carbonylation reaction is carried out in the presence of water (or aliphatic alcohols), a second alkyl group in the intermediate 226 migrates to the adjacent carbon yielding, after the oxidative work-up, the corresponding ketone. This feature allowed to produce a number of unsymmetrically substituted and cyclic ketones, when thexylborane (1,1,2-trimethylpropylborane) was used as a hydroboration agent for the synthesis of mixed trialkylboranes and cyclic boranes respectively (Scheme 49). Since the thexyl moiety exhibits low migratory tendency, it serves as an anchor group.[144]

![Synthesis of unsymmetrically substituted ketones](image1)

**Scheme 49.** Synthesis of ketones via hydroboration/carbonylation sequence.[144]

Carbonylation of trialkylboranes in the presence of ethylene glycol results in migration of the second and the third alkyl group to give, after oxidation, the corresponding tert-alcohols. Hydroboration of polyenes followed by carbonylation and oxidation provides access to the complex carbocyclic systems and therefore serves as a valuable synthetic tool for constructing the core terpene structures.

1.4.3 Asymmetric Tandem Borylation-Allylation Reactions

The groundwork in the field of catalytic enantioselective diboration of alkenes, dienes and allenes has been done by Morken and co-workers in the past decades. With reporting new methodologies, scope, and limitations of the mentioned catalytic methods, Morken’s group has begun a new chapter in history of boron-mediated chemistry. In the course of this thesis, a special emphasis is put on catalytic enantioselective 1,2-diboration of 1,3-diienes and further transformation of the produced organoboron species.

On the one hand, the newly generated by 1,2-diboration of 1,3-diene 237 allyl boron reagent 239 exhibits its corresponding reactivity towards carbonyl groups, allowing the generation of homoallylic alcohols 240.[145] On the other hand, 239 can be oxidatively converted into the corresponding chiral 1,2-diols 238 providing a straightforward access to this class of compounds (see Scheme 50).[146]
Being of utmost interest to our research, stereoselective addition of the corresponding chiral allyl boron reagents to prochiral carbonyls is further extensively discussed. According to the reported classification of allylmetal-carbonyl condensations by Denmark and Weber,[147] allyl boron reagents belong to the type I allylation agents. That means that the addition to the carbonyl group is carried out through closed transition states (TS) which allows the reaction not only to establish appropriate oxygenation patterns, but also, due to its stereochemical predictability, provides a ready access to the stereochemically pure homoallylic alcohols 240. In a vast majority of known allylation reactions, the obtained products bear a terminal alkene moiety which strongly limits functionalization of this part of the molecule. However, additional synthetic operations are often required. One of the most important reactions reported to resolve this problem is the vinylogous aldol reaction which yields enoate-derived homoallylic alcohols.[148] Despite the great effort that has been made in developing catalytic enantioselective vinylogous aldol reactions, a syn-selective asymmetric propionate version is still unavailable, as is a version that yields asymmetric quaternary centers.[149]

When considering the initial addition product 240, it was reported that with a suitable oxidative work-up it can be converted into vinylogous aldol equivalents 241, resolving limitations of the previously reported vinylogous aldol reactions. Furthermore, the newly formed allyl boron fragment in the allylation product 240 can be employed in other bond-forming reactions (e.g. cross coupling, allylation). For example, this feature allows applying the 1,2-diboration of 1,3-dienes methodology for the enantioselective synthesis of polyketides (Scheme 51).[145]

In fact, considering the huge number of transformations that are available to organoboronates, allylation intermediates 240 may be directly transformed into a variety of other useful building blocks.
blocks. For example, the allylboronate 240 can be subjected to the Matteson homologation protocol,[150] Suzuki coupling[151] or protodeboronation protocol reported by Aggarwal.[152] Lastly, the obtained chiral intermediate 240 can react in a similar manner with another carbonyl compound, affording diol 243 which bears four consecutive stereocenters. Interestingly, the latter reaction exhibits still a type I allylation reaction and provides a great stereochemical predictability allowing an access to a range of asymmetric diols.

Based on the extensive previously reported studies, in 2013, the Morken group published a novel catalytic enantioselective diboration strategy followed by cascade allylboration of dicarbonyls.[153] The above mentioned strategy offered a rapid access to the optically pure carbocyclic reaction products with dense and diverse functionalization patterns, and a native terpene stereochemistry at selected positions. As it was broadly demonstrated in earlier studies, an α-chiral allylboron reagent derived from the corresponding 1,3-dienes can be engaged in asymmetric carbonyl allylation (see TS 245) subsequently with two carbonyl groups (see Scheme 50 and 51).[145]

Morken and co-workers anticipated that if the second carbonyl was tethered to the first one, the corresponding allylboron 244 might attack the second carbonyl intramolecularly (see TS 246). This in turn would lead to the formation of the cyclic product 247, which bears four contiguous stereocenters similarly to the intermolecular variant demonstrated on diol 243 (Scheme 51).[153] It was also presumed that the second allylation would exceedingly comply with the conformational preferences of intermediate 246 and thus, the reaction would proceed through the defined bicyclic transition state delivering the desired level of stereoinduction. Remarkably, the reaction products exhibit noticeable structural features, which in turn strongly resemble some structural motifs found in terpene natural products.
The pioneering work to develop the strategy described above was performed on the coupling reaction between geranial-derived diene 248 and succinic dialdehyde. The general procedure employing B2(pin)2, Pt(dba)3 as a catalyst and TADDOL-derived chiral ligand 250 in toluene was found to be the most effective for an enantioselective 1,2-diboration. Following the addition of the dicarbonyl, stirring at elevated temperature and alkaline workup, cyclic diol 249 was obtained in 80% yield, 15:1 d.r. and 96% e.e. (Scheme 53).

A series of other dienes and dicarbonyls were subjected to the same conditions. As a result, several valuable observations regarding the reaction scope were postulated: a) tertiary centers and spiro centers can be accessed with excellent diastereo- and enantioselectivity; b) high level of regioselectivity can be reached with non-symmetric carbonyls (including ketoaldehydes); c) extension of the scope to seven-membered rings leads to the formation of complex mixtures; d) stereoisomers are often readily separable by chromatography. Morken and co-workers also reported a model for stereoinduction in tandem allylations based on a trans-decalin-like transition state with intramolecular allylboration occurring in a chairlike six-membered fashion (type I allylation) (Scheme 54).

Mechanistic considerations led to the building of the corresponding transition states TS1 and TS2 and revealed a strong preference of the CS-OB(pin) group for an axial orientation in most of the investigated systems. It was also shown that the axial disposition of the OB(pin) group
acts in concert with the larger R’ preferring to reside in an equatorial site and thus enhancing the selectivity to react through TS1. In contrast, systems bearing R” larger than R’ at C4 managed to counteract the axial preference of the OB(pin) group sufficiently to turn over the diastereoselectivity and direct the reaction to proceed over TS2. Morken and co-workers postulated several reasonable explanations for a rather unusual preference of an axial orientation of the C5-OB(pin) group. Firstly, they suggested this unordinary feature could arise from electrostatic attraction between the axial oxygen and either the carbonyl group or axial hydrogens in α-position to the carbonyl. Secondly, it could also be caused by hyperconjugative interactions between the C−O σ* and an adjacent axial CH donor.

Based on the thorough investigation of the mechanism and origin of the stereoinduction, a certain predictability for the stereoselective synthesis through the above described tandem allylation strategy was reached. Relying on that, Morken’s group performed a number of enantioselective syntheses of valuable densely functionalized building blocks and showed their direct application in the short and enantioselective total synthesis of pumilaside aglycon.\[153\]

In 2019, Gademann et al. reported the synthesis of a key fragment of the complex polyhalogenated marine meroterpenoid azamerone based on Morken’s tandem allylation strategy.\[154\] The key transformation leading to formation of the core structure of the desired fragment was reported to be an asymmetric tandem borylation-allylation reaction. In the course of the following reaction (Scheme 55), diene 253 was subjected to the typical reaction conditions developed by Morken’s group. The one-pot coupling of the corresponding 1,2-diborated intermediate with 4-oxopentanal delivered the targeted carbocycle 254 in 60% yield, 9:1 d.r. and 88% e.e.

Scheme 55. Synthesis of carbocycle 254 following Morken’s tandem allylation strategy.\[154\]

In summary, the reported enantioselective synthesis of carbocycle 254 evoked our attention due to its structural features. The triol 254 strongly resembles the taxane C-ring fragment regarding its unique oxidation and substitutional pattern (Figure 10).
To our delight, the obtained enantioenriched triol 254 has the required stereochemistry at C2 and C3 (cyclohexane numbering, at C3 and C8 – taxane numbering), a suitable substitution design and an advanced oxidation pattern allowing it to be considered as a potential taxane C-ring precursor. Moreover, those features are readily accessible in the course of a single one-pot process.

Morken’s studies on the tandem allylation strategy has provided the foundation for developing short and scalable stereoselective synthetic methods towards advanced and heavily oxygenated taxane C-ring precursors, which are discussed in detail in the following chapter.
2 Results and Discussion

In the course of this thesis, the synthesis of a small library of taxane C-ring precursors was aimed for. This was to be accomplished by synthesis and proper modification of the initial borylation-allylation reaction products. Herein, we report the design of the numerous diverse building blocks, relying on the previously reported methods for the C-ring system modification (see chapter 1.3.4).

Furthermore, their application in the “pinacol” and “Diels-Alder” approach towards the taxane synthesis was planned to be widely investigated. This was to reveal some unexpected limitations to both described approaches with regards to the structure of the corresponding C-ring precursors.

2.1 Enantioselective Synthesis of Taxane C-Ring Precursors

2.1.1 First Generation of C-Ring Precursors

The first generation C-ring precursors reported in this thesis comprise direct derivatives of the literature known compound 254. Even though the latter has a vast of required structural features, in order to be used as a C-ring precursor, some important functional group transformations had to be performed. To help understanding the nature of the required operations, Figure 10 was converted into the simplified retrosynthetic scheme indicating the positioning of the retrosynthetic disconnections (RDs) (Scheme 56).

![Scheme 56](image)

Based on the thorough analysis of the earlier reported routes towards taxanes, which commenced with preassembled C-rings (C → ABC, AC → ABC approaches), the corresponding retrosynthetic disconnections were proposed (RD1–RD4) (Scheme 56). Thus, the initial cyclization product 254 had to be modified in a way that complies with the retrosynthetic approach presented in Scheme 56. For this purpose, some synthetic goals were established:
a) placing orthogonal reactive sites at C10, C9, C2 or C14/C1 suitable for further creating the respective C-C bonds; b) establishing a sustainable protecting group pattern for the functionalities not involved in C-C bond formation reactions; c) maintaining the native absolute stereochemistry at C3 and C8 position; d) developing a rapid, high-yielding accesses to the targeted C-ring precursor; e) implementing a multi-gram scale synthesis of the C-ring intermediates while keeping the overall material cost low.

The synthetic efforts began with reproducing the literature known synthesis of the valuable intermediate 254 (Scheme 55). For this purpose, a set of starting compounds (diene 253 and 4-oxapentanal) was prepared in deca-gram scale according to the literature reported procedures. Due to high price and poor availability, the TADDOL-based chiral ligand 250, required for the enantioselective 1,2-diboration, was also produced in multi-gram scale. A perfect reproducibility of the reported procedures allowed us to access ligand 250 in high quantity within a short period of time. With all prerequisite compounds in hand, the enantioselective synthesis of 254 was reproduced delivering the targeted carbocycle in yields varying from 54% to 78% (9:1 d.r. at C1 position).

*all reactions were performed on 5–8 g scale; ** starting diene 253 was recovered

Since our initial goal was to broadly investigate the possible synthetic routes towards the variety of the C-ring precursors starting from diol 254, logically, the deca-gram scale optimization of the above mentioned chemical step was required. The main upscaling limitation was the amount of catalyst/ligand required for the sufficient 1,2-diboration. The high price of the catalyst/ligand couple strongly restrained the possibility of the proportional upscaling. It was reported to use
3 mol% of Pt(dba)_3 and 3.5 mol% of ligand 250 in a single batch to provide the highest yield and enantiomeric excess.\textsuperscript{153} In practice, proportional usage of the catalyst/ligand couple in the deca-gram batch would result in large amounts of reagents (\~{} 1.0 g of Pt(dba)_3 and \~{} 1.2 g of ligand 250). Due to the described economic reasons, a screening for the conditions optimized for the large scale reaction was initiated (Table 1). It was found that prolonging the reaction time along with slightly increasing the reaction temperature compared to the reported 60 °C positively impacted the yield of the reaction when reduced amounts of catalyst and chiral ligand were used (Table 1, entries 3,4). The most significant improvement was observed when the concentration of the corresponding reaction mixture was changed to 2 M (in toluene) allowing to perform a catalytic reaction with only 0.5 mol% of Pt(dba)_3 and 0.6 mol% of ligand 250 (Table 1, entry 5,6). Further reducing of the catalyst/ligand amount resulted in a negative impact on the overall yield (Table 1, entry 7). Thus, the optimal conditions for the multi-gram scale synthesis of diol 254 were discovered providing readily available large quantities of the important intermediate.

Unfortunately, isolation of the single diastereomer of diol 254 through flash column chromatography was not possible. In order to obtain the desired single isomer of compound 254, the latter was treated with TBAF affording an easily separable mixture of the isomeric diols 255 and 256 (Scheme 57).\textsuperscript{154}

![Scheme 57. Synthesis of diastereomerically pure triol 255.\textsuperscript{154}](image)

With intermediate 255 in hand, we proceeded with its modification in order to install the necessary reactive sites. Since the molecule 255 bears three free alcohol functionalities, we had to apply an elegant protecting group strategy to be able to perform site-selective modifications. Fortunately, all three alcohols significantly differ in reactivity, which allowed us to differentiate them by protecting with orthogonal protecting groups.

In order to pursue this goal, the primary and secondary alcohol of triol 255 were capped with acetyl groups. In the following step, the most sterically hindered tertiary alcohol was protected as a MOM-ether, followed by alkaline work-up, which smoothly removed the capped acetyl groups yielding diol 257 in 82% yield over two steps (Scheme 58).
Differentiation of the two alcohol functionalities in diol 257 did not cause any problems, since the primary alcohol could be selectively oxidized to the corresponding β-hydroxy aldehyde 258 with PIDA/TEMPO. With this achieved, the first taxane C-ring precursor 258 bearing a reactive site at C9 as well as its TES protected derivative 259 were synthesized.

It is noteworthy that for the majority of the naturally occurring taxane natural products, the stereochemistry at C7 is opposite to the one present in the above depicted C-ring precursors 258 and 259. Strategically speaking, when applying the selected C-rings in the total synthesis of taxanes, additional steps for adjusting the C7 native stereochemistry would be required at a later stage. Since at this stage of our research, the starting material 255 was readily accessible in large quantities, we decided to attempt inverting the stereocenter at C7. The presence of the adjacent quaternary center at C8 drastically limited our options of strategy choice. After extensive analysis of the literature known precedents for the stereocenter inversion on similar substances, we chose an oxidation/reduction strategy (Scheme 59).

The main precondition for choosing this strategy was the suitable presence of the masked hydroxy functionality in the β-position to the C7 stereocenter. Thus, the Evans-Saksena reduction protocol could be applied to deliver the right stereochemistry. In its essence, this reduction method exhibits a diastereoselective reduction of β-hydroxy ketones to the corresponding anti-diols employing tetramethylammonium triacetoxyborohydride (Me₄NHB(OAc))₃ as a mild reducing agent. When applying the described methodology onto our system, the synthesis of the diastereoselective reduction precursor 262 became a primary goal as the β-hydroxy functionality is essential for the overall reduction process (Scheme 60).
In the first step of the reduction process, the acetate group from the reducing agent is substituted by the free hydroxy group delivering boronate derivative 264a. In the second step, the intramolecular hydride delivered from the boronate species forces the reduction to proceed strictly from the chelating face resulting in diol 264.\[^{[156]}\]

Unfortunately, the proposed synthetic strategy employing the Evans-Saksena reduction protocol did not deliver the desired inverted diol 264 (Scheme 60). Instead, as a result of the TBDPS-deprotection reaction, ketone 263 was obtained. Presumably, a retro-aldol reaction took place as soon as the free alcohol/alcoholate was formed at the β-position to the ketone functionality, as depicted in Scheme 60.

We also attempted to produce the corresponding β-hydroxy ketone 265 bearing the free tertiary alcohol at C4 and submit the latter to the before mentioned Evans-Saksena reduction protocol (Scheme 61). For this purpose, we tried to convert the previously synthesized intermediate 260 into the desired reduction precursor 265. An extensive screening for the suitable TBDPS deprotection agent gave no positive result, since all attempted reactions led to the complete decomposition of the starting ketone 260.

In parallel, we screened for more “classical” reduction protocols which were applied to compound 261. As a result, over ten different reduction protocols were tested affording exclusively the undesired epimer at C7. Even though in the case of Evans-Saksena reduction the
bicyclic transition state 264a (see Scheme 60) could not be adopted due to the sterical overload, we hoped that the smaller and more reactive reducing agents might be directed by the β-oxygen containing group and deliver the targeted C7 epimer 264. Despite the negative result of the above described screening process, we stayed on track of the proposed oxidation/reduction strategy (see Scheme 59).

From the previously obtained results, we concluded that the reduction of the corresponding ketone functionality must occur way faster than the coordination of the reducing agent and therefore leading to an undesired product explained by the axial hydride attack. In fact, we assumed that the coordination of the reducing agent could be stalled by the high sterical overload on the shielded face of the molecule (Figure 11). After analyzing earlier obtained results, we have come to the conclusion that: a) the MOM-ether group at C4 position might prevent the system from adopting the necessary conformation 264a; b) the reduction of the ketone proceeds prior to the reducing agent coordination; c) without prior coordination, an equatorial approach of the reducing agent is shielded hence hardly possible.

At last, to perform the diastereoselective ketone reduction, we have come to another approach representing the manner of stereoinduction similar to the Evans-Saksena method. In terms of the new route, dicarbonyl 266 was prepared and subsequently subjected to various reduction conditions (Scheme 62). We anticipated that in case of the following reaction the reduction of the aldehyde would occur first, leading to intermediate 267. This intermediate would have the reducing agent covalently attached to the β-oxy group. This in turn would induce the subsequent intramolecular reduction of the neighboring ketone to proceed in the desired diastereoselective fashion. The main difference to the Evans-Saksena reduction protocol is that more reactive and less stereo demanding reducing agents could be used. These agents would be attached to the β-oxy functionality during the reduction process, therefore ensuring the formation of the prerequisite transition state 267 (see Scheme 62).
The ketoaldehyde 266, obtained by PCC oxidation of the triol 255, showed rather moderate stability in solution and complete instability upon concentration. In order to be able to characterize the valuable reduction precursor 266, we treated a sample of dicarbonyl 266 (solution in DCM) with MOMCl/DIPEA in the presence of catalytic amount of DMAP. The resulting dicarbonyl 269 showed great stability. The reason for the instability of precursor 266 remained unclear. Nevertheless, the requirement for minor purification and solvent change prior the reduction step encouraged us to develop a special procedure for the oxidation step work-up. This comprised a fast filtration of the reaction mixture through a short plug of silica followed by low-temperature concentration under vacuum. After dissolving the residue in dry THF, the resulting solution of ketoaldehyde 266 could be stored in the fridge for several days.

Table 2. Screening for the suitable reduction conditions towards 268.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RA, eq.</th>
<th>$T$, t</th>
<th>Solvent, conc.</th>
<th>Yield*</th>
<th>d.r.**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH$_4$, 1 eq</td>
<td>0 °C, 15 min</td>
<td>THF, 0.1 M</td>
<td>12%</td>
<td>1:3</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH$_4$, 1 eq</td>
<td>-20 °C, 1 h</td>
<td>THF, 0.1 M</td>
<td>5%</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$, 0.5 eq</td>
<td>0 °C, 1 h</td>
<td>THF, 0.05 M</td>
<td>18%</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH$_4$, 0.5 eq</td>
<td>22 °C, 5 min</td>
<td>THF, 0.05 M</td>
<td>20%</td>
<td>1:9</td>
</tr>
<tr>
<td>5</td>
<td>NaBH$_4$, 1 eq</td>
<td>0 °C, 1 h</td>
<td>THF/MeOH, 0.05 M</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>NaBH$_4$, 1 eq</td>
<td>23 °C, 15 min</td>
<td>THF/MeOH, 0.05 M</td>
<td>23%</td>
<td>8:1</td>
</tr>
<tr>
<td>7</td>
<td>NaBH$_4$, 0.5 eq</td>
<td>23 °C, 15 min</td>
<td>THF/MeOH, 0.05 M</td>
<td>19%</td>
<td>13:1</td>
</tr>
</tbody>
</table>

*over two steps; RA = reducing agent; ** for 268:255.

With a stock solution of precursor 266 in hand, we proceeded with screening for suitable reduction conditions following the above described idea (Scheme 62). To our delight, the conditions which provided the desired diastereoselectivity were found rather quickly (Table 2, entries 6, 7). Even though the yield over two steps (oxidation and reduction, Scheme 62) was low (~23%), the observed results marked a possibility for the synthesis of the taxane C-ring.
precursor with the native taxane stereochemistry at C7 by submitting triol 268 to the same sequence demonstrated in Scheme 58.

Having developed a ready access to the taxane C-ring precursors 258 and 259 (see Scheme 58), we further attempted to perform C1-elongation at the C9 position (aldehyde) in order to shift the reactive electrophilic site away from the quaternary center. This in turn would provide a shortcut to another class of C-ring precursors bearing the reactive center at C10 and therefore allowing the construction of the taxane core along RD1 (see Scheme 56).

A huge number of methods for one-carbon homologation-functionalization of aldehydes have been reported with the further advancement of preparative organic synthesis. In the course of this thesis, some selected methods were probed that would ensure the shifting of the reactive site to C10.

In order to install a soft electrophilic center at C10, the corresponding TES-protected aldehyde 259 was submitted to the Johnson–Corey–Chaykovsky reaction protocol yielding the desired epoxide 270 in an acceptable yield of 79% (Scheme 63).

![Scheme 63. Synthesis of the epoxide 270.](image)

Furthermore, we planned to install a hard electrophilic center at C10 providing variability in the future choice of coupling partners for the synthetic route towards taxanes. Since all the attempts of selective opening of the epoxide 270 to the corresponding aldehyde at C10 failed, we turned our attention to other homologation methods. In pursuing this goal, previously obtained aldehyde 258 was hydroxymethylated in accordance with the procedure developed by Tamao. In the course of this transformation, freshly prepared Grignard reagent 273 was stereoselectively added to aldehyde 258 affording the thermally unstable product 271 (Scheme 64). The latter was then submitted to the typical Tamao oxidation protocol converting the respective organosilicon compound 271 into the corresponding primary alcohol, which in our system equals to tetraol 272 (see Scheme 64).
We also tried to perform the same reaction sequence on C7-protected aldehydes. Unfortunately, when a protected hydroxy aldehyde was used, only formation of complex mixtures was observed. With compound 272 in hand, we attempted to differentiate the present free alcohol functionalities. All our efforts to selectively oxidize the primary alcohol at C10 led to either decomposition (complex mixture formation) or formation of the cyclic keto-lactone 274. Also, the other efforts to differentiate the three alcohols through full protection/selective deprotection strategy failed (Scheme 64). Even though we succeeded in installation of the C10 hydroxy functionality, further transformation of this center to the suitable hard electrophilic site did not give any positive result.

Starting from compound 255, a couple of taxane C-ring precursors bearing the reactive site at C2 position have been prepared. In accordance with the previously proposed retrosynthetic concept (see Scheme 56), the alkene moiety of triol 255 was converted into an aldehyde, providing an electrophilic center. It could serve as a reactive site for further synthetic operations towards the taxane structure along RD3.

The corresponding compounds 278 and 280 were obtained in a short reaction sequence from triol 255 comprising subsequent protection of the free alcohol groups with concomitant cleavage of the alkene to generate the desired aldehyde functionality (Scheme 65). In case of intermediate 279, direct cleavage of alkene 255 by means of ozonolysis resulted in a low-yield formation (15%) of the trihydroxy aldehyde 279. It is worth to notice, that the most efficient synthesis of the C2-electrophilic C-ring precursor was demonstrated on compound 280,
delivering the target molecule in the yield of 79% over three chemical steps starting from the literature known compound 255 (Scheme 65).

Scheme 65. Synthesis of taxane C-ring precursors 278, 279 and 280.

With the concise stereoselective syntheses of 278 and 280 developed, we attempted to extend the functional group patterns of the particular C-ring precursors by attachment of a vinyl group at the C2 position. By accomplishing that, we planned to enter the next valuable class of C-ring precursors having the C14 and C1 carbon atoms incorporated, with the main reactive site being fixed back at C9 position. The rapid access to the corresponding C-rings would create the possibility of the taxane core construction along the RD2/RD4 within the earlier described retrosynthetic proposal (see Scheme 56).

Scheme 66. Synthesis of taxane C-ring precursor 282.

Surprisingly, the reaction of aldehyde 280 with vinylmagnesium bromide resulted in diol 281 following a two-step process – addition of the Grignard reagent to the carbonyl group and selective opening of the cyclic silyl ether. Remarkably, the ring opening occurred regioselectively releasing the less sterically hindered primary alcohol (Scheme 66).
This kind of chemical behavior has already been described by Sammakia for diisopropylsilylenes derived from 1,3-diols in the presence of alkyl lithium reagents.\[^{[160]}\] To the best of our knowledge, the formation of alcohol \textit{281} marks the first precedent of the regioselective cyclic silyl ether opening by a Grignard reagent. However, the unexpectedly obtained diol \textit{281} was the undesired product. Since the differentiation between primary and secondary alcohols by subsequent installation of proper protecting groups would require additional synthetic steps, we tried to perform a selective oxidation of one of the two alcohols present in diol \textit{281}. After numerous unsuccessful attempts, we have discovered that treatment of diol \textit{281} with a huge excess of Dess-Martin periodinane in a diluted solution delivered the dicarbonyl \textit{282} smoothly in 78% yield (see Scheme 66). To our delight, compound \textit{282} bears the desired features of the advanced taxane C-ring precursor with the most reactive site at C9 position. In addition to that, the enone moiety provides the prerequisite C14 and C1 carbon atoms for assembling the taxane core in accordance with the RD4 concept. Moreover, the above described synthetic sequence comprises only five chemical steps from the literature known compound \textit{255} and gives rise to intermediate \textit{282} in 59% overall yield.

Despite the presence of the desired significant features in dicarbonyl \textit{282}, we anticipated chemoselectivity issues upon subjecting \textit{282} to the respective coupling reactions along the RD3. The origin of those issues could arise from the presence of two reactive (electrophilic) centers in the molecule at C9 (aldehyde moiety) and C14/C2 (enone moiety). In order to avoid this problem, we produced the analogous building block \textit{284} with electrophilic activity narrowed down to C9 position (Scheme 67).

Scheme 67. Synthesis of taxane C-ring precursor \textit{284}.

The reaction sequence towards aldehyde \textit{284} commenced by treating the previously obtained aldehyde \textit{278} with vinylmagnesium bromide, followed by protection of the resulting allylic alcohol as a pivaloyl ester and cleaving both TBS-ethers with an excess of TBAF. The resulting diol \textit{283} was then subjected to the selective oxidation protocol affording the desired β-hydroxy aldehyde \textit{284} in 23% yield over six chemical steps starting from the known compound \textit{255} (Scheme 67). With producing the building block \textit{284}, we prevented two possible synthetic issues which could appear if dicarbonyl \textit{282} is used in taxane total synthesis. Firstly, we avoided a
possible chemoselectivity clash between the C9 and C2 reactive sites. Secondly, we kept the C7 hydroxy group intentionally unprotected to reduce the potential sterical hindrance of the C9 electrophilic center. Additionally, the unprotected C7 hydroxy functionality could serve as a coordination site and therefore tuning the diastereoselectivity for the upcoming steps.

2.1.2 Second Generation of C-Ring Precursors

As it was discussed in the previous chapter, the synthesis of building blocks bearing a reactive site at C10 position via elongation of the existing site at C9 position proved to be inefficient. Only epoxide 270 was obtained in acceptable yield (see Scheme 63). All attempts to install an aldehyde functionality at C10 position via deriving its precursors from the earlier synthesized C-ring intermediates failed.

Nevertheless, in order to pursue our goal of synthesizing the suitable C-ring precursor for the RD1 approach (see Scheme 56), we decided to incorporate the desired C10 atom prior to the bisborylation/allylation sequence. That implies an elongation of the side chain in the starting diene by one carbon atom (Scheme 68). Furthermore, having an oxygen-containing functionality pre-installed at the C10 position (and at C9 if possible) is essential for rapid access to the reactive site.

![Scheme 68. New approach towards C-ring precursors bearing a functional group at C10.](image)

At first, the respective dienes 285 and 286 were synthesized. The unprotected diene precursor 291 was accessed in a short literature known sequence (see Scheme 69). Followed by TBDPS-protection of the obtained alcohol 291, the corresponding diene 285 was delivered in 56% yield over three steps.
In contrast to compound 285, diene 286 is not literature known. After extensive analysis of the published studies on the scalable synthesis of 1,2-diols, we have developed an efficient route towards the double TBDPS-protected 1,2-diol 286 comprising only three chemical steps starting from literature known aldehyde 292 (Scheme 70).

Employing the previously tested sequence for the Tamao hydroxymethylation protocol,[159] the readily accessible aldehyde 292 was treated with the Grignard reagent 273 followed by Tamao oxidation to yield the desired 1,2-diol 293 in excellent yield of 85%. In the final step, the protection of both alcohol functionalities as TBDPS-ethers was performed giving diene 286 in 79% over the whole sequence.

With both starting dienes in hand, we attempted to synthesize the corresponding C-ring precursors 287 and 288. Whereas submitting diene 285 to the modified bisborylation/tandem allylation protocol delivered the targeted molecule 287 in up to 67% yield, no conversion of starting material was observed when diene 286 was used (Scheme 71).
Despite the only partial success in synthesis of the targeted building blocks, with diol 287 in hand, we continued pursuing our goal of producing the C-ring precursor bearing the reactive site at C10 position.

For this purpose, diol 287 was treated with excess of MOMCl yielding the double MOM-protected product. In the following steps, the TBDPS-ether was cleaved and the resulting primary alcohol was oxidized delivering the taxane C-ring precursor 293 which bears the hard electrophilic center (aldehyde) at C10 position (Scheme 72).

The above described reaction sequence proved to be highly efficient providing an overall yield of 79% starting from cyclic product 287. Having an efficient route towards this class of C-ring precursors developed, we turned our focus to the synthesis of other C-rings which could be derived from the valuable intermediate 287.

By ozonizing the previously obtained double MOM-protected product 294, aldehyde 295 was produced in 96% yield representing an important C-ring intermediate with a reactive site placed at the C2 position, which is suitable for construction of the taxane core along RD3 (see Scheme 56). Reduction of the latter gave a rise to alcohol 296, which in turn was converted to another C-ring precursor 297 in a short three-step sequence (Scheme 73).
Compound 297 was of the highest importance to us in terms of further synthesis of taxane natural products. When considering the structure of precursor 297, it is necessary to point out the presence of the electrophilic site at C10 position along with the “masked” reactive site at C2 (pivaloyl protected primary alcohol). Strategically speaking, such arrangement of two reactive sites allowed us further planning of the synthesis along RD2 with subsequent RD3 connection strategy (see Scheme 56). Actually, building block 297 holds the potential to be used as the common precursor in both previously discussed approaches – namely the “Diels-Alder” and “pinacol” approach (see chapters 1.3.2 and 1.3.3, respectively).

At last, aldehyde 295 was treated with vinylmagnesium bromide resulting in alcohol 298, which was further converted into compound 299 providing a rapid entry to another class of C-ring precursors bearing the reactive site at C10 with having both C14 and C1 carbon atoms already incorporated (see Scheme 73).

![Scheme 74. Synthesis of C-ring precursors 302, 303, 304 and 307.](image)

In terms of further derivatization of the corresponding C-ring fragments, we planned to eliminate the hydroxy functionality at the C4 position in order to install an unsaturated fragment at this part of the molecule. The presence of an unsaturation unit at C4 is essential for later functionalizations of the taxane core (e.g. C–H oxidation, dihydroxylation, photocyclization) and required for the completion of the natural product total synthesis. Therefore, performing this
type of transformation at an early stage of the C-ring synthesis would enhance the convergency of the respective total synthesis.

Initially, diol 287 was selectively protected with pivaloyl chloride at the secondary alcohol yielding the desired pivaloyl-ester 300 in a low yield of 35%. Alternatively, protection of the secondary alcohol as a benzyl ether delivered the protected diol 301 in 66% yield. Having the mono-protected diol 301 in hand, we proceeded towards our initial goal to eliminate the tertiary alcohol at C4 position. For this purpose, compound 301 was firstly ozonized delivering aldehyde 303 in 51% yield along with the undesired benzoate 302 (18%). In the following step, aldehyde 303 was subjected to the Burgess elimination protocol which provided rather poor exo/endo elimination selectivity. The elimination product 304 was further reduced with NaBH₄ to give alcohol 305. The compound 305 was further protected as pivaloyl ester followed by TBDPS-deprotection which resulted in primary alcohol 306. At last, alcohol 306 with oxidized with the aid of PIDA and TEMPO. This sequence delivered another C-ring precursor 307 as a mixture of two isomeric compounds (exo/endo 2:1). In overall, four different readily available C-rings (302, 303, 304 and 307) were synthesized in the course of the described low-yielding sequence (see Scheme 74).

An interesting result was observed when protection of aldehyde 303 as a cyclic thioacetal was attempted. Submitting compound 303 to the typical thioacetal protection protocol resulted in formation of dithiane 308 resulting from an one-pot three-step process – dithiane formation, TBDPS-deprotection and C4 alcohol elimination. The unexpectedly obtained alcohol 308 was further oxidized to deliver C-ring precursor 309. Remarkably, the synthesized C-ring 309 bears the reactive electrophilic site at C10 along with the “masked” nucleophilic center at C2. To the best of our knowledge, the synthesis of such C-ring precursor has not yet been reported (Scheme 75).

In order to render the previously discussed reaction sequence more efficient (see Scheme 74), we decided to slightly change the protecting group installation strategy en route to the desired C-ring building blocks. Starting with TBDPS-deprotection of compound 287, we obtained triol
310, which structurally resembles intermediate 255. Inspired by earlier success of implementing a cyclic silyl ether as a protecting group for 1,3-diols, we protected the respective triol 310 as a cyclic silyl ether to afford bicycle 311 in excellent yield (see Scheme 76). In the following step, compound 311 was ozonized delivering the aldehyde 312 in 74% yield. Analogously to the previous sequence, the tertiary alcohol at C4 position was eliminated upon treatment of 312 with Burgess reagent, surprisingly giving a separable mixture of enone 313 and a pair of aldehydes 314 (exo/endo 9:1). By reduction of 314 with NaBH₄, the alcohols 315 were obtained.

As successful regioselective cyclic silyl ether ring opening by the Grignard reagent has been previously observed (see Scheme 66), we attempted to convert the Piv-protected alcohol 316 into the corresponding alcohol 317. Unfortunately, even under harsh conditions (refluxing in THF with an excess of vinylmagnesium bromide), no conversion was observed. However, selective cleavage of the silyl ether at the primary position with TBAF resulted in the formation of diol 318 in a yield of 89%. Further extensive oxidation efforts towards the C-ring precursor 319 gave no positive result. With this result in hand, no further attempts of accessing 319-like C-ring precursor were made.

Scheme 76. Synthesis of the C-rings 312 and 314, and synthetic efforts towards precursor 319.
Thorough examination of the isolated taxane structures revealed that some of them do not bear a functionality at the C7 position. Since all of the above discussed building blocks were synthesized via bisborylation/allylation sequence and thus bear the hydroxy functional group at C7, our next goal was to perform an early stage defunctionalization at this particular position. In our opinion, developing a high-yielding early-stage C7 defunctionalization method applied to the initial cyclization products (254 or 287) would provide the most rapid entry to a variety of C7-defunctionalized C-ring precursors, which were thought to be produced in the same manner as their C7-hydroxy analogues.

In pursuing this goal, cyclic compound 320 was obtained in the course of the Barton-McCombie deoxygenation reaction,[163] At first, compound 287 was converted into the corresponding phenyl thionoformate, which was then heated in the presence of AIBN and an excess of nBu3SnH to deliver the C7-defunctionalized derivative 320. Further synthesis of the corresponding C-ring precursor 321 following the already established procedure was completed by MSc Yulia Krivolapova (PhD student, AG Gaich) providing an entry to the class of principally novel C-ring intermediates (Scheme 77).

![Scheme 77: Synthesis of the C7-defunctionalized C-ring precursor 321.](image)

In summary, a small library of readily available C-ring precursors (19 examples) bearing reactive sites at either C10, C9 or C2 positions was produced. A divergent approach to the synthesis of the reported building blocks was demonstrated utilizing intermediates 254 and 287 as common precursors. These compounds in turn were produced in the course of a single step bisborylation/allylation reaction from the simple and readily accessible starting dienes 253 and 285. It is worth to mention that the described C-ring precursors were designed strictly in compliance with the proposed retrosynthetic approach towards taxane natural products allowing further construction of the taxane scaffold along the RD1–RD4 connectivity sites (see Scheme 56). Moreover, the logically arranged positioning of the respective reactive sites makes the selected C-ring intermediates ideally suitable for their further employment in the “Diels-Alder” or “pinacol” synthetic strategy on the route to the advance taxane natural products.
2.1.3 C-Ring Precursors with Advanced Side Chain

Based on the successful C10 atom incorporation prior to the borylation/allylation sequence (see Scheme 71), installation of advanced side chains was attempted in the same manner. Especially the introduction of a dienyl moiety (marked with blue in Scheme 78) appeared to be interesting as this would provide an access to the advanced C-ring building block 323 which could be readily transformed into the valuable IMDA precursor 322 in a four-step reaction sequence. In terms of the “Diels-Alder” synthetic strategy towards taxanes, a short linear reaction sequence delivering the advanced C-ring intermediate 323 would provide a significant shortcut to the desired DA precursor 322 (Scheme 78). Moreover, we assumed that installation of the dienyl moiety at an early stage of the synthesis could help to avoid a number of earlier reported synthetic problems observed on similar systems (see chapter 1.3.2).

In accordance with the proposed retrosynthetic analysis which leads back to the linear intermediate 324, we put our efforts on producing the advanced C-ring intermediate 323. In order to do so, the starting diene 324 had to be prepared in significant quantity. To the best of our knowledge, no syntheses of compound 324 or related derivatives have been reported to this date.

Extensive analysis of the available literature concerning the synthesis of dienyl structures resulted in proposing two approaches towards the synthesis of compound 324, both starting
from literature known aldehyde 327 (Scheme 79). Following the retrosynthetic proposal, compound 324 was to be derived from the corresponding vinyl iodide 325, which in turn could either be prepared by iododesilylation of the vinyl silane 326 (1st pathway) or via applying the Negishi carboalumination protocol to the corresponding alkyne 328 (2nd pathway).

In terms of the first pathway, aldehyde 327, prepared via literature known procedure,\textsuperscript{[164]} was subjected to the LA-catalyzed Sakurai reaction protocol using freshly prepared allyl silane 331 and SnCl\textsubscript{4} as a strong Lewis acid (Scheme 80). Allyl silane 331 was prepared in accordance to literature reported procedures in a two-step reaction sequence.\textsuperscript{[165]} In the following step, the Sakurai reaction protocol was applied delivering alcohol 326 in a low yield of 25%. The main side product of the described reaction was an 1,4-addition product, since aldehyde 327 represents an enone system. Using other Lewis acids proved to give the 1,4-addition product as the major product.

Nevertheless, with compound 326 in hand, we performed an iododesilylation reaction to give the vinyl iodide 332 in 51% yield. Unfortunately, extensive 2D NMR analysis of the obtained iodide 332 revealed an undesired cis relative stereochemistry at the newly formed vinyl iodide fragment. Thus, with respect to the proposed retrosynthetic approach (see Scheme 79), utilization of vinyl iodide 332 was irrelevant to our purposes.

In contrast to the first pathway, the second approach towards vinyl iodide 325 relied on a stereospecific carboalumination/iodination sequence. The predictable trans stereospecificity originates from reported mechanistic studies on zirconium-catalyzed carboalumination of alkynes.\textsuperscript{[166]} The following synthetic route commences with the same aldehyde 327 which is treated with Grignard reagent, freshly prepared from bromide 337, followed by TMS-cleavage with TBAF to give the 1,2-addition product 333 in excellent yield over three steps.\textsuperscript{[167]}

\textit{Scheme 80.} Preparation of vinyl iodide 332.
Next, the Negishi carboalumination conditions were applied to alkyne 333 followed by quenching of the organoaluminum intermediate with iodine to deliver vinyl iodide 325.[168] In the following step, the iodide was subjected to the typical Stille coupling reaction protocol employing tributyl(vinyl)tin as a coupling partner to afford an alcohol, which was subsequently protected as TBDPS-ether resulting in the desired diene 324. The described sequence could be reproduced repeatedly delivering diene 324 in large quantities and good overall yield (Scheme 81). Next, we tried to employ the obtained diene 324 as a starting material in the course of the bisborylation/allylation sequence to get an access to the desired C-ring 335. Submitting diene 324 to the above discussed cyclization reaction conditions showed full conversion of the starting material. However, no desired cyclic structure 335 was observed after treating the reaction mixture with 4-oxopentanal. Since the bisborylation/allylation was reported to be a one pot multi-step process, we figured that the reaction stopped after the enantioselective bisborylation step (initial step). The previous statement was proven experimentally by isolating the corresponding diol 336 derived from the bisborylated diene 334. We concluded that under the typical reaction conditions, the second step – tandem allylation of the dicarbonyl – does not proceed in the reported course (Scheme 82).

Further attempts to set the right reaction conditions for the tandem allylation step by variating the temperature protocol, concentration or amount of the corresponding dicarbonyl gave no result.
2.2 “Diels-Alder Approach” towards Taxanes

With having a number of suitably decorated taxane C-ring intermediates synthesized, we moved on to testing their application in one of the aforementioned known strategies of taxane natural product synthesis. Herein, we report our synthetic efforts towards the construction of the taxane core structure via type II IMDA reaction.

2.2.1 Synthesis of the IMDA Precursor

Structurally speaking, the IMDA reaction precursor is a C-ring intermediate with properly incorporated diene and dienophile moieties as side chains. Consequentially, we planned to synthesize the DA precursor by modifying the previously produced C-ring precursors.

The overall retrosynthetic analysis of the desired IMDA precursor 339 is summarized as depicted in *Scheme 83* below.

*Scheme 83*. Retrosynthetic analysis of the DA precursor 339.

In accordance with the proposed retrosynthetic analysis, the DA precursor 339 is to be derived from either the first generation C-ring precursor 340 by attaching dienyl 341 to the C9 reactive site followed by modification of the C2 position (1st generation retrosynthetic approach), or from the respective second generation C-ring intermediate 342 by incorporation of diene 343 at the C10 position followed by modification of the C2 position (2nd generation retrosynthetic approach).
approach). Depending on the chemical structure of the selected starting C-ring intermediate, the C2 position either had to be decorated with the vinyl rest with subsequent oxidation or, in case of the C-rings with previously incorporated C14 and C1 atoms, properly oxidized to yield the targeted DA precursor. In the following chapter, we report our synthetic efforts towards the construction of compound 339.

In order to attach the corresponding diene fragment 341 to the building block 340, hence creating a C10–C9 bond, we planned to perform a metal-mediated allylation of aldehyde 340 with an organometallic species 343, which should be generated from halide 341. By its nature, dienyl halide 341 resembles an allyl (prenyl) halide bearing an additional vinyl substituent at the β-position. Thus, we anticipated the newly formed dienyl metallic species 343 to exhibit similar reactivity towards carbonyls as numerous reported allyl metallic compounds before.

![Scheme 84](image)

_Scheme 84._ Anticipated reactivity courses of organometallic species 343 towards aldehydes.

Based on the available reports on metal-mediated allylations of carbonyls, we have concluded that the generated organometallic species 343 could take one of the two possible reaction pathways (Scheme 84). In the vast majority of the reported cases, the metal-mediated allylation of carbonyl compounds with allylic halides occurs regioselectively at the γ-position (through path I).\textsuperscript{169} Furthermore, the most common metal-mediated allylations involving allylmagnesium and allyllithium species are often very difficult to handle due to high instability and tendency of isomerization. The metal-mediated Barbier type allylation reaction provides an alternative to overcome the stability and isomerization problems. Under typical Barbier allylation conditions metals, such as indium, zinc, and tin, are commonly used.\textsuperscript{170} It was also shown that the corresponding organometallic species 343 (M = In, Zn or Sn) are stable at ambient temperatures and can be generated in environmentally benign solvents such as water or ethanol. The main limitation of this type of allylation is the undesired γ-regioselectivity thereby providing exclusively 344-like products.
Logically, in order to access the desired DA precursor 339, the corresponding allylation of aldehyde 340 must proceed via path II to afford the α-adduct 345 as a major product (Scheme 84). To the best of our knowledge, there are only a few metal-mediated allylation methods that have been reported to deliver a high α-regioselectivity. The known published methods involve usage of a combination of AlCl₃ and the respective allyl stannane reagent,[171] allyl barium compounds[172-173] or the corresponding organocerium species.[174] Furthermore, a number of cases utilizing indium-mediated allylations to deliver 345-like α-adducts were reported in the past decades.[175-176] Also, there are described cases of indium-mediated allylation applied to systems similar to 343. Considering the ready availability, relative stability, low toxicity and the presence of the reported precedents, our choice of metal for generating the organometallic species 343 was put on indium.

Extensive studies on In-mediated Barbier type allylation reactions by Loh and Cheng showed the pathway preferences (depicted in Scheme 84) to be strongly dependent on the solvent polarity.[176-177] The greatest α-regioselectivity was demonstrated when the corresponding allylation reaction was carried out in water or a 1:1 DCM/water mixture. Also, for the majority of the performed experiments, a significantly prolonged reaction time was required (up to 72 h). The temperature protocol varied from room temperature to reflux, depending on the starting aldehyde reactivity.[178]

Having the important procedural information gathered, we proceeded towards our synthetic goal – introduction of the dienyl moiety to one of the first generation C-ring precursors. According to the literature known procedures,[179-180] the respective dienyl halides 347 and 348 were produced from the synthetically available alcohol 346. With the respective halides in hand, the formation of the corresponding dienylindium compounds 349 and 350 was carried out by subjecting them to the literature reported reaction protocol utilizing indium powder and sodium iodide in a 1:1 DCM/water solvent mixture. Full conversion of the starting dienyl halides was observed within 3 to 5 h. In order to test the reactivity of the generated dienyl metallic species 349 and 350, the yellowish reaction suspension was treated with commercially available acetaldehyde to yield a mixture of addition products 351 and 352 (5:1 ratio in favor of α-adduct 351, see Scheme 85).
Scheme 85. Generation and reactivity of the dienylindium compounds 349 and 350.

Despite the relatively low yield (49%) of the allylation reaction that was observed for the test reaction (Scheme 85), the great regioselectivity favoring the α-adduct convinced us to move forward with the same reaction conditions and start our synthetic efforts towards the introduction of the desired dienyl fragment to the C9 reactive site of the selected C-ring precursors.

For this purpose, 1 M solutions of the C-ring intermediates 258, 259, 282 and 284 in DCM were prepared and subsequently added to vigorously stirred suspensions of the freshly generated organoindium compounds 349 or 350 at room temperature (23 °C) with concomitant stepwise increasing of the reaction temperature. The summarized results of the performed experimental screening are shown in Table 3.

Table 3. Synthetic efforts towards intermediates 353-356.

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>Reagent</th>
<th>T, t</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>258</td>
<td>349 or 350</td>
<td>23 °C, 18 h</td>
<td>NR, SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>258</td>
<td>349 or 350</td>
<td>reflux, 18 h</td>
<td>NR, SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>259</td>
<td>349 or 350</td>
<td>23 °C, 18 h</td>
<td>NR, SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>259</td>
<td>349 or 350</td>
<td>reflux, 5 h</td>
<td>TES-ether cleavage, no further reaction</td>
</tr>
<tr>
<td>5</td>
<td>282</td>
<td>349</td>
<td>23 °C, 18 h</td>
<td>NR, SM recovered</td>
</tr>
<tr>
<td>6</td>
<td>282</td>
<td>350</td>
<td>23 °C, 18 h</td>
<td>traces of 355, SM recovered</td>
</tr>
<tr>
<td>7</td>
<td>282</td>
<td>350</td>
<td>reflux, 18 h</td>
<td>full decomposition</td>
</tr>
<tr>
<td>8</td>
<td>282</td>
<td>349</td>
<td>reflux, 14 h</td>
<td>traces of MOM-cleaved product, no further conversion</td>
</tr>
</tbody>
</table>
To our disappointment, none of the screened reaction protocols resulted in the formation of the desired products 353–356 (see Table 3). In some particular cases (entry 6, 11) trace amounts (<5%) of 355 could be observed. Based on those results, we assumed that the aldehyde moiety at C9 position (present in the screened starting building blocks) exhibits rather low reactivity towards the respective organoindium compounds 349 and 350 due to its significant sterical hindrance caused by an α-quaternary carbon center. Moreover, the nucleophilic activity of the generated organometallic compounds was not sufficient enough to overcome the sterical effects of the respective carbonyl substrates. A similar problem was reported earlier by Loh and co-workers[178] thereby postulating a low efficiency of the In-mediated allylations when applied to the sterically demanding substrates.

![Scheme 86. Synthesis of dithiane 358.](image)

Alternatively, we searched for another synthetic equivalent of organometallic species 343. In pursuing this goal, dithiane derivative 358 was prepared from alcohol 346 in a two-step reaction sequence. The latter was then deprotonated by nBuLi to deliver the nucleophilic surrogate 359 (Scheme 86).

![Table 4. Synthetic efforts towards 360–363.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>Additive</th>
<th>C, T, t</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>258</td>
<td>-</td>
<td>1 M, −78 to 0 °C, 1 h</td>
<td>NR, SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>258</td>
<td>HMPA</td>
<td>1 M, −78 °C, 3 h</td>
<td>360 (17%), γ-adduct (20%)</td>
</tr>
<tr>
<td>3</td>
<td>258</td>
<td>HMPA</td>
<td>2 M, −78 °C, 3 h</td>
<td>360 (21%), γ-adduct (44%)</td>
</tr>
<tr>
<td>4</td>
<td>258</td>
<td>DMPU</td>
<td>2 M, −78 to 0 °C, 3 h</td>
<td>NR, SM recovered</td>
</tr>
</tbody>
</table>
A freshly prepared solution of 359 (stable at −40 °C) in dry THF was treated with a solution of the respective aldehyde (258, 259, 282 or 284) in dry THF/Et₂O. A variety of reaction conditions using different additives, concentration or temperature protocols were screened. The summarized experimental results are shown in Table 4.

Based on the obtained experimental results, we concluded that the electrophilic reactivity of the carbonyl (aldehyde) group towards nucleophile 359 is strongly limited, presumably due to the high sterical hindrance of the reaction site. Only in some particular cases when stoichiometric amounts of HMPA were added prior to the addition of aldehyde (Table 4, entry 2, 3, 6), insignificant quantities of the desired product 360 were isolated along with its undesired isomeric γ-adducts. Also, in cases when reaction products could be identified and the isolated yield could be calculated (Table 4, entry 2, 3, 5, 6), we observed a predominant formation of the undesired γ-adducts as major products over the desired α-adducts.

We planned to avoid the above mentioned reactivity and regioselectivity problems when proceeding in accordance with the 2nd generation retrosynthetic approach (see Scheme 83). Since the corresponding 2nd generation C-ring building blocks 342 bear the reactive site at C10 position, we anticipated no sterical influence on the carbonyl reactivity from the rest of the molecule. Furthermore, utilizing the bromodiene 364 (vinyl bromide analog) instead of the dienyl halide 341 (allyl halide analog) should resolve the α/γ-regioselectivity issue naturally occurring when the metal-mediated allylation protocol is employed.

Conversion of diene 364 to the corresponding organolithium compound 365 by metal-halogen exchange (Scheme 87) followed by its addition to a preassembled C-ring has been reported to be an useful synthetic tool for the one-step introduction of the diene moiety during the synthesis of taxane derivatives via IMDA reaction.[103, 109, 181] However, in most of the reported cases the reaction is majorly complicated by the emergence of side products arising from the metallo-allenyl species 366. It was also reported that the product ratio of dienyl/allenyl derivatives (368/367) randomly depends on many factors such as solvent, concentration, structure of the
aldehyde substrate and metal additives. Despite the extensive studies made on that matter, the reaction outcome regarding the diene/allene product ratio remains poorly predictable.

Scheme 87. Formation and dienyl/allenyl equilibrium of the metallo diene 365.

Addition of anhydrous CeCl₃ to the freshly formed organolithium 365 prior to aldehyde addition was reported to minimize the formation of the corresponding allenyl alcohol 367. Being aware of the possible regioselectivity issue, we started our condition screening efforts with regards to the previously synthesized C-ring precursors 293, 297 and 299. It is worth mentioning that the respective bromodiene 364 was prepared in large scale according to a literature known two-step procedure. Addition of organolithium 365 was in turn generated via metal-halogen exchange reaction from bromodiene 364 by treating its solution in dry THF with two equivalents of tBuLi at −78 °C. In order to proceed with the planned condition screening, 1 M solutions of 293, 297 and 299 in dry THF were prepared and subsequently added to the freshly generated organolithium 365. In terms of the screening process, additives, temperature protocols and duration of the addition reaction were varied. The resulting experimental data is summarized in Table 5.

Table 5. Synthetic efforts towards adducts 369 – 371.

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>Additive</th>
<th>T, t</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>293</td>
<td>-</td>
<td>−78 to 0 °C, 1 h</td>
<td>369 + allene (80%), 2:3</td>
</tr>
<tr>
<td>2</td>
<td>293</td>
<td>CeCl₃</td>
<td>−78 to 0 °C, 1 h</td>
<td>369 + allene (41%), 2:1</td>
</tr>
<tr>
<td>3</td>
<td>297</td>
<td>-</td>
<td>−78 to 0 °C, 3 h</td>
<td>370 + allene (10%), 1:1</td>
</tr>
<tr>
<td>4</td>
<td>297</td>
<td>-</td>
<td>−78 °C, 3 h</td>
<td>370 + allene (74%), 1:3</td>
</tr>
</tbody>
</table>
In contrast to the previously described indium-mediated allylations (see Table 4), the above described efforts (Table 5) delivered successful results. It was observed that addition of CeCl₃ tuned the reactivity of the organolithium towards the formation of the desired dienyl alcohols. Undoubtedly, the addition of CeCl₃ to the freshly formed organolithium compound resulted in formation of the organocerium species which in turn has a relatively low tendency towards the diene/allene equilibration depicted in Scheme 87. Since the obtained inseparable mixtures of dienyl/allenyl alcohols contained four different compounds (dienyl/allenyl alcohols and their diastereomers), full characterization of the initial addition products proved to be rather complicated and was in some cases fully omitted.

The best result was obtained when C-ring precursor with CeCl₃ as an additive was employed affording the targeted compound as an inseparable mixture of dienyl/allenyl alcohols in a ratio of 7:1 (Table 5, entry 5). The isolated mixture of four compounds was further treated with TESCl to give the mixture of two diastereomeric TES-protected dienyl alcohols, which could be easily separated from their allenyl isomers. Subsequently, the C2 position was modified by subsequent Piv-ester cleavage followed by oxidation of the resulting alcohol to an aldehyde, addition of vinylmagnesium bromide and oxidation of the newly formed allylic alcohol to give rise to the desired IMDA precursor (Scheme 88).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Additive</th>
<th>Temperature, Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>297</td>
<td>CeCl₃</td>
<td>−78 °C, 3 h</td>
<td>370 + allene (71%), 7:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>297</td>
<td>HMPA</td>
<td>−78 °C, 2 h</td>
<td>complex mixture</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>297</td>
<td>DMPU</td>
<td>−78 °C, 2 h</td>
<td>complex mixture</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>299</td>
<td>-</td>
<td>−78 °C, 2 h</td>
<td>allene (81%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>299</td>
<td>CeCl₃</td>
<td>−78 °C, 2 h</td>
<td>complex mixture</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>299</td>
<td>CeCl₃</td>
<td>−78 °C, 15 min</td>
<td>371 + allene (25%), 1:11</td>
<td></td>
</tr>
</tbody>
</table>

SM = starting material; *diene/allene ratio

Scheme 88. Synthesis of the DA precursor 375.
To our delight, the synthetic route towards 375 proved to be reproducible and easily scalable delivering significant quantities of the IMDA precursor required for further screening of the DA conditions. The overall synthetic sequence involves only seven steps and gives compound 375 in 37% overall yield starting from cyclization product 287.

The IMDA reaction precursor 375 was obtained as a mixture of two diastereomers of which separation was omitted intentionally. Since there were no reported cases of a successful IMDA reaction performed on a system similar to 375, we planned to submit the mixture of diastereomers to the DA reaction protocol to study a possible effect of the stereochemistry at the C10 position on the reaction outcome.

2.2.2 IMDA Reaction Efforts

Herein, we report our attempts to establish the ABC taxane core via IMDA reaction following the “C → ABC” synthetic approach. With the properly decorated DA precursor 375 in hand, we proceeded towards the construction of the classical taxane core via the “Diels-Alder approach” (see chapter 1.3.2). Based on earlier reported IMDA reaction procedures, we planned to test both thermally initiated and LA-catalyzed variants of the cycloaddition reaction. To carry out the thermally induced IMDA reaction we explored many conditions (Table 6).

Table 6. Thermal IMDA reaction condition screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzene (0.01 M), 80–90 °C, 18 h</td>
<td>NR, SM recovered (97%)</td>
</tr>
<tr>
<td>2</td>
<td>toluene (0.01 M), 140 °C, 8 h</td>
<td>NR, SM recovered (95%)</td>
</tr>
<tr>
<td>3</td>
<td>toluene (0.01 M), 140 °C, 3 d</td>
<td>NR, SM recovered (95%)</td>
</tr>
<tr>
<td>4</td>
<td>toluene (0.01 M), 180 °C, 22 h</td>
<td>377 (15%), 378 (18%), 380 (60%)</td>
</tr>
<tr>
<td>5</td>
<td>toluene (0.01 M), Proton Sponge® (30 mol%), 180 °C, 18 h</td>
<td>377 (10%), SM recovered (60%)</td>
</tr>
<tr>
<td>6</td>
<td>toluene (0.01 M), Proton Sponge® (1.1 eq), 180 °C, 18 h</td>
<td>NR, SM recovered (99%)</td>
</tr>
<tr>
<td>7</td>
<td>toluene (0.01 M), Proton Sponge® (1.1 eq), 180–190 °C, 4 d</td>
<td>NR, SM recovered (80%)</td>
</tr>
<tr>
<td>8</td>
<td>xylene (0.01 M), Proton Sponge® (1.1 eq), 220–230 °C, 14 h</td>
<td>NR, slow decomposition, SM recovered (25%)</td>
</tr>
</tbody>
</table>

SM = starting material; NR = no reaction
While no desired product 376 (or its C1 epimer) could be detected in any case, the side products 377, 378 and 379 (Table 6, entry 4, 5) were isolated in sufficient quantities for the characterization (Figure 12).

In general, the formation of the depicted side products 378 and 379 complies with the reactivity behavior previously reported for the DA precursors bearing oxygen-containing functionality at C10 position.\textsuperscript{[106]} Undoubtedly, the tricycle 378 is formed from 375 through a thermally induced and further TESOH-catalyzed 1,4-elimination followed by a type I IMDA reaction. Indeed, when the proton scavenger (Proton Sponge\textsuperscript{®}) was added, formation of 378 and 379 was no longer observed (Table 6, entries 5–8). Side product 377 exhibits a product of thermal MOM-ether degradation followed by an intramolecular cyclization. Interestingly, we also observed a formation of significant amounts of 380 (E/Z mixture) which derives from 375 via 1,2-elimination of TESOH.

Furthermore, Lewis acid catalysis of the IMDA reaction was examined. To our disappointment, the desired taxane core structure 376 was not observed. In some of the performed experiments we detected a formation of the same side products 377 and 379 depicted in Figure 12. Presumably, the 1,4-elimination product 379 could also be formed under LA-catalyzed reaction conditions. However, further conversion of 379 to the type I IMDA reaction product 378 was not observed (see Table 7).

In contrast to the thermal variant of the corresponding cycloaddition process, the LA-catalyzed reaction induced a rapid conversion of the starting material which led to the formation of extremely complex mixtures. We assume that the oxygenated C-ring fragment in combination with the oxygen-containing functionality at the C10 position made the synthesized cycloaddition precursor 375 extremely sensitive towards oxophilic Lewis acids. Moreover, the LA-labile MOM-ethers at C4 and C7 position could be easily cleaved during the reaction which would result in further complications of the reaction outcome.
Table 7. LA-catalyzed IMDA reaction condition screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM (0.01 M), BF₃·Et₂O (5 eq.), −78 °C, 30 min</td>
<td>377 (13%), 379 (traces) c.m.</td>
</tr>
<tr>
<td>2</td>
<td>DCM (0.01 M), BF₃·Et₂O (1.1 eq.), 0 °C, 5 min</td>
<td>377 (25%), c.m.</td>
</tr>
<tr>
<td>3</td>
<td>DCM (0.01 M), BF₃·Et₂O (1.1 eq.), 0 °C, 5 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>DCM (0.01 M), EtAlCl₂ (1.1 eq.), −78 to 0 °C, 5 min</td>
<td>379 (traces), c.m.</td>
</tr>
<tr>
<td>5</td>
<td>DCM (0.01 M), EtAlCl₂ (1.1 eq.), 0 °C, 5 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>DCM (0.01 M), Cu(OTf)₂ (1.1 eq.), 23 °C, 1 min</td>
<td>c.m.</td>
</tr>
<tr>
<td>7</td>
<td>DCM (0.01 M), Cu(OTf)₂ (1.1 eq.), 2,2'-Bipyridyl (2.4 eq.), 23 °C, 5 min</td>
<td>full conversion</td>
</tr>
<tr>
<td>8</td>
<td>DCM (0.01 M), ZnCl₂ (1.1 eq.), 23 °C, 5 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>DCM/py (0.01 M), ZnCl₂ (1.1 eq.), 23 °C, 18 h</td>
<td>NR, slow decomposition SM recovered (~50%)</td>
</tr>
<tr>
<td>10</td>
<td>DCM (0.01 M), TiCl₄ (2 eq.), −78 °C, 30 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>11</td>
<td>DCM (0.01 M), SnCl₄ (2 eq.), −78 °C, 30 min</td>
<td>377 (~5%), 378 (traces) c.m.</td>
</tr>
<tr>
<td>12</td>
<td>DCM (0.01 M), TMSOTf (1.1 eq.), −78 °C to −40 °C, 1 h</td>
<td>c.m.</td>
</tr>
</tbody>
</table>

*c.m. = complex mixture*

In conclusion, we could confirm that the reported and summarized limitations of the IMDA approach (see chapter 1.3.2) strongly restrict an application of the heavily oxygenated C-ring building blocks described in this thesis. Even though we developed a short and efficient route to the advance oxygenated DA precursor 375, we could not apply it further in the synthesis of the targeted taxane core.
2.3 “Pinacol Approach” towards Taxanes

As widely discussed in chapter 1.3.3, in the “pinacol approach” the targeted taxane core structure 381 is to be assembled via intramolecular pinacol coupling reaction applied to the dicarbonyl intermediate 382 (Scheme 89). Generally speaking, the overall synthetic strategy towards the final taxane core represents the “AC→ABC” approach, meaning assembling of the corresponding AC-fragment needs to happen beforehand. With regards to our main goal – demonstrating the applicability of the readily available C-ring precursors – we planned to access the desired AC-system (dicarbonyl intermediate 382) via coupling of the previously synthesized C-ring building block 384 with the corresponding achiral A-ring precursor 383.

![Scheme 89. Retrosynthetic analysis of taxane core 381.](image)

2.3.1 Synthesis of the Pinacol Coupling Precursors

The above mentioned A-ring intermediate 383 was prepared in large scale according to the literature known procedures.[122, 183] In the following step, the organolithium compound 385 was prepared through the lithium-iodine exchange reaction followed by treatment with the corresponding aldehyde 297 to deliver the coupling product 386 in 67% yield as a mixture of two inseparable diastereomers (d.r. 1:1.2). Next, we attempted to protect the newly formed secondary alcohol at C10 position as TES-ether. To our surprise, applying the standard protection conditions involving TESCl and imidazole gave no result. However, when TESOTf was employed, the desired TES-protected derivative 387 could be isolated in a low yield of 15%. We assumed that the high Lewis acidity of the TESOTf reagent could cause a number of side reactions such as elimination, MOM-ether cleavage, cationic rearrangements etc., thus leading to the increased amount of unidentified decomposed products. Furthermore, we managed to isolate one of the side products and confirm its structure. The isolated side product 388 indeed was a product of MOM-ether cleavage at the C7 position which then underwent intramolecular cyclization (Scheme 90).
Scheme 90. Initial attempts towards synthesis of 387.

To solve this problem, the lithium alcoholate 389, which was initially formed during the addition reaction, was treated with an excess of TESCl at \(-78 \, ^\circ\text{C}\) smoothly delivering the TES-protected derivative 387 in 78% yield. In the following step, the Piv-ester at the C2 position was removed and the resulting primary alcohol 390 was oxidized to the corresponding aldehyde using TPAP/NMO yielding compound 391 in excellent yield of 84% over two steps (Scheme 91).

Scheme 91. Synthesis of the pinacol coupling precursor 392.

Finally, the dithiane moiety was removed with the aid of HgCl\(_2\) according to the literature known procedure\(^{[122]}\) delivering the targeted compound 392 in a moderate yield of 49%.

Alternatively, we planned to synthesize another pinacol coupling precursor bearing a principally different substitution pattern at the C4 and C7 position. For this purpose, earlier synthesized C-ring intermediate 307 was coupled in a similar manner to the corresponding vinyl lithium 385.
Remarkably, the previously employed one-pot TES-protection protocol of the hydroxy functionality at the C10 position did not show any desired conversion. Instead, the unprotected coupling product 393 was isolated in 61% yield (d.r. 1:1.1) (Scheme 92).

\[
\begin{align*}
\text{Scheme 92.} & \text{ Synthesis of intermediate 394.} \\
\end{align*}
\]

The obtained intermediate 393 was further treated with TBSOTf and DIBAL-H at −78 °C to result in a separable mixture of the desired product 394 and diene 395. With sufficient amounts of 394 in hand, we attempted to remove the dithiane protecting group with the aid of HgCl₂. Surprisingly, we observed the formation of a complex mixture of compounds from which only one single product, the organomercury compound 396, could be isolated (Scheme 93).

\[
\begin{align*}
\text{Scheme 93.} & \text{ Formation of the organomercury species 396.} \\
\end{align*}
\]

Presumably, compound 396 was formed via Hg(II)-promoted intramolecular cyclization of the initially formed ketone 397 depicted in Scheme 93. We also tested a number of other dithiane
cleavage protocols including oxidative conditions\cite{184-185} which could deliver the desired pinacol coupling precursor in a single step. In addition to that, we also tried to employ a previously reported methylation protocol.\cite{186} Unfortunately, none of the above mentioned methods afforded the desired deprotected ketone 397 or the corresponding dicarbonyl intermediate. In case of the applied methylation protocols, no conversion of the starting material was observed. In contrast to that, the oxidative deprotection conditions rapidly gave a complex mixture of undefined products.

Nevertheless, with the synthetic route towards precursor 392 established, we were able to perform a deca-milligram scale synthesis of the precursor setting the stage for an extensive pinacol coupling screening process.

### 2.3.2 Pinacol Coupling Reaction

With rapid and scalable access to the key intermediate 392, the crucial pinacol coupling reaction of ketoaldehyde 392 (see Scheme 94) was studied under a variety of different reaction conditions. At first, literature known pinacol coupling procedures, which were earlier successfully employed in the taxane ring closure, were investigated (Table 8).\cite{83, 96, 121-123}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄ (30 eq), Zn (60 eq), THF (0.25 M), rt then pyridine (30 eq), rt then ketoaldehyde (over 2 h), rt</td>
<td>NR, SM recovered (95%)</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄ (30 eq), Zn (60 eq), THF (0.25 M), rt then pyridine (30 eq), rt then ketoaldehyde (over 3 h), 50 °C</td>
<td>NR, SM recovered (85%)</td>
</tr>
<tr>
<td>3</td>
<td>Sm (50 eq), CH₂I₂ (15 eq), THF (0.25 M), rt, 14 h then ketoaldehyde (over 5 min), rt</td>
<td>unidentified unpolar products</td>
</tr>
<tr>
<td>4</td>
<td>Sm (50 eq), CH₂I₂ (15 eq), THF (0.05 M), rt, 2 h then ketoaldehyde (over 2 h), −78 °C to rt</td>
<td>400 (80%), 399 (traces)</td>
</tr>
<tr>
<td>5</td>
<td>Sm (50 eq), CH₂I₂ (15 eq), THF (0.05 M), rt, 2 h then ketoaldehyde (over 2 h), 0 °C to rt</td>
<td>400 (64%), 399 (traces)</td>
</tr>
<tr>
<td>6</td>
<td>Sm (50 eq), CH₂I₂ (15 eq), THF (0.05 M), rt, 2 h then ketoaldehyde (over 2 h), 60 °C</td>
<td>400 (40%), 399 (traces)</td>
</tr>
</tbody>
</table>

NR = no reaction; SM = starting material
Unfortunately, none of the screened reaction conditions delivered the desired taxane core 399. Instead, the compound 400 as a result of selective aldehyde reduction was isolated in reasonable yields when ketoaldehyde 392 was treated with freshly generated SmI$_2$/Sm suspension in THF (Table 8, entries 4–6). Interestingly, the change of the temperature protocol during the ketoaldehyde addition process from −78 to 60 °C only resulted in a decrease of the isolated yield of alcohol 400. Furthermore, treating dicarbonyl 392 with a low-valent titanium system (TiCl$_4$, zinc dust and pyridine) did not affect the starting material in any way allowing us to recover the ketoaldehyde from the reaction mixture (Table 8, entry 1, 2). At last, the fast addition of the corresponding aldehyde to the freshly prepared SmI$_2$/Sm suspension in THF at room temperature resulted in a complex mixture of unidentified unpolar compounds (Table 8, entry 3). Since the reported reaction conditions gave no positive result, we launched an extensive screening process in order to determine the proper conditions for the synthesis of taxane 399. During the screening, a number of electron donor systems, untypical for the pinacol coupling reaction, such as VCl$_3$/Zn, Li/naphthalene/NiCl$_2$, CrCl$_2$/TMSCl and Mn/CrCl$_2$ were examined. To our disappointment, none of the screened conditions delivered tricycle 399. In most of the conducted experiments, compound 400 was isolated in significant amounts as the major product. Remarkably, the full reduction of the ketoaldehyde was never observed.

To explain the origin of the extraordinary selectivity for the aldehyde reduction over pinacol coupling, we proposed the following mechanism of the reaction depicted in Scheme 95. In our mechanistic considerations, we propose that the transition state 401 required for successful intramolecular pinacol coupling is in an equilibrium with the corresponding six-membered chelate 402 whereby the proposed equilibrium is strongly shifted towards intermediate 402. In the course of the reaction, the energetically more favorable system 402 undergoes the first single electron transfer (SET) generating a secondary radical which is incorporated into the six-membered chelate 403. At this point, the system could undergo an intramolecular radical cyclization to result in the desired tricycle 399. Instead, a second SET occurs yielding a stable anionic compound 404 which is transformed into the primary alcohol 392 upon aqueous reaction quench.
We assume that the radical intermediate \( 403 \) does not take a pathway of intramolecular cyclization due to sterical reasons. Presence of a quaternary center adjacent to the ketone combined with the fixed position of the secondary radical (due to chelation) restricts the system’s ability to adopt the configuration required for the cyclization in which the two reaction sites (ketone and alkyl radical) would be in sufficient proximity for the recombination.

Based on our investigation, we concluded that the presence of coordinating functional groups such as MOM-ether in the precursor structure \( 392 \) strongly influences the course of the attempted intramolecular pinacol coupling reaction. With regards to this, synthetic design of the building blocks required for the synthesis of taxanes via pinacol coupling has to be adjusted.
2.4 Boron-Mediated Formal CO Insertion

In the following chapter, we report our efforts towards developing a novel methodology for a formal carbon monoxide insertion into the carbon-boron bonds present in alkylboranes which are in turn derived from dienes. Hence, providing a rapid one-step access to the respective ketones. The main focus is put on the synthesis of the bridgehead ketones which exhibit a strained bicyclic system.

As it is reported in the literature, cyclic ketones can be obtained from organoboron compounds using toxic cyanides or carbon monoxide.\cite{187-190} These methods are inconvenient as a common synthetic tool in the laboratory due to the high toxicity of the required reagents. To the best of our knowledge, no boron-mediated CO insertion methodology using dimethoxycarbene (DMC) as a carbon monoxide surrogate has been reported yet.

\[\text{Scheme 96. Proposed mechanism for the formal CO insertion employing dimethoxycarbene 405 as a CO surrogate.}\]

In accordance with the proposed mechanism, we planned to exploit the electrophilic nature of alkylboranes 407 by reacting them with the aforementioned electron-rich, nucleophilic dimethoxycarbene 405 (Scheme 96). Thereby, a boronate complex 408 would be formed, that in turn would undergo several further rearrangements resulting in the boronate 411. Upon standard oxidation conditions,\cite{190} boronate 411 would be transformed into another ate-complex 412 that features a leaving group (OH-) in \(\alpha\)-position to the boron center. This would allow a 1,2-metallate rearrangement whereat one substituent migrates from the boron atom to the vicinal oxygen atom cleaving off the hydroxide as a leaving group.\cite{191} Subsequent attack of the hydroxide anion on boronate 413 would lead to the formation of the boronic acid derivative 414 and the targeted ketone 415. In the case when alkyl substituents \(R^1\) and \(R^2\) are tethered in the former organoboron compound 407, the respective cyclic ketones are obtained.
In conclusion, in order to obtain a ketone from an alkylborane, formation of the boronate complex 408 is compulsory. Subsequently, two alkyl groups (R1 and R2) with sufficient migration tendency are required to perform a 1,2-migration from the boron center of this boronate complex to the DMC vicinal carbon atom. However, the third alkyl rest (R3) should not migrate, otherwise a complex mixture of products will be obtained as the course of the reaction could take three different pathways. Meeting the mentioned prerequisite well 1,1,2-trimethylpropyl (theeryl), was previously used by Brown and co-workers as the third substituent for the carbonylation reaction of trialkyl boranes with carbon monoxide.[188]

Bis(alkoxy)carbenes such as dimethoxycarbene 405 are generally considered as an acetal of carbon monoxide. The carbene 405 can be prepared in situ via thermolysis of the oxadiazoline derivative 418 with release of N2 and acetone as the only side products (Scheme 97).[192]

\[
\begin{array}{c}
\text{418} \\
\xrightarrow{\Delta} \text{405} & \text{406} \\
\text{N}_2 & \text{acetone} \\
\text{416} & \text{417}
\end{array}
\]

Scheme 97. Generation of DMC and its properties compared to carbon monoxide.

The corresponding oxadiazoline 418 is relatively stable at ambient temperatures[192-193] and can be prepared in only two single steps. Rapid and scalable access to its precursor makes dimethoxycarbene (DMC) 405 a desirable non-toxic surrogate for carbon monoxide.

We aimed to investigate the reaction of oxadiazoline 418 with organoborons under practically feasible reaction conditions. Furthermore, it seemed worthwhile to explore the scope of the reaction in order to investigate its potential application to preparative organic synthesis.

The main objective of the described investigation was to develop a principally new synthetic approach towards the classical taxane core skeleton. This employs the suitably modified taxane C-ring precursor in a boron-mediated cyclization/CO insertion sequence accessing an extremely strained bicyclo[5.3.1]undecene ring system with a bridgehead ketone moiety at C15 position (taxane numbering, see Scheme 101 below).
2.4.1 The Scope of the Formal CO Insertion

In several known procedures,\textsuperscript{194-195} oxadiazoline reagents in the form of 420 were reported to be obtained via oxidative cyclization of the corresponding (methoxycarbonyl)hydrazine derivative 418 by treatment with (diacetoxyiodo)benzene (PIDA) 419 (Scheme 98).

\[ \text{NHS_2O} \xrightarrow{\text{OAc}} \text{O} \]
\[ R = \text{Me, p-MeO-phenyl} \]

\textbf{Scheme 98.} Synthesis of oxadiazoline reagents 420.

In terms of this thesis, we investigated the reaction of different organoboron compounds with \textit{in situ} generated dimethoxycarbene. Thereby, we examined a novel methodology for the formal CO insertion as a general method for the synthesis of ketones. A replacement of the highly toxic carbon monoxide was considered to be a major advantage of the investigated method over the previously reported methodologies.\textsuperscript{190, 196-197} Dimethoxycarbene 406, generated \textit{via} thermolysis of 420, served as a CO-surrogate, instead of e.g. toxic cyanides.\textsuperscript{189} Reaction with an organoboron substrate 407 followed by a common workup with alkaline hydrogen peroxide solution\textsuperscript{190} delivers ketone 415 (Scheme 99).

\[ \begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N}
\end{align*} \]
\[ R = \text{Me, p-MeO-phenyl} \]

\textbf{Scheme 99.} Novel formal CO insertion reaction accessing ketones 415.

Numerous organoboron compounds were prepared according to literature known procedures comprising hydroboration of the corresponding alkenes/dienes. Subsequently, the obtained substrates were screened in terms of the formal CO insertion reaction protocol. The variety of different organoboron species ranges from thexyldialkylboranes 421, 424, 426 to siamyldialkylborane 427, borinic esters 422, 423, 425, 428, 429 and borinic acid 430 (Figure 13).
Figure 13. Synthesized and examined variety of organoboron substrates.

Formation of the organoboron precursors was confirmed by $^{11}$B-NMR. For some selected substrates, it was possible to convert the trialkylboranes into the desired ketones and isolate the product. Dimethylphenoxy- and methoxyborinic esters 422 and 423 have been found to deliver the best results, giving the desired ketone 431 in yield up to 71% in a one-pot reaction (Scheme 100).

After the first successful runs of the reaction, various conditions were examined to improve the yield and suppress the formation of side products. This included different stoichiometries, reaction times as well as different reagents and consequently, varied temperatures. Also, different concentrations from 0.15 M to 1.82 M in aprotic unpolar solvent and even neat conditions were tested. Higher concentration up to 1.82 M turned out to be crucial for the formation of products. Neat conditions did not show any improvement compared to the 1.82 M solution. Usually, reactions with dimethoxycarbene generated in situ from oxadiazolines 420 are
carried out in refluxing toluene or benzene at 110 °C in a sealed tube.\textsuperscript{[193, 198]} Therefore, all reactions in the present work were performed in either toluene or benzene, both being aromatic, unpolar solvents. Interestingly, in the CO insertion reaction with carbon monoxide reported by Brown and co-workers uses more polar solvents, such as THF or diglyme.\textsuperscript{[197],[188]} Moreover, water was often required to afford the desired ketones.\textsuperscript{[190]}

However, for all other organoborons, the ketone could not be efficiently isolated from the crude material or no ketone formation was observed at all (in case of 421). In this respect, the scope of the new reaction is quite limited and a general methodology cannot be claimed available. Another obstacle on the way to its broad applicability is the formation of numerous side products during the formal CO insertion. This renders the identification and isolation of the desired ketones difficult. Ideal methods and conditions for the ketone purification still need to be explored. Characterization of the byproducts could help finding a suitable protocol for isolating the products from the crude reaction mixture.

2.4.1 Application of Boron-Mediated CO Insertion to the Synthesis of Taxanes

In parallel to our boron-mediated CO insertion methodology studies, we were planning to apply the aforementioned method to construct the highly strained bicyclo[5.3.1]undecene taxane ring system. Since one of the examined experiments showed a positive result providing a rapid access to the bridgehead carbonyl 431 (see Scheme 100), we proposed an alternative route towards the taxane-like structure 432. This commences with the readily available C-ring precursor 258. The targeted molecule 432 was to be obtained via boron-mediated CO insertion from the cyclic intermediate 433, ideally employing the earlier developed hydroboration/formal CO insertion method using oxadiazoline 420 as a source of dimethoxycarbene (Scheme 101).

\begin{center}
\textbf{Scheme 101.} Retrosynthetic analysis of the taxane-like intermediate 432.
\end{center}
The α-hydroxyallene **433** was intended to be obtained from cyclic alkyne **434** via submitting the latter to the literature known Cu–H promoted diastereoselective S$_{N}$2´ reduction protocol of propargyl oxiranes developed by Krause and co-workers.$^{[199]}$ The alkyne **434** in turn was planned to be synthesized via ring-closing metathesis (RCM) reaction from the monocyclic precursor **435**. Finally, the latter was planned to be synthesized from the preassembled C-ring precursor **258** via coupling with the corresponding organolithium reagent derived from the terminal alkyne **436** (Scheme 101).

At first, alkyne **436** was prepared. Relying on the literature reported procedures, the enantioenriched alcohol **439** was rapidly accessed.$^{[200]}$

The obtained epoxy alcohol **439** was further oxidized with TPAP/NMO to aldehyde **440**, which in turn was converted into the terminal alkyne **436** by treating the epoxy aldehyde with Ohira-Bestmann reagent (Scheme 102).$^{[201]}$ With having both building blocks in hand, the terminal alkyne **436** was deprotonated by LDA and subsequently added to the cooled premixed suspension of aldehyde **258** with an excess of anhydrous CeCl$_3$ to give the desired addition product **441** in excellent yield as a mixture of two inseparable diastereomers (d.r. 3:1) (Scheme 103). In the following step, the resulting diol **441** was capped with acetyl groups followed by treatment with TBAF yielding alcohol **442**. In order to obtain the RCM precursor **435**, alcohol **442** was firstly oxidized with the Dess-Martin periodinane to result in the corresponding aldehyde which was further submitted to various literature known olefination protocols. Surprisingly, the desired olefin **435** could only be isolated in minor amounts, whereas diene **444** was always detected as a major product of the respective olefination reaction (Scheme 103).
The best result was observed when the aldehyde intermediate was subjected to typical Wittig olefination conditions\(^{[202]}\) employing the inverse addition technique – slow addition of the prior generated methyl phosphonium ylide to a solution of the aldehyde at low temperatures. In this way, the desired alkene 435 was isolated in 14% yield. Due to the low yield, we could not carry on with the proposed synthetic route without a proper optimization of the olefination reaction or changing the whole approach towards the targeted RCM precursor 435. Furthermore, with launching a wide screening process we ran out of the valuable starting aldehyde before we could find optimized reaction conditions. As extensive searching for an acceptable solution did not deliver any positive result, the above described project was put on hold for an undetermined period of time.
3. Summary and Outlook

In the first part of this thesis, an efficient preparation of a small library of novel enantioenriched taxane C-ring precursors has been widely described. As far as the corresponding library of 19 individual compounds is concerned, the respective taxane C-ring building blocks were categorized into three groups (A–C) depending on their position of the reactive site (at C2, C9 or C10 position respectively). According to our retrosynthetic considerations, the reactive sites were properly incorporated into the precursors’ structure to make them applicable to the convergent synthetic strategies of the total synthesis of taxane natural products (C → ABC, AC → ABC approaches).

![Figure 14. Group A of building blocks bearing a reactive site at C2 position (marked with blue).](image)

Group A exhibits a number of building blocks bearing a reactive (electrophilic) site at the C2 position. Compounds 278 and 280 originate from the common cyclic precursor 254 and could be rapidly accessed in a four-step reaction sequence each, representing the first generation of C2-reactive C-ring precursors. Furthermore, intermediates 295, 303, 304 and 312–314 originate from precursor 287 and therefore represent the second generation of C2-reactive C-ring intermediates. Synthetic accessibility of those relies on the respective two- to four-step reaction sequences. Great overall yields along with repetitive reproducibility allowed us to obtain the above mentioned intermediates in significant quantities (scale up to 5 g) (Figure 14). Additionally, an orthogonal protecting group pattern creates a possibility for the selective functional group transformation. The last feature allowed us a subsequent site-selective modification of the C-ring precursors en route to polycyclic taxane-like structures.
Group B consists of five C-ring intermediates (258, 258, 269, 284 and 282) which bear a reactive site at the C9 position. Each of the above depicted (see Figure 15) building blocks was accessed through a short reaction sequence (three to eight chemical steps) in gram-scale. Furthermore, due to the elegant protecting group strategy, the same synthetic features as for group A compounds are available, allowing us a direct usage of the respective building blocks in the taxane total synthesis.

Group C comprises six C-ring precursors (270, 293, 297, 299, 307 and 309) bearing an electrophilic site at the C10 position (Figure 16). Compound 270, derived from aldehyde 259, represents the only example of a first generation C-ring intermediate with reactive center at the C10 position. In contrast, compounds 293, 297, 299, 307 and 309 of the second generation originate from their common precursor – cyclic intermediate 287. Each of these precursors was obtained in the course of a short reaction sequence (three to six chemical steps) in significant quantities (up to 500 mg). Having orthogonal protecting groups properly in place, the group C building blocks perfectly match features required for general synthetic applicability.

In conclusion, the library of densely functionalized taxane C-ring precursor featuring the native taxane stereochemistry was rapidly accessed starting from the common cyclic precursors 287 and 254. These precursors in turn were produced in large quantities relying on the
bisborylation/tandem allylation synthetic methodology starting from synthetically available starting materials. Due to their rapid accessibility, high reproducibility and great enantiomeric excess (>94%), the corresponding building blocks depicted in Figures 14–16 could be extensively examined as taxane C-ring scaffolds.

Subsequently, the possible application of the respective building blocks was broadly examined within the course of two synthetic strategies of our interest – the “Diels-Alder” (C → ABC) and the “pinacol” (AC→ABC) approach. As a matter of fact, compound 297 demonstrated its common applicability to both of the synthetic strategies allowing us to develop a short and efficient route towards the strategic key precursors 375 and 392 (Scheme 104). Although the construction of the targeted taxane tricyclic core was not achieved, the rapid accessibility of the key precursors 375 and 392 demonstrated a great potential of using the produced C-rings as starting points in various synthetic sequences besides the ones described in this work.

![Scheme 104](image)

Alternatively, boron-mediated formal CO insertion as a novel synthetic tool for constructing the taxane skeleton was investigated. Having some positive results obtained on simple systems, it was planned to apply the same methodology employing dimethoxycarbene as carbon monoxide surrogate in the course of the boron-mediated CO insertion. Some initial steps towards formation of the suitable CO insertion precursor have been achieved delivering the intermediate 443 in an unacceptably low yield (see chapter 2.4.1).

We strongly believe that applying the readily accessible C-ring precursors to the total synthesis of taxane natural products remains a promising research field. As shown in this work, usage of the properly preassembled C-ring intermediates provides a rapid access to the strategic key intermediates en route to the taxane core structures. Since those C-ring building blocks can be generally considered synthetically available compounds, their elegant employment to total synthesis can significantly simplify and improve an overall synthetic sequence. Moreover, easy preparation procedures provide a scaling-up opportunity, essential for multi-step synthetic sequences.
As we observed several application problems arising from the dense functionalization pattern, particularly at C4 and C7 position in the respective building blocks, when the compounds were subjected to the taxane core synthesis (see chapters 2.2.2 and 2.3.2), our future synthetic goal is to reduce the functionalization load of the corresponding C-ring precursors. Whereas their core synthesis would still rely on the successfully developed bisborylation/allylation methodology, further modification of the initial cyclic products must involve several defunctionalization events. Based on that idea, the synthesis of the respective defunctionalized C-ring precursor 321 (with C4-hydroxy eliminated and C7-hydroxy deoxygenated) has already been done by MSc Yuliia Krivolapova. Starting from that point, new attempts on synthesis of the desired taxane-like structures are currently being performed (Scheme 105). Moreover, an employment of the C7-defunctionalized C-ring precursors creates a further opportunity to enter the class of cyclotaxane natural products.

Scheme 105. A promising approach towards the classical taxane scaffold.

For more detailed information regarding the cyclotaxane chemistry and the chemical bridge between classical taxanes and complex cyclotaxane structures, see Schneider’s PhD dissertation on “The Total Synthesis of Canataxpropellane” published in 2021.
Part B. Enantiodivergent Synthesis of Cyclohepta[b]indole Derivatives
1.1 Cyclohepta[b]indole Motif in Alkaloids and Drugs

Alkaloids represent a large group of naturally occurring compounds with over 20,000 individual substances isolated to this date. Alkaloids are mostly isolated from plants, although there are plenty of reported examples of alkaloids found in other organisms such as fungi or marine microorganisms. Among the alkaloid family of natural products, the indole alkaloid group consists of more than 4,000 substances. It is no surprise that over the past decades, indole-containing molecules have sparked the interest of medicinal chemists. A large variety of crucial ligand-receptor interactions mediated by indole-containing subunits has been discovered and widely investigated in the last years, making the indole motif a “privileged motif” in medicinal chemistry. The cyclohepta[b]indole-based natural products comprise a large subgroup of the indole alkaloids. Biosynthetically they are mainly derived from the amino acid tryptophan. Interestingly, the vast majority of cyclohepta[b]indoles shows a wide spectrum of biological activities, such as the inhibition of the adipocyte fatty-acid binding protein (A-FABP), deacetylation of histones, inhibition of p53 production, antituberculosis and anti-HIV activities as well as anti-inflammatory effects. Furthermore, a remarkable number of non-natural cyclohepta[b]indole derivatives demonstrated various pharmaceutical activities therefore underlining the role of cyclohepta[b]indole as a motif of interest in indole-based drug development. The chemical structures referred to as cyclohepta[b]indoles exhibit a tricyclic scaffold in which an alicyclic seven-membered ring (partially or fully saturated) is fused to the indole moiety.

1.1.1 Biologically Relevant Cyclohepta[b]indole-Based Derivatives

In the past decades, several natural products bearing the cyclohepta[b]indole structure motif have been isolated and subsequently investigated. The selected natural products of this family – aristolasene (448) and aristolasol (449) – were isolated in 1988 by Husson and co-workers (see Figure 17). Although their chemical structure was easily elucidated by NMR techniques, no further biological investigations were conducted till nowadays. One of the most structurally complex cyclohepta[b]indole containing natural products – actinophyllic acid (447) – was isolated in 2005 by Carrol and co-workers. Due to its unique structural features and potential biological relevance, the molecule has immediately drawn high attention from several research groups, which further resulted in developing a number of successful total
Another two cyclohepta[b]indole natural products – exotine A (445) and exotine B (446) – were isolated recently in 2015 by Jiang and co-workers. Interestingly, the plant from which they were isolated – the jasmine tree *Murraya exotica* – is broadly used in traditional medicine and is reported to exhibit antimicrobial, antifungal and anti-inflammatory activities. It has also been shown that exotine A and B can act as inhibitors of the lipopolysaccharide-induced nitric oxide (NO) production in BV-2 microglial cells. Having an astonishing range of biological activities demonstrated, the exotines have rapidly become target molecules for several research groups including ours. Naturally, a few years after its isolation, the first total synthesis of (±)-exotine B was published by Cheng and co-workers in 2018.

![Figure 17. Selected cyclohepta[b]indole containing natural products.](image)

As mentioned before, cyclohepta[b]indole alkaloids can also be isolated from marine microbial sources. For example, the ambiguine family of natural products comprises 18 indole-containing compounds. More than ten of them are individual cyclohepta[b]indole derivatives which were isolated from cyanobacteria.

The monoterpenoid indole alkaloids isolated from plants of the genus *Ervatamia* represent another large family of cyclohepta[b]indole-based natural products (*Figure 18*). Like other indole-containing alkaloids, this group of natural compounds exhibits a broad range of biological activity and their natural sources are widely used in traditional medicine. Shortly after the isolation of the first member of this family by Knox and co-workers, the newly isolated alkaloid ervatamine (450) was found to demonstrate a cell membrane activity as sodium channel blocker. In the following years, a number of other representative *Ervatamia* alkaloids was isolated from different natural sources (*Figure 18*). Multiple biological assays confirmed the strong pharmacological relevance of these derivatives making them attractive synthetic targets.
As for non-natural cyclohepta[b]indole derivatives, a number of potent biologically relevant compounds have been synthesized over the past years (Figure 19). Naturally, the wide range of biological activities has encouraged medicinal chemists to search for more synthetically available non-natural cyclohepta[b]indole derivatives with comparable activity to the natural compounds. For example, compound 454 was found to be a potential antidepressant and showed a significant cytotoxicity (LD$_{50}$ = 85 mg/kg in mice).\cite{234} The derivative 455 in turn was shown to have a great affinity to the human androgen receptor (IC$_{50}$ = 0.92 μM).\cite{235} Another non-natural derivative 456 demonstrated great inhibition potency towards aurora kinases A (IC$_{50}$ = 4 nM) and kinases B (IC$_{50}$ = 5 nM). At last, the chlorinated cyclohepta[b]indole derivative 457 was shown to act as a potent SIRT1 (sirtuin 1, also known as NAD-dependent deacetylase sirtuin-1) inhibitor.\cite{236} The scalable enantioselective synthesis of the latter has been reported by Gaich and co-workers in 2013 (Figure 19).\cite{237}

Considering derivative 457, it is worth to mention that only its (S)-enantiomer exhibits an outstanding biological activity with an IC$_{50}$ value of 60–100 nM. A great difference in activity between two enantiomers can be explained by the influence of the only chiral element on ligand/receptor interactions, even though the indole part of the molecule is achiral.
1.2 Assembling of the Cyclohepta[b]indole Core

Due to their broad diversity and unique pharmacological relevance, highly functionalized and unsymmetrically substituted cyclohepta[b]indole derivatives have rapidly become a primary synthetic target to many research groups. Over the past two decades, numerous methodologies accessing the cyclohepta[b]indole scaffold have been developed. In terms of this chapter, only selected asymmetrical (enantioselective) methodologies are discussed. For a comprehensive overview on the cyclohepta[b]indole core construction methodologies see a review published by Gaich and co-workers\textsuperscript{[211]} and published doctoral dissertations by Stempel\textsuperscript{[238]} and Häfner\textsuperscript{[239]}

1.2.1 Enantioselective Approaches

The enantioselective synthesis of cyclohepta[b]indole derivatives is a relatively new field of research. The first enantioselective method featuring a combination of organo- and gold-catalysis was only published in 2011 by Enders and co-workers\textsuperscript{[240]} They reported a novel, efficient and highly enantioselective indole C2/C3-annulation method. Starting with the bifunctional ortho-alkyne-substituted nitrostyrene 458, the two follow-up Friedel-Crafts type reactions took place smoothly giving rise to the corresponding cyclohepta[b]indole derivatives 459. In the one-pot process, the alkene is activated by the corresponding chiral organocatalyst 460 through hydrogen bond formation, providing a valuable stereoselective induction for the first Friedel-Crafts reaction (Scheme 106).

![Scheme 106](image_url)

\textit{Scheme 106.} The first enantioselective synthesis of cyclohepta[b]indole derivatives.\textsuperscript{[240]}

Next, the gold-catalyzed second Friedel-Crafts/ring expansion cascade took place affording the desired tetracyclic products 459 as single enantiomers with e.e.>95\% (Scheme 106). Thus, the above described methodology provides a rapid access to the enantioenriched...
cyclohepta[b]indole derivatives in the course of a catalytic one-pot process.\cite{240} However, the mentioned protocol is strictly limited to the formation of benzocyclohepta[b]indoles. Moreover, the proper stereochemical outcome can only be provided when the reaction conditions are applied to the specific nitromethyl-containing aryls 458 due to the defined hydrogen-bonding nature of the chosen organocatalyst 460.\cite{240}

Another asymmetric organocatalytic synthesis of cyclohepta[b]indole derivatives was published by Hong and co-workers in 2013.\cite{241} In terms of the reported method, the respective aldehyde 462 was converted into the Schiff base with chiral L-proline derivative 465 followed by a nucleophilic 1,4-addition of the corresponding indolyalkyl malononitrile 461. Hereby, the nucleophilic attack occurred from the face determined by the chirality of the proline derivative 465 resulting in the Michael addition product 463 with up to 96% e.e. (Scheme 107).

![Scheme 107. Sequential organocatalytic Michael addition/double Friedel-Crafts alkylation approach.\cite{241}](image)

In the next step, the corresponding N-Bn-protected indole 466 was added to aldehyde 463 followed by Brønstedt-acid treatment. This induced a double Friedel-Crafts alkylation reaction delivering the desired enantioenriched cyclohepta[b]indole derivatives 464 in fair yields of approximately 60% and as a mixture of two diastereomers (ca. 70:30 syn/anti). In conclusion, the above described method provides a one-pot access to the enantioenriched densely substituted cyclohepta[b]indole derivatives 464 via sequential organocatalytic Michael addition/double Friedel-Crafts alkylation reaction (Scheme 107).\cite{241}

In the search for effective synthetic methods for the construction of cyclohepta[b]indole derivatives cycloadDITION reactions again proved to be a powerful tool for the construction of cyclic molecules. Moreover, being a concerted process which proceeds through a defined cyclic
transition state, cycloaddition reactions usually deliver a high degree of diastereoselectivity to the stereochemical outcome of the reaction. However, the situation completely changes when it comes to the enantioselective variant. In a majority of the reported cases, either a chiral substrate or a specific, often synthetically challenging chiral catalyst is required. The situation is becoming even more complex when it comes to less investigated cycloaddition processes such as [4+3] or [5+2] cycloadditions, which are required for the construction of seven-membered rings. Naturally, a number of research groups challenged themselves to develop a method for the synthesis of cyclohepta[b]indole derivatives, which relied on the cycloaddition process as a key transformation step.

In the past years, a significant amount of published syntheses offered an access to the cyclohepta[b]indole scaffold via (formal) cycloaddition processes. However, only a few of them could provide an enantioselective method which could be applied on the relatively broad spectrum of substrates.

One of such asymmetric cycloaddition methods was reported by Masson and co-workers in 2018. Their method relied on the chiral phosphoric acid catalyzed formal [4+3]-cycloaddition of 1,3-diene-1-carbamate with 3-indolylmethanol (Scheme 108). Based on the developed methodology, a small library of 6-aminotetrahydrocyclohepta[b]indoles was synthesized (21 examples, up to 83% yield, 83 to 99% e.e.).

![Scheme 108. Synthesis of enantioenriched 6-aminotetrahydrocyclohepta[b]indoles 470.](image)

The authors also performed a mechanistic study which confirmed that the cycloaddition process proceeds in a stepwise fashion.

Sun and co-workers reported a unified method for the synthesis of the dearomatized cyclohepta[b]indole derivatives 474 and 475 via rhodium-catalyzed enantioselective formal [4+3]-cycloaddition of vinylindoles 472/473 with various vinyldiazoacetates 471 (Scheme 109).
The authors proposed the formal [4+3]-cycloaddition process to proceed via asymmetric cyclopropanation with concomitant Cope rearrangement of the unstable divinylcyclopropane intermediates 476 and 477 analogously to the previously reported method by our group.\(^{237}\)

The application of the Cope-type [3,3]-rearrangement of the divinylcyclopropane derivatives, more commonly referred to as divinylcyclopropane rearrangement (DVCPR), to the synthesis of cyclohepta[b]indoles has been initially demonstrated by our research group in 2013.\(^{237}\) It was shown that an asymmetric synthesis of cyclohepta[b]indoles could be achieved in the course of a short reaction sequence. Starting with chiral cyclopropyl alcohol 477, obtained via asymmetric Charette cyclopropanation or via enantioselective carbenoid cyclopropanation using bis(oxazoline) ligands, followed by an oxidation/olefination sequence, the desired divinylcyclopropane derivative 478 was rapidly accessed (Scheme 110).

In the following step, the thermally induced rearrangement proceeded smoothly to deliver the dearomatized intermediate 479. Subsequent rearomatization under acidic conditions afforded
the respective cyclohepta[b]indole 480 (Scheme 110). In the above shown strategy, the synthesis relied on the aforementioned DVCPR, employing an indole moiety as 2π-unit. Being a particular case of Cope-type [3,3]-sigmatropic rearrangement, the DVCPR proceeds stereospecifically due to orbital symmetry considerations. Thus, in the course of the rearrangement, the chirality is smoothly transferred from the cyclopropane ring to the benzylic position (depicted in Scheme 110 with blue double headed arrows). In conclusion, the above described strategy suggests a fast access to a variety of enantioenriched cyclohepta[b]indoles starting from the synthetically accessible chiral cyclopropane derivatives 477, from which the chirality is being stereospecifically transferred to the corresponding rearrangement products. Based on the developed strategy, Gaich and co-workers completed an efficient, enantioselective, and gram-scale synthesis of SIRT1-inhibitor IV (457).

For a comprehensive overview of the application of the divinylcyclopropane-cycloheptadiene rearrangement in synthetic organic chemistry, its biosynthetic applications and its mechanistic considerations including transition state analysis see a review published by Gaich and co-workers in 2014. 

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1.3 The Pd-Catalyzed C(sp³)–H Activation

Over the last two decades, plenty of studies concerning metal-catalyzed C–H activation were published. Being an emerging field in organic synthesis, C(sp³)–H activation methods find their application in recently published total syntheses, methodologies and small molecule library preparation. In its essence, the C(sp³)–H activation process provides an unique access to the conversion of non-activated carbon-hydrogen bonds into carbon-carbon or carbon-heteroatom bonds. The aforementioned process exhibits a functionalization of the relatively inert C(sp³)–H bond and therefore requires a certain activation energy. It is known, that due to the relatively low bond dissociation enthalpies (97–101 kcal/mol), the functionalization of the C−H bonds at the sp³-hybridized carbon via homolytic bond cleavage is an easier process compared to the C−H bond cleavage at the sp²- and sp-hybridized carbons.\cite{252-253} However, for metal-catalyzed activations the strength of the carbon-metal bond should be taken into consideration as well.\cite{252-253} Moreover, considering the C(sp³)–H activation compared to the relatively well investigated C(sp²)–H activation, additional conformational freedom along the single σ-bond together with the lack of π-orbital interactions with the respective metal make the activation energy for this process significantly higher.\cite{254} In order to overcome the activation energy barrier, metal coordination groups which direct the metal atom towards the C−H bond and therefore circumvent the problems caused by the inertness of the C(sp³)–H have been discovered. Furthermore, the application of the various coordination groups allowed to strictly determine the site selectivity of the respective C−H activation reaction. In other words, the directing group (DG) binds to the metal center (catalyst) and selectively delivers it to a proximal C–H bond.\cite{255}

In the following chapter, the directing group-mediated Pd-catalyzed C(sp³)-H activation process is broadly discussed. The main focus is put on mechanistic aspects of the C(sp³)-H activation and the variability of the directing groups. However, due to irrelevance to this thesis, the application of Pd-catalyzed C(sp³)–H activation to the C–C bond formation in total syntheses is intentionally omitted.

1.3.1 The Directed Pd-Catalyzed C(sp³)–H Activation: Mechanism and Scope

Within the past years of the metal-catalyzed C(sp³)–H activation development, selective functionalization of a single C–H bond within a complex molecule has become a major synthetic challenge. As mentioned above, an employment of properly designed ligands (directing groups) helps to provide the desired selectivity and therefore makes the C−H activation reaction more predictable. Furthermore, reproducibility and high efficacy of the described functionalization method allowed to employ the C(sp³)–H activation reactions in various synthetic methodologies
and multi-step syntheses.\cite{256-257} Stoichiometric ligand-directed C–H activation reactions are often referred to as cyclometalation reactions due to the cyclic nature of the C–H insertion intermediate – the five-membered chelate complex (Scheme 111).\cite{258}

![Scheme 111. Ligand-directed cyclometalation process.\cite{258}](image)

A number of different transition metals such as Ru, Rh, Pt and Pd have been widely reported to participate in directed C–H activation reactions.\cite{258} However, the Pd-based catalysts are being used more frequently and thus are better investigated for several reasons. First, due to the compatibility of Pd(II) catalysts with oxidants and the ability of the cyclopalladated chelates to be selectively functionalized, the Pd-catalyzed C(sp\(^3\))–H activation can be used for the installation of carbon-heteroatom bonds. Secondly, a variety of directing groups can be used with Pd-based catalysts to readily promote C–H activation. At last, lots of Pd-catalyzed directed C–H functionalization reactions tolerate the presence of air and moisture providing a significant advantage over the other transition metal-based catalysts.\cite{255}

In 2005, Daugulis and co-workers reported a novel Pd-catalyzed arylation method which relied on the regioselective C–H activation method, marking the first application of the directed Pd-catalyzed C(sp\(^3\))–H activation to a preparative organic synthesis.\cite{259} The authors showed an efficient employment of pyridine-containing derivatives of carboxylic acids (8-aminoquinoline amides 481 or picolinamides 483) as directing groups (Scheme 112).

![Scheme 112. Daugulis’ pioneering work on directed Pd-catalyzed C(sp\(^3\))–H activation.\cite{259}](image)

When the 8-aminoquinoline auxiliary was employed, a highly regioselective catalytic β-arylation of carboxylic acids took place affording derivatives 482 in 60% to 92% yield. Additionally, a similar approach was applied for the arylation of amine derivatives 483. Interestingly, when
2-picolinic acid as an auxiliary was used, the C–H activation process resulted in formation of the γ-arylated amine derivatives 484 in up to 81% yield.

Besides the two mentioned coordination groups (8-aminoquinoline and 2-picolinamidine), a significant number of other directing groups have been broadly used in various C(sp³)–H functionalizations (Figure 20).[[260-269]]

![Figure 20. Typical directing groups for the C(sp³)–H functionalization.](image)

Since its discovery, the Pd-catalyzed C–H activation has been suggested to proceed through Pd(II)-Pd(IV) catalysis. However, the exact mechanism of the directed Pd-catalyzed C(sp³)–H cyclometalation remained undefined for several years. The evidential studies on Pd(IV) complexes by Canty[[270-271]] followed by experimental mechanistic studies by the Daugulis group[[272]] further supported a Pd(IV)-mediated mechanism for the directed C–H insertion. Finally, a number of computational studies[[273-275]] confirmed the previously suggested Pd(II)-Pd(IV) catalytic mechanism allowing to postulate the general mechanism for the Pd-catalyzed C–H arylation as depicted in Scheme 113.
Commencing with the initial coordination of the Pd(II)-species to the directing group (8-aminoquinoline) the catalytic cycle proceeds towards the five-membered cyclopalladated chelate. The latter is formed as a result of an agnostic interaction between the Pd(II)-species and the C-H bond at the γ-position (with respect to the coordination group), consequentially leading to weakening of the respective C-H bond and Pd(II) insertion. Next, the precomplexation of the respective aryl iodide is taking place by replacement of the weakly bound acetic acid followed by oxidative addition of the aryl iodide affording the Pd(IV)-species. In the next step, an octahedral Pd(IV) intermediate is formed by iodine-acetate ligand exchange setting stage for the reductive elimination followed by dissociation of the arylated product and catalyst regeneration. Remarkably, computational and experimental studies revealed the formation of Pd(II)-Ag(I) heterodimeric complexes, which could play a crucial role in stabilization of energetically disfavored intermediates throughout the catalytical circle.\[275\]
Over the last decade, directed Pd-catalyzed C(sp$^3$)–H activation reactions found their application in the total synthesis of complex natural products. As an unique synthetic tool for the selective C(sp$^3$)–H functionalization, the C(sp$^3$)–H activation was successfully employed in a number of completed total syntheses (Figure 21).[276-283]
2 Results and Discussion

Despite the great number of synthetic methodologies employed in the cyclohepta[b]indole core construction, only a few of them could provide access to the enantioenriched derivatives (see chapter 1.2.1). However, an enantioselective synthesis of cyclohepta[b]indoles is particularly essential when it comes to the preparation of the biologically relevant, natural product-like derivatives (see Figures 17-19).

One of the pioneering contributions in the field of enantioselective cyclohepta[b]indole synthesis was published by our research group in 2013. The reported methodology relied on a [3,3]-sigmatropic divinylcyclopropane/Cope-rearrangement applied to the properly preassembled chiral cyclopropane derivatives 477 (see chapter 1.2.1, Scheme 110). In the course of this previously published work, a highly efficient enantioselective synthesis of the SIRT1 inhibitor 457 was accomplished. In case of the disubstituted cyclopropanes 477, the chirality was introduced via Charette’s asymmetric cyclopropanation providing an acceptable enantiomeric excess of up to 89%.

For the construction of the trisubstituted chiral cyclopropanes 477, enantioselective carbenoid cyclopropanation using bis(oxazoline) ligands was employed providing a rather poor enantiomeric excess of 60%. An application of the respective cyclopropane derivatives to the aforementioned cyclohepta[b]indole construction methodology eventually enabled the total synthesis of a number of Ervatamia alkaloids reported by Dr. Erik Stempel in his PhD thesis. Even though an excellent diastereoselectivity was provided by the described method, the poor overall enantioselectivity (~60% e.e.) strongly limited the opportunities for further natural product syntheses.

2.1 General Methodology Strategy and Background

In this work, we aimed to develop a general methodology to access variously substituted, enantioenriched cyclohepta[b]indole derivatives employing the DVCPR as a key construction step (analogously to the previous studies reported by our group). Moreover, we envisioned to develop an enantiodivergent approach granting access to both enantiomeric cyclohepta[b]indoles from a common precursor. Counting on the highly specific chirality transfer during the sigmatropic rearrangement, we focused on developing a method for the highly enantioselective construction of an indol-containing trisubstituted cyclopropane. It was also intended to commence the synthetic route with maximally simplified and synthetically available
chiral disubstituted cyclopropane derivatives, overcoming the restrictions of intermolecular cyclopropanation mentioned in previous reports.\[237]\ The indole moiety is to be installed later by stereospecific, directed Pd-catalyzed C(sp\(^3\))–H arylation.

Retrosynthetically speaking, we planned to access both enantiomeric forms of the respective cyclohepta[b]indole derivative 485 via a short reaction sequence starting from the common precursor 487, which in turn must exhibit a “hidden” symmetry plane (Scheme 114).

\[ \text{Scheme 114. Enantiodivergent plan towards both enantiomeric forms of cyclohepta[b]indole 485.} \]**

The direct, stereospecific introduction of indole 488 to the chiral cyclopropane derivative 489 via Pd-catalyzed directing-group-mediated C(sp\(^3\))–H activation is considered to be the key step of our enantiodivergent approach (Scheme 114). It is noteworthy that previous studies on the related (cyclopropane-based) systems only described an introduction of iodobenzenes to the cyclopropane ring during the C–H activation process.\[^{265, 285-291}\] To the best of our knowledge, iodoindole 488 as well as its substituted analogues have not been previously investigated as coupling partners in this reaction. Following our retrosynthetic planning, the C–H activation product 487 is to be further transformed in the DVCPR with participation of the indole as the 2π-unit. It is worth mentioning that benzene rings do not participate in the DVCPR due to their high dearomatization energy barrier in contrast to the aforementioned indole.

Naturally, the C–H activation product derived from the cis-1,2-disubstituted cyclopropane derivative 489 possesses a fully cis-1,2,3-trisubstituted cyclopropane ring. The all-cis-relationship is a direct result of the reaction mechanism of the C–H activation process, in which the palladium is pre-coordinated to the substrate via the aminquinoline unit (NHQ) in intermediate 490 (accordingly to the postulated Pd-catalyzed C–H arylation mechanism, Scheme
As a consequence, the coupling of the heteroaromatic ring occurs from the same side of the cyclopropane ring (cis fashion).

Scheme 115. The origin of cis-selectivity in the respective C–H-activation process.

If the cyclopropane substrate already contains two cis-oriented substituents, the C–H activation will introduce the third substituent (the indole coupling partner 488) in cis manner to give the all-cis-1,2,3-cyclopropane product 487 (Scheme 115).

2.1.1 The Concept of “Hidden Symmetry” as a Tool for Enantiodivergency

When subjecting compound 487 to subsequent functional group transformations, indole-vinylcyclopropanes 486 are to be obtained, which would then undergo the DVCPR to afford, after rearomatization, the targeted cyclohepta[b]indoles 485. Importantly, both enantiomeric forms of 485 can be obtained selectively from a single optical antipode of the C–H activation product 487. For this to be accomplished, we established two parallel synthetic routes. The first route exhibits the transformation of the amide functionality to the olefin in cyclopropane 487, giving enantiomer (−)-486. This route is referred to as amide-to-olefin route. The second route exhibits the transformation of the protected alcohol fragment to the olefin resulting in enantiomer (+)-486 and therefore is referred to as alcohol-to-olefin route (Scheme 114). Employment of these two routes reveals a “hidden symmetry” based on the σ symmetry plane present in compound 487 (marked with green at the C–H arylation product 487 in Scheme 114). Based on the proposed parallel synthetic routes, we assumed that the hidden σ symmetry plane would act as an “enantiomeric switch” providing a useful tool for the enantiodivergent synthesis. Utilizing of this tool would allow us to spare the need to synthesize both enantiomeric forms of cyclopropane 487 and thus provide a substantial synthetic asset.
2.2 Enantiodivergent Synthesis of Cyclohepta[b]indoles

2.2.1 Preparation of the C(sp³)−H Activation Precursor 489

As noted before, we planned to commence our synthetic route towards cyclohepta[b]indoles with maximally simplified and, more importantly, easily accessible chiral cyclopropane derivative 489 in order to avoid the earlier reported cyclopropanation restrictions.

To our delight, the method for the stereoselective hydrolysis of synthetically available meso-cyclopropane-1,2-dicarboxylates with porcine liver esterase (PLE) developed by Tamm and co-workers[292] could provide us an easy access to the desired enantioenriched cyclopropane derivatives. The preparation of the suitable substrate for the enzymatic reaction involved only four chemical steps. At first, a mixture of cis- and trans-cyclopropyl-1,2-diesters was prepared via base-induced condensation of methyl chloroacetate 491 with methyl acrylate 492. In the next step, saponification with subsequent acidification afforded the corresponding diacid 493 as a mixture of cis/trans isomers. Treating the latter with acetic anhydride under equilibrating conditions resulted in formation of a cis-bicyclic anhydride.[293] This bicycle was subsequently opened with methanol under acidic conditions to provide the desired dimethyl cis-cyclopropyl-1,2-diester 494 setting the stage for the planned enzymatic saponification (Scheme 116).

\[ \text{Scheme 116. Multi-gram preparation of the chiral cyclopropane derivative 495.} \]

Finally, an enzymatic saponification protocol was performed strictly according to the literate reported procedure[292] yielding the enantioenriched acid 495 in 97% yield (Scheme 116).

Having a large quantity of enantiopure compound 495 in hand, we proceeded towards the synthesis of the precursor 489 required for the C-H activation. For this purpose, compound 495 was treated with BH₃·THF resulting in formation of alcohol 496. Next, the primary alcohol was protected with the respective protecting group and the resulting compounds were further converted into the cyclopropylamides 489a-e via treating the previously obtained esters 497a-e with deprotonated 8-aminoquinoline at −78 °C (Scheme 117).[294]
At this point, we were able to introduce a number of different protecting groups to the primary alcohol of the C-H activation precursor 489 setting the stage for the key coupling step. It is worth to mention, that during the preliminary conditions screening for the C–H activation, performed by MSc Paul Gamerdinger and Dr. Maximilian Häfner, suitable conditions were found as follows: cyclopropane precursor 489 (1.0 eq.), N-tosylated 3-iodoindole 488 (3.0 eq.), Pd(OAc)₂ (10 mol%), and Ag₂CO₃ (1.2 eq.) in anhydrous toluene (1 M solution) under inert gas atmosphere at 110 °C for 4–6 h. As a model substrate in their studies, MOM-protected compound 489 was employed showing moderate reaction yields of up to 54%.

In terms of this work, we further studied the variability of the protecting group of the C–H activation precursor 489 as we planned to improve the moderate reaction yields shown for the model MOM-protected substrate. For this purpose, compounds 489a-e with two orthogonal sets of typical O-protecting groups were synthesized. The first set comprises silyl protecting groups, which are typically very stable to a variety of reaction conditions. We also envisioned to investigate the influence of the relative size of the respective protecting group. Therefore, TMS-ether as small, TES-ether as medium, and TBDPS-ether as a large protecting group were incorporated into the precursor structure. As second set, the trityl-based protecting groups MMTr- and DMTr-ether were introduced as easier removable analogs of the trityl group. At this point, our main goal was to examine each of the mentioned protecting groups on the matter of their stability during the C–H activation, their influence on the yield and possible applicability for further functional group transformation in the course of the planned synthetic route towards cyclohepta[b]indoles 485.

Scheme 117. Synthesis of the C-H activation precursors 489a-e.
2.2.2 Preparation of 487 via the C(sp³)–H Activation

Having the C-H activation precursors 489a-e in hand, we subjected them to the previously optimized C-H arylation protocol in order to examine the influence of the various protecting groups on the overall reaction yield (Table 9).

Table 9. Preparation of cyclopropanes 487a-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG (substrate)</th>
<th>Yield (product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS (489a)</td>
<td>23% (487a)*</td>
</tr>
<tr>
<td>2</td>
<td>TES (489b)</td>
<td>38% (487b)*</td>
</tr>
<tr>
<td>3</td>
<td>TBDPS (489c)</td>
<td>67% (487c)*</td>
</tr>
<tr>
<td>4</td>
<td>TBDPS (489c)</td>
<td>47% (487c)**</td>
</tr>
<tr>
<td>5</td>
<td>MMTr (489d)</td>
<td>60% (487d)*</td>
</tr>
<tr>
<td>6</td>
<td>DMTr (489e)</td>
<td>62% (487e)*</td>
</tr>
</tbody>
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*Scale 1.0 mmol; **Scale 5.5 mmol.

Surprisingly, relatively low reaction yields (23–38%) were observed when substrates with TMS- and TES-ether were employed (Table 9, entry 1, 2). We assumed that the corresponding silyl protecting groups did not tolerate the respective C–H activation reaction conditions due to their poor stability. In contrast, when TBDPS-protected substrate 489c was used, a significantly increased reaction yield of 67% was observed (Table 9, entry 3). However, a multi-gram reaction attempt resulted in decrease of the reaction yield to 47% (Table 9, entry 4). At last, employment of the C–H activation precursors bearing trityl-based protecting groups 489d-e showed acceptable reaction yields of 60–62% (Table 9, entry 5, 6). Based on the obtained experimental results, we decided to proceed with our synthesis towards cyclohepta[b]indoles 485 employing the TBDPS-protected C–H activation product 487c as its preparation delivered the highest reaction yield.

2.2.3 Enantiodivergent Synthesis of Cyclohepta[b]indoles

With sufficient quantities of the C-H activation product 487c produced, we continued our synthetic efforts. In the following step, the directing group was removed via imide formation (Boc-protection) and subsequent reduction with an excess of LiBH₄ following the literature reported protocol[294] and affording the corresponding alcohol 490 in 88% yield over two steps (Scheme 118). The structure of the obtained mono-protected diol 490 exhibits an
enantioselectively desymmetrized trisubstituted cyclopropane moiety allowing us to further pursue the before described concept of “hidden symmetry”.

Scheme 118. Removal of the 8-aminoquinoline moiety to afford alcohol 490.

The optically enriched compound 490 was prepared in gram-scale and further converted to the respective (−)-cyclohepta[b]indole 485 in accordance with the previously proposed “amide-to-olefin” route (see Scheme 114). This was accomplished in the course of a five-step reaction sequence involving Ley–Griffith oxidation and subsequent Wittig olefination delivering precursor 491 which further underwent the DVCPR. To our delight, the rearrangement proceeded smoothly at 120 °C in toluene to yield the desired (−)-cyclohepta[b]indoline 492 quantitatively. Further TBDPS-deprotection with the aid of HF in pyridine and subsequent aromatization induced by pTsOH afforded the targeted (−)-cyclohepta[b]indole 485 (Scheme 119).


In accordance with our synthetic plan, we envisioned to obtain both enantiomeric forms of 485 by exploiting the “hidden symmetrical” nature of the compounds 487c/490 (see Scheme 114). In fact, by submitting the common precursor 490 to the proposed “alcohol-to-olefin” route with concomitant DVCPR and functional group transformation, the opposite enantiomer (+)-cyclohepta[b]indole 485 was readily accessed. At first, Piv-protection and subsequent TBDPS-deprotection resulted in alcohol 493, which was further converted into the respective olefin 494 in analogous manner. The following DVCPR at 110 °C afforded the
(+)-cyclohepta[b]indoline 495 in excellent yield. Finally, Piv-deprotection followed by induced by pTsOH aromatization yielded the desired enantiopure (+)-cyclohepta[b]indole 485 in 91% over three steps (Scheme 120).

As expected, the NMR spectra of both compounds (−)-485 and (+)-485 were identical. However, their optical rotation values were of opposite sign (with [α]_D^-12 and +12 respectively). In fact, this proved the postulated stereospecific mechanism of the DVCPR and the ability to obtain both enantiomers from a single precursor confirming the overall synthetic strategy as enantiodivergent.

2.2.4 Methodology Scope and Limitations

In order to demonstrate the broad utility of our synthetic methodology, we attempted to synthesize a number of enantioenriched cyclohepta[b]indoles bearing various substituents on the aliphatic seven-membered ring. In other words, we aimed to create a small library of compounds with general structure 498. For this purpose, different olefination protocols utilizing different reagents and reaction conditions were applied to the earlier produced in the course of amide-to-olefin sequence intermediate 496 (Table 10).

Table 10. Synthesis of substituted cyclohepta[b]indoles 498 via olefination/DVCPR sequence.
In order to obtain the corresponding divinylcyclopropane precursors 497, two different olefination protocols were employed. The first reaction protocol (protocol A) involved a Wittig olefination using various phosphonates as olefination reagents resulting in the formation of the respective DVCPR precursors 497a-c. These intermediates were further submitted to the optimized rearrangement conditions (at ~120 °C). Remarkably, whereas precursors 497b and 497c were smoothly converted into the cyclohepta[b]indoles 499 and 500 respectively (Table 10, entry 2, 3), olefin 497a did not undergo any conversion during the DVCPR even under significantly elevated temperatures (~220 °C) (Table 10, entry 1). The second protocol (protocol B) involved the olefination employing stabilized phosphonium ylides and therefore required elevated reaction temperatures (typically from 80 °C to 110 °C). In contrast to protocol A, the second procedure did not allow us to isolate the corresponding divinylcyclopropane precursors. Instead, the DVCPR products were readily formed under the olefination reaction conditions and were further converted into the corresponding cyclohepta[b]indoles 501 and 502 in an analogous manner (Table 10, entry 4, 6). Once again, we observed that the corresponding divinylcyclopropane intermediate 497d bearing a cis-methyl group in its structure did not undergo a rearrangement even when submitted to harsher reaction conditions (~220 °C) (Table 10, entry 5).

Naturally, the noticeable unreactivity of the olefins 497a and 497d under the DVCPR reaction conditions drew our attention, as it marks the first defined limitation of the above described synthetic methodology. The initial analysis of their chemical structure revealed a common feature – the presence of the cis-methyl group (as R1). To understand the nature of the cis-methyl substituent’s impact on the reactivity, we had to consider some DVCPR’s mechanistic aspects with regard to its transition state preferences.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefination cond.</th>
<th>R1</th>
<th>R2</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>protocol A (497a)</td>
<td>Me</td>
<td>H</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>protocol A (497b)</td>
<td>H</td>
<td>Vinyl</td>
<td>44% (499)</td>
</tr>
<tr>
<td>3</td>
<td>protocol A (497c)</td>
<td>H</td>
<td>Ph</td>
<td>66% (500)</td>
</tr>
<tr>
<td>4</td>
<td>protocol B</td>
<td>H</td>
<td>CO2Me</td>
<td>48% (501)</td>
</tr>
<tr>
<td>5</td>
<td>protocol B (497d)</td>
<td>Me</td>
<td>CO2Me</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>protocol B</td>
<td>H</td>
<td>Ac</td>
<td>58% (502)</td>
</tr>
<tr>
<td>7</td>
<td>protocol B</td>
<td>H</td>
<td>CN</td>
<td>21% (511)</td>
</tr>
</tbody>
</table>

*isolated yield over four steps.
It was reported, that unlike the Cope rearrangement which typically proceeds though the chair-like transition state, the DVCPR only proceeds via boat-like transition state $506c$ with both $2\pi$-units (vinyl moieties) being in endo-orientation with regard to the cyclopropane part \textit{(Scheme 121)}.$^{[251,295]}$ Even though the calculations revealed that the preferred orientation of the \textit{cis}-divinylcyclopropane $503$ is \textit{exo/exo} $504a$ \textit{(Scheme 121)}.\textsuperscript{[251]} The other possible transition states would hypothetically result in a cycloheptadiene (after DVCPR) with at least one $E$-configured double bond ($506a$-$b$), making the formation of the respective DVCPR-products strongly disfavored.

Projecting the reported mechanistic considerations on the corresponding substrates $497a$ and $497d$, we assumed that adopting the \textit{endo/endo} orientation $508$ required for the DVCPR is strongly disfavored due to the significant steric repulsion (marked in red) between the third substituent on the cyclopropane ring (-CH$_2$OTBDPS) and the respective \textit{cis}-methyl group \textit{(Scheme 122)}. 
Scheme 122. Rationalization of the unreactivity of the cis-substituted precursors 497a and 497d.

The rationalization of the unreactivity of the cis-substituted DVCPR-precursors, depicted in Scheme 122, is entirely based on the previously reported mechanistic considerations.\textsuperscript{[251]} Even though no further calculations were performed to confirm the above described suggestion, we assumed that the substitution pattern present in the core structure 510 with various combinations of $R^1$ and $R^2$ (except for $R^1 = H$) could not be accessed through the above described DVCPR-based synthetic methodology.

Additionally, the scope of the C–H activation was broadened by Dr. Maximilian Häfner. By applying the C–H activation protocol to the unsymmetrical cyclopropane precursors and varying the substitution pattern on the heteroaromatic coupling partner, a diversity of C–H activation products was obtained. Furthermore, by applying the two previously established synthetic routes – amide-to-olefin and alcohol-to-olefin, a number of DVCPR-precursors and further derived cyclohepta[b]indoles were synthesized. The combined synthetic efforts including the enantiodivergent synthesis, its further diversification as well as the aforementioned expanded scope of the C–H activation were published by our group in 2019.\textsuperscript{[296]}

For most of the synthetic applications, EWG-N-protected indole substrates are highly relevant since these derivatives demonstrate higher stability and tolerance to a plenty of reaction conditions. However, the vast majority of biologically active indole-based compounds (see Figures 17–19) do not bear any protecting group. Since only N-Ts-protected indoles were employed throughout the developed methodology, this creates the necessity to test the effective and selective late stage Ts-deprotection to yield the biologically more relevant $N$-H-indole derivatives.
To our delight, subjecting (–)-485 to the standard SET deprotection protocol\textsuperscript{[297–298]} smoothly resulted in selective Ts-deprotection leaving other functional groups untouched and delivering the cyclohepta[b]indole 512 in 85% yield as a thermally unstable, strongly fluorescent compound (Scheme 123).
3. Summary and Outlook

In this part of the thesis, a synthetic methodology exhibiting a general, enantiodivergent access to cyclohepta[b]indoles is broadly described. Relying on the Pd-catalyzed directing group-mediated cyclopropane C(sp\(^3\))\text{-}H activation, valuable synthetic precursors with the general structure 487 were obtained in good yields (up to 67%), large quantities and excellent enantioselectivity (Scheme 124).

Moreover, the specific mechanism of the directing group-mediated C(sp\(^3\))\text{-}H activation process which generally proceeds via cyclopalladated complex 490 allowed us to introduce the indole moiety in a \textit{cis}-fashion exclusively. This in turn provided an entry to the future enantiodivergent cyclohepta[b]indole synthesis through the “hidden symmetry”.

Further transformation of the initial C\text{-}H activation product 487 by submitting the latter to the previously established parallel synthetic routes eventually delivered both enantiomeric forms of the targeted cyclohepta[b]indole derivative 485. This in turn confirmed the efficacy of the enantiodivergent strategy whereby the “hidden symmetry” plane acts as an enantiomeric switch.
Further diversification of the methodology by varying the olefination reagents eventually led to the synthesis of a small library of diversely substituted cyclohepta[b]indoles (Figure 22).

Complementary studies by Dr. Maximilian Häfner on the application of unsymmetrically substituted C–H activation precursors and diversely substituted heteroaromatic coupling partners enabled to significantly expand the scope of the described methodology. Eventually, the combined synthetic methodology has been published as research article “Enantioselective Synthesis of Cyclohepta[b]indoles via Pd-Catalyzed Cyclopropane C(sp^3)−H Activation as a Key Step”.[296]

The practical application of this methodology to the total synthesis of Ervatamia alkaloids is currently underway in our research group (Scheme 126).

In conclusion, we have successfully applied the cyclopropane C–H activation to the synthesis of cyclohepta[b]indoles with high enantiomeric excess (>92%). The symmetry properties of the core cyclopropane system allowed product diversification with regard to the absolute stereochemistry starting from a single precursor. In addition, the stereoselective introduction of an additional substituent on the cyclohepta[b]indole (at C2 benzyl position) was accomplished.
Part C. Experimental Section
1 General Information

All sensitive reactions were carried out using standard inert gas Schlenk-techniques under an inert atmosphere of nitrogen/argon in oven-dried/flame-dried glassware, unless otherwise stated. Reactions were stirred using magnetic stirrers. The reaction completion was usually monitored by thin-layer chromatography (TLC), using silica gel coated aluminium plates impregnated with a fluorescent indicator (254 nm; Merck 60-F254). The used TLC plates were visualized by staining with basic potassium permanganate solution (KMnO₄), acidic ceric ammonium molybdate solution (CAM), acidic vanillin solution or acidic 2,4-dinitrophenylhydrazine solution followed by external heating if required. Molecular sieves with the pore diameter of 4 Å were used when needed. Flash column chromatography was carried out on silica gel (40-63 μm, 240-400 mesh, Merck). Solvents for the flash chromatography were freshly distilled prior to use. Triethylamine (NEt₃), diisopropylamine (DIPA) and diisopropylethylamine (DIPEA) were distilled under nitrogen from CaH prior to use. Extra dry solvents were purchased from Acros Organics, used as received and stored over molecular sieves (4 Å). Solvents (as well as some solutions) were transferred via syringe or stainless steel cannula through a rubber septum. The commercially available reagents were purchased from chemical suppliers (Sigma-Aldrich, Merck, Acros Organics, Alfa Aesar, TCI Europe, ABCR, Carbolution) and used as received unless otherwise stated. The experimental procedures for the self-prepared reagents can be found in section “3 Experimental Procedures”.

2 Analytical Methods

**Nuclear magnetic resonance (NMR):** measured on a Bruker Avance III 400, Avance III 600 or JEOL RESONANCE ECZ 400S. Chemical shifts are given in ppm and referenced to the solvent residual peaks (Chloroform-d1 ¹H δ = 7.26 ppm, ¹³C δ = 77.0 ppm; DMSO-d6 ¹H, δ = 2.50 ppm, ¹³C, δ = 39.5 ppm). Reports are presented in order: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, se=sextet, h=heptet, m=multiplet), coupling constant J, integration. For the combined multiplicities, the one with the larger coupling constant is stated first. All raw data files were processed and analyzed using MestReNova v12.0.3-21384 from Mestrelab Research S.L.

**High resolution mass spectra (HRMS):** measured on a LTQ Orbitrap Velos spectrometer from Thermo Fisher Scientific (Velos Pro) with or without loop-mode injection from a Waters (RP18) HPLC system or a Micromass LCT spectrometer via loop-mode injection from a Waters (Alliance
HPLC system. Method of ionisation - electrospray ionization (ESI). Ionisation mode, calculated and found mass are provided.

**IR spectra:** measured on a Perkin Elmer Spectrum 100 FT-IR spectrometer. All raw data files were processed and analyzed using ACD Labs 6.0. Data are represented in frequency of absorption in wavenumber [cm⁻¹]. Samples were applied as a neat film.

**Optical rotation:** measured on a Jasco P-2000 polarimeter using the sodium D line (589nm). Concentration and solvent are indicated.

**Chiral HPLC analysis:** performed on an Agilent 1100 series HPLC-System with ChiralPAK AD or CHIRALCEL® OD-H column.

3 Experimental Procedures

3.1 Enantioselective Synthesis of Taxane C-Ring Precursors and Their Application to the Total Synthesis

3.1.1 First Generation of C-Ring Precursors

**Ethyl (E)-2-methylpenta-2,4-dienoate**

Prepared in accordance with modified literature known procedure.[154]

Ethyl 2-(triphenylphosphoranylidene)propionate (11.52 g, 31.80 mmol, 1.1 eq.) was dissolved in anhydrous DCM (60 mL) and freshly distilled acrolein (1.62 g, 28.90 mmol, 1.0 eq.) was added dropwise to the solution, maintaining a vigorous reflux. After the addition was finished, the resulting mixture was further refluxed for 1 h. After which time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure followed by addition of pentane (100 mL) which precipitated triphenylphosphine oxide. The mixture was filtered and the filter cake was rinsed with cold pentane (50 mL). The solvent was removed under reduced pressure to afford ester (2.37 g, 3.57 mmol, 59%) as a colorless liquid which was used in the next step without further purification.

**¹H NMR** (400 MHz, CDCl₃) δ = 7.18 (d, J = 11.3 Hz, 1H), 6.70 – 6.62 (m, 2H), 5.56 (d, J = 16.8 Hz, 1H), 5.45 (d, J = 10.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.96 (d, J = 1.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 1H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.
(E)-2-methylpenta-2,4-dien-1-ol

Prepared in accordance with modified literature known procedure. The freshly prepared ethyl (E)-2-methylpenta-2,4-dienoate (2.37 g, 16.91 mmol, 1.0 eq.) was dissolved in dry DCM, cooled down to -78 °C and the solution was treated with DIBAL-H (1 M in hexanes, 37.19 mL, 37.19 mmol, 2.2 eq.). The resulting solution was further stirred for 30 min at -78 °C. The cooling bath was then removed and the mixture was allowed to warm up to room temperature. Then diethyl ether (10 mL), water (5 mL) and aqueous sodium hydroxide solution (1 M, 1 mL) were added to the reaction mixture subsequently. A white precipitate was formed and the suspension was stirred for 1 h at 25 °C. Magnesium sulphate was added and the mixture was filtered and concentrated to afford a colourless liquid. The crude product was purified via flash column chromatography on silica gel (EA / PE 1:4) to afford desired alcohol (1.28 g, 13.02 mmol, 77%) as a colourless liquid.

\[\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 6.59 \text{ (ddd, } J = 16.8, 10.9, 10.2 \text{ Hz, } 1\text{H}) , \quad 6.07 \text{ (dqd, } J = 10.9, 1.4, 0.7 \text{ Hz, } 1\text{H}), \quad 5.28 - 5.16 \text{ (m, } 1\text{H}), \quad 5.10 \text{ (dddt, } J = 10.2, 1.9, 1.3, \text{ 0.6 Hz, } 1\text{H}), \quad 4.06 \text{ (s, } 2\text{H}), \quad 1.78 \text{ (dt, } J = 1.3, 0.6 \text{ Hz, } 3\text{H) ppm.}

The obtained NMR data is consistent with the values reported in the respective literature.

(E)-tert-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane (253)

Prepared in accordance with modified literature known procedure. (E)-2-methylpenta-2,4-dien-1-ol (1.28 g, 13.02 mmol, 1.0 eq.) was dissolved in DCM (90 mL) and the mixture was cooled to 0 °C. TBDPSCI (3.71 g, 14.32 mmol, 1.1 eq.) was added followed by addition of imidazole (1.95 g, 28.65 mmol, 2.2 eq.). The ice bath was removed and the mixture was stirred at 25 °C for 5 h. The reaction was diluted with water (20 mL) and DCM (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified via flash column chromatography on silica gel (100% pentane to 2% ethyl acetate in pentane) to afford diene (4.14 g, 12.30 mmol, 95%) as a colorless liquid.

\[\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.69 - 7.64 \text{ (m, } 1\text{H}), \quad 7.42 - 7.34 \text{ (m, } 1\text{H}), \quad 6.60 \text{ (dd, } J = 16.8, 10.6 \text{ Hz, OH}), \quad 6.17 \text{ (d, } J = 11.1 \text{ Hz, OH}), \quad 5.21 - 5.13 \text{ (m, } 0\text{H}), \quad 5.09 - 5.04 \text{ (m, } 0\text{H}), \quad 4.10 \text{ (s, } 0\text{H}), \quad 1.71 \text{ (s, } 1\text{H}), \quad 1.06 \text{ (d, } J = 0.9 \text{ Hz, } 2\text{H) ppm.}

The obtained NMR data is consistent with the values reported in the respective literature.
(1S,2S,3R,4R)-3-(((tert-butyldiphenylsilyloxy)methyl)-1,3-dimethyl-2-vinylcyclohexane-1,4-diol (254)

Prepared in accordance with modified literature known procedure.\[^{154}\] Pt(dba)\(_3\) (97.8 mg, 0.11 mmol, 0.02 equiv), (R,R)-TADDOLPPh \(^{250}\) (119 mg, 0.131 mmol, 0.03 eq.) and bis(pinacolato)diboron (1.17 g, 4.59 mmol, 1.05 eq.) were transferred to a Schlenk flask in the glove box. The flask was taken out of the glove box and dry PhMe (4 mL) was added to the mixture. The flask was sealed and heated at 80 °C for 20 min under an inert atmosphere. Then the reaction mixture was cooled down to room temperature and diene \(^{253}\) (1.22 g, 4.37 mmol, 1.0 eq.) was added. The flask was again sealed and heated to 60 °C under an inert atmosphere for 18 h. The flask was then cooled to 25 °C and 4-oxopentanal (1.09 g, 10.93 mmol, 2.50 eq.) was added. The mixture was heated at 60 °C for next 24 h. Then the mixture was cooled to 0 °C and THF (5 mL) was added followed by pH 7 phosphate buffer (5 mL) and H\(_2\)O\(_2\) (30% in water) (5.14 mL, 54.4 mmol, 12.0 eq.). The mixture was slowly allowed to warm to room temperature over 6 h. After which time, saturated aqueous sodium thiosulfate solution (10 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified via flash column chromatography (EA/PE 2:3) to afford diol \(^{254}\) (d.r. = 9:1, 1.33 g, 3.03 mmol, 69%) as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.68 – 7.64\) (m, 4H), 7.46 – 7.36 (m, 6H), 5.68 (dt, \(J = 16.1\), 10.6 Hz, 1H), 5.16 – 5.11 (m, 2H), 3.79 (dd, \(J = 5.0\), 2.8 Hz, 1H), 3.73 (d, \(J = 10.3\) Hz, 1H), 3.44 (d, \(J = 10.3\) Hz, 1H), 2.50 (d, \(J = 10.5\) Hz, 1H), 1.96 (td, \(J = 12.4\), 4.2 Hz, 1H), 1.82 (dq, \(J = 9.5\), 4.8 Hz, 1H), 1.72 (ddt, \(J = 14.5\), 11.8, 3.4 Hz, 1H), 1.56 (ddd, \(J = 12.8\), 5.1, 3.9 Hz, 1H), 1.16 (s, 3H), 1.08 (s, 9H), 0.85 (s, 3H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

(1S,2S,3R,4R)-3-(hydroxymethyl)-1,3-dimethyl-2-vinylcyclohexane-1,4-diol (255)

Prepared in accordance with modified literature known procedure.\[^{154}\] Diol \(^{254}\)
(6.84 g, 15.60 mmol, 1.0 eq.) was dissolved in THF (40 mL) and cooled down to 0 °C. TBAF (1 M in THF, 20 mL, 20.00 mmol, 1.3 eq.) was added dropwise and the mixture was allowed to warm up to room temperature. After 6 h, the reaction was complete and quenched by the addition of saturated aqueous sodium bicarbonate (100 mL) followed by addition of ethyl acetate (100mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic layer was washed with brine.
(100 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified via flash column chromatography on silica gel (100% EA) at this stage separating the two diastereomers to afford triol (1.27, 6.34 mmol, 41%) as a colorless solid (m.p. 124 °C).

\(^1\)H NMR (400 MHz, DMSO-\(\text{D}_6\)) \(\delta = \) 5.66 (dt, \(J = 16.8, 10.3\) Hz, 1H), 5.04 – 4.89 (m, 2H), 4.51 (d, \(J = 4.4\) Hz, 1H), 4.21 (t, \(J = 5.7\) Hz, 1H), 4.10 (s, 1H), 3.57 (dd, \(J = 10.6, 5.9\) Hz, 1H), 3.48 (dt, \(J = 7.8, 3.8\) Hz, 1H), 3.38 (dd, \(J = 9.9, 4.5\) Hz, 1H), 2.17 (d, \(J = 10.6\) Hz, 1H), 1.82 – 1.58 (m, 2H), 1.58 – 1.49 (m, 1H), 1.46 – 1.30 (m, 1H), 0.99 (s, 3H), 0.79 (s, 3H) ppm.

\(^13\)C NMR (101 MHz, DMSO-\(\text{D}_6\)) \(\delta = \) 136.9, 117.4, 71.9, 70.2, 67.1, 54.6, 41.1, 34.8, 27.8, 27.2, 20.3 ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

**\((1R,2R,3S,4S)-2-(hydroxymethyl)-4-(methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexan-1-ol (257)**

Triol **255** (138 mg, 0.69 mmol, 1.0 eq.) was dissolved in dry pyridine (1 mL) and subsequently treated with Ac\(_2\)O (1 mL). The resulting mixture was stirred at room temperature for 18 h. After which time, water (2 mL) and Et\(_2\)O (5 mL) were added subsequently to the vigorously stirred reaction mixture. The organic layer was separated, washed with brine (1 mL), dried over magnesium sulfate, filtered and concentrated. The crude was dissolved in DCM (1 mL) and cooled to 0 °C. DIPEA (0.86 mL, 4.92 mmol, 7.0 eq.), DMAP (86 mg, 0.69 mmol, 1.0 eq.) and MOMCl (0.28 mL, 3.52 mmol, 5.0 eq.) were added subsequently. The mixture was stirred at room temperature for 15 h, after which time, aqueous saturated NH\(_4\)Cl (10 mL) and DCM (10 mL) were added. The organic layer was separated, washed with aqueous 0.1 M HCl solution (5 mL), aqueous saturated NaHCO\(_3\) solution (10 mL), brine (2 × 10 mL), dried over MgSO\(_4\), filtered and concentrated. The residue was dissolved in MeOH (3 mL) followed by addition of water (1 mL) and KOH (225 mg, 4.02 mmol, 6.0 eq.) at room temperature. The mixture was stirred at ambient for 1 h until the reaction was finished (monitored by TLC, eluted with EA/PE 1:1). Next, the mixture was diluted with cold EtOAc (10 mL) and washed with water (10 ml x 2). Organic layer was separated, dried over MgSO\(_4\), filtered and concentrated affording the desired diol **257** (135 mg, 0.55 mmol, 82%). The compound was used in the next step without further purification.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = \) 5.75 – 5.60 (m, 1H), 5.18 – 5.09 (m, 2H), 4.73 (s, 2H), 3.85 (d, \(J = 11.5\) Hz, 1H), 3.72 (dd, \(J = 8.0, 4.0\) Hz, 1H), 3.60 (d, \(J = 11.5\) Hz, 1H), 3.37 (s, 3H), 2.72 (s, 1H), 2.54
– 2.47 (m, 1H), 2.43 – 2.36 (m, 1H), 2.03 – 1.94 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.56 (ddd, \( J = 13.5, 9.2, 4.2 \) Hz, 1H), 1.20 (s, 3H), 0.94 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta = 135.5, 119.2, 90.5, 78.1, 75.2, 69.6, 55.63 53.5, 41.7, 31.9, 27.6, 24.2, 21.0 \) ppm.

HRMS (ESI, \( m/z \)) calculated for \( C_{13}H_{24}NaO_4^+ \) [M+Na]: 267.1567; found: 267.1572.

\([\alpha]_D^{23}\): –3.2 (c 0.08, CHCl\(_3\)).

IR (film): uninformative.

\((15,25,35,6R)-6\text{-hydroxy-3-\{methoxymethoxy\}-1,3\text{-dimethyl-2-vinylcyclohexane-1-carbaldehyde (258)}\)

To a solution of diol 257 (528 mg, 2.16 mmol, 1.0 eq.) in DCM (20 mL), water (20 mL) was added. The resulting suspension was treated with TEMPO (372 mg, 2.38 mmol, 1.1 eq.) and PIDA (765 mg, 2.38 mmol, 1.1 eq.). The resulting biphasic system was stirred vigorously at room temperature for 3 h, and then quenched with \( \text{Na}_2\text{S}_2\text{O}_3 \) (saturated aqueous solution), followed by addition of \( \text{NaHCO}_3 \) (saturated aqueous solution). After stirring at room temperature for 10 minutes, the organic layer was separated, and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried over MgSO\(_4\) and filtered. The filtrate was concentrated to yield the crude product as an orange oil. The crude product was then purified via flash chromatography (EA/PE 1:1) to provide the title compound 258 (410 mg, 1.69 mmol, 78%) as a colorless oil.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \( \delta = 9.48 – 9.23 \) (m, 1H), 5.54 (dt, \( J = 16.6, 10.4 \) Hz, 1H), 5.32 – 5.16 (m, 2H), 4.65 (d, \( J = 7.3 \) Hz, 1H), 4.60 (d, \( J = 7.3 \) Hz, 1H), 3.56 – 3.45 (m, 2H), 3.34 (s, 3H), 2.52 (dd, \( J = 10.7, 2.3 \) Hz, 1H), 1.97 – 1.79 (m, 3H), 1.55 – 1.42 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta = 205.2, 132.9, 121.5, 90.3, 77.4, 72.9, 59.2, 56.1, 50.2, 30.4, 28.4, 24.9, 18.6 \) ppm.

HRMS (ESI, \( m/z \)) calculated for \( C_{13}H_{22}NaO_4^+ \) [M+Na]: 265.1410; found: 265.1409.

\([\alpha]_D^{25}\): –2.9 (c 0.25, CHCl\(_3\)).

IR (film): \( \lambda_{\text{max}} = 3471, 2936, 2877, 2823, 1709, 1452, 1132, 1056, 1028, 921 \text{ cm}^{-1} \).
(1S,2S,3S,6R)-3-(methoxymethoxy)-1,3-dimethyl-6-((triethylsilyl)oxy)-2-vinylcyclohexane-1-carbaldehyde (259)

A solution of aldehyde 258 (130 mg, 0.54 mmol, 1 eq.) in DCM (1 mL) was treated with imidazole (146 mg, 2.15 mmol, 4 eq.) and TESCl (161 mg, 1.07 mmol, 2 eq.) subsequently at room temperature. The resulting mixture was further stirred for 2 h at room temperature, then aqueous saturated NH₄Cl (5 mL) and DCM (5 mL) were added. The layers were separated and the aqueous layer was extracted with DCM (5 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried (MgSO₄) and concentrated. The residual oil was purified via flash column chromatography (PE/Et₂O 4:1) to afford TES-protected aldehyde 259 (180 mg, 0.51 mmol, 94%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 10.03 (s, 1H), 5.53 (ddd, J = 16.6, 10.8, 10.2 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.61 (d, J = 7.5 Hz, 1H), 4.42 (d, J = 7.5 Hz, 1H), 3.73 (dd, J = 11.9, 5.0 Hz, 1H), 3.31 (s, 3H), 2.52 (dd, J = 10.9, 2.2 Hz, 1H), 2.25 – 2.10 (m, 1H), 1.85 – 1.71 (m, 2H), 1.57 – 1.46 (m, 1H), 1.09 (s, 3H), 0.99 – 0.91 (m, 12H), 0.64 – 0.55 (m, 6H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 206.7, 134.1, 120.6, 90.3, 76.3, 72.8, 59.7, 55.6, 50.2, 32.0, 28.3, 24.7, 22.2, 7.0, 5.2 ppm.

HRMS (ESI, m/z) calculated for C₁₉H₃₆NaO₄Si⁺ [M+Na]⁺: 379.2275; found: 379.2273.

[α]ᵢ °: --8.6 (c 0.37, CHCl₃).

IR (film): λmax = 2954, 2877, 1716, 1458, 1378, 1090, 1034, 1017, 922, 830, 744, 727 cm⁻¹.

(2R,3S,4S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxy-2,4-dimethyl-3-vinylcyclohexan-1-one (260)

A round bottomed flask was charged with PCC (332 mg, 1.54 mmol, 1.5 eq.) and SiO₂ (600 mg). Into the reaction flask dry DCM (25 mL) was added and the formed suspension was vigorously stirred for 10 min. After which time, a solution of 254 (450 mg, 1.03 mmol, 1.0 eq.) in DCM (5 mL) was added dropwise at room temperature. After a certain time (aprx. 10 min) the color of the suspension turned black. The resulting mixture was stirred for additional 3 h until the reaction was finished (completion monitored by TLC). After that, the reaction mixture was filtered through a celite pad and filtrate was concentrated. The crude was purified via flash column chromatography (PE/EA 2:1) to afford pure 260 (435 mg, 1.00 mmol, 97%) as a colorless oil.
\(^1\)H NMR (400 MHz, CDCl\(_3\))  δ = 7.71 – 7.62 (m, 4H), 7.47 – 7.33 (m, 6H), 5.65 (d,  J = 16.8 Hz, 1H), 5.19 (dd,  J = 10.1, 2.1 Hz, 1H), 5.10 (ddd,  J = 16.7, 2.1, 0.7 Hz, 1H), 3.90 (d,  J = 9.5 Hz, 1H), 3.46 (d,  J = 9.5 Hz, 1H), 2.79 (d,  J = 10.5 Hz, 1H), 2.69 (ddd,  J = 16.3, 7.9, 6.8 Hz, 1H), 2.39 (dt,  J = 16.3, 6.9 Hz, 1H), 2.27 (s, 2H), 2.02 – 1.96 (m, 2H), 1.26 (s, 3H), 1.04 (s, 9H), 0.90 (s, 3H) ppm.

\(^13\)C NMR (101 MHz, CDCl\(_3\)) δ = 213.8, 135.9, 135.9, 134.8, 133.3, 133.0, 129.9, 127.8, 120.6, 70.9, 69.1, 57.0, 56.1, 42.3, 37.4, 34.1, 24.2, 12.3 ppm.

HRMS (ESI, \(m/z\)) calculated for \(C_{27}H_{36}NaO_3Si\)[M+Na]\(^{+}\): 459.2326; found: 459.2339.

\([\alpha]_D^{23}\): +1.4 (c 0.16, CHCl\(_3\)).

IR (film): \(\lambda_{\text{max}} = 3435, 2931, 2857, 1706, 1428, 1111, 1084, 915, 825, 741, 702\) cm\(^{-1}\).

(2R,3S,4S)-4-(methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexan-1-one (263)

A solution of 260 (435 mg, 1.00 mmol, 1 eq.) in DCM (10 mL) was cooled to 0 °C and subsequently treated with DIPEA (1.19 mL, 6.97 mmol, 7 eq.), DMAP (127 mg, 1.00 mmol, 1.0 eq.) and MOMCl (0.38 mL, 4.98 mmol, 5 eq.). The resulting mixture was stirred for 15 h at room temperature. After which time, aqueous saturated NH\(_4\)Cl (10 mL) and DCM (10 mL) were added. The organic layer was separated, washed with aqueous 0.1 M HCl solution (5 mL), aqueous saturated NaHCO\(_3\) solution (10 mL), brine (2 × 10 mL), dried over MgSO\(_4\), filtered and concentrated. The crude was further dissolved in MeOH (10 mL) and NH\(_4\)F (736 mg, 19.89 mmol, 20 eq.) was added to the mixture in one portion at room temperature. The resulting slurry reaction mixture was heated at 60 °C for 10 h. When the starting material was consumed, the mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (50 mL), brine (15 mL), dried (MgSO\(_4\)) and concentrated. The residual oil was purified via flash column chromatography (PE/EA 2:1) to afford undesired compound 263 (110 mg, 0.45 mmol, 45%) as a yellowish oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\))  δ = 5.27 (dt,  J = 16.3, 10.1 Hz, 1H), 5.19 – 5.07 (m, 2H), 4.90 – 4.83 (m, 2H), 3.44 (s, 3H), 3.26 (qdd,  J = 6.8, 4.9, 1.3 Hz, 1H), 2.71 (tdd,  J = 14.0, 6.8, 1.3 Hz, 1H), 2.63 (ddd,  J = 10.3, 5.0, 2.7 Hz, 1H), 2.20 (ddd,  J = 14.1, 5.2, 1.8 Hz, 1H), 2.09 (ddt,  J = 14.4, 6.8, 2.2 Hz, 1H), 1.81 (td,  J = 14.2, 5.2 Hz, 1H), 1.22 (s, 3H), 0.88 (d,  J = 6.8 Hz, 3H) ppm.

\(^13\)C NMR (101 MHz, CDCl\(_3\)) δ = 213.4, 134.5, 120.5, 91.2, 77.4, 59.8, 56.1, 42.3, 37.4, 34.1, 24.2, 12.3 ppm.

HRMS (ESI, \(m/z\)) not found.
(1R,2S,3S)-3-(methoxymethoxy)-1,3-dimethyl-6-oxo-2-vinylcyclohexane-1-carbaldehyde (269)

A round bottomed flask was charged with PCC (160 mg, 0.75 mmol, 1.5 eq.) and SiO$_2$ (300 mg). Into the reaction flask dry DCM (20 mL) was added and the formed suspension was vigorously stirred for 10 min. After which time, a solution of 255 (100 mg, 0.50 mmol, 1.0 eq.) in DCM (5 mL) was added dropwise at room temperature. After a certain time (aprx. 10 min) the color of the suspension turned black. The resulting mixture was stirred for additional 3 h until the reaction was finished (completion monitored by TLC). After that, the reaction mixture was filtered through a celite pad and filtrate was immediately cooled to 0 °C and subsequently treated with DIPEA (0.59 mL, 3.46 mmol, 7.0 eq.), DMAP (60 mg, 0.49 mmol, 1.0 eq.) and MOMCl (200 mg, 2.47 mmol, 5.0 eq.). The resulting mixture was stirred for 18 h at room temperature. After which time, aqueous saturated NH$_4$Cl (10 mL) and DCM (10 mL) were added. The organic layer was separated, washed with aqueous 0.1 M HCl solution (5 mL), aqueous saturated NaHCO$_3$ solution (10 mL), brine (2 × 10 mL), dried over MgSO$_4$, filtered and concentrated. The residual oil was purified via flash column chromatography (PE/EA 3:1) to afford compound 269 (30 mg, 0.12 mmol, 25%) as a yellowish oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 9.39$ (s, 1H), 5.36 – 5.17 (m, 3H), 4.79 (d, $J = 7.6$ Hz, 1H), 4.73 (d, $J = 7.6$ Hz, 1H), 3.39 (s, 4H), 2.91 (dd, $J = 9.6$, 2.7 Hz, 1H), 2.77 (ddd, $J = 14.9$, 14.0, 6.9 Hz, 1H), 2.30 (ddd, $J = 14.9$, 5.2, 1.9 Hz, 1H), 2.11 (dddd, $J = 14.9$, 6.9, 2.8, 1.9 Hz, 1H), 1.78 (ddd, $J = 14.9$, 14.0, 5.2 Hz, 1H), 1.27 (s, 3H), 0.98 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 208.8$, 197.8, 132.6, 121.9, 90.9, 77.4, 61.6, 60.9, 56.6, 36.0, 32.0, 24.2, 16.1 ppm.

(15R,25R,3R,4S)-3-(hydroxymethyl)-1,3-dimethyl-2-vinylcyclohexane-1,4-diol (268)

A round bottomed flask was charged with PCC (160 mg, 0.75 mmol, 1.5 eq.) and SiO$_2$ (300 mg). Into the reaction flask dry DCM (20 mL) was added and the formed suspension was vigorously stirred for 10 min. After which time, a solution of 255 (100 mg, 0.50 mmol, 1 eq.) in DCM (5 mL) was added dropwise at room temperature. After a certain time (aprx. 10 min) the color of the suspension turned black. The resulting mixture was stirred for additional 3 h until the reaction was finished (completion monitored by TLC). After that, the reaction mixture was filtered through a celite pad and filtrate was immediately cooled to 0 °C and exposed to the reduced pressure performing
slow concentration process over 5 h. The residue was then dissolved in THF (10 mL) making 0.05M solution which was kept at 0 to 4 °C.

Next, a solution of 266 (0.05 M, 1 mL, 1.0 eq.) in dry THF was treated with NaBH₄ (1.9 mg, 0.05 mmol, 1.0 eq.) at room temperature and the mixture was stirred for 15 min. After which time, the mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The organic layer was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified via flash column chromatography on silica gel (EtOAc) to afford triol 268 (2.3 mg, 0.01 mmol, 23%).

^1H NMR (400 MHz, DMSO-D₆) δ = 5.78 – 5.66 (m, 1H), 5.08 – 4.97 (m, 2H), 4.29 (d, J = 31.5 Hz, 2H), 3.58 – 3.50 (m, 1H), 3.24 (d, J = 10.2 Hz, 1H), 3.04 (d, J = 10.1 Hz, 1H), 2.12 (d, J = 10.1 Hz, 1H), 1.57 (tdt, J = 7.1, 4.9, 2.6 Hz, 2H), 1.45 – 1.33 (m, 2H), 1.05 (s, 3H), 0.63 (s, 3H) ppm.

triethyl((1R,2R,3S,4S)-4-(methoxymethoxy)-2,4-dimethyl-2-(oxiran-2-yl)-3-vinylcyclohexyl)oxy)silane (270)

To a cooled to 0 °C solution of Me₃Si (160 mg, 0.79 mmol, 1.6 eq.) in dry THF (8 mL) was added a solution of KHMDS (0.5 M in PhMe, 1.4 mL, 0.69 mmol, 1.4 eq.) dropwise over 10 min. The resulting reaction mixture was stirred for 1 h. A solution of aldehyde 259 (175 mg, 0.49 mmol, 1 eq.) in THF (3 mL) was transferred to the reaction vessel via cannula. The resulting mixture was stirred for 1 h (completion monitored by TLC PE/Et₂O 4:1). After which time, water (10 mL) was added and the mixture was extracted with Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (50 mL). The combined organic extracts were washed with water (35 mL), brine (25 mL), dried (MgSO₄) and concentrated. The residual oil was purified via flash column chromatography (PE/Et₂O 4:1) to afford an inseparable mixture of epoxides 270 (163 mg, 0.43 mmol, 89%) as a colorless oil.

^1H NMR peak listing of the mixture of diastereomers (d.r. 2:1) is uninformative, see NMR spectrum below for the graphic representation.
1-((15,25,35,6R)-6-hydroxy-3-(methoxymethoxy)-1,3-dimethyl-2-vinylcyclohexyl)ethane-1,2-diol (272)

A solution of the aldehyde 258 (50 mg, 0.21 mmol, 1.0 eq.) in THF (1 mL) was treated with corresponding Grignard reagent 273 (1 M in THF, 0.93 mL, 0.93 mmol, 4.5 eq.) at 0 °C. The resulting solution was further stirred for 30 min at 0 °C and for 30 min at room temperature. After which time, the reaction mixture was cooled down to 0 °C and quenched by addition of aqueous NH₄Cl (2 mL) and the resulting suspension was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum at 0 °C to yield the crude addition product, which was subsequently dissolved in THF (1 mL). To the resulting solution, MeOH (1 mL), NaHCO₃ (86 mg, 1.03 mmol, 5.0 eq.), KF (35 mg, 0.62 mmol, 3.0 eq.) and H₂O₂ (0.7 mL, 30% in water, 30.0 eq.) were added subsequently strictly in the described order. The resulting suspension was stirred for 18 h at room temperature, quenched with aqueous solution of Na₂S₂O₃ (5 mL) at 0 °C and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as an orange oil. This oil was then purified by using silica gel flash chromatography (eluted with pure EA) to provide the desired compound 272 (40 mg, 0.15 mmol, 70%) as a colorless oil.

$^{1}H$ NMR (400 MHz, CDCl₃) δ = 5.67 (dt, $J = 16.7$, 10.4 Hz, 1H), 5.24 – 5.10 (m, 2H), 4.79 – 4.67 (m, 2H), 4.40 – 4.21 (s, 1H), 3.89 (dd, $J = 10.7$, 3.2 Hz, 1H), 3.74 (dd, $J = 8.1$, 3.4 Hz, 1H), 3.69 (s, 1H), 3.64 (dd, $J = 10.7$, 8.6 Hz, 1H), 3.38 (s, 3H), 2.64 (d, $J = 10.2$ Hz, 1H), 2.42 (s, 1H), 2.08 – 1.97 (m, 1H), 1.92 – 1.82 (m, 1H), 1.71 (dddd, $J = 13.9$, 7.8, 4.2, 3.3 Hz, 1H), 1.54 (ddd, $J = 14.0$, 8.9, 4.2 Hz, 1H), 1.19 (s, 3H), 0.95 (s, 3H) ppm.

$^{13}C$ NMR (101 MHz, CDCl₃) δ = 135.0, 119.9, 90.3, 78.3, 75.9, 75.5, 63.2, 55.7, 53.6, 42.6, 31.5, 27.6, 24.3, 18.7 ppm.

HRMS (ESI, m/z) calculated for C₁₄H₂₆NaO₅⁺ [M+Na]^+: 297.1672; found: 297.1669.

$[\alpha]^{23}$: +5.5 (c 0.06, CHCl₃).

IR (film): uninformative.
1-((1S,2S,3S,4S,6R)-6-acetoxy-3-(methoxymethoxy)-1,3-dimethyl-2-vinylcyclohexyl)ethane-1,2-diyldiacetate (275)

To a solution of 272 (50 mg, 0.18 mmol, 1.0 eq.) in pyridine (1 mL), was added Ac₂O (0.86 mL, 9.11 mmol, 50.0 eq.) at room temperature. The resulting mixture was stirred for 18 h at ambient temperature. After which time, water (10 mL) was added and the mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as an orange oil. The crude was then purified by using silica gel flash chromatography (eluted with EA/PE 1:1) to provide the desired compound 275 (70 mg, 0.17 mmol, 96%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 6.11 (s, 1H), 5.73 (dt, J = 16.7, 10.3 Hz, 1H), 5.20 (dd, J = 10.1, 1.9 Hz, 1H), 5.10 (dd, J = 16.7, 2.0 Hz, 1H), 4.86 (dd, J = 10.4, 3.6 Hz, 1H), 4.78 (d, J = 7.6 Hz, 1H), 4.72 – 4.67 (m, 2H), 4.12 – 4.07 (m, 1H), 3.43 (s, 3H), 2.45 – 2.37 (m, 1H), 2.14 – 2.07 (m, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 – 1.94 (m, 1H), 1.67 – 1.62 (m, 1H), 1.60 – 1.56 (m, 1H), 1.14 (s, 3H), 1.01 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 171.1, 170.6, 170.4, 134.9, 120.6, 90.6, 77.9, 72.2, 64.6, 56.2, 42.9, 31.6, 31.1, 23.6, 21.6, 21.5, 21.0 ppm.


[α]D²⁵ +6.4 (c 0.11, CHCl₃).

IR (film): uninformative.

(3aS,4S,5S,7aR)-5-(methoxymethoxy)-3a,5-dimethyl-4-vinylhexahydrobenzofuran-2,3-dione (274)

The triol 272 (10 mg, 0.04 mmol, 1.0 eq.) was dissolved in DCM (1 mL) and subsequently treated with aqueous solution of NaHCO₃ (0.5 mL), KBr (13 mg, 0.1 mmol, 3.0 eq.) and TEMPO (2.8 mg, 0.02 mmol, 0.5 eq.). To the resulting solution, 6% NaClO (0.1 mL, 0.09 mmol, 2.5 eq.) was added and the dark-red reaction mixture was stirred for 1 hour until the mixture color faded to pale orange. After approximately 20 min, the reaction mixture was quenched with aqueous solution of Na₂S₂O₃ (1 mL) and extracted with DCM (2 x 10 mL). To the combined organic phases were dried over MgSO₄ and concentrated in vacuum affording the compound 274 (7 mg, 0.03 mmol, 70%) as a yellowish oil.
**1H NMR** (400 MHz, CDCl₃) δ = 5.55 – 5.44 (m, 1H), 5.35 – 5.25 (m, 2H), 4.59 – 4.55 (m, 1H), 4.53 – 4.45 (m, 2H), 3.24 – 3.22 (m, 3H), 2.68 (dd, J = 10.6, 1.7 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.10 – 2.01 (m, 1H), 1.91 – 1.84 (m, 1H), 1.52 – 1.48 (m, 1H), 1.21 (s, 3H), 1.10 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 195.6, 161.9, 133.0, 122.7, 89.9, 81.2, 76.6, 59.5, 55.8, 44.0, 26.77, 24.8, 23.9, 22.3 ppm.

(15,2S,3R,4R)-4-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-1,3-dimethyl-2-vinylcyclohexan-1-ol

The triol 255 (312 mg, 1.56 mmol, 1.0 eq.) and imidazole (530 mg, 7.79 mmol, 5.0 eq.) were dissolved in dry DMF (15 mL) followed by addition of TBSCI (516 mg, 3.43 mmol, 2.2 eq.) at room temperature. The resulting mixture was stirred for 48 h at 60 °C. After which time, the reaction mixture was diluted with aqueous NH₄Cl (10 mL) and water (20 mL). The mixture was then extracted with Et₂O (3 x 50 ml). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as a brownish oil. The crude was then purified by using silica gel flash chromatography (eluted with PE/EA 6:1) to provide the desired compound (285 mg, 0.66 mmol, 43%) as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ = 5.67 (dt, J = 16.8, 10.1 Hz, 1H), 5.13 – 4.97 (m, 2H), 3.64 (m, 2H), 3.41 (d, J = 9.7 Hz, 1H), 2.26 (d, J = 10.3 Hz, 2H), 1.88 (d, J = 8.8 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.63 – 1.46 (m, 2H), 1.10 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.84 (s, 3H), 0.05 – 0.02 (m, 12H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 136.7, 118.5, 72.9, 70.7, 68.7, 56.6, 42.5, 34.3, 27.5, 26.2, 26.1, 18.5, 18.3, -3.9, -4.9, -5.2, -5.4 ppm.

**HRMS** (ESI, m/z) calculated for C₂₃H₄₉O₅Si₂⁺ [M+H]⁺: 429.3215; found: 429.3209.

[α]D²³: −9.7 (c 0.19, CHCl₃).

**IR (film):** λmax = 3615, 2929, 2856, 1472, 1256, 1086, 836, 774 cm⁻¹.

(15,2R,3R,6S)-3-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-(methoxymethoxy)-2,6-dimethylcyclohexane-1-carbaldehyde (278)

A double TBS-protected alcohol (285 mg, 0.66 mmol, 1.0 eq.), DMAP (89 mg, 0.73 mmol, 1.1 eq.) and DIPEA (1.04 mL, 5.98 mmol, 9.0 eq.) were dissolved in dry DCM (5 mL). To the resulting solution MOMCl (0.3 mL, 3.99 mmol, 6.0 eq.) was added dropwise at room temperature and the mixture was stirred further for 48 h. After which time, the reaction mixture was diluted with
aqueous NH₄Cl (10 mL) and water (20 mL). The mixture was then extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄ and placed into the 3-necked flask equipped with inlet-outlet tubes system. Next, a stream of ozone was bubbled through a cold (−78 °C) solution of the alkene. After the reaction mixture turned dark blue, the solution was further bubbled with ozone for 5 min. In order to remove an excess of ozone, a stream of oxygen was bubbled through the solution for 10 min. To the resulting colorless solution, PPh₃ powder (350 mg, 1.33 mmol, 2 eq.) was added in one portion at −78 °C. The resulting cloudy solution was stirred for another 1 h at −78 °C and for 2 h at room temperature. After this time, solvent was removed under reduced pressure and the crude was submitted to the flash column chromatography (PE/EA 9:1) affording a pure aldehyde 278 (220 mg, 0.46 mmol, 70 % over two steps).

^1H NMR (400 MHz, CDCl₃) δ = 9.83 (d, J = 4.8 Hz, 1H), 4.76 (d, J = 7.7 Hz, 1H), 4.65 (d, J = 7.6 Hz, 1H), 3.83 (d, J = 8.9 Hz, 1H), 3.66 (m, 1H), 3.41 (d, J = 9.3 Hz, 1H), 3.32 (s, 3H), 2.85 (d, J = 4.6 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.78 – 1.66 (m, 2H), 1.64 – 1.56 (m, 1H), 1.35 (s, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 – 0.02 (m, 12H) ppm.

^13C NMR (101 MHz, CDCl₃) δ = 204.4, 133.9, 128.9, 90.4, 77.4, 57.8, 55.3, 44.1, 27.1, 26.1, 25.9, 18.5, 18.2, -4.1, -4.9, -5.4, -5.4 ppm.

HRMS (ESI, m/z) calculated for C₂₄H₅₀NaO₅Si₂⁺ [M+Na]⁺: 497.3089; found: 497.3091.

[α]D²³: −13.7 (c 0.26, CHCl₃).

IR (film): uninformative.

(4aR,5S,6S,8aR)-2,2-diisopropyl-6-(methoxymethoxy)-4a,6-dimethyl-5-vinylhexahydro-4H-benzo[d][1,3,2]dioxasiline

A solution of 255 (348 mg, 1.74 mmol, 1.0 eq.), DMAP (10 mg, 0.09 mmol, 0.05 eq.) and Et₃N (0.6 mL, 4.34 mmol, 2.5 eq.) in dry DMF (20 mL) was treated with diisopropylchlorosilane (0.4 mL, 2.26 mmol, 1.3 eq.) at room temperature. The resulting suspension was further stirred for 30 min. After with time, the reaction mixture was diluted with aqueous NH₄Cl (10 mL) and water (50 mL). The mixture was then extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as a yellowish oil. The crude was then purified by using silica gel flash chromatography (eluted with PE/EA 4:1) to provide the desired compound (530 mg, 1.70 mmol, 98%) as a colorless oil.
**1H NMR** (400 MHz, CDCl₃) δ = 5.78 (dtd, J = 16.7, 10.3, 0.8 Hz, 1H), 5.40 – 5.31 (m, 2H), 3.95 (t, J = 2.9 Hz, 1H), 3.66 (d, J = 11.8 Hz, 1H), 3.52 (d, J = 11.6 Hz, 1H), 2.90 (d, J = 10.7 Hz, 1H), 2.09 – 1.94 (m, 1H), 1.79 – 1.68 (m, H), 1.59 – 1.54 (m, 1H), 1.26 (m, 5H), 1.15 – 1.07 (m, 12H), 0.74 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 133.5, 122.2, 76.8, 71.7, 71.3, 50.4, 40.5, 33.5, 27.6, 25.1, 17.8, 17.6, 17.4, 17.2, 17.0, 12.9, 12.3 ppm.


[α]$_{D}^{23}$: –16.1 (c 1.42, CHCl₃).

**IR** (film): λ max = 3432, 2943, 2866, 1465, 1389, 1165, 1085, 1052, 1004, 918, 883, 797, 691, 643 cm$^{-1}$.

(4aR,5S,6S,8aR)-2,2-diisopropyl-6-(methoxymethoxy)-4a,6-dimethylhexahydro-4H-benzo[d][1,3,2]dioxasiline-5-carbaldehyde (280)

The (iPr)$_2$Si-protected alcohol (530 mg, 1.70 mmol, 1.0 eq.), DMAP (207 mg, 1.70 mmol, 1 eq.) and DIPEA (2.36 mL, 13.57 mmol, 8.0 eq.) were dissolved in dry DCM (5 mL). To the resulting solution MOMCl (682 mg, 8.48 mmol, 5.0 eq.) was added dropwise at room temperature and the mixture was stirred further for 48 h. After which time, the reaction mixture was diluted with aqueous NH₄Cl (10 mL) and water (20 mL). The mixture was then extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄ and placed into the 3-necked flask equipped with inlet-outlet tubes system. Next, a stream of ozone was bubbled through a cold (−78 °C) solution of the alkene. After the reaction mixture turned dark blue, the solution was further bubbled with ozone for 5 min. In order to remove an excess of ozone, a stream of oxygen was bubbled through the solution for 10 min. To the resulting colorless solution, PPh₃ powder (867 mg, 3.31 mmol, 2 eq.) was added in one portion at −78 °C. The resulting cloudy solution was stirred for another 1 h at −78 °C and for 2 h at room temperature. After this time, solvent was removed under reduced pressure and the crude was submitted to the flash column chromatography (PE/EA 9:1) affording a pure aldehyde 280 (500 mg, 1.39 mmol, 84% over two steps).

**1H NMR** (400 MHz, CDCl₃) δ = 10.04 (d, J = 1.8 Hz, 1H), 4.81 (dd, J = 7.7, 0.6 Hz, 1H), 4.77 (dd, J = 7.6, 0.6 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 3.80 (t, J = 3.1 Hz, 1H), 3.55 (d, J = 11.9 Hz, 1H), 3.36 (s, 3H), 3.33 (s, 1H), 2.20 (dd, J = 12.4, 5.2 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.64 (dt, J = 12.8, 3.9 Hz, 1H), 1.45 (s, 3H), 1.13 – 1.02 (m, 14H), 0.93 (s, 3H) ppm.

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**13C NMR** (101 MHz, CDCl₃) δ = 205.1, 89.9, 77.9, 77.1, 70.3, 55.2, 40.4, 31.4, 26.9, 22.4, 17.8, 17.4, 17.2, 16.9, 16.9, 12.3, 12.1 ppm.

**HRMS** (ESI, m/z) calculated for C₁₈H₃₆O₅Si₂⁺ [M+H₂]⁺: 180.1161; found: 180.1141.

[α]D²³: +0.7 (c 1.36, CHCl₃).

**IR (film):** λmax = 2943, 2867, 1731, 1465, 1148, 1087, 1031, 1007, 918, 885, 796, 689 cm⁻¹.

1-[(1R,2R,3R,6S)-3-((diisopropyl(vinyl)silyl)oxy)-2-(hydroxymethyl)-6-(methoxymethoxy)-2,6-dimethylcyclohexyl]prop-2-en-1-ol (281)

A solution of aldehyde 280 (220 mg, 0.61 mmol, 1.0 eq.) in dry THF (4 mL) was treated with VinylMgBr (1 M in THF, 0.92 mL, 0.92 mmol, 1.5 eq.) at −78 °C. The resulting mixture was allowed to warm up to room temperature and subsequently diluted with aqueous NH₄Cl (1 mL) and water (5 mL). The mixture was then extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as a yellowish oil. The crude was then purified by using silica gel flash chromatography (eluted with PE/EA 2:1) to provide the desired compound 281 (230 mg, 0.59 mmol, 96%) as a colorless oil (d.r. 2:9).

**1H NMR** peak listing of the mixture of diastereomers (d.r. 2:9) is uninformative, see NMR spectrum below for the graphic representation.

**13C NMR** peak listing of the mixture of diastereomers (d.r. 2:9) is uninformative, see NMR spectrum below for the graphic representation.

**HRMS** (ESI, m/z) calculated for C₂₂H₄₂NaO₅Si⁺ [M+Na]⁺: 437.2694; found: 431.2698.

**IR (film):** λmax = 3335, 2943, 2867, 1463, 1407, 1133, 1089, 1028, 917, 704, 669 cm⁻¹.

(1S,2S,3S,6R)-2-acryloyl-6-((diisopropyl(vinyl)silyl)oxy)-3-(methoxymethoxy)-1,3-dimethylcyclohexane-1-carbaldehyde (282)

A solution of 281 (166 mg, 0.4 mmol, 1.0 eq.) in dry DCM (28 mL) was treated with a solution of Dess-Martin periodinate (0.3 M in DCM, 3.47 mL, 1.04 mmol, 2.6 eq.) at room temperature. The resulting cloudy mixture was further stirred for 2 h and quenched by addition of aqueous Na₂S₂O₃ (5 mL) and NaHCO₃ (5 mL). The biphasic mixture was extracted with DCM (50 mL) and the organic layer was separated, dried over MgSO₄ and filtered. The
filtrate was concentrated in vacuum to yield the crude product as a dark brownish oil. The crude was then purified by using silica gel flash chromatography (eluted with PE/EA 4:1) to provide the desired compound 282 (109 mg, 0.27 mmol, 66%) as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 10.06 (d, J = 1.9 \text{ Hz}, 1\text{H}), 6.44 (ddd, J = 17.4, 10.4, 2.1 \text{ Hz}, 1\text{H}), 6.28 (dd, J = 17.5, 1.2 \text{ Hz}, 1\text{H}), 6.12 – 6.01 (m, 2\text{H}), 5.90 – 5.77 (m, 2\text{H}), 4.66 – 4.61 (m, 1\text{H}), 4.47 (dd, J = 7.6, 2.1 \text{ Hz}, 1\text{H}), 4.43 – 4.36 (m, 1\text{H}), 3.63 (s, 1\text{H}), 3.32 (s, 3\text{H}), 2.16 – 1.87 (m, 3\text{H}), 1.74 – 1.62 (m, 1\text{H}), 1.08 (s, 3\text{H}), 1.02 (m, 14\text{H}), 0.97 (s, 3\text{H}) \text{ ppm.}

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 205.6, 201.2, 139.7, 134.7, 133.7, 129.5, 90.2, 77.2, 76.0, 72.3, 59.6, 55.7, 50.0, 31.4, 27.9, 23.9, 20.4, 17.7, 17.6, 17.6, 12.8, 12.7 \text{ ppm.}

HRMS (ESI, \(m/z\)) calculated for C\(_{22}\)H\(_{38}\)NaO\(_5\)Si\(^+\) [M+Na\(^+\)]: 433.2381; found: 433.2383.

\([\alpha]_D^{22} = -3.8 (c 0.38, \text{CHCl}_3)\).

IR (film): \(\lambda_{\text{max}} = 2942, 2869, 1713, 1665, 1466, 1461, 1096, 1029, 1007, 883 \text{ cm}^{-1}\).

1-((1R,2R,3R,6S)-3-hydroxy-2-(hydroxymethyl)-6-(methoxymethoxy)-2,6-dimethylcyclohexyl)allyl pivalate (283)

A solution of aldehyde 278 (220 mg, 0.46 mmol, 1.0 eq.) in dry THF (5 mL) was treated with VinylMgBr (1 M in THF, 0.92 mL, 0.92 mmol, 2.0 eq.) at \(-78 \degree\text{C}\). The resulting mixture was allowed to warm up to room temperature and subsequently diluted with aqueous NH\(_4\)Cl (1 mL) and water (5 mL). The mixture was then extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were dried over MgSO\(_4\) and filtered. The filtrate was concentrated in vacuum to yield the crude product as a yellowish oil. The crude was then dissolved in dry DCM (1.5 mL) and Et\(_3\)N (0.32 mL, 2.23 mmol, 5.0 eq.), DMAP (6 mg, 0.04 mmol, 0.1 eq.) and PivCl (0.18 mL, 1.39 mmol, 3.0 eq.) were added subsequently to the mixture at room temperature. The resulting mixture was stirred for another 14 h, after which time, only 30% completion was observed. Another portions of Et\(_3\)N (0.32 mL, 2.23 mmol, 5 eq.), and PivCl (0.18 mL, 1.39 mmol, 3 eq.) were added to the mixture subsequently and the reaction was stirred for additional 72 hours. After this time, full completion was indicated. The reaction mixture was diluted with DCM (10 mL), washed with aqueous NH\(_4\)Cl and the organic phase was dried over MgSO\(_4\) and concentrated in vacuum. To the crude residue TBAF (1 M in THF, 4 mL) was added and the resulting mixture was heated to 63 \degree\text{C} for the next 18 h. After this time, aqueous NH\(_4\)Cl (5 mL) and water (5 mL) were added to the mixture and the resulting biphasic mixture was extracted with EtOAc (2 x 10 mL). The organic layers were separated, combined, dried over MgSO\(_4\) and concentrated in vacuum. The crude was purified
via flash chromatography (eluted with PE/EA 1:1) affording the desired compound 283 (130 mg, 0.36 mmol, 79%, d.r. 1:2) as a colorless oil.

$^1$H NMR peak listing of the mixture of diastereomers (d.r. 1:2) is uninformative, see NMR spectrum below for the graphic representation.

$^{13}$C NMR peak listing of the mixture of diastereomers (d.r. 1:2) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, $m/z$) calculated for C$_{19}$H$_{34}$NaO$_6$ $^+ [M+Na]^+$: 381.2248; found: 381.2249.

IR (film): $\lambda_{\text{max}} = 3388, 2939, 2874, 1727, 1480, 1279, 1147, 1032, 914 \text{ cm}^{-1}$.

1-((1R,2S,3R,6S)-2-formyl-3-hydroxy-6-(methoxymethoxy)-2,6-dimethylcyclohexyl)allyl pivalate (284)

To a solution of diol 283 (79 mg, 0.22 mmol, 1.0 eq.) in DCM (2 mL), water (2 mL) was added. The resulting suspension was treated with TEMPO (38 mg, 0.24 mmol, 1.1 eq.) and PIDA (78 mg, 0.24 mmol, 1.1 eq.). The resulting biphasic system was stirred vigorously at room temperature for 5 h, and then quenched with Na$_2$S$_2$O$_3$ (saturated aqueous solution), followed by addition of NaHCO$_3$ (saturated aqueous solution). After stirring at room temperature for 10 minutes, the organic layer was separated, and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried over MgSO$_4$ and filtered. The filtrate was concentrated to yield the crude product as an orange oil. The crude product was then purified via flash chromatography (EA/PE 1:2) to provide the title compound 284 (70 mg, 0.20 mmol, 89%) as a colorless oil (d.r. 1:2).

For the analytical purposes compound 284 was purified via HPLC to give the sample with d.r. 9:1, which was further characterized.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 9.31$ (d, $J = 2.7 \text{ Hz}, 1\text{H}$), 5.94 – 5.84 (m, 1H), 5.81 (m, 1H), 5.18 – 5.08 (m, 2H), 4.62 (d, $J = 7.4 \text{ Hz}, 1\text{H}$), 4.49 (d, $J = 7.4 \text{ Hz}, 1\text{H}$), 3.96 – 3.86 (m, 1H), 3.45 (s, 1H), 3.30 (s, 3H), 2.33 (s, 1H), 1.87 – 1.67 (m, 3H), 1.50 – 1.40 (m, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.21 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 204.1, 177.3, 137.7, 115.7, 89.6, 78.4, 72.8, 72.4, 55.8, 53.5, 51.5, 38.9, 31.1, 27.7, 27.2, 24.3, 18.2 \text{ ppm}$.

HRMS (ESI, $m/z$) calculated for C$_{19}$H$_{33}$O$_6^+$ [M+H]$^+$: 357.2272; found: 357.2278.
IR (film): $\lambda_{\text{max}} = 3450, 2934, 2875, 1724, 1713, 1480, 1451, 1277, 1137, 1020, 918 \text{ cm}^{-1}$.

3.1.2 Second Generation of C-Ring Precursors

(E)-4-iodo-3-methylbut-3-en-1-ol (290)

Prepared in accordance with modified literature known procedure.\footnote{Reference 161} To a stirred solution of zirconocene dichloride (3.86 g, 13.2 mmol, 0.22 eq.) in anhydrous DCM (260 mL) at $-23^\circ\text{C}$ was added trimethylaluminum (2 M in PhMe, 93 mL, 186 mmol, 3.1 eq.) dropwise. After stirring the resulting yellow mixture for 10 min at $-25^\circ\text{C}$, water (1.68 mL, 93.0 mmol, 1.55 eq.) was cautiously added. After an additional 10 min stirring, commercially available 3-butyn-1-ol (4.21 g, 60.0 mmol, 1.0 eq.), pretreated with trimethylaluminum (2 M in PhMe, 9.3 mL, 18.6 mmol, 0.31 eq.) in anhydrous DCM (50 mL) at 0 °C, was added drop-wise via cannula. The reaction mixture was allowed to warm to ambient temperature and the resulting yellow thick slurry was stirred overnight. The reaction mixture was then cooled to $-25^\circ\text{C}$ and a solution of I$_2$ (22.8 g, 90.0 mmol, 1.5 eq.) in anhydrous Et$_2$O (100 mL) was added dropwise via cannula. The mixture was allowed to warm to ambient temperature and was stirred for additional 2 h. The reaction mixture was slowly quenched with saturated aqueous solution of potassium tartrate (50 mL). The aqueous phase was extracted with Et$_2$O (3 x 200 mL) and washed with Na$_2$S$_2$O$_3$ and brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (PE/Et$_2$O 1:1) provided the desired vinyliodide 290 (10.5 g, 49.52 mmol, 83%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 6.02 (s, 1H), 3.72 ($t, J = 6.3 \text{ Hz}, 2H$), 2.48 ($t, J = 6.3 \text{ Hz}, 2H$), 1.87 ($d, J = 1.0 \text{ Hz}, 3H$), 1.43 (s, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 144.7, 77.0, 60.3, 42.6, 23.9 ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

(E)-3-methylhexa-3,5-dien-1-ol (291)

To a degassed and stirred solution of 290 (1.0 g, 4.72 mmol, 1.0 eq.) in THF (10 mL), vinyltributyltin (1.45 mL, 4.95 mmol, 1.05 eq.) and PPh$_3$ were added followed by Pd$_2$(dba)$_3$ (300 mg) at room temperature. The reaction mixture was then heated at 50 °C for 8h. Water (10 mL) was added and the reaction mixture was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure (280 mbar, temperature of bath 35 °C). After column
chromatography (Et₂O/PE 1:6) diene 291 (400 mg, 3.57 mmol, 76%) was obtained as an orange oil.

^1^H NMR (400 MHz, CDCl₃) δ = 6.58 (dt, J = 16.8, 10.5 Hz, 1H), 5.94 (d, J = 10.8 Hz, 1H), 5.15 (d, J = 16.9 Hz, 1H), 5.05 (d, J = 10.2 Hz, 1H), 3.73 (q, J = 6.1 Hz, 2H), 2.33 (t, J = 6.3 Hz, 2H), 1.80 (d, J = 1.0 Hz, 3H), 1.32 (t, J = 5.7 Hz, 1H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

(E)-tert-butyl((3-methylhexa-3,5-dien-1-yl)oxy)diphenylsilane (285)

Alcohol 291 (486 mg, 4.33 mmol, 1.0 eq.) dissolved in DCM (18.5 mL) was cooled to 0°C and followed by addition of TBDPSCI (1.12 mL, 4.10 mmol, 1.2 eq.) and imidazole (884 mg, 13.00 mmol, 2.2 eq.). The mixture was stirred at room temperature for 12 h. The solution was quenched with water (3.5 mL) and DCM (3.5 mL) was added. The aqueous layer was extracted with DCM (3 x 5 mL) and collected organic phases were washed with brine (5 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude product was then purified via flash chromatography (EA/PE 3:97) to provide the title compound 285 (1.22 g, 3.48 mmol, 80%) as a colorless oil.

^1^H NMR (400 MHz, CDCl₃) δ = 7.67 (dd, J = 7.8, 1.5 Hz, 4H), 7.40 (dd, J = 11.9, 7.1 Hz, 6H), 6.56 (dt, J = 16.8, 10.5 Hz, 1H), 5.92 – 5.81 (m, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 3.76 (t, J = 6.8 Hz, 2H), 2.30 (t, J = 6.8 Hz, 2H), 1.69 (s, 3H), 1.05 (s, 9H) ppm.

^13^C NMR (101 MHz, CDCl₃) δ = 36.5, 135.8, 134.1, 133.4, 129.7, 127.7, 127.5, 115.1, 62.9, 42.9, 26.9, 19.3, 17.1 ppm.

HRMS (ESI, m/z) calculated for C₂₃H₃₁OSi⁺ [M+H]^⁺: 351.2139; found: 351.2144.

The obtained NMR data is consistent with the values reported in the respective literature.

(E)-2-methylpenta-2,4-dienal (292)

The alcohol 291 (100 mg, 1.02 mmol, 1 eq.) was dissolved in DCM (2 mL), vigorously stirred and treated with MnO₂ (452 mg, 5.2 mmol, 5.1 eq.). The resulting mixture was stirred at room temperature for 1 h and treated with further portion of MnO₂ (603 mg, 6.9 mmol, 7 eq.). The solution was stirred for 1 h at room temperature followed by addition of another portion of MnO₂ (452 mg, 5.2 mmol, 5.1 eq.). After stirring for another 1 h, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure giving the desired aldehyde 292 contaminated with significant amount of DCM. Nevertheless, the compound was used in the next step without further purification.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 9.48\) (s, 1H), 6.94 – 6.76 (m, 2H), 5.78 – 5.55 (m, 2H), 1.86 (d, \(J = 0.9\) Hz, 3H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

\((E)-3\text{-methylhexa-3,5-diene-1,2-diol (293)}\)

\[
\begin{align*}
\text{Aldehyde 292} & \text{ (400 mg, 4.16 mmol, 1 eq.) was dissolved in dry Et}_2\text{O (5 mL)} \\
& \text{treated with Grignard reagent 273 (1 M in THF, 8.32 mL, 8.32 mmol, 2.0 eq.) at 0°C. The mixture was further stirred at 0°C for 1 h and quenched with cold saturated NH}_4\text{Cl aqueous solution (5 mL). The organic layer was separated, washed with water (5 mL) and dried using MgSO}_4. \\
& \text{The solvent was removed over the course of 2 h using nitrogen influx. The residue was dissolved in MeOH/THF 1:1 (8 mL) and the resulting solution was treated with NaHCO}_3 (350 mg, 4.16 mmol, 1.0 eq.), KF (484 mg, 8.32 mmol, 2.0 eq.) and 30\% \text{H}_2\text{O}_2 (2.36 mL, 20.8 mmol, 5.0 eq.) at room temperature. The mixture was then heated at 50°C for 2 h and quenched with aqueous Na}_2\text{S}_2\text{O}_3 (10 mL). The reaction mixture was then extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over MgSO}_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (eluted with pure EA) provided the desired diol 293 (453 mg, 3.54 mmol, 85\%) as a colorless oil.}
\end{align*}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 6.59\) (dt, \(J = 16.8, 10.5\) Hz, 1H), 6.17 (d, \(J = 10.9\) Hz, 1H), 5.22 (s, 1H), 5.15 (d, \(J = 10.2\) Hz, 1H), 4.29 – 4.10 (m, 1H), 3.69 (ddd, \(J = 10.7, 6.9, 3.6\) Hz, 1H), 3.57 (ddd, \(J = 11.3, 7.7, 3.9\) Hz, 1H), 2.12 (d, \(J = 3.3\) Hz, 1H), 1.86 – 1.80 (m, 1H), 1.78 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 136.9, 132.4, 126.9, 118.0, 77.0, 65.4, 13.5\) ppm.

HRMS (ESI, m/z) calculated for C\(_7\)H\(_{13}\)O\(_2\)+ [M+H]+: 129.0910; found: 129.0911.

IR (film): uninformative.

\((E)-2,2,9,9\text{-tetramethyl-5-(penta-2,4-dien-2-yl)-3,3,8,8-tetraphenyl-4,7-dioxa-3,8-disiladecane (286)}\)

\[
\begin{align*}
\text{Diol 293} & \text{ (63 mg, 0.50 mmol, 1.0 eq.) was dissolved in dry DCM and treated with imidazole (135 mg, 1.98 mmol, 4.0 eq.) and TBDPSCI (0.25 mL, 1.04 mmol, 4.0 eq.) at room temperature. The resulting mixture was stirred for 12 h at ambient temperature, After which time, the reaction mixture was diluted with water (4 mL) and extracted with Et}_2\text{O (3 x 5 mL). The combined organic layers were dried over MgSO}_4, filtered and concentrated under reduced pressure. Purification of the}
\end{align*}
\]
residue by flash chromatography on silica gel (eluted with PE/Et2O 20:1) provided the desired compound 286 (280 mg, 0.46 mmol, 93%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.71 – 7.60 (m, 4H), 7.59 – 7.56 (m, 4H), 7.44 – 7.37 (m, 4H), 7.36 – 7.31 (m, 8H), 6.47 (dt, $J$ = 16.8, 10.5 Hz, 1H), 5.86 (d, $J$ = 10.9 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.21 (t, $J$ = 5.9 Hz, 1H), 3.65 (dd, $J$ = 10.1, 5.6 Hz, 1H), 3.55 (dd, $J$ = 10.1, 6.4 Hz, 1H), 1.57 (s, 3H), 1.07 (s, 9H), 0.98 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 138.0, 136.2, 136.1, 135.8, 135.7, 134.4, 133.9, 133.8, 133.8, 132.9, 129.7, 129.6, 128.1, 127.7, 127.6, 127.6, 127.5, 116.5, 79.1, 66.7, 27.2, 26.9, 19.5, 19.3, 12.6 ppm.

HRMS (ESI, $m/z$) calculated for C$_{23}$H$_{29}$OSi$^+$ [M without OTBDPS]$^+$: 349.1982; found: 349.1988.

IR (film): $\lambda_{max}$ = 3073, 3048, 2957, 2931, 2858, 1472, 1427, 1111, 1105, 1079, 822, 737, 698, 610, 601 cm$^{-1}$.

(1S,2S,3S,4R)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1,3-dimethyl-2-vinylcyclohexane-1,4-diol (287)

Pt(db)$_3$ (93 mg, 0.11 mmol, 1.5 mol%), (R,R)-TADDOLPh (116 mg, 0.13 mmol, 1.7 mol%) and bis(pinacolato)diboron (1.9 g, 7.49 mmol, 1.05 eq.) were transferred to a Schlenk flask in the glove box. The flask was taken out of the glove box and dry PhMe (7.1 mL) was added. The flask was sealed and heated to 80 °C for 20 min under an inert atmosphere. Then the reaction mixture was cooled down to room temperature and the diene 285 (2.5 g, 7.13 mmol, 1.0 eq.) was added. The flask was again sealed and heated to 60 °C under an inert atmosphere for 18 h. The flask was then cooled to 25 °C and 4-oxopentanal (2 mL, 14.26 mmol, 2.5 eq.) was added. The mixture was heated at 60 °C for further 24 h. Then the mixture was cooled to 0 °C and THF (15 mL) was added followed by pH 7 phosphate buffer (15 mL) and H$_2$O$_2$ (30% in water) (10 mL, 0.11 mol, 15 eq.). The mixture was slowly allowed to warm to room temperature over 6 h. After which time, saturated aqueous sodium thiosulfate solution (15 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified via flash column chromatography (EA/PE 2:3) to afford diol 287 (2.16 g, 4.78 mmol, 67%) as a yellowish oil containing 5% to 10% of 4-oxopentanal.
The enantiomeric excess was determined to be 94% by chiral HPLS analysis (Chiralcel® OD-H, 0.1 mL/min, 99:1 Hexanes/isopropanol, λ = 254 nm) t.(major) = 18.53 min, t.(minor) = 16.48 min.

\[ ^{1}\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.67 \ (t, J = 7.8 \text{ Hz, } 4\text{H}), 7.47 - 7.39 \ (m, 6\text{H}), 5.73 \ (dt, J = 16.9, 10.4 \text{ Hz, } 1\text{H}), 5.27 - 5.13 \ (m, 2\text{H}), 3.82 \ (s, 1\text{H}), 3.77 - 3.71 \ (m, 2\text{H}), 3.68 - 3.62 \ (m, 1\text{H}), 2.42 - 2.37 \ (m, 1\text{H}), 2.13 \ (s, 1\text{H}), 1.99 - 1.90 \ (m, 2\text{H}), 1.87 - 1.80 \ (m, 1\text{H}), 1.75 \ (t, J = 13.2 \text{ Hz, } 1\text{H}), 1.63 - 1.58 \ (m, 1\text{H}), 1.55 - 1.44 \ (m, 1\text{H}), 1.20 \ (s, 3\text{H}), 1.06 \ (s, 9\text{H}), 0.87 \ (s, 3\text{H}) \text{ ppm.} \]

\[ ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 135.8, 135.7, 135.2, 132.7, 132.5, 130.1, 130.0, 128.0, 120.7, 71.7, 71.6, 60.6, 58.1, 40.9, 40.7, 34.0, 26.9, 26.3, 25.5, 19.1 \text{ ppm.} \]

\[ \text{HRMS} \ (\text{ESI, } m/z) \text{ calculated for } \text{C}_{28}\text{H}_{40}\text{NaO}_{3}\text{Si}^{+} [\text{M+Na}^{+}] : 475.2639; \text{ found: 475.2636}. \]

\[ [\alpha]_{D}^{23}: +7.7 \ (c 0.32, \text{CHCl}_3). \]

\[ \text{IR (film)}: \lambda_{\text{max}} = 3337, 2971, 2938, 1469, 1379, 1303, 1162, 1129, 1108, 952, 817 \text{ cm}^{-1}. \]

**The diol 287 (980 mg, 2.23 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and cooled to 0 °C. DIPEA (3.89 mL, 22.34 mmol, 10.0 eq.), DMAP (272 mg, 2.23 mmol, 1.0 eq.) and MOMCl (1.19 mL, 15.64 mmol, 7.0 eq.) were added subsequently. The mixture was stirred at room temperature for 48 h, after which time, aqueous saturated NH₄Cl (10 mL) and DCM (10 mL) were added. The organic layer was separated, washed with aqueous 0.1 M HCl solution (5 mL), aqueous saturated NaHCO₃ solution (10 mL), brine (2 × 10 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified via flash column chromatography (EA/PE 1:5) to afford the title 2 x MOM-protected compound (1.17 g, 2.22 mmol, 99%) as a yellowish oil.**

\[ ^{1}\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.72 - 7.67 \ (m, 4\text{H}), 7.44 - 7.35 \ (m, 6\text{H}), 5.62 \ (dt, J = 16.8, 10.4 \text{ Hz, } 1\text{H}), 5.05 \ (dd, J = 10.1, 2.3 \text{ Hz, } 1\text{H}), 4.95 \ (dd, J = 16.8, 2.2 \text{ Hz, } 1\text{H}), 4.70 - 4.61 \ (m, 3\text{H}), 4.51 \ (d, J = 6.9 \text{ Hz, } 1\text{H}), 3.80 \ (dt, J = 28.8, 9.5, 5.8 \text{ Hz, } 2\text{H}), 3.37 - 3.33 \ (m, 1\text{H}), 3.33 \ (s, 3\text{H}), 3.31 \ (s, 3\text{H}), 2.24 \ (d, J = 10.7 \text{ Hz, } 1\text{H}), 2.17 - 2.12 \ (m, 1\text{H}), 1.94 - 1.79 \ (m, 3\text{H}), 1.70 - 1.57 \ (m, 1\text{H}), 1.52 - 1.40 \ (m, 1\text{H}), 1.11 \ (s, 3\text{H}), 1.03 \ (s, 9\text{H}), 0.85 \ (s, 3\text{H}) \text{ ppm.} \]

\[ ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 136.4, 135.8, 134.5, 134.4, 129.6, 127.7, 118.6, 95.9, 90.3, 80.4, 77.8, 61.3, 56.5, 55.9, 55.5, 39.7, 37.9, 32.0, 31.1, 27.0, 24.9, 24.2, 23.6, 19.3 \text{ ppm.} \]

\[ \text{HRMS} \ (\text{ESI, } m/z) \text{ calculated for } \text{C}_{32}\text{H}_{49}\text{O}_{3}\text{Si}^{+} [\text{M+H}^{+}] : 541.3344; \text{ found: 541.3366}. \]
[α]$_D$$^{23}$: −14.5 (c 0.41, CHCl$_3$).

IR (film): $\lambda_{max} = 2931, 2887, 1461, 1428, 1147, 1104, 1081, 1031, 916, 823, 740, 702$ cm$^{-1}$.

2-((15,25,35,6R)-3,6-bis(methoxymethoxy)-1,3-dimethyl-2-vinylcyclohexyl)ethan-1-ol

The respective MOM-protected diol (127 mg, 0.23 mmol, 1.0 eq.) was dissolved in THF (0.1 mL) and treated with excess of TBAF (1 M in THF, 0.94 mL, 0.94 mmol, 4.0 eq.) at room temperature. The resulting reddish mixture was stirred further for 3 h at ambient temperature (completion monitored by TLC), quenched with aqueous NH$_4$Cl and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography (EA/PE 1:2) to afford the title alcohol (71 mg, 0.23 mmol, 100%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 5.62$ (dt, $J = 16.7, 10.5$ Hz, 1H), 5.14 – 4.96 (m, 2H), 4.80 – 4.66 (m, 3H), 4.58 (d, $J = 6.9$ Hz, 1H), 3.73 (q, $J = 5.6$ Hz, 2H), 3.48 (d, $J = 10.4$ Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 3.16 (s, 1H), 2.42 (d, $J = 10.7$ Hz, 1H), 1.94 (ddt, $J = 50.6, 24.7, 12.6$ Hz, 4H), 1.74 – 1.66 (m, 1H), 1.47 (t, $J = 13.1$ Hz, 1H), 1.12 (s, 3H), 0.93 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 136.5, 118.8, 95.8, 90.4, 80.6, 78.4, 59.4, 58.3, 56.1, 55.8, 39.9, 37.6, 31.6, 26.0, 25.1, 23.7$ ppm.

HRMS (ESI, m/z) calculated for C$_{16}$H$_{30}$NaO$_5$ $^{[M+Na]}^{+}$: 325.1985; found: 325.1989.

[α]$_D$$^{23}$: −13.3 (c 1.02, CHCl$_3$).

IR (film): $\lambda_{max} = 3388, 2954, 2933, 2889, 1463, 1428, 1379, 1147, 1111, 1026, 917, 868, 743, 702, 608$ cm$^{-1}$.

2-((15,25,35,6R)-3,6-bis(methoxymethoxy)-1,3-dimethyl-2-vinylcyclohexyl)acetaldehyde

(293)

To a solution of respective alcohol (71 mg, 0.23 mmol, 1.0 eq.) in DCM (2 mL), water (2 mL) was added. The resulting suspension was treated with TEMPO (40 mg, 0.26 mmol, 1.1 eq.) and PIDA (83 mg, 0.26 mmol, 1.1 eq.). The resulting biphasic system was stirred vigorously at room temperature for 5 h, and then quenched with Na$_2$S$_2$O$_3$ (saturated aqueous solution), followed by addition of NaHCO$_3$ (saturated aqueous solution). After stirring at room temperature for 10 minutes, the organic layer was separated, and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried over MgSO$_4$ and filtered. The filtrate was concentrated to
yield the crude product as an orange oil. The crude product was then purified via flash chromatography (EA/PE 1:2) to provide the title compound 293 (55 mg, 0.19 mmol, 79%) as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ = 9.89 (t, J = 2.6 Hz, 1H), 5.63 (dt, J = 16.7, 10.4 Hz, 1H), 5.16 – 5.03 (m, 2H), 4.70 (dd, J = 12.5, 7.1 Hz, 2H), 4.64 (d, J = 7.3 Hz, 1H), 4.55 (d, J = 6.9 Hz, 1H), 3.48 (dd, J = 9.6, 4.1 Hz, 1H), 3.34 (d, J = 0.5 Hz, 6H), 2.83 – 2.70 (m, 2H), 2.53 (d, J = 10.8 Hz, 1H), 1.93 – 1.69 (m, 3H), 1.55 – 1.43 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H) ppm.

13C NMR (101 MHz, CDCl₃) δ = 204.3, 135.8, 119.5, 95.7, 90.4, 79.8, 77.7, 57.2, 55.9, 55.6, 50.0, 40.8, 32.1, 25.2, 25.0, 23.8 ppm.

HRMS (ESI, m/z) calculated for C₁₆H₂₈NaO₅⁺ [M+Na]⁺: 323.1829; found: 323.1837.

[a]D²³: –28.3 (c 1.72, CHCl₃).

IR (film): λmax = 2935, 2888, 1713, 1456, 1379, 1209, 1148, 1099, 1019, 916 cm⁻¹.

(1S,2S,3R,6S)-2-((tert-butyldiphenylsilyl)oxy)ethyl)-3,6-bis(methoxymethoxy)-2,6-dimethylcyclohexane-1-carbaldehyde (295)

Ozone was bubbled through a cooled (−78 °C) solution of the alkene (1.4 g, 2.59 mmol, 1.0 eq.) in methanol (5 mL) and DCM (40 mL) until a blue color persisted. The solution was then sparged with O₂ for 10 minutes and PPh₃ (2.04 g, 7.77 mmol, 3.0 eq.) was added portionwise, and the reaction mixture was allowed to slowly reach room temperature over the period of 14 h. After this time, solvent was removed under reduced pressure and the crude was submitted to the flash column chromatography (PE/EA 5:1) affording a pure aldehyde 295 (1.35 g, 2.49 mmol, 96%) as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ = 9.78 (d, J = 4.9 Hz, 1H), 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.43 – 7.35 (m, 6H), 4.68 – 4.60 (m, 3H), 4.52 (d, J = 6.9 Hz, 1H), 3.84 – 3.69 (m, 2H), 3.51 (dd, J = 9.2, 3.4 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 2.66 (dd, J = 4.9, 1.3 Hz, 1H), 2.20 (dt, J = 14.3, 7.3 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.96 – 1.86 (m, 2H), 1.78 – 1.69 (m, 1H), 1.63 (dd, J = 14.1, 10.3, 3.8 Hz, 1H), 1.21 (s, 3H), 1.03 (s, 9H), 1.00 (s, 3H) ppm.

13C NMR (101 MHz, CDCl₃) δ = 204.1, 135.8, 134.1, 129.7, 127.8, 95.9, 90.1, 80.6, 62.8, 60.9, 55.9, 55.7, 40.0, 33.2, 27.0, 24.6, 23.4, 23.0, 19.3 ppm.

HRMS (ESI, m/z) calculated for C₃₁H₴₆NaO₆Si⁺ [M+Na]⁺: 565.2956; found: 565.2958.
Aldehyde 295 (1.35 g, 2.49 mmol, 1.0 eq.) was dissolved in MeOH (5 mL) and the resulting solution was cooled down to 0 °C. To the reaction mixture, NaBH₄ (94 mg, 2.49 mmol, 1.0 eq.) was added portionwise at 0 °C. After addition, the reaction mixture was allowed to warm up to room temperature over 15 min. After this time, water (5 mL) was added and the cloudy mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated to yield the crude product which was then purified via flash chromatography (Et₂O/PE 1:1) to provide the title compound 296 (1.33 g, 2.44 mmol, 98%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 7.71 – 7.66 (m, 4H), 7.39 (q, J = 7.6, 6.3 Hz, 6H), 4.80 – 4.70 (m, 2H), 4.46 (dd, J = 6.9, 1.0 Hz, 1H), 4.40 (dd, J = 6.9, 0.9 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.76 (dt, J = 17.7, 9.9 Hz, 3H), 3.37 (d, J = 1.3 Hz, 3H), 3.28 (d, J = 1.3 Hz, 3H), 3.19 – 3.12 (m, 1H), 2.07 – 1.95 (m, 3H), 1.86 – 1.75 (m, 2H), 1.66 – 1.59 (m, 1H), 1.48 (t, J = 14.3 Hz, 1H), 1.39 (s, 3H), 1.04 (d, J = 1.1 Hz, 9H), 0.79 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 35.7, 134.1, 129.6, 127.7, 96.0, 89.8, 81.5, 79.1, 61.1, 60.4, 56.2, 55.7, 50.0, 41.4, 40.2, 31.3, 27.0, 23.1, 21.7, 20.2, 19.2 ppm.

HRMS (ESI, m/z) calculated for C₃₁H₄₈NaO₆Si⁺ [M+Na⁺]: 567.3112; found: 567.3118.

[α]D₂₃: –11.8 (c 0.76, CHCl₃).

IR (film): λmax = 2932, 2889, 2857, 1728, 1428, 1145, 1105, 1085, 1031, 919, 823, 740, 702, 614 cm⁻¹.

((1R,2S,3R,6S)-2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3,6-bis(methoxymethoxy)-2,6-dimethylcyclohexyl)methanol (296)
reaction mixture was allowed to warm up to room temperature and stirred for 2 h. After which time, the reaction mixture was carefully quenched with aqueous NaHCO₃, and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. To the neat residue, TBAF (1 M in THF, 2.43 mL, 2.43 mmol, 2.0 eq.) was added at room temperature and the mixture was stirred for 14 h, quenched with aqueous NaHCO₃, and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Next, the residue was dissolved in DCM (5 mL) followed by addition of water (5 mL). To the resulting biphasic mixture, TEMPO (227 mg, 1.46 mmol, 1.2 eq.) and PIDA (469 mg, 1.46 mmol, 1.2 eq.) were added at ambient temperature. The resulting suspension was stirred for 3 h, with aqueous Na₂S₂O₅ and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure affording the crude aldehyde which was further purified via flash column chromatography (EA/PE 2:3) to give **297** (368 mg, 0.95 mmol, 78%) as a colorless oil. **1H NMR** (400 MHz, CDCl₃) δ = 9.89 (dd, J = 3.4, 1.4 Hz, 1H), 4.75 – 4.68 (m, 2H), 4.66 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.43 (dd, J = 12.3, 2.5 Hz, 1H), 4.20 (dd, J = 12.3, 5.5 Hz, 1H), 3.57 (dd, J = 7.2, 3.0 Hz, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.77 – 2.68 (m, 1H), 2.57 (d, J = 16.3 Hz, 1H), 2.42 (dd, J = 5.2, 2.1 Hz, 1H), 1.99 (ddd, J = 13.2, 9.1, 3.9 Hz, 1H), 1.86 (ddt, J = 15.0, 7.6, 3.8 Hz, 1H), 1.77 – 1.58 (m, 2H), 1.26 (s, 3H), 1.19 (s, 9H), 1.17 (s, 3H) ppm. **13C NMR** (101 MHz, CDCl₃) δ = 203.0, 178.6, 95.9, 90.2, 80.2, 78.1, 63.1, 56.1, 55.6, 51.6, 47.1, 41.7, 38.7, 32.6, 27.3, 23.4, 23.3, 22.9 ppm. **HRMS** (ESI, m/z) calculated for C₂₀H₃₆NaO₇ [M+Na]⁺: 411.2353; found: 411.2364. [α]D²³: −24.3 (c 1.44, CHCl₃). **IR (film):** λ max = 2981, 2889, 1725, 1480, 1462, 1383, 1252, 1150, 1088, 1030, 956 cm⁻¹. **1-((1R,2S,3R,6S)-2-((tert-butyldiphenylsilyl)oxy)ethyl)-3,6-bis(methoxymethoxy)-2,6-dimethylcyclohexyl)prop-2-en-1-ol (298)** A solution of aldehyde **295** (100 mg, 0.18 mmol, 1.0 eq.) in dry THF (1 mL) was treated with vinylmagnesium bromide (1 M in THF, 0.22 mL, 0.22 mmol, 1.2 eq.) at −78 °C. The resulting mixture was stirred for 10 min at −78 °C and warmed up to room temperature over 30 min. After this time, the reaction mixture was quenched with aqueous NH₄Cl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Next, the residue was dissolved in DCM (5 mL) followed by addition of water (5 mL). To the resulting biphasic mixture, TEMPO (227 mg, 1.46 mmol, 1.2 eq.) and PIDA (469 mg, 1.46 mmol, 1.2 eq.) were added at ambient temperature. The resulting suspension was stirred for 3 h, with aqueous Na₂S₂O₅ and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure affording the crude aldehyde which was further purified via flash column chromatography (EA/PE 2:3) to give **297** (368 mg, 0.95 mmol, 78%) as a colorless oil. **1H NMR** (400 MHz, CDCl₃) δ = 9.89 (dd, J = 3.4, 1.4 Hz, 1H), 4.75 – 4.68 (m, 2H), 4.66 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.43 (dd, J = 12.3, 2.5 Hz, 1H), 4.20 (dd, J = 12.3, 5.5 Hz, 1H), 3.57 (dd, J = 7.2, 3.0 Hz, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.77 – 2.68 (m, 1H), 2.57 (d, J = 16.3 Hz, 1H), 2.42 (dd, J = 5.2, 2.1 Hz, 1H), 1.99 (ddd, J = 13.2, 9.1, 3.9 Hz, 1H), 1.86 (ddt, J = 15.0, 7.6, 3.8 Hz, 1H), 1.77 – 1.58 (m, 2H), 1.26 (s, 3H), 1.19 (s, 9H), 1.17 (s, 3H) ppm. **13C NMR** (101 MHz, CDCl₃) δ = 203.0, 178.6, 95.9, 90.2, 80.2, 78.1, 63.1, 56.1, 55.6, 51.6, 47.1, 41.7, 38.7, 32.6, 27.3, 23.4, 23.3, 22.9 ppm. **HRMS** (ESI, m/z) calculated for C₂₀H₃₆NaO₇ [M+Na]⁺: 411.2353; found: 411.2364. [α]D²³: −24.3 (c 1.44, CHCl₃). **IR (film):** λ max = 2981, 2889, 1725, 1480, 1462, 1383, 1252, 1150, 1088, 1030, 956 cm⁻¹.
filtered and concentrated under reduced pressure affording the crude aldehyde which was further purified via flash column chromatography (PE/EA 5:1) to give 298 (99 mg, 0.18 mmol, 95%) as a colorless oil (d.r. 1:3).

\(^1\text{H NMR}\) peak listing of the mixture of diastereomers (d.r. 1:3) is uninformative, see NMR spectrum below for the graphic representation. For analytical purposes, two diastereomers were separated via HPLC. With regards to the relevance to our research the absolute stereochemistry of the resulting allylic alcohols was not determined.

Minor diastereomer of 298: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.70 – 7.60 \text{ (m, 4H)}, 7.45 – 7.33 \text{ (m, 6H)}, 6.16 \text{ (ddd, } J = 17.1, 10.5, 5.1 \text{ Hz, 1H)}, 5.22 \text{ (dt, } J = 17.2, 1.7 \text{ Hz, 1H)}, 5.06 \text{ (dt, } J = 10.5, 1.8 \text{ Hz, 1H)}, 4.78 – 4.65 \text{ (m, 3H)}, 4.46 \text{ (d, } J = 6.9 \text{ Hz, 1H)}, 4.38 \text{ (d, } J = 6.9 \text{ Hz, 1H}), 3.75 \text{ (ddq, } J = 19.2, 9.7, 5.8, 5.0 \text{ Hz, 2H)}, 3.35 (s, 3H), 3.27 (s, 3H), 3.10 (d, } J = 3.3 \text{ Hz, 1H}), 2.72 (d, } J = 6.8 \text{ Hz, 1H}), 1.99 – 1.74 \text{ (m, 6H)}, 1.47 (s, 3H), 1.02 (s, 12H) ppm.

Major diastereomer of 298: \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.70 – 7.62 \text{ (m, 4H)}, 7.42 – 7.34 \text{ (m, 6H)}, 6.02 \text{ (ddd, } J = 17.0, 10.2, 6.6 \text{ Hz, 1H)}, 5.18 \text{ (dt, } J = 17.1, 1.4 \text{ Hz, 1H)}, 5.03 \text{ (dt, } J = 10.2, 1.3 \text{ Hz, 1H)}, 4.79 – 4.69 \text{ (m, 2H)}, 4.51 – 4.33 \text{ (m, 3H)}, 3.90 (s, 1H), 3.78 – 3.65 \text{ (m, 2H)}, 3.36 (s, 3H), 3.28 (s, 3H), 3.21 – 3.12 (m, 1H), 2.07 – 2.02 (m, 3H), 1.90 (t, } J = 7.4 \text{ Hz, 2H}), 1.57 (dd, } J = 9.7, 6.2 \text{ Hz, 1H}), 1.51 (s, 3H), 1.01 (s, 9H), 0.95 (s, 3H) ppm.

\(^1\text{C NMR}\) peak listing of the mixture of diastereomers (d.r. 1:3) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, \(m/z\)) calculated for C\(_{33}\)H\(_{50}\)NaO\(_6\)Si\(_6\)^+ \([\text{M}+\text{Na}]^+\)\): 593.3269; found: 593.3273.

\(\text{IR (film): } \lambda_{\text{max}} = 3459, 2931, 2888, 1468, 1452, 1428, 1146, 1110, 1086, 1035, 918, 704 \text{ cm}^{-1}.\)

1-((1R,2S,5R,6S)-2-(2-hydroxyethyl)-3,6-bis(methoxymethoxy)-2,6-dimethylcyclohexyl)allyl pivalate

A solution of 298 (99 mg, 1.22 mmol, 1.0 eq.) in dry DCM (1 mL) was treated with DMAP (21 mg, 0.17 mmol, 1.0 eq.) and Et\(_3\)N (0.12 mL, 0.87 mmol, 5.0 eq.). To the resulting solution, PivCl (0.05 mL, 0.34 mmol, 2.0 eq.) was added dropwise at \(-78 \text{ °C}\) and the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. After which time, the reaction mixture was carefully quenched with aqueous NaHCO\(_3\), and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. To the neat residue, TBAF (1 M in THF, 0.35 mL, 0.35 mmol, 2.0 eq.)
was added at room temperature and the mixture was stirred for 14 h, quenched with aqueous NaHCO₃, and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was used in the next step without further purification.

For analytical purposes, the major diastereomer of the title product was purified via HPLS and characterized.

**¹H NMR** (400 MHz, CDCl₃) δ = 6.03 – 5.92 (m, 2H), 5.06 – 4.95 (m, 2H), 4.73 – 4.66 (m, 3H), 4.56 (d, J = 6.8 Hz, 1H), 3.82 – 3.66 (m, 2H), 3.42 – 3.39 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.36 (s, 1H), 2.07 – 2.01 (m, 2H), 1.99 (s, 1H), 1.85 – 1.69 (m, 2H), 1.62 (s, 1H), 1.44 (s, 3H), 1.24 (s, 9H), 1.11 (s, 3H) ppm.

**¹³C NMR** (101 MHz, CDCl₃) δ = 177.2, 139.2, 113.4, 95.6, 90.1, 80.0, 79.5, 73.3, 59.4, 56.1, 55.9, 53.3, 41.8, 39.6, 38.9, 33.7, 27.4, 25.6, 23.4, 22.9 ppm.

**HRMS** (ESI, m/z) calculated for C₂₂H₄₀NaO₇⁺ [M+Na]⁺: 439.2666; found: 439.2658.

1-((1R,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-(2-oxoethyl)cyclohexyl)allyl pivalate (299)

The respective alcohol (72 mg, 0.17 mmol, 1.0 eq.) was dissolved in DCM (1 mL) followed by addition of water (1 mL). To the resulting biphasic mixture, TEMPO (32 mg, 0.21 mmol, 1.2 eq.) and PIDA (67 mg, 0.21 mmol, 1.2 eq.) were added at ambient temperature. The resulting suspension was stirred for 3 h, with aqueous Na₂S₂O₅ and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure affording the crude aldehyde which was further purified via flash column chromatography (EA/PE 1:3) to give 299 (48 mg, 0.12 mmol, 67%) as a colorless oil (d.r. 1:1.5).

**¹H NMR** peak listing of the mixture of diastereomers (d.r. 1:1.5) is uninformative, see NMR spectrum below for the graphic representation.

**¹³C NMR** peak listing of the mixture of diastereomers (d.r. 1:1.5) is uninformative, see NMR spectrum below for the graphic representation.

**HRMS** (ESI, m/z) calculated for C₂₂H₃₈NaO₇⁺ [M+Na]⁺: 437.2510; found: 437.2516.

**IR** (film): λmax = 2956, 2892, 1728, 1480, 1450, 1277, 1148, 1101, 1035, 919 cm⁻¹.
(1R,2S,3S,4S)-2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-hydroxy-2,4-dimethyl-3-vinylcyclohexyl pivalate (300)

A solution of 287 (15 mg, 0.03 mmol, 1.0 eq.) in dry DCM (1 mL) was treated with DMAP (4 mg, 0.03 mmol, 1.0 eq.) and Et$_3$N (0.04 mL, 0.33 mmol, 10.0 eq.). To the resulting solution, PivCl (0.01 mL, 0.10 mmol, 3.0 eq.) was added dropwise at −78 °C and the reaction mixture was allowed to warm up to room temperature and stirred for 48 h. After which time, the reaction mixture was carefully quenched with aqueous NaHCO$_3$, and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:4) to give 300 (6 mg, 0.01 mmol, 35%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.70 – 7.63$ (m, 4H), 7.46 – 7.35 (m, 6H), 5.75 (dt, $J = 16.8$, 10.3 Hz, 1H), 5.17 – 5.03 (m, 2H), 4.73 (dd, $J = 9.2$, 3.4 Hz, 1H), 3.71 (tq, $J = 10.4$, 4.9 Hz, 2H), 3.16 (s, 1H), 2.57 – 2.39 (m, 2H), 2.04 – 1.90 (m, 1H), 1.74 – 1.54 (m, 4H), 1.15 (s, 9H), 1.13 (s, 3H), 1.05 (s, 9H), 0.81 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.8$, 135.7, 133.1, 132.9, 129.9, 127.8, 119.0, 75.8, 71.2, 60.9, 58.7, 39.1, 39.1, 33.7, 27.9, 27.4, 27.2, 26.9, 23.3, 19.0 ppm.

HRMS (ESI, $m/z$) calculated for C$_{33}$H$_{48}$NaO$_4$Si$^+$ [M+Na]$^+$: 559.3214; found: 559.3231.

[α]$_D^{23}$ = −2.2 (c 0.59, CHCl$_3$).

IR (film): $\lambda$ max = 3467, 2932, 2858, 1724, 1479, 1458, 1428, 1284, 1164, 1111, 984, 739, 702 cm$^{-1}$.

(1S,2S,3S,4R)-4-(benzyloxy)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1,3-dimethyl-2-vinylcyclohexan-1-ol (301)

A solution of 287 (143 mg, 0.32 mmol, 1.0 eq.) in dry THF (3 mL) was treated with KHMDS (0.5 M in PhMe, 1.39 mL, 0.69 mmol, 2.2 eq.) at −78 °C and the resulting reddish solution was stirred for another 15 min at the same temperature followed by addition of BnBr (0.1 mL, 0.82 mmol, 2.6 eq.). The resulting mixture was kept for another 30 min at −78 °C and for 1 h at 0 °C. After this time, the reaction mixture was quenched with aqueous NH$_4$Cl and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure affording the crude aldehyde.
which was further purified via flash column chromatography (EA/PE 1:5) to give \(301\) (113 mg, 0.21 mmol, 66%) as a colorless oil.

\[ ^1H \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.71 – 7.68 \text{ (m, 2H)}, 7.66 – 7.64 \text{ (m, 2H)}, 7.43 – 7.33 \text{ (m, 8H)}, 7.29 – 7.27 \text{ (m, 3H)}, 5.72 \text{ (dt, } J = 16.8, 10.3 \text{ Hz, 1H)}, 5.19 – 5.05 \text{ (m, 2H)}, 4.57 \text{ (d, } J = 11.6 \text{ Hz, 1H}), 4.25 \text{ (d, } J = 11.6 \text{ Hz, 1H}), 3.79 – 3.71 \text{ (m, 2H)}, 3.24 \text{ (dd, } J = 8.1, 3.0 \text{ Hz, 1H}), 2.52 \text{ (d, } J = 10.6 \text{ Hz, 1H}), 2.26 \text{ (m, 1H)}, 2.00 \text{ (dt, } J = 12.5, 8.7, 3.8 \text{ Hz, 1H}), 1.84 – 1.76 \text{ (m, 2H)}, 1.72 – 1.64 \text{ (m, 1H)}, 1.51 \text{ (ddd, } J = 13.0, 8.9, 3.8 \text{ Hz, 1H}), 1.15 \text{ (s, 3H)}, 1.05 \text{ (s, 9H)}, 0.90 \text{ (s, 3H)} \text{ ppm.} \]

\[ ^13C \text{ NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 139.2, 135.8, 135.8, 129.8, 128.3, 127.8, 127.4, 71.4, 71.0, 61.3, 58.4, 40.2, 33.8, 27.0, 22.1, 19.2 \text{ ppm.} \]

\[ \text{HRMS (ESI, m/z) calculated for } C_{35}H_{47}O_3Si^+ [M+H]^+: 543.3289; \text{ found: 543.3303.} \]

\[ [\alpha]_D^{23} : -12.3 \text{ (c 0.50, CHCl}_3). \]

\[ \text{IR (film): uninformative.} \]

\(1S,2S,3R,6S)-3\)-(benzyloxy)-2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-hydroxy-2,6-dimethylcyclohexane-1-carboxaldehyde (303)

\(1R,2S,3S,4S)-2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-formyl-4-hydroxy-2,4-dimethylcyclohexyl benzoate (302)

Ozone was bubbled through a cooled (−78 °C) solution of \(301\) (568 mg, 1.05 mmol, 1.0 eq.) in methanol (5 mL) and dichloromethane (40 mL) until a blue color persisted. The solution was then sparged with \(O_2\) for 10 minutes and \(PPh_3\) (548 mg, 2.09 mmol, 2.0 eq.) was added portionwise, and the reaction mixture was allowed to slowly reach room temperature over the period of 14 h. After this time, solvent was removed under reduced pressure and the crude was submitted to the flash column chromatography (PE/EA 5:1) affording a readily separable compound \(303\) (290 mg, 0.53 mmol, 51%) as a colorless oil and compound \(302\) (105 mg, 0.19 mmol, 18%) as a yellowish oil.

Aldehyde \(303\):

\[ ^1H \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 9.80 \text{ (d, } J = 4.6 \text{ Hz, 1H}), 7.72 – 7.68 \text{ (m, 2H)}, 7.66 – 7.63 \text{ (m, 2H)}, 7.46 – 7.36 \text{ (m, 6H)}, 7.30 – 7.23 \text{ (m, 5H)}, 4.62 \text{ (d, } J = 11.6 \text{ Hz, 1H}), 4.32 \text{ (d, } J = 11.6 \text{ Hz, 1H}), 3.84 – 3.68 \text{ (m, 3H)}, 3.48 \text{ (dd, } J = 9.8, 2.9 \text{ Hz, 1H}), 2.93 \text{ (d, } J = 4.4 \text{ Hz, 1H}), 2.67 – 2.47 \text{ (m, 1H)}, 2.16 – 2.00 \text{ (m, 1H)}, 1.95 – 1.76 \text{ (m, 3H)}, 1.71 – 1.59 \text{ (m, 1H)}, 1.19 \text{ (s, 3H)}, 1.06 \text{ (s, 9H)}, 0.99 \text{ (s, 3H)} \text{ ppm.} \]
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 204.6, 138.8, 135.8, 135.7, 132.9, 130.1, 130.0, 128.4, 128.0, 128.0, 127.6, 127.5, 81.8, 71.3, 70.4, 64.7, 61.2, 40.3, 36.6, 35.1, 29.4, 27.0, 23.4, 22.1, 19.1 ppm.

HRMS (ESI, $m/z$) calculated for C$_{34}$H$_{44}$NaO$_4$Si$^+$ [M+Na]$^+$: 567.2901; found: 567.2913.

$[\alpha]_D^{23}$: $-27.0$ (c 1.00, CHCl$_3$).

IR (film): $\lambda_{\text{max}} =$ 3402, 2933, 2858, 1719, 1462, 1428, 1112, 1069, 739, 702 cm$^{-1}$.

Aldehyde 302:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 9.90 (d, $J = 5.0$ Hz, 1H), 7.98 (dd, $J = 8.4$, 1.3 Hz, 2H), 7.73 $-$ 7.69 (m, 2H), 7.69 $-$ 7.65 (m, 2H), 7.58 $-$ 7.52 (m, 1H), 7.46 $-$ 7.39 (m, 8H), 5.28 (dd, $J = 10.5$, 3.4 Hz, 1H), 3.81 (h, $J = 5.7$ Hz, 2H), 3.69 (s, 1H), 3.11 $-$ 2.99 (m, 1H), 2.93 $-$ 2.77 (m, 1H), 2.24 (m, 1H), 1.96 $-$ 1.78 (m, 4H), 1.23 (s, 3H), 1.08 (s, 9H), 0.99 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 203.2, 165.9, 135.8, 135.7, 133.2, 132.6, 132.5, 130.3, 130.1, 130.0, 129.6, 128.5, 128.0, 128.0, 77.3, 70.1, 64.9, 60.9, 39.4, 36.6, 35.1, 29.7, 27.0, 23.4, 23.2, 19.1 ppm.

HRMS (ESI, $m/z$) calculated for C$_{34}$H$_{42}$NaO$_5$Si$^+$ [M+Na]$^+$: 581.2694; found: 581.2708.

$[\alpha]_D^{23}$: $-24.8$ (c 1.70, CHCl$_3$).

IR (film): $\lambda_{\text{max}} =$ 3434, 2932, 2889, 1717, 1462, 1452, 1382, 1256, 1112, 956, 740, 703 cm$^{-1}$.

((1R,2S,3R)-3-(benzoyloxy)-2-(2-((tert-butyldiphenylsilyloxy)ethyl)-2-methyl-6-methylenecyclohexyl)methanol (305)

A solution of 303 (447 mg, 0.82 mmol, 1.0 eq.) in PhMe/dioxane 1:1 (10 mL) was treated with the Burgess reagent (205 mg, 0.86 mmol, 1.05 eq.) at room temperature. The resulting reaction mixture was heated at 50 °C for 2 h. After which time, the reaction was quenched with water (2 mL) and extracted with Et$_2$O (3 x 10 mL). The organic layer was dried (MgSO$_4$) and concentrated. The residue was further dissolved in MeOH (20 mL), and the solution was cooled down to 0 °C followed by treatment with NaBH$_4$ (155 mg, 4.10 mmol, 5.0 eq.). After vigorous gas evolution was over, the reaction mixture was allowed to slowly reach room temperature over 14 h. After which time, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was then washed with brine (3 x 50 mL), dried (MgSO$_4$) and concentrated.
The crude NMR showed formation of mixture of two isomeric compounds 305 (exo/endo 2:1) which was used in the following step without purification/separation. For the analytical purposes, a pure sample of exo-305 was obtained via HPLS and further characterized.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.68 – 7.62 (m, 4H), 7.42 – 7.32 (m, 6H), 7.29 – 7.23 (m, 5H), 4.96 (s, 1H), 4.70 (s, 1H), 4.55 (d, \(J = 11.7\) Hz, 1H), 4.28 (d, \(J = 11.7\) Hz, 1H), 3.78 – 3.71 (m, 2H), 3.65 (dd, \(J = 10.2, 4.0\) Hz, 1H), 3.55 (t, \(J = 10.5\) Hz, 1H), 3.23 (dd, \(J = 9.6, 3.8\) Hz, 1H), 2.40 (dd, \(J = 10.6, 4.4\) Hz, 1H), 2.31 – 2.22 (m, 1H), 2.11 (dd, \(J = 17.1, 7.8\) Hz, 1H), 2.00 – 1.91 (m, 1H), 1.86 – 1.77 (m, 1H), 1.70 (d, \(J = 6.3\) Hz, 1H), 1.57 (dd, \(J = 15.0, 7.8\) Hz, 1H), 1.02 (s, 9H), 0.91 (s, 3H) ppm.

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 145.9, 139.2, 135.7, 134.2, 129.6, 128.4, 127.7, 127.4, 113.2, 81.4, 71.3, 60.8, 59.3, 53.9, 40.5, 36.9, 30.5, 29.6, 27.0, 26.3, 21.4, 19.3\) ppm.

HRMS (ESI, m/z) calculated for C\(_{34}\)H\(_{44}\)NaO\(_3\)Si\([M+Na]^+\): 551.2952; found: 551.2961.

IR (film): \(\lambda_{\text{max}} = 3450, 2931, 2858, 1473, 1458, 1428, 1111, 724, 701\) cm\(^{-1}\).

\(((1R,2S,3R)-3-(benzyloxy)-2-(2-hydroxyethyl)-2-methyl-6-methylenecyclohexyl)methyl\) pivalate (306)

Crude mixture of compounds 305 (433 mg, 0.82 mmol, 1.0 eq.) was dissolved in dry DCM (5 mL) and the solution was treated with DMAP (200 mg, 1.64 mmol, 2.0 eq.) and Et\(_3\)N (0.58 mL, 4.09 mmol, 5.0 eq.). To the resulting mixture, PivCl (0.3 mL, 2.46 mmol, 3.0 eq.) was added dropwise at \(-78\) °C, after white precipitate was formed, the solution was allowed to warm up to room temperature and was stirred for additional 2 h. After which time, the reaction mixture was carefully quenched with NaHCO\(_3\) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The neat residue TBAF (2.46 mL, 2.46 mmol, 3.0 eq.) was added at room temperature and the mixture was stirred for 14 h, quenched with NaHCO\(_3\), and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The crude mixture of isomeric products was used in the next step without further purification.

For the analytical purposes, a pure sample of exo-306 was obtained via HPLS and further characterized.
The mixture of isomeric alcohols 306 (306 mg, 0.82 mmol, 1.0 eq.) was dissolved in DCM (3 mL) followed by addition of water (3 mL). To the resulting biphasic mixture, TEMPO (141 mg, 0.90 mmol, 1.1 eq.) and PIDA (315 mg, 0.98 mmol, 1.2 eq.) were added at ambient temperature. The resulting suspension was stirred for 3 h, with aqueous Na$_2$S$_2$O$_3$ and extracted with DCM (3 x 15 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure affording the crude mixtures of aldehyde which was further purified via flash column chromatography (Et$_2$O/PE 1:2) to give inseparable mixture of two isomeric aldehydes 307 (221 mg, 0.59 mmol, 72%) as a colorless oil (exo/endo 2:1).

$^1$H NMR peak listing of the mixture of two isomers (exo/endo 2:1) is uninformative, see NMR spectrum below for the graphic representation.

$^{13}$C NMR peak listing of the mixture of two isomers (exo/endo 2:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C$_{23}$H$_{32}$NaO$_4$ [M+Na]$^+$: 395.2193; found: 395.2202.

IR (film): $\lambda_{max} = 2974, 2939, 2870, 1725, 1479, 1456, 1284, 1152, 1078, 1030$ cm$^{-1}$. 

1$^H$ NMR (400 MHz, CDCl$_3$) $\delta = 7.34 – 7.28$ (m, 5H), 4.85 (s, 1H), 4.68 – 4.62 (m, 2H), 4.41 (d, $J = 11.4$ Hz, 1H), 4.28 – 4.11 (m, 2H), 3.74 (td, $J = 12.2$, 4.5 Hz, 1H), 3.62 – 3.53 (m, 1H), 3.45 (dd, $J = 10.0$, 3.9 Hz, 1H), 2.86 – 2.71 (m, 1H), 2.39 (dd, $J = 9.2$, 4.9 Hz, 1H), 2.30 (dt, $J = 13.9$, 4.8 Hz, 1H), 2.23 – 2.19 (m, 1H), 2.16 – 2.04 (m, 2H), 1.96 – 1.86 (m, 1H), 1.82 – 1.74 (m, 1H), 1.14 (s, 9H), 1.05 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 178.7, 144.8, 128.6, 128.0, 128.1, 127.8, 112.5, 81.5, 71.9, 62.4, 58.9, 57.0, 40.9, 39.7, 38.8, 30.5, 30.0, 29.9, 27.4, 26.5, 21.3 ppm.

HRMS (ESI, m/z) calculated for C$_{23}$H$_{34}$NaO$_4$ [M+Na]$^+$: 397.2349; found: 397.2357.
2-((1S,2R,6R)-6-(benzyloxy)-2-(1,3-dithiolan-2-yl)-1,3-dimethylcyclohex-3-en-1-yl)ethan-1-ol (308)

A solution of 303 (75 mg, 0.14 mmol, 1.0 eq.) and 1,2-ethandithiol (0.11 mL, 1.24 mmol, 9.0 eq.) in dry DCM (2 mL) was treated with BF₃·Et₂O (85 mmL, 0.69 mmol, 5.0 eq.) at 0 °C. The resulting yellowish mixture was further stirred at 0 °C for 1 h and allowed to warm up to room temperature over 2 h. After which time, the reaction was carefully quenched with 50% aqueous KOH (2 mL) and the suspension was further vigorously stirred for another 2 h. After this time, the mixture was extracted with Et₂O (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:2) to give desired alcohol 308 (28 mg, 0.08 mmol, 56%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 7.38 – 7.29 (m, 5H), 5.47 – 5.38 (m, 1H), 4.92 (d, J = 1.8 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 3.82 – 3.73 (m, 2H), 3.54 (dd, J = 14.0, 6.0 Hz, 1H), 3.34 – 3.21 (m, 3H), 3.18 – 3.08 (m, 2H), 2.60 – 2.46 (m, 1H), 2.38 (s, 1H), 2.19 – 2.06 (m, 2H), 1.90 (d, J = 1.7 Hz, 3H), 1.23 (dd, J = 7.4, 3.0 Hz, 1H), 1.16 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 138.0, 134.1, 128.128.0, 127.9, 127.9, 127.8, 121.7, 78.4, 72.1, 59.0, 55.7, 54.5, 40.7, 39.2, 39.1, 37.9, 29.7, 26.0, 20.8 ppm.

2-((1S,2R,6R)-6-(benzyloxy)-2-(1,3-dithiolan-2-yl)-1,3-dimethylcyclohex-3-en-1-yl)acetaldehyde (309)

A solution of 308 (37 mg, 0.1 mmol, 1.0 eq.) and DIPEA (0.18 mL, 1.01 mmol, 10.0 eq.) in dry DCM (1 mL) was cooled down to 0 °C and treated with a solution of pyridine·SO₃ complex (48 mg, 0.31 mmol, 3.0 eq.) in dry DMSO (0.6 mL). The resulting yellowish mixture was further stirred at the same temperature for 2 h, after which time, it was quenched with aqueous NH₄Cl (1 mL), warmed up to room temperature and the mixture was extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give compound 309 sufficiently pure for the next step. The compound showed the thermal instability, therefore it was stored at −20 °C. Any attempts to purify the crude product resulted in rapid decomposition of the corresponding aldehyde 309.

¹H NMR (400 MHz, CDCl₃) δ = 9.81 – 9.76 (m, 1H), 7.24 (m, 5H), 5.40 (s, 1H), 4.85 (s, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.24 – 3.13 (m, 2H), 3.13 – 3.06 (m,
2H), 2.62 (dd, J = 14.6, 3.0 Hz, 1H), 2.48 (s, 1H), 2.13 (dd, J = 14.6, 3.0 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.83 (s, 3H), 1.27 (s, 3H) ppm.

(15,25,35,4R)-3-(2-hydroxyethyl)-1,3-dimethyl-2-vinylcyclohexane-1,4-diol (310)

To pre-cooled neat 287 (1.23 g, 2.72 mmol, 1 eq.), TBAF (1 M in THF, 4.09 mL, 4.09 mmol, 1.5 eq.) was added and the resulting dark solution was warmed up to room temperature and further stirred for 14 h. After which time, the reaction was quenched with NaHCO₃, and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (pure EA) to give desired triol 310 (496 mg, 2.32 mmol, 85%) as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ = 5.75 (dt, J = 16.8, 10.4 Hz, 1H), 5.28 – 5.15 (m, 2H), 3.84 – 3.72 (m, 2H), 3.67 (dd, J = 4.9, 2.9 Hz, 1H), 3.26 (s, 1H), 2.60 (s, 1H), 2.35 (d, J = 10.6 Hz, 1H), 2.12 (s, 1H), 1.89 – 1.73 (m, 4H), 1.64 – 1.54 (m, 2H), 1.20 (s, 3H), 0.94 (s, 3H) ppm.

13C NMR (101 MHz, CDCl₃) δ = 135.3, 120.6, 72.0, 71.7, 58.7, 57.9, 40.8, 40.4, 34.0, 26.6, 26.1, 20.3 ppm.


[α]D²³: −25.8 (c 0.20, CHCl₃).

IR (film): uninformative.

(5aS,6S,7S,9aR)-2,2-diisopropyl-5a,7-dimethyl-6-vinloctahydrobenzo[d][1,3,2]dioxasilepin-7-ol (311)

A solution of 310 (186 mg, 0.87 mmol, 1.0 eq.) and Et₃N (0.75 mL, 5.21 mmol, 6 eq.) in dry DMF (20 mL) was treated with diisopropylchlorosilane (0.2 mL, 1.13 mmol, 1.3 eq.) at 0 °C. The resulting suspension was further stirred for 30 min. After with time, the reaction mixture was diluted with aqueous NH₄Cl (10 mL) and water (50 mL). The mixture was then extracted with Et₂O (3 x 50 ml). The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum to yield the crude product as a yellowish oil. The crude product 311 (269 mg, 0.82 mmol, 95%) was used in the next step without further purification.

1H NMR (400 MHz, CDCl₃) δ = 5.75 (dt, J = 16.9, 10.3 Hz, 1H), 5.28 (dd, J = 10.2, 2.4 Hz, 1H), 5.23 – 5.13 (m, 1H), 3.97 – 3.84 (m, 3H), 2.42 (d, J = 10.7 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.96 (s, 1H),
1.77 (ddt, J = 10.6, 6.8, 3.8 Hz, 3H), 1.57 – 1.52 (m, 1H), 1.35 (ddd, J = 15.7, 6.2, 2.2 Hz, 1H), 1.21 (s, 3H), 1.09 – 0.98 (m, 14H), 0.92 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 134.6, 121.2, 73.7, 71.6, 60.7, 56.5, 45.1, 41.5, 33.6, 27.4, 24.7, 20.7, 17.8, 17.7, 17.4, 13.1, 13.1 ppm.

HRMS (ESI, m/z) calculated for C$_{18}$H$_{34}$NaO$_3$Si$^+$ [M+Na]$^+$: 349.2169; found: 349.2182.

[α]$^D_23$ = –11.9 (c 0.28, CHCl$_3$).

IR (film): uninformative.

(5a$S$,6$S$,7$S$,9a$R$)-7-hydroxy-2,2-diisopropyl-5a,7-dimethyl octahydrobenzo[d][1,3,2]dioxasilepine-6-carbaldehyde (312)

Ozone was bubbled through a cooled (−78 °C) solution of 311 (286 mg, 0.88 mmol, 1 eq.) in methanol (5 mL) and dichloromethane (50 mL) until a blue color persisted. The solution was then sparged with O$_2$ for 10 minutes and PPh$_3$ (689 mg, 2.63 mmol, 3.0 eq.) was added portionwise, and the reaction mixture was allowed to slowly reach room temperature over the period of 14 h. After this time, solvent was removed under reduced pressure and the crude was submitted to the flash column chromatography (PE/EA 3:1) affording the desired aldehyde 312 (253 mg, 0.77 mmol, 88%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 10.01 (d, J = 2.1 Hz, 1H), 4.06 – 3.94 (m, 2H), 3.85 (t, J = 3.0 Hz, 1H), 2.72 (d, J = 2.0 Hz, 1H), 2.54 (s, 1H), 2.14 – 2.02 (m, 2H), 1.83 – 1.70 (m, 3H), 1.53 (dt, J = 12.7, 3.6 Hz, 1H), 1.41 (s, 3H), 1.12 (s, 3H), 1.06 – 1.02 (m, 14H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 207.0, 73.7, 72.7, 62.4, 60.5, 44.2, 41.8, 35.3, 27.3, 25.2, 21.1, 17.8, 17.6, 17.4, 17.2, 17.2, 13.2, 13.1, 13.1 ppm.

HRMS (ESI, m/z) calculated for C$_{17}$H$_{33}$O$_4$Si$^+$ [M+H]$^+$: 329.2143; found: 329.2148.

[α]$^D_23$ = –4.4 (c 0.34, CHCl$_3$).

IR (film): λmax = 3427, 2944, 2867, 1703, 1463, 1390, 1105, 1033, 995, 885, 695 cm$^{-1}$.
(5aS,9aR)-2,2-diisopropyl-5a,7-dimethyl-4,5,5a,8,9,9a-hexahydrobenzo[d][1,3,2]dioxasilepine-6-carbaldehyde (313)

A solution of 312 (62 mg, 0.19 mmol, 1.0 eq.) in PhMe/dioxane 2:1 (1.5 mL) was treated with the Burgess reagent (67 mg, 0.28 mmol, 1.5 eq.) at room temperature. The resulting reaction mixture was heated at 80 °C for 2 h. After which time, the reaction was quenched with water (2 mL) and extracted with Et₂O (3 x 10 mL). The organic layer was dried (MgSO₄) and concentrated. The crude was submitted to the flash column chromatography (EA/PE 1:4) delivering compound 313 (7 mg, 0.02 mmol, 12%) as a minor product and 314 (42 mg, 0.13 mmol, 71%, exo/endo 9:1) as an inseparable mixture of two isomeric olefins which was submitted to the next step without full characterization.

¹H NMR (400 MHz, CDCl₃) δ = 10.16 (s, 1H), 3.99 – 3.90 (m, 2H), 3.73 (ddd, J = 12.2, 7.0, 1.7 Hz, 1H), 2.74 – 2.61 (m, 1H), 2.45 (dd, J = 15.6, 9.1 Hz, 1H), 2.16 (s, 3H), 2.08 (ddd, J = 19.5, 5.3, 2.6 Hz, 1H), 1.98 (dd, J = 15.7, 6.1 Hz, 1H), 1.87 – 1.77 (m, 2H), 1.16 (s, 3H), 1.04 (m, 7H), 0.97 (m, 7H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 192.4, 158.7, 137.3, 75.9, 62.2, 42.0, 40.9, 31.0, 25.8, 25.7, 19.4, 17.9, 17.5, 17.5, 13.2, 13.1 ppm.

HRMS (ESI, m/z) calculated for C₁₇H₃₁O₃Si⁺ [M+H]⁺: 351.2037; found: 311.2041.

IR (film): uninformative.

((5aS,6R,9aR)-2,2-diisopropyl-5a-methyl-7-methyloctahydrobenzo[d][1,3,2]dioxasilepin-6-yl)methanol (315)

A mixture of 314 (42 mg, 0.13 mmol, 1.0 eq.) was dissolved in MeOH (1 mL) and the resulting solution was cooled down to 0 °C. To the mixture, NaBH₄ (26 mg, 0.07 mmol, 5.0 eq.) was added portionwise at 0 °C. After the addition was finished, the reaction mixture was allowed to warm up to room temperature over 2 h. After this time, water (2 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:2) to give the desired compound 315 (30 mg, 0.09 mmol, 71%, exo/endo 9:1).
1H NMR (400 MHz, CDCl₃) δ = 4.99 (s, 1H), 4.71 (s, 1H), 4.00 (ddd, J = 12.2, 7.6, 1.7 Hz, 1H), 3.90 (ddd, J = 12.2, 8.3, 1.5 Hz, 1H), 3.83 – 3.74 (m, 2H), 3.70 (d, J = 10.1 Hz, 1H), 2.69 (dd, J = 9.4, 3.6 Hz, 1H), 2.50 (dt, J = 13.1, 8.3 Hz, 1H), 2.18 – 2.12 (m, 1H), 2.03 (ddd, J = 15.7, 8.3, 1.6 Hz, 1H), 1.77 (dd, J = 8.0, 3.6 Hz, 2H), 1.50 – 1.42 (m, 2H), 1.04 (m, 14H), 0.80 (s, 3H). ppm.

13C NMR peak listing of the mixture of two isomers (exo/endo 9:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C₁₇H₃₃O₃Si+ [M+H]+: 313.2193; found: 313.2198.

IR (film): λ max = 3368, 2940, 2866, 1465, 1446, 1100, 1057, 1027, 1012, 885, 748, 692 cm⁻¹.

((1R,2S,3R)-3-hydroxy-2-(2-hydroxyethyl)-2-methyl-6-methylene cyclohexyl)methyl pivalate (318)

A solution of 315 (47 mg, 0.15 mmol, 1.0 eq.) in dry DCM (1 mL) was treated with DMAP (18 mg, 0.15 mmol, 1 eq.), Et₃N (0.11 mL, 0.75 mmol, 5 eq.) and PivCl (54 mg, 0.45 mmol, 3 eq.) at 0 °C. The resulting mixture was stirred for 3 h at 0 °C. After which time, water (3 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further treated with TBAF (1 M in THF, 0.3 mL, 0.3 mmol, 2 eq.) and the resulting mixture was stirred for 8 h at room temperature, quenched with NaHCO₃, and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 2:1) to give the desired compound 318 (38 mg, 0.13 mmol, 89%, exo/endo 3:1).

1H NMR peak listing of the mixture of two isomers (exo/endo 3:1) is uninformative, see NMR spectrum below for the graphic representation.

13C NMR peak listing of the mixture of two isomers (exo/endo 3:1) is uninformative, see NMR spectrum below for the graphic representation.


IR (film): λ max = 3311, 2967, 2938, 2876, 1727, 1481, 1462, 1287, 1159, 1065, 1036 cm⁻¹.
(15,25,35)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1,3-dimethyl-2-vinylcyclohexan-1-ol (320)

To a pre-heated to 80 °C solution of 287 (50 mg, 0.11 mmol, 1.0 eq.) in dry DCE (2 mL), phenyl thionochloroformate (25 mg, 0.14 mmol, 1.3 eq.) was added. The resulting mixture was further stirred at 80 °C for 30 min, after which time, water (3 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was dissolved in dry dioxane (5 mL) and the resulting mixture was treated with catalytic amount of AIBN (3-5 mg) and nBu₃SnH (160 mg, 0.55 mmol, 5 eq.). The reaction mixture was heated to reflux for 3 h, after with time the reaction was diluted with water (3 mL) and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:4) to give the desired compound 320 (37 mg, 0.09 mmol, 78%).

$^1$H NMR (400 MHz, CDCl₃) δ = 7.72 – 7.64 (m, 4H), 7.44 – 7.36 (m, 6H), 5.73 (dt, J = 16.9, 10.3 Hz, 1H), 5.16 (dd, J = 10.2, 2.3 Hz, 1H), 5.08 – 5.01 (m, 1H), 3.82 – 3.61 (m, 2H), 2.44 (s, 1H), 2.01 (d, J = 10.4 Hz, 1H), 1.74 – 1.58 (m, 2H), 1.43 – 1.32 (m, 4H), 1.24 (dd, J = 13.2, 6.1 Hz, 2H), 1.15 (s, 3H), 1.05 (s, 9H), 0.83 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl₃) δ = 36.4, 135.8, 133.8, 133.7, 129.8, 127.8, 119.4, 71.6, 60.8, 60.4, 45.1, 38.5, 37.1, 35.7, 27.0, 22.8, 19.3, 19.2 ppm.

HRMS (ESI, m/z) calculated for C₂₈H₄₁O₂Si⁺ [M+H]^⁺: 437.2870; found: 437.2870.

$[^{[α]}]_{D}^2$: +0.3 (c 0.49, CHCl₃).

IR (film): λmax = 2931, 2857, 1461, 1428, 1111, 1083, 915, 823, 739, 701 cm⁻¹.

3.1.3 C-Ring Precursors with Advanced Side Chain

3-methyl-2-(prop-1-en-2-yl)but-2-en-1-ol

Prepared in accordance with the literature known procedure.¹⁰⁰

$^1$H NMR (400 MHz, CDCl₃) δ = 5.06 (dq, J = 3.1, 1.6 Hz, 1H), 4.70 (dq, J = 2.8, 0.9 Hz, 1H), 4.16 (s, 2H), 1.82 (dd, J = 1.5, 0.9 Hz, 3H), 1.76 (s, 3H), 1.71 (s, 3H), 1.32 (s, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl₃) δ = 144.9, 130.0, 115.1, 60.5, 22.8, 22.1, 19.7 ppm.

The obtained NMR data is consistent with the values reported in the respective literature.
3-methyl-2-{prop-1-en-2-yl}but-2-enal (327)

To a solution of respective alcohol (544 mg, 4.31 mmol, 1.0 eq.) and Et₃N (3.61 mL, 25.86 mmol, 6.0 eq.) in dry DMSO (10 mL), a solution of pyridine SO₃ complex (1.72 g, 10.78 mmol, 2.5 eq.) in dry DMSO (10 mL) was added dropwise at room temperature. The resulting yellowish mixture was stirred for 2 h at room temperature, quenched by addition of water (20 mL) and extracted with Et₂O (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude 327 was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ = 10.07 (s, 1H), 5.19 (dt, J = 3.2, 1.6 Hz, 1H), 4.66 (dq, J = 2.1, 1.0 Hz, 1H), 2.21 (s, 3H), 1.97 (s, 3H), 1.81 (dd, J = 1.6, 0.9 Hz, 3H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

(2-methylprop-2-ene-1,1-diyl)bis(trimethylsilane) (331)

Prepared in accordance with the literature known procedure.[165]

¹H NMR (400 MHz, CDCl₃) δ = 4.65 (dh, J = 2.8, 1.4 Hz, 1H), 4.39 (dq, J = 2.2, 0.8 Hz, 1H), 1.72 (dd, J = 1.4, 0.7 Hz, 3H), 0.84 – 0.81 (m, 1H), 0.06 (s, 18H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

2,6-dimethyl-5-{prop-1-en-2-yl}-1-{trimethylsilyl}hepta-1,5-dien-4-ol (326)

To a solution of 327 (304 mg, 2.45 mmol, 1.0 eq.) in dry DCM (3 mL), SnCl₄ (1 M in DCM, 2.69 mL, 2.69 mmol, 1.1 eq.) was added at −78 °C. The resulting mixture was stirred for 5 min before a solution of 331 (736 mg, 3.67 mmol, 1.5 eq.) in dry DCM (1 mL) was added at the same temperature. After 5 min, the reaction was quenched with MeOH at −78 °C and further diluted with DCM (5 mL). When the reaction is allowed to stand for longer periods of time (longer than 5 min), formation of proto-desilylation product was also observed. The crude product solution was placed on a beaker containing a saturated aqueous solution of Rochelle’s salt and was stirred for 2 h until the layers were well separated. The phases were separated and the aqueous phase was extracted DCM (2 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was directly used in the next step without full characterization.

¹H NMR (400 MHz, CDCl₃) δ = 5.45 – 5.38 (m, 1H), 5.11 (dt, J = 3.0, 1.5 Hz, 1H), 4.77 (dd, J = 10.8, 1.7 Hz, 1H), 4.64 (dq, J = 2.6, 0.9 Hz, 1H), 2.57 (dd, J = 13.6, 10.8 Hz, 1H), 2.11 (dd, J = 13.6, 2.9
Hz, 1H), 1.96 – 1.92 (m, 3H), 1.89 (dd, J = 1.4, 1.0 Hz, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.50 (d, J = 4.6 Hz, 1H), 0.10 (s, 9H) ppm.

(Z)-1-iodo-2,6-dimethyl-5-(prop-1-en-2-yl)hepta-1,5-dien-4-ol (332)

A solution of 326 (150 mg, 0.59 mmol, 1.0 eq.) in dry CH₃CN (12 mL), NIS (200 mg, 0.89 mmol, 1.5 eq.) was added at 0 °C. The reaction flask was wrapped in aluminum foil and let stirring for 3 h at the same temperature. After which time, the reaction was quenched with aqueous Na₂S₂O₃ (10 mL) and extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:4) to give compound 332 (91 mg, 0.30 mmol, 50%).

¹H NMR (400 MHz, CDCl₃) δ = 6.00 (dp, J = 1.5, 0.7 Hz, 1H), 5.16 (dd, J = 2.6, 1.5 Hz, 1H), 4.85 – 4.76 (m, 1H), 4.71 (dd, J = 2.6, 0.9 Hz, 1H), 2.63 (dd, J = 13.7, 10.3 Hz, 1H), 2.27 (dd, J = 13.7, 3.5 Hz, 1H), 2.00 (d, J = 1.4 Hz, 3H), 1.92 (dd, J = 1.5, 0.9 Hz, 3H), 1.78 (s, 3H), 1.69 (s, 3H), 1.54 (d, J = 6.8 Hz, 1H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 145.5, 144.2, 138.2, 128.3, 115.9, 76.6, 69.20, 45.4, 25.4, 24.7, 22.3, 19.7 ppm.

6-methyl-5-(prop-1-en-2-yl)-1-(trimethylsilyl)hept-5-en-1-yn-4-ol

Preparation of TMS-propargyl magnesium bromide: The flask charged with ZnBr₂ (50 mg, 0.22 mmol) and Mg turnings (505 mg) was heated under deep vacuum, flushed with N₂ and charged with Et₂O (6 mL).

Next, addition of TMS-propargyl bromide (2.0 g, 10.4 mmol) initiated an exothermic reaction and the reaction mixture was cooled down to 0 °C. After the addition was finished, the resulting mixture was further stirred for 2 h at the same temperature to afford a light yellow supernatant and pulverized Mg precipitates. The concentration of supernatant was determined to be 0.56 M by titration using methyl orange as an indicator.

To a solution of 327 (191 mg, 1.54 mmol, 1.0 eq.) in dry Et₂O, a solution of TMS-propargyl magnesium bromide (0.56 M in Et2O, 6.15 mL, 3.08 mmol, 2.0 eq.) was added at 0 °C. The resulting mixture was stirred for 15 min at the same temperature and 10 min at room temperature. After this time, the reaction was quenched with aqueous NH₄Cl and extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via
flash column chromatography (Et₂O/PE 1:3) to give the desired compound (246 mg, 1.04 mmol, 68%).

**1H NMR** (400 MHz, CDCl₃) δ = 5.11 (dq, J = 3.0, 1.5 Hz, 1H), 4.77 (ddd, J = 7.9, 6.3, 5.1 Hz, 1H), 4.65 (dq, J = 2.8, 0.9 Hz, 1H), 2.58 (dd, J = 16.7, 7.9 Hz, 1H), 2.39 (dd, J = 16.7, 6.3 Hz, 1H), 1.94 (d, J = 5.2 Hz, 1H), 1.88 (dd, J = 1.6, 0.9 Hz, 3H), 1.76 (s, 3H), 1.69 (s, 3H), 0.14 (s, 9H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 143.8, 136.5, 130.1, 115.8, 104.0, 87.0, 28.0, 25.2, 22.3, 19.7, 0.2 ppm.

**HRMS** (ESI, m/z) calculated for C₁₄H₂₅OSi⁺ [M+H]⁺: 237.1669; found: 237.1675.

**IR (film)**: λmax = 3387, 2932, 2177, 1445, 1421, 1022, 837, 758, 699, 645 cm⁻¹.

**6-methyl-5-{(prop-1-en-2-yl)hept-5-en-1-yn-4-ol (333)}**

A solution of the respective alcohol (246 mg, 1.04 mmol, 1.0 eq.) in dry THF (2 mL) was treated with TBAF (1 M in THF, 1.25 mL, 1.25 mmol, 1.2 eq.) at 0 °C. The resulting yellowish solution was stirred further for 45 min at the same temperature and was allowed to warm up to room temperature. After stirring for 1 h at room temperature, the reaction was quenched by addition of aqueous NaHCO₃ (2 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:3) to give 333 (169 mg, 1.03 mmol, 99%) as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ = 5.12 (dd, J = 2.5, 1.6 Hz, 1H), 4.79 (dt, J = 8.3, 5.1 Hz, 1H), 4.66 (dt, J = 1.7, 0.9 Hz, 1H), 2.53 (ddd, J = 16.7, 8.4, 2.6 Hz, 1H), 2.35 (ddd, J = 16.7, 5.7, 2.7 Hz, 1H), 2.02 (t, J = 2.6 Hz, 1H), 1.90 (d, J = 5.0 Hz, 1H), 1.88 (dd, J = 1.5, 0.9 Hz, 3H), 1.77 (s, 3H), 1.69 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 143.7, 136.6, 130.3, 115.9, 81.7, 70.2, 69.1, 26.5, 25.2, 22.3, 19.6 ppm.

**HRMS** (ESI, m/z) calculated for C₁₁H₁₇O⁺ [M+H]⁺: 165.1274; found: 165.1277.

**IR (film)**: λmax = 3409, 3306, 2945, 2916, 1443, 1373, 1032, 1014, 898, 633 cm⁻¹.
(E)-1-iodo-2,6-dimethyl-5-(prop-1-en-2-yl)hepta-1,5-dien-4-ol (325)

To a flame-dried N₂-purged 50 mL Schlenk flask, zirconocene dichloride (37 mg, 0.13 mmol, 0.3 eq.) was added followed by addition of dry DCE (1 mL). The resulting solution was cooled down to 0 °C followed by dropwise addition of trimethylaluminium (2 M in PhMe, 1.07 mL, 2.13 mmol, 5.0 eq.). While stirring at 0 °C, a solution of 333 (70 mg, 0.43 mmol, 1.0 eq.) in dry DCE (1 mL) was added dropwise. After addition, the reaction was allowed to warm up to room temperature and stirred for 48 h. After which time, the mixture was cooled down to 0 °C followed by addition of a solution I₂ (140 mg, 0.55 mmol, 1.3 eq.) in dry THF (2 mL) via cannula at the same temperature. After the addition was finished, the reaction mixture was kept for 1 h at 0 °C, then diluted with Et₂O (3 mL) and quenched aqueous NH₄Cl (10 mL). The resulting mixture was extracted with Et₂O (2 x 10 mL) and combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:3) to give 325 (69 mg, 0.23 mmol, 53%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ = 6.01 (s, 1H), 5.10 (s, 1H), 4.73 – 4.67 (m, 1H), 4.62 (s, 1H), 2.49 (dd, J = 14.0, 9.6 Hz, 1H), 2.32 (dd, J = 14.1, 3.5 Hz, 1H), 1.91 (s, 3H), 1.86 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.58 (d, J = 3.6 Hz, 1H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 45.3, 144.1, 137.8, 128.7, 115.7, 77.4, 68.3, 46.3, 25.3, 24.3, 22.2, 19.5 ppm.

HRMS (ESI, m/z) calculated for C₁₂H₁₉O⁺ [M without I]⁺: 179.1430; found: 179.1432.

IR (film): λmax = 3429, 2914, 1626, 1443, 1373, 1273, 1143, 1042, 878, 774, 746 cm⁻¹.

(E)-2,6-dimethyl-3-(propan-2-ylidene)nona-1,6,8-trien-4-ol

To a degassed and stirred solution of 325 (94 mg, 0.30 mmol, 1.0 eq.) in THF (4 mL), vinyltributyltin (0.1 mL, 0.34 mmol, 1.1 eq.) and PPh₃ (32 mg, 0.12 mmol, 0.4 eq.) were added followed by Pd₂(dba)₃ (20 mg) at room temperature. The reaction mixture was then heated at 50 °C for 8h. Water (10 mL) was added and the reaction mixture was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. After column chromatography (Et₂O/PE 1:6) the title diene (53 mg, 0.26 mmol, 84%) was obtained as an orange oil.

¹H NMR (400 MHz, CDCl₃) δ = 6.58 (dt, J = 16.8, 10.5 Hz, 1H), 5.94 (d, J = 10.9 Hz, 1H), 5.17 – 5.06 (m, 2H), 5.06 – 4.99 (m, 1H), 4.75 – 4.68 (m, 1H), 4.65 – 4.57 (m, 1H), 2.31 (dd, J = 13.8, 9.7 Hz,
1H), 2.21 (dd, J = 13.9, 3.6 Hz, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.61 (d, J = 4.6 Hz, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 144.5, 138.3, 136.2, 133.1, 128.5, 128.1, 115.8, 115.2, 68.4, 47.0, 25.3, 22.2, 19.4, 16.9 ppm.

HRMS (ESI, m/z) calculated for C$_{14}$H$_{22}$NaO$^+$ [M+Na]$^+$: 229.1563; found: 229.1568.

IR (film): $\lambda_{\text{max}}$ = 3446, 2959, 2918, 2856, 1443, 1373, 1048, 988, 898 cm$^{-1}$.

(E)-tert-butyl(2,6-dimethyl-3-(propan-2-ylidene)nona-1,6,8-trien-4-yl)oxy)diphenylsilane (324)

The respective alcohol (40 mg, 0.19 mmol, 1.0 eq.) dissolved in DCM (1 mL) was cooled to 0 °C followed by addition of TBDPSCI (64 mg, 0.23 mmol, 1.2 eq.) and imidazole (40 mg, 0.58 mmol, 3.0 eq.). The mixture was stirred at room temperature for 12 h. The reaction was quenched with water (3.5 mL) and DCM (3.5 mL) was added. Phases were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The collected organic phases were washed with brine (5 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was then purified via flash chromatography (EA/PE 3:97) to provide the title compound 324 (84 mg, 0.19 mmol, 98%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.73 – 7.67 (m, 4H), 7.44 – 7.35 (m, 6H), 6.39 (dt, J = 16.8, 10.5 Hz, 1H), 5.64 (d, J = 10.9 Hz, 1H), 5.10 (s, 1H), 5.01 – 4.90 (m, 2H), 4.69 (t, J = 6.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 2.30 (tt, J = 13.4, 7.2 Hz, 2H), 1.97 (s, 3H), 1.68 (s, 3H), 1.49 (s, 3H), 1.19 (s, 3H), 1.08 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 144.7, 138.1, 136.5, 136.2, 135.8, 134.5, 134.5, 133.5, 129.7, 129.5, 128.5, 128.5, 127.6, 127.4, 115.5, 114.7, 70.6, 47.2, 27.3, 25.3, 22.6, 20.1, 19.4, 16.4 ppm.

HRMS (ESI, m/z) calculated for C$_{30}$H$_{41}$OSi$^+$ [M+Na]$^+$: 445.2921; found: 445.2928.

IR (film): $\lambda_{\text{max}}$ = 2959, 2930, 2857, 1472, 1445, 1428, 1111, 1050, 897, 739, 701, 614 cm$^{-1}$.
3.1.4 Diels-Alder Approach towards Taxanes

3-(chloromethyl)-2,4-dimethylpenta-1,3-diene (347)

Prepared in accordance with the literature known procedure. [179]

\[ \text{1H NMR (400 MHz, CDCl}_3\] \delta = 5.04 (dq, J = 3.1, 1.6 Hz, 1H), 4.74 (dq, J = 1.9, 0.9 Hz, 1H), 4.17 (s, 2H), 1.85 (dd, J = 1.6, 0.9 Hz, 3H), 1.82 (s, 3H), 1.76 (s, 3H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

2-(2,4-dimethylpenta-1,3-dien-3-yl)-1,3-dithiane (358)

A solution of 357 (534 mg, 4.30 mmol, 1.0 eq.) in DCM (10 mL) was treated with propane-1,3-dithiol (0.44 mL, 4.30 mmol, 1.0 eq.) at room temperature. The resulting solution was cooled down to 0 °C and BF$_3$·Et$_2$O (1.06 mL, 8.60 mmol, 2.0 eq.) was added to the mixture dropwise. The reaction was stirred for 5 min at 0 °C and for 1 h at room temperature. After which time, the reaction was quenched by addition of 10 % aqueous KOH (50 mL) and diluted with Et$_2$O (70 mL). The layers were separated and the organic phase was dried over MgSO$_4$ and concentrated to give the crude product 358 as a yellowish liquid. The crude product was then purified via flash chromatography (EA/PE 1:9) to provide the title compound 358 (783 mg, 3.66 mmol, 85%) as a colorless oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\] \delta = 5.06 (dq, J = 3.0, 1.5 Hz, 1H), 5.04 (s, 1H), 4.71 (dd, J = 2.4, 0.9 Hz, 1H), 3.02 – 2.93 (m, 2H), 2.84 – 2.77 (m, 2H), 2.12 – 2.04 (m, 1H), 1.93 – 1.91 (m, 3H), 1.89 (s, 3H), 1.86 – 1.79 (m, 1H), 1.70 (s, 3H) ppm.

\[ \text{13C NMR (101 MHz, CDCl}_3\] \delta = 144.0, 133.6, 132.5, 115.7, 50.2, 32.3, 25.6, 24.3, 22.4, 20.6 ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

(1R,2S,3S,4S)-2-((2-(2,4-dimethylpenta-1,3-dien-3-yl)-1,3-dithian-2-yl)(hydroxy)methyl)-4-(methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexan-1-ol (360)

Dithiane 358 (188 mg, 0.88 mmol, 2.5 eq.) and HMPA (0.15 mL, 0.88 mmol, 2.5 eq.) were dissolved in dry THF (5 mL) and the resulting solution was cooled down to -78 °C followed treatment with nBuLi (1.6 M in hexane, 0.48 mL, 0.77 mmol, 2.2 eq.). The mixture was further stirred at -78 °C for 15 min, after which time a solution of aldehyde 258 (85 mg, 0.35 mmol, 1.0 eq.) in dry THF (2 mL) was added dropwise. The resulting mixture was stirred for another 30 min at the same time and quenched with aqueous NH$_4$Cl (2 mL). The reaction mixture
was allowed to warm up to room temperature and extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:1) to give 360 (33 mg, 0.07 mmol, 21%) as a colorless oil (d.r. 1:2).

1H NMR peak listing of the mixture of diastereomers (d.r. 1:2) is uninformative, see NMR spectrum below for the graphic representation.

13C NMR peak listing of the mixture of diastereomers (d.r. 1:2) is uninformative, see NMR spectrum below for the graphic representation.

3-bromo-2,4-dimethylpenta-1,3-diene (364)

Prepared in accordance with the literature known procedure.[299]

\[ \text{Br} \]

1H NMR (400 MHz, CDCl₃) δ = 5.07 – 5.03 (m, 3H), 4.93 – 4.90 (m, 3H), 1.90 (s, 9H), 1.89 (dd, J = 1.4, 0.8 Hz, 9H), 1.81 (s, 9H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

1-((1S,2S,3S,6R)-3,6-bis(methoxymethoxy)-1,3-dimethyl-2-vinylcyclohexyl)-4-methyl-3-(prop-1-en-2-yl)pent-3-en-2-ol (369)

A solution of 364 (116 mg, 0.67 mmol, 5.0 eq.) in dry THF (1 mL) was treated with tBuLi (1.9 M in pentane, 0.65 mL, 9.5 eq.) at −78 °C. The resulting yellowish solution was stirred for 15 min at the same temperature and a solution of aldehyde 293 (40 mg, 0.13 mmol, 1 eq.) in dry THF (0.5 mL) was added dropwise at −78 °C. The resulting mixture was allowed to warm up to 0 °C, quenched with aqueous NH₄Cl (1 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:1) to give a complex inseparable mixture of four isomeric products including two diastereomers of 369 and their allenyl isomers (80% overall yield).

For the analytical purposes, a single diastereomer of 369 was isolated via HPLS and further characterized.

1H NMR (400 MHz, CDCl₃) δ = 5.71 – 5.55 (m, 1H), 5.14 – 5.06 (m, 2H), 5.00 (dd, J = 2.9, 1.5 Hz, 1H), 4.80 (d, J = 7.7 Hz, 1H), 4.72 (d, J = 7.7 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.63 (dd, J = 2.9, 0.9 Hz, 1H), 4.56 (d, J = 6.9 Hz, 1H), 4.00 (d, J = 6.0 Hz, 1H), 3.49 (dd, J = 11.3, 4.7 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.99 (dd, J = 10.8, 2.1 Hz, 1H), 2.50 (dd, J = 15.0, 10.7 Hz, 1H), 1.93 (dq, J = 15.0,
3.3 Hz, 1H), 1.90 – 1.86 (m, 3H), 1.78 – 1.72 (m, 1H), 1.70 (s, 3H), 1.63 (s, 3H), 1.54 (dd, \( J = 15.0 \), 1.2 Hz, 1H), 1.51 – 1.44 (m, 1H), 1.32 – 1.26 (m, 1H), 1.12 (s, 3H), 1.03 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta = 146.0, 141.2, 136.8, 124.5, 118.9, 113.7, 95.8, 90.3, 80.9, 79.6, 67.8, 57.4, 56.4, 55.7, 40.0, 39.0, 30.4, 26.7, 26.6, 25.7, 23.7, 22.2, 19.2 \) ppm.

\((1R,2S,3R,6S)-2-(2-hydroxy-4-methyl-3-(prop-1-en-2-yl)pent-3-en-1-yl)-3,6-bis(methoxymethoxy)-2,6-dimethylcyclohexyl)methyl pivalate (370)

A solution of 364 (365 mg, 2.09 mmol, 3.0 eq.) in dry THF (5 mL) was treated with tBuLi (1.9 M in pentane, 2.20 mL, 6.0 eq.) at –78 °C. In parallel, anhydrous CeCl\(_3\) (559 mg, 2.23 mmol, 3.2 eq.) was placed in the separate Schlenk flask, followed by addition of dry THF (3 mL). The resulting colorless suspension was cooled down to –78 °C and kept stirring vigorously under inert atmosphere. After 15 min of stirring, the freshly generated solution of organolithium compound transferred to the vial with CeCl\(_3\) suspension via cannula. The resulting light brown suspension was further stirred for 1 h at –78 °C, after which time a solution of 297 (200 mg, 0.69 mmol, 1.0 eq.) in dry THF (1 mL) was added dropwise at the same temperature and the reaction mixture was stirred for another 30 min. After this time, the reaction was quenched by addition of aqueous NH\(_4\)Cl (5 mL) and the reaction mixture was allowed to warm up to room temperature over 2 h. Next, the reaction mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with water, brine, and dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et\(_2\)O/PE 1:1) to give a complex inseparable mixture of four isomeric products including two diastereomers of 370 and their allenyl isomers (395 mg, 71% overall yield, diene/allene 7:1).

For the analytical purposes, a single diastereomer of 370 was isolated via HPLS and further characterized.

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 5.01 (dd, \ J = 2.9, 1.5 \) Hz, 1H), 4.82 (d, \( J = 7.7 \) Hz, 1H), 4.76 – 4.70 (m, 1H), 4.70 – 4.66 (m, 2H), 4.63 (dd, \( J = 2.9, 0.9 \) Hz, 1H), 4.54 (d, \( J = 6.8 \) Hz, 1H), 4.29 – 4.15 (m, 2H), 3.69 (dd, \( J = 9.7, 5.2 \) Hz, 1H), 3.52 (s, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.70 – 2.64 (m, 1H), 2.45 (dd, \( J = 14.9, 10.8 \) Hz, 1H), 2.01 – 1.92 (m, 1H), 1.90 – 1.84 (m, 3H), 1.73 – 1.64 (m, 6H), 1.62 (s, 3H), 1.60 – 1.53 (m, 1H), 1.26 (s, 3H), 1.20 (m, 12H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta = 146.0, 141.2, 136.8, 124.5, 118.9, 113.7, 95.8, 90.3, 80.9, 79.6, 67.8, 57.4, 56.4, 55.7, 40.0, 39.0, 30.4, 26.7, 26.6, 25.7, 23.7, 22.2, 19.2 \) ppm.

HRMS (ESI, \( m/z \)) calculated for C\(_{27}\)H\(_{48}\)NaO\(_7\) [M+Na]**: 507.3292, found: 507.3287
The diene/allene mixture (7:1) 370 (395 mg, 0.81 mmol, 1.0 eq.) was dissolved in dry DCM (5 mL) and the solution was treated with imidazole (222 mg, 3.26 mmol, 4.0 eq.) and DMAP (99 mg, 0.81 mmol, 1.0 eq.) at room temperature. To the resulting mixture, TESCl (0.27 mL, 1.63 mmol, 2.0 eq.) was added dropwise at room temperature. The suspension was further stirred for 14 h at room temperature, after which time, aqueous NH₄Cl (2 mL) was added and the mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:5) to afford an inseparable mixture of two diastereomers 372 (327 mg, 0.55 mmol, 67%, d.r. 1:1.4) and separating off their allenyl isomers.

¹H NMR peak listing of the mixture of diastereomers (d.r. 1:1.4) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C₃₃H₆₂NaO₇Si⁺ [M+Na]⁺: 621.4157; found: 621.4163.

IR (film): λmax = 2955, 2878, 1728, 1458, 1367, 1283, 1149, 1088, 1031, 918, 738, 722 cm⁻¹.

A solution of 372 (327 mg, 0.55 mmol, 1.0 eq.) in dry DCM (2 mL) was treated with DIBAL-H (1.64 mL, 1.64 mmol, 3.0 eq.) at −78 °C. The resulting solution was further stirred at −78 °C for 2 h and quenched with aqueous NaOH (1 M, 1 mL). The resulting heterogeneous mixture was allowed to warm up to room temperature over 30 min, after which time it was diluted with Et₂O (5 mL) and the mixture was kept stirring vigorously for another 15 min at ambient temperature. Next, a certain amount of MgSO₄ (required for drying off remaining water) was added directly into the reaction vessel and the mixture was further stirred vigorously for 20 min. After this time, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:1) to afford an inseparable mixture of diastereomers 373 (239 mg, 0.46 mmol, 85%, d.r. 1:1.4).

¹H NMR peak listing of the mixture of diastereomers (d.r. 1:1.4) is uninformative, see NMR spectrum below for the graphic representation.
$^{13}$C NMR peak listing of the mixture of diastereomers (d.r. 1:1.4) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for $C_{28}H_{64}NaO_6Si^+ [M+Na]^+$: 537.3582; found: 537.3590.

IR (film): $\lambda_{\text{max}} = 3456, 2949, 2878, 1454, 1149, 1086, 1027, 916, 738, 725 \text{ cm}^{-1}$.

(1S,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-(4-methyl-3-(prop-1-en-2-yl)-2-((triethylsilyloxy)pent-3-en-1-yl)cyclohexane-1-carbaldehyde (374)

To a flask charged with 373 (100 mg, 0.19 mmol, 1.0 eq.), NMO (35 mg, 0.29 mmol, 1.5 eq.) and MS 4Å (100 mg) was added dry DCM (2 mL) and the resulting suspension was stirred vigorously for 15 min at room temperature. After this time, a catalytical amount of TPAP (~2 mg) was added to the reaction mixture and resulting dark suspension was further stirred for 1 h at room temperature. After which time, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et$_2$O/PE 1:1) to afford an inseparable mixture of diastereomers 374 (80 mg, 0.16 mmol, 80%, d.r. 1:2.6).

$^1$H NMR peak listing of the mixture of diastereomers (d.r. 1:2.6) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for $C_{28}H_{64}NaO_6Si^+ [M+Na]^+$: 535.3425; found: 535.3433.

IR (film): $\lambda_{\text{max}} = 2952, 2880, 1722, 1457, 1379, 1147, 1083, 1039, 918, 744 \text{ cm}^{-1}$.

1-((1S,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-(4-methyl-3-(prop-1-en-2-yl)-2-((triethylsilyloxy)pent-3-en-1-yl)cyclohexyl)prop-2-en-1-one (375)

A solution of 374 (80 mg, 0.16 mmol, 1.0 eq.) in dry THF (1 mL) was treated with vinylmagnesium bromide solution (1 M in THF, 0.31 mL, 2.0 eq.) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and quenched with aqueous NH$_4$Cl (1 mL). The mixture was warmed up to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was then dissolved in dry DCM (2 mL) and treated with Dess-Martin periodinane solution (0.3 M in DCM, 0.78 mL, 0.23 mmol, 1.5 eq.) at room temperature. The resulting cloudy solution was stirred for another 2 h at room temperature. After this time, aqueous NaHCO$_3$ (2 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The
combined organic layers were washed with water, brine, and dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et$_2$O/PE 1:4) to afford an inseparable mixture of two diastereomers 375 (59 mg, 0.11 mmol, 71%, d.r. 1:1.3).

$^1$H NMR peak listing of the mixture of diastereomers (d.r. 1:1.3) is uninformative, see NMR spectrum below for the graphic representation.

$^{13}$C NMR peak listing of the mixture of diastereomers (d.r. 1:1.3) is uninformative, see NMR spectrum below for the graphic representation.

For the structure conformation see 2D HSQC and 2D HMBC spectra attached.

HRMS (ESI, m/z) calculated for C$_{28}$H$_{54}$NaO$_6$Si$^+$ [M+Na]$^+$: 537.3582; found: 537.3590.

IR (film): $\lambda_{\text{max}} = 2951, 2878, 1693, 1460, 1398, 1147, 1079, 1025, 918, 739, 723$ cm$^{-1}$.

(1S,4R,4aS,8aS,9aS,10aR)-1,4-bis(methoxymethoxy)-1,4a,6-trimethyl-5-(prop-1-en-2-yl)-1,3,4,4a,7,8,8a,9a,10,10a-decahydroanthracen-9(2H)-one (378)

A solution of 375 (10 mg, 0.02 mmol, 1.0 eq.) in dry PhMe (2 mL) was heat at 180 °C for 22 h. After which time, solvent was removed under reduced pressure and the residue was submitted to the flash column chromatography affording compound 378 (1.5 mg, 0.004 mmol, 18%) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 4.96$ (dd, $J = 2.6, 1.4$ Hz, 1H), 4.85 (d, $J = 7.7$ Hz, 1H), 4.73 (d, $J = 7.0$ Hz, 1H), 4.60 (dd, $J = 9.2, 7.4$ Hz, 2H), 4.56 (dd, $J = 2.6, 0.8$ Hz, 1H), 3.39 (s, 3H), 3.31 (t, $J = 2.5$ Hz, 1H), 3.29 (s, 3H), 3.09 (s, 1H), 2.31 (d, $J = 14.8$ Hz, 1H), 2.27 – 2.22 (m, 1H), 2.07 (d, $J = 12.9$ Hz, 1H), 2.00 (d, $J = 11.3$ Hz, 1H), 1.94 – 1.86 (m, 2H), 1.75 (dd, $J = 11.6, 4.8$ Hz, 2H), 1.70 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.47 – 1.41 (m, 2H), 1.30 (s, 2H), 0.92 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 211.5, 144.5, 136.5, 127.6, 113.7, 95.3, 90.6, 76.5, 57.8, 56.2, 55.3, 53.9, 44.6, 42.6, 33.7, 31.2, 29.9, 28.5, 23.4, 21.6, 21.5, 20.5, 20.3$ ppm.

HRMS (ESI, m/z) calculated for C$_{24}$H$_{39}$O$_5^+$ [M+H]$^+$: 407.2792; found: 407.2788.

[$\alpha$]$_D^{23}$: –28.0 (c 0.05, CHCl$_3$).

IR (film): uninformative.
3.1.5 Pinacol Approach towards Taxanes

7-iodo-6,6,8-trimethyl-1,4-dithiaspiro[4.5]dec-7-ene (383)

Prepared in accordance with the literature known procedure.[122]

\[ \text{1H NMR (400 MHz, CDCl}_3 \text{)} \delta = 3.26 (m, 4H), 2.49 – 2.37 (m, 2H), 2.36 – 2.25 (m, 2H), 1.89 (s, 3H), 1.42 (s, 6H) ppm. \]

The obtained NMR data is consistent with the values reported in the respective literature.

((1R,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-(2-((triethylsilyl)oxy)-2-(6,6,8-trimethyl-1,4-dithiaspiro[4.5]dec-7-en-7-yl)ethyl)cyclohexyl)methyl pivalate (387)

A solution of 383 (160 mg, 0.47 mmol, 2 eq.) in dry THF (2 mL) was treated with tBuLi (1.9 M in pentane, 0.96 mmol, 4.1 eq.) at −78 °C and the mixture was stirred for another 15 min at the same temperature. After which time, a solution of 297 (91 mg. 0.24 mmol, 1 eq.) in dry THF (1 mL) was added dropwise at −78 °C. The resulting mixture was stirred for 30 min and treated with TESCl (0.08 mL, 0.47 mmol, 2 eq.) −78 °C and the mixture was stirred for 1 h at the same temperature after which time it was allowed to warm up to 0 °C, quenched with aqueous NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 3:2) to afford an inseparable mixture of two diastereomers 387 (128 mg, 0.18 mmol, 78%, d.r. 5:1).

\[ \text{1H NMR peak listing of the mixture of diastereomers (d.r. 5:1) is uninformative, see NMR spectrum below for the graphic representation.} \]

\[ \text{13C NMR peak listing of the mixture of diastereomers (d.r. 5:1) is uninformative, see NMR spectrum below for the graphic representation.} \]

\[ \text{HRMS (ESI, m/z) calculated for C}_{37}\text{H}_{68}\text{NaO}_{7}\text{Si}^+ \text{ [M+H]}^+: 739.4068; found: 739.4086.} \]

\[ \text{IR (film): } \lambda_{\text{max}} = 2952, 2878, 1727, 1463, 1283, 1153, 1091, 1035, 739 \text{ cm}^{-1}. \]
((1R,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-((triethylsilyl)oxy)-2-(6,6,8-trimethyl-1,4-dithiaspiro[4.5]dec-7-en-7-yl)ethyl)cyclohexyl)methanol (390)

A solution of 387 (128 mg, 0.18 mmol, 1.0 eq.) in dry DCM (3 mL) was treated with DIBAL-H (1.64 mL, 1.64 mmol, 3.0 eq.) at −78 °C. The resulting solution was further stirred at −78 °C for 2 h and allowed to warm up to 0 °C, quenched with aqueous NaOH (1 M, 1 mL). The resulting heterogeneous mixture was allowed to warm up to room temperature over 30 min, after which time it was diluted with Et2O (5 mL) and the mixture was kept stirring vigorously for another 15 min at ambient temperature. Next, a certain amount of MgSO4 (sufficient for drying off remaining water) was added directly into the reaction vessel and the mixture was further stirred vigorously for 20 min. After this time, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et2O/PE 1:1) to afford an inseparable mixture of diastereomers 390 (107 mg, 0.17 mmol, 95%, d.r. 7:1).

1H NMR peak listing of the mixture of diastereomers (d.r. 7:1) is uninformative, see NMR spectrum below for the graphic representation.

13C NMR (101 MHz, CDCl3) δ = 139.9, 131.4, 98.4, 89.8, 81.5, 81.3, 79.2, 70.3, 61.6, 56.0, 55.6, 49.1, 44.1, 41.3, 41.2, 39.4, 39.3, 39.2, 37.0, 32.9, 32.8, 31.0, 24.7, 23.0, 21.2, 17.1, 7.3, 5.4 ppm.

HRMS (ESI, m/z) calculated for C32H60NaO6S2Si+ [M+Na]+: 655.3493; found: 655.3505.

IR (film): λmax = 3482, 2939, 2878, 1468, 1447, 1092, 1042, 743 cm−1.

To a flask charged with 390 (107 mg, 0.17 mmol, 1.0 eq.), NMO (40 mg, 0.34 mmol, 2.0 eq.) and MS 4Å (100 mg) was added dry DCM (2 mL) and the resulting suspension was stirred vigorously for 15 min at room temperature. After this time, a catalytical amount of TPAP (~4 mg) was added to the reaction mixture and resulting dark suspension was further stirred for 1 h at room temperature. After which time, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et2O/PE 1:1) to afford an inseparable mixture of diastereomers 391 (85 mg, 0.14 mmol, 80%, d.r. 7:1).
\textsuperscript{1}H NMR peak listing of the mixture of diastereomers (\textit{d.r.} 7:1) is uninformative, see NMR spectrum below for the graphic representation.

\textsuperscript{13}C NMR peak listing of the mixture of diastereomers (\textit{d.r.} 7:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, \textit{m/z}) calculated for C\textsubscript{32}H\textsubscript{58}NaO\textsubscript{6}S\textsubscript{2}Si\textsuperscript{+} [M+Na]\textsuperscript{+}: 653.3336; found: 653.3350.

IR (\textit{film}): \(\lambda_{\text{max}} = 2953, 2878, 1720, 1467, 1453, 1153, 1092, 1037, 918, 740 \text{ cm}^{-1}\).

(15,2S,3R,6S)-3,6-bis(methoxymethoxy)-2,6-dimethyl-2-((triethylsilyl)oxy)-2-(2,6,6-trimethyl-5-oxocyclohex-1-en-1-yl)ethyl)cyclohexane-1-carbaldehyde (392)

A solution of aldehyde 391 (51 mg, 0.08 mmol, 1.0 eq.) in CH\textsubscript{3}CN/water (4:1) mixture (2.5 mL) was treated with HgCl\textsubscript{2} (90 mg, 0.33 mmol, 4.0 eq.) and CaCO\textsubscript{3} (99 mg, 0.99 mmol, 12.0 eq.) at room temperature. The resulting heterogeneous mixture was stirred for 4 h, after which time it was filtered through a celite pad, diluted with brine (5 mL) and the solution was extracted with Et\textsubscript{2}O (3 x 30 mL). The combined organic layers were washed with water, brine, and dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et\textsubscript{2}O/PE 3:2) to afford an inseparable mixture of two diastereomers 392 (20 mg, 0.04 mmol, 45%, \textit{d.r.} 7:1).

\textsuperscript{1}H NMR peak listing of the mixture of diastereomers (\textit{d.r.} 7:1) is uninformative, see NMR spectrum below for the graphic representation.

\textsuperscript{13}C NMR peak listing of the mixture of diastereomers (\textit{d.r.} 7:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, \textit{m/z}) calculated for C\textsubscript{30}H\textsubscript{54}NaO\textsubscript{7}Si\textsuperscript{+} [M+Na]\textsuperscript{+}: 577.3531; found: 577.3539.

IR (\textit{film}): uninformative.

3-(2-((15,2R,3S,6R)-2-(hydroxymethyl)-3,6-bis(methoxymethoxy)-1,3-dimethylcyclohexyl)-1-((triethylsilyl)oxy)ethyl)-2,2,4-trimethylcyclohex-3-en-1-one (400)

To a solution of CH\textsubscript{2}I\textsubscript{2} (37 mg, 0.14 mmol, 14.0 eq.) in dry THF (3 mL), were added Sm pieces (55 mg, 0.37 mmol, 40.0 eq.) and the reaction mixture was stirred vigorously at room temperature for 2 h under inert atmosphere until a persistent dark blue solution is formed. After this time, the reaction mixture s cooled down to \(-78 ^\circ\text{C}\) followed be addition of a solution
of the respective ketoaldehyde 392 (5 mg, 0.01 mmol, 1.0 eq.) in dry THF (0.6 mL) via automated syringe pump over 2 h. After an addition was completed, the reaction mixture was allowed to warm up to room temperature and quenched by addition of aqueous NaHCO₃ (3 mL) and the resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et₂O/PE 1:1) to afford undesired alcohol 400 (4 mg, 0.009 mmol, 80%, d.r. 7:1).

¹H NMR peak listing of the mixture of diastereomers (d.r. 7:1) is uninformative, see NMR spectrum below for the graphic representation.

¹³C NMR peak listing of the mixture of diastereomers (d.r. 7:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C₃₀H₇₆NaO₇Si⁺ [M+Na]⁺: 579.3688; found: 579.3696.

IR (film): λmax = 3501, 2955, 2928, 1715, 1465, 1382, 1092, 1042, 1019, 736 cm⁻¹.

3.1.6 Boron-Mediated Formal CO Insertion

2,2-dimethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole

Prepared in accordance with the literature known procedure.[300]

¹H NMR (400 MHz, CDCl₃) δ = 3.42 – 3.32 (m, 6H), 1.57 – 1.37 (m, 6H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

One-pot procedure for the synthesis of bicyclo[3.3.1]nonan-9-one (431)

To a flame-dried Schlenk flask charged with dry DCM (20 mL), Me₂S·BH₂Cl (1.17 g, 10.6 mmol, 1.0 eq.) was added under inert atmosphere followed by dropwise addition of 1,4-cyclooctadiene (1.2 g, 11.09 mmol, 1.0 eq.) at room temperature. The resulting solution was stirred for 30 min at ambient temperature, after which time, a solvent along with other volatilities was pumped off and the residues was neat heated at 140 °C for 2 h. Next, the reaction vessel was cooled down to room temperature and Me₂S (5 mL) was added to the mixture. After stirring the resulting mixture for 5 min, hexane (20 mL) was added and the mixture was heated to reflux for 1 h, after which time it was let to cool down to room temperature over 2 h. The white precipitate was formed and the supernatant was sucked out of the reaction vessel. Crystalline residue was washed with hexane (3 x 10 mL) in the
same manner another and was let drying under reduced pressure for 18 h without external heating affording the reaction intermediate as a white powder.

Next, the previously obtained chloroborane (1.18 g, 5.4 mmol, 1.0 eq.) was dissolved in dry DCM (5 mL) and the resulting solution was treated with a solution of 2,6-dimethylphenol (692 mg, 5.67 mmol, 1.05 eq.) in dry DCM (5 mL) at room temperature. After stirring for 15 min, all the volatilities were pumped off forming a colorless oil as a residue, which was subsequently dissolved in dry PhMe (3 mL). To the newly formed reaction mixture, an excess of 2,2-dimethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (1.73 g, 10.8 mmol, 2.0 eq.) was added at room temperature and the reaction mixture was heated in an open-air apparatus equipped with reflux condenser at 130 °C for 15 h. After which time, the red colored reaction mixture was cooled down with an ice bath and EtOH (2 mL), NaOH (1.08 g, 26.99 mmol, 5.0 eq.) and 30% H₂O₂ (3 mL, 26.99 mmol, 5 eq.) were added subsequently. After the vigorous initial reaction was finished, the reaction mixture was heated at 40 °C for additional 2 h. After this time, the resulting mixture was diluted with brine (10 mL) and subsequently extracted with EtOAc (3 × 15 mL). The combined organic extract was washed with brine (100 mL), dried over MgSO₄, filtered through a coarse frit, and concentrated under reduced pressure. Obtained crude ketone was recrystallized in PE at -78 °C to give the desired ketone as a yellowish crystals with 71% yield.

\(^{1}H\) NMR (400 MHz, CDCl₃) δ = 2.42 (m, 2H), 2.17 – 1.99 (m, 10H), 1.59 – 1.49 (m, 2H) ppm.

The obtained NMR data is consistent with the values reported in the respective literature.

((2R,3S)-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-methyloxiran-2-yl)methanol (439)

Prepared in accordance with the literature known procedure.\(^{[200]}\)

\(^{1}H\) NMR (400 MHz, CDCl₃) δ = 3.87 (ddd, J = 10.3, 4.5, 3.7 Hz, 1H), 3.76 (ddd, J = 10.9, 10.4, 2.8 Hz, 1H), 3.67 (dd, J = 11.7, 10.4 Hz, 1H), 3.53 (dd, J = 11.7, 2.9 Hz, 1H), 3.08 (dd, J = 10.1, 3.1 Hz, 1H), 2.81 (dd, J = 9.4, 4.0 Hz, 1H), 2.04 (dq, J = 14.5, 3.7 Hz, 1H), 1.73 (ddddd, J = 14.3, 11.0, 9.5, 4.6 Hz, 1H), 1.44 (s, 3H), 0.92 (s, 9H), 0.11 (d, J = 2.5 Hz, 6H) ppm.

\(^{13}C\) NMR (101 MHz, CDCl₃) δ = 64.7, 62.6, 60.8, 60.7, 31.4, 26.1, 20.5, 18.7, -5.3, -5.4 ppm.

The obtained NMR data is consistent with the values reported in the respective literature.
**tert-butyl(2-((2S,3R)-3-ethynyl-3-methyloxiran-2-yl)ethoxy)dimethylsilane (436)**

Prepared in accordance with the literature known procedure[200] respective aldehyde 440 (60 mg, 0.25 mmol, 1.0 eq.) was dissolved in MeOH (1 mL) and the resulting solution was subsequently treated with K$_2$CO$_3$ (135 mg, 0.98 mmol, 4.0 eq.) and Ohira-Bestmann reagent (162 mg, 0.74 mmol, 3.0 eq.) at room temperature. The reaction mixture was further stirred for 4 h at ambient temperature, diluted with water (4 mL), and extracted with Et$_2$O (3 x 3 mL). The combined organic layers were washed with water, brine, and dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (Et$_2$O/PE 1:5) to afford 436 (38 mg, 0.16 mmol, 64%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 3.81$ (dd, $J = 6.8, 5.5$ Hz, 2H), 3.02 (dd, $J = 6.3, 5.6$ Hz, 1H), 2.35 (s, 1H), 2.02 – 1.83 (m, 2H), 1.56 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 82.0, 72.7, 62.6, 60.1, 52.2, 33.6, 26.1, 23.3, 18.5, -5.3 ppm.

HRMS (ESI, m/z) calculated for C$_{13}$H$_{24}$NaO$_2$Si$^+$ [M+Na]$^+$: 263.1438; found: 263.1433.

[α]$_D$$^{23}$: $-3.9$ (c 0.16, CHCl$_3$).

IR (film): $\lambda_{max} =$ 3311, 2955, 2929, 2858, 1473, 1257, 1093, 835, 777 cm$^{-1}$.

(1R,2S,3S,4S)-2-((S)-3-((2R,3S)-3-((tert-butyl(dimethyl)silyl)oxy)ethyl)-2-methyloxiran-2-yl)-1-hydroxyprop-2-yn-1-yl)-4-(methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexan-1-ol (441)

At first, an anhydrous CeCl$_3$ (121 mg, 0.49 mmol, 1.0 eq.) was added to a solution of aldehyde 258 (119 mg, 0.49 mmol, 1.0 eq.) in dry THF (2 mL) and the resulting suspension was stirred at ambient temperature for 1 h.

In a separate reaction vessel, LDA was prepared by addition of nBuLi (2.5 M in hexanes, 0.29 mL, 0.74 mmol, 1.5 eq.) to a solution of diisopropylamine (0.21 mL, 1.47 mmol, 3.0 eq.) in dry THF (3 mL) at $-78$ °C. The freshly formed solution of LDA was further stirred at 0 °C for 15 min and cooled down to $-78$ °C. A solution of 436 (141 mg, 0.59 mmol, 1.2 eq.) in dry THF (1 mL) was added dropwise to the previously prepared LDA solution and the mixture was stirred further at $-78$ °C for 10 min. In parallel, a suspension containing CeCl$_3$ and the respective aldehyde 258 was cooled down to 0 °C and a solution of the deprotonated alkyne was transferred to the reaction mixture via cannula maintaining vigorous stirring. The resulting mixture was stirred at 0 °C for 30 min, after which time it was quenched by addition of aqueous saturated NH$_4$Cl.
and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:2) to afford 441 (222 mg, 0.46 mmol, 94%) as a colorless oil (d.r. 3:1).

The compound was used in the next step without full characterization.

HRMS (ESI, m/z) calculated for C₂₆H₄₆NaO₆Si⁺ [M+Na]⁺: 505.2956; found: 505.2950.

(1R,2S,3S,4S)-2-((S)-1-acetoxy-3-((2R,3S)-3-(2-hydroxyethyl)-2-methyloxiran-2-yl)prop-2-yn-1-yl)-4-(methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexyl acetate (442)

Diol 441 (100 mg, 0.21 mmol, 1.0 eq.) was dissolved in pyridine/Ac₂O 2:1 mixture and was let stirring for 22 h at room temperature. After this time, reaction mixture was diluted with water (2 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further dissolved in dry THF (1 mL) and the mixture was treated with TBAF (1M in THF, 0.41 mL, 0.41 mmol, 2.0 eq.) at room temperature. The reaction mixture was further stirred for 5 h at ambient temperature, diluted with water and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:2) to afford 442 (73 mg, 0.16 mmol, 78%) as a colorless oil (d.r. 3:1).

¹H NMR peak listing of the mixture of diastereomers (d.r. 3:1) is uninformative, see NMR spectrum below for the graphic representation.

¹³C NMR peak listing of the mixture of diastereomers (d.r. 3:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C₂₄H₃₇O₈⁺ [M+H]⁺: 453.2483; found: 453.2489.

IR (film): λmax = 3491, 2938, 1734, 1444, 1369, 1230, 1132, 1018, 919 cm⁻¹.
(1R,2S,3S,4S)-2-((S)-1-acetoxy-3-(((2R,3S)-3-allyl-2-methyloxiran-2-yl)prop-2-yn-1-yl)-4- (methoxymethoxy)-2,4-dimethyl-3-vinylcyclohexyl acetate (443)

A solution of 442 (45 mg, 0.1 mmol, 1.0 eq.) in dry DCM (2 mL) was treated with a solution of Dess-Martin periodinolate (0.3 M in DCM, 0.5 mL, 0.15 mmol, 1.5 eq.) at room temperature. The reaction mixture was stirred further at room temperature for 2 h, then diluted with aqueous NaHCO₃ and extracted with DCM (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further dissolved in dry THF (1 mL) and the resulting solution was submitted to the next step. In a separate reaction vessel, a solution of methyltriphenylphosphonium bromide (61 mg, 0.17 mmol, 1.7 eq.) in dry THF (2 mL) was treated with NaHMDS (1 M in THF, 0.1 mL, 0.1 mmol, 1.0 eq.) at −78 °C. The resulting suspension was further stirred for 1 h at 0 °C and transferred via cannula to the precooled to 0 °C solution of the aldehyde intermediate. After the addition was finished, the resulting mixture was stirred for 30 min at 0 °C, diluted with aqueous NH₄Cl (2 mL) and extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with water, brine, and dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was further purified via flash column chromatography (EA/PE 1:7) to afford 443 as a minor product (5 mg, 0.01 mmol, 14%) as a colorless oil (d.r. 3:1).

H NMR peak listing of the mixture of diastereomers (d.r. 3:1) is uninformative, see NMR spectrum below for the graphic representation.

13C NMR peak listing of the mixture of diastereomers (d.r. 3:1) is uninformative, see NMR spectrum below for the graphic representation.

HRMS (ESI, m/z) calculated for C₂₄H₃₇O₈ [M+H]⁺: 453.2483; found: 453.2489.
3.2 Enantiodivergent Synthesis of Cyclohepta[b]indole Derivatives

3.2.1 C–H Activation Precursors Preparation

(1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide (489c)

Corresponding cyclopropane (3.4 g, 26.1 mmol, 1.0 eq.), imidazole (2.14 g, 31.3 mmol, 1.2 eq.) and DMAP (160 mg, 1.3 mmol, 0.05 eq.) were dissolved in anhydrous DCM (10 mL). TBDPSCI (7.54 g, 27.4 mmol, 1.05 eq.) was added dropwise at room temperature. The mixture was stirred overnight, diluted with water (15 mL) and phases were separated. The organic layer was subsequently washed with water (10 mL), 1 M HCl (5 mL), aqueous NaHCO₃ (10 mL) and dried over magnesium sulfate, after the solvent was removed in vacuo. The crude product was used in the next step without purification. TBDPS-protected cyclopropane was converted into compound 489c via literature known procedure[294] (11.3 g, over two steps 87%)

The enantiomeric excess was determined to be 91% by chiral HPLC analysis (Chiral Pack IA, 0.3 mL/min, 91:9 Hexanes/ethanol, λ = 254 nm) tᵣ (major) = 139.2 min, tᵣ (minor) = 169.2 min.

¹H NMR (400 MHz, CDCl₃) δ = 10.09 (s, 1H), 8.81 (d, J = 2.8 Hz, 1H), 8.78 (d, J = 7.6 Hz, 1H), 8.16 (dd, J = 8.2, 1.5 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.60 – 7.56 (m, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 7.33 (q, J = 7.2 Hz, 2H), 7.24 (t, J = 7.6 Hz, 4H), 4.04 (dd, J = 11.0, 5.6 Hz, 1H), 3.84 (dd, J = 11.0, 8.9 Hz, 1H), 2.02 (td, J = 8.1, 5.6 Hz, 1H), 1.67 (dt, J = 14.7, 7.7 Hz, 1H), 1.27 – 1.21 (m, 1H), 1.05 (ddd, J = 8.9, 7.6, 4.8 Hz, 1H), 0.85 (s, 9H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 169.7, 148.1, 138.4, 136.4, 135.7, 135.7, 135.1, 134.3, 133.9, 129.5, 128.1, 127.6, 127.6, 121.6, 121.1, 116.5, 62.4, 29.9, 26.8, 23.9, 21.3, 19.2, 10.5 ppm.

HRMS (ESI, m/z) calculated for C₃₀H₃₂N₂O₂Si⁺ [M+H]⁺: 481.2306; found: 481.2286.

[α]D²⁵: +34.4 (c 0.37, CHCl₃).
3-iodo-1-tosyl-1H-indole (488)

To a solution of the corresponding indole (14.3 mmol, 1.0 eq.) in DMF (22 mL) was added freshly powdered KOH (35.7 mmol, 2.5 eq.). The mixture was stirred for 30 min at room temperature. A solution of iodine (15.0 mmol, 1.05 eq.) in DMF (22 mL) was added dropwise and the reaction was stirred for 1 h. Powdered KOH (35.7 mmol, 2.5 eq.) was added followed by TsCl (30.0 mmol, 2.1 eq.). The reaction was stirred overnight and was then poured into water (200 mL). The product was filtered off, washed with water, a small amount of isopropanol and finally with petrol ether and dried in air to yield the corresponding 3-iodoindole.

According to general procedure starting from indole (100 mmol), 36.0 g (90.6 mmol, 91%) were obtained as a colorless solid after recrystallization from ethanol. Analytical data were in accordance to literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.96 (d, $J$ = 8.5 Hz, 1H), 7.78 (d, $J$ = 8.1 Hz, 2H), 7.69 (s, 1H), 7.29 – 7.38 (m, 3H), 7.24 (d, $J$ = 8.1 Hz, 2H), 2.35 (s, 3H).

3.2.2 Pd-Catalyzed C–H Activation/Preparation of the Common Precursor

Corresponding cyclopropane (5.31 mmol, 1.0 eq.), silver carbonate (6.37 mmol, 1.2 eq.), iodoindole (15.9 mmol, 3.0 eq.) and palladium acetate (0.53 mmol, 10% mol, 0.1 eq.) were mixed up under nitrogen atmosphere in a Schleck flask and toluene (5.3 mL) was added under a nitrogen flow. The seal tube was protected from light and heated in an oil bath at 110 $^\circ$C for 2 – 6 h. Completion of the reaction was controlled by TLC (PE/EA 3:1) After cooling down to room temperature, the reaction mixture was filtered over a pad of celite using ethyl acetate as eluent. The filtrate was dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was purified by column chromatography (PE/EA 3:1) to yield the desired product as a yellowish foam.
2-(((tert-butylidiphenylsilyl)oxy)methyl)-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (487c) (1.87 g, 47%)

\[ \text{[a]_D^{23} = -4.9 \text{ (c 0.2, CHCl}_3) } \]

To a solution of trisubstituted cyclopropane (3.81 mmol, 1.0 eq.) in CH\(_3\)CN (35 mL) were added DMAP (7.63 mmol, 2.0 eq.) and Boc\(_2\)O (11.4 mmol, 3.0 eq.) at room temperature, and the mixture was heated at 40° C for 2 h. The solvent was evaporated, and the residue was partitioned between EtOAc (100 mL) and aqueous HCl (1 M, 50 mL). The organic layer was washed with saturated aqueous NaHCO\(_3\) (50 mL) and brine (50 mL), dried over anhydrous MgSO\(_4\), and evaporated to give a crude product as a brown oil. To a solution of the crude product in THF (50 mL) were added MeOH (11.4 mmol, 3.0 eq.) and LiBH\(_4\) (13.35 mmol, 3.5 eq.) at 0 °C, and the mixture was stirred at room temperature for 90 min. The solvent volume was doubled with Et\(_2\)O (50 mL) and the solution was cooled to 0 °C. Saturated aqueous NH\(_4\)Cl (30 mL) was added dropwise followed by addition of water (20 mL). The resulting mixture was extracted with Et\(_2\)O, and the organic layer was washed with brine, dried over anhydrous MgSO\(_4\), and evaporated. The residue was purified by silica gel column chromatography (PE/EA 3:1) to give the corresponding alcohol as a slightly green foam.

\[ \text{[a]_D^{23} = -4.9 \text{ (c 0.2, CHCl}_3) } \]

\[ \text{[(1R,2S,3S)-2-(((tert-butylidiphenylsilyl)oxy)methyl)-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methanol (513) (2.03 g, 02s 88%)} \]
11.6, 9.8, 6.0 Hz, 1H), 3.67 – 3.55 (m, 1H), 3.41 (t, J = 10.6 Hz, 1H), 2.78 (d, J = 8.0 Hz, 1H), 2.32 (s, 3H), 2.11 (td, J = 8.7, 1.3 Hz, 1H), 1.84 (qd, J = 8.9, 6.1 Hz, 1H), 1.73 – 1.59 (m, 1H), 1.07 (s, 9H) ppm.

13C NMR (101 MHz, CDCl3) δ = 144.9, 135.7, 135.5, 135.2, 135.1, 133.1, 132.9, 132.0, 129.9, 129.8, 127.9, 124.9, 124.7, 123.3, 119.6, 117.6, 113.7, 61.7, 59.9, 26.9, 22.1, 21.6, 21.4, 19.1, 15.1 ppm.

HRMS (ESI, m/z) calculated for C36H39NO4SSi+ [M+H]+: 609.2364; found: 609.2372.

[α]D23: +26.5 (c 0.35, CHCl3).

3.2.3 Amide-to-Olefin Route

(1R,2S,3R)-2-(((tert-butylidiphenylsilyl)oxy)methyl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carbaldehyde (496) (445 mg, 84%)

To a solution of alcohol (533 mg, 0.873 mmol, 1.0 eq.) in anhydrous DCM (10 mL), NMO (154 mg, 1.31 mmol, 1.5 eq.) and was freshly powdered MS 4Å (450 mg) were added subsequently. To the stirring reaction mixture TPAP (30 mg, 0.08 mmol, 0.1 eq.) was added and the mixture was stirred at room temperature until consumption of the starting material (about 1–2 h). The reaction was diluted with DCM (20 mL) and filtered through a pad of celite, and eluted with another amount of DCM (50 mL). The solvent was removed under reduced pressure and the crude foam was purified by column chromatography (PE/EA 3:1) to obtain the desired aldehyde (445 mg, 0.728 mmol, 84%) as a white foam.

1H NMR (400 MHz, CDCl3) δ = 8.88 (d, J = 7.0 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.72 – 7.62 (m, 6H), 7.47 – 7.36 (m, 7H), 7.32 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 4.13 (dd, J = 11.5, 9.1 Hz, 1H), 3.96 (dd, J = 11.5, 6.4 Hz, 1H), 2.73 (t, J = 8.4 Hz, 1H), 2.32 (s, 3H), 2.22 (q, J = 8.5 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.11 (s, 9H) ppm.

13C NMR (101 MHz, CDCl3) δ = 199.7, 144.8, 135.4, 135.4, 135.0, 134.9, 133.1, 132.9, 131.2, 129.7, 129.7, 127.7, 127.7, 126.6, 125.7, 125.1, 123.5, 119.5, 114.8, 113.6, 59.3, 30.7, 28.5, 26.7, 21.4, 21.1, 19.0 ppm.

HRMS (ESI, m/z) calculated for C36H37NO5SSi+ [M+H]+: 608.2285; found: 608.2272.

[α]D23: +5.3 (c 0.58, CHCl3).
3-((1S,2R,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3-vinylcyclopropyl)-1-tosyl-1H-indole (491) (432 mg, 98%).

Methyltriphenylphosphonium bromide (1.86 mmol, 2.6 eq.) was suspended in anhydrous THF (10 mL) and stirred for 5 min at room temperature. Then the mixture was cooled down to -78 °C and NaHMDS (1 M in THF, 1.43 mmol, 2.0 eq.) was added dropwise at -78 °C. Reaction mixture stirred for 20 min at -78 °C and 30 min at 0 °C, after which time, was further re-cooled to -78 °C. In parallel, aldehyde 52 (0.873 mmol, 1.0 eq.), was dissolved in anhydrous THF (10 mL) and added dropwise to the reaction mixture at -78 °C. The resulting mixture was stirred additionally for 20 min at -78 °C and 60 min at 0 °C. After starting material is consumed (monitored by TLC), 40 mL of ice-cold water were added and mixture was extracted with EtOAc (100 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo to give the crude product as a yellowish oil, which was purified by column chromatography (PE/EA 3:1) to obtain the desired alkene as a slightly yellowish foam.

¹H NMR (400 MHz, CDCl₃) δ = 7.99 (d, J = 8.3 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, J = 7.2, 4.9 Hz, 4H), 7.61 (d, J = 7.1 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.46 – 7.27 (m, 7H), 7.15 (dd, J = 22.5, 7.8 Hz, 3H), 5.24 – 5.06 (m, 2H), 4.85 (dd, J = 9.4, 2.6 Hz, 1H), 3.82 (dd, J = 11.3, 5.6 Hz, 1H), 3.75 – 3.62 (m, 1H), 2.31 (s, 3H), 2.25 (t, J = 8.7 Hz, 1H), 2.04 (q, J = 8.9 Hz, 1H), 1.70 (qd, J = 9.1, 5.8 Hz, 1H), 1.09 (s, 9H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 144.6, 135.7, 135.6, 135.4, 135.2, 134.2, 133.9, 133.7, 132.3, 129.7, 129.6, 127.7, 126.7, 126.7, 125.5, 124.7, 123.1, 120.6, 116.1, 113.6, 61.1, 26.9, 24.6, 23.9, 21.5, 19.2, 17.3 ppm.

HRMS (ESI, m/z) calculated for C₃₇H₃₉NO₃Si⁺ [M+H]⁺: 606.2493; found: 606.2474.

[α]D²₃: -13.9 (c 0.45, CHCl₃).

(5aR,9R)-9-(((tert-butyldiphenylsilyl)oxy)methyl)-5-tosyl-5a,6,9-tetrahydrocyclohepta[b]indole (492) (409 mg, 95%)

To perform divinylcyclopropane-cycloheptadiene rearrangement, the corresponding vinyl-cyclopropane (0.709 mmol) was dissolved in anhydrous toluene (10 mL), placed in a sealed tube and heated at 120 °C for 3h. After starting material is consumed (monitored by TLC), the solvent was removed in vacuo to give the crude product, which was purified by column
chromatography (PE/EA 3:1) to obtain the desired cyclohepta[b]indoline as a slightly yellowish foam.

\[ ^1H \text{NMR} \] (400 MHz, CDCl\textsubscript{3}) \( \delta = 7.69 \) (t, \( J = 7.5 \) Hz, 3H), 7.63 (d, \( J = 7.3 \) Hz, 2H), 7.41 (td, \( J = 11.2, 8.0 \) Hz, 6H), 7.29 (t, \( J = 7.5 \) Hz, 2H), 7.24 – 7.17 (m, 2H), 7.00 (t, \( J = 7.5 \) Hz, 1H), 6.92 (d, \( J = 8.1 \) Hz, 2H), 6.02 – 5.94 (m, 1H), 5.94 – 5.83 (m, 1H), 5.82 – 5.72 (m, 1H), 4.72 (d, \( J = 11.1 \) Hz, 1H), 3.64 (dd, \( J = 9.3, 6.6 \) Hz, 2H), 3.56 (t, \( J = 8.5 \) Hz, 1H), 3.28 – 3.16 (m, 1H), 3.01 (ddd, \( J = 15.8, 8.1, 2.9 \) Hz, 1H), 2.54 – 2.43 (m, 1H), 2.21 (s, 3H), 1.03 (s, 9H) ppm.

\[ ^{13}C \text{NMR} \] (101 MHz, CDCl\textsubscript{3}) \( \delta = 143.9, 142.8, 140.5, 135.6, 135.5, 133.8, 133.6, 130.0, 129.8, 129.6, 129.5, 129.4, 127.8, 127.7, 127.3, 126.7, 124.3, 120.1, 117.1, 116.4, 67.1, 64.6, 43.6, 34.5, 26.8, 21.5, 19.3 \) ppm.

HRMS (ESI, \( m/z \)) calculated for C\textsubscript{37}H\textsubscript{39}NO\textsubscript{3}SSi\textsuperscript{+} [M+H]\textsuperscript{+}: 606.2493; found: 606.2478.

\([\alpha]_D^{23}\) : \(-106.5 \) (c 1.04, CHCl\textsubscript{3}).

\((S)-(5\text{-tosyl}-5,6,9,10\text{-tetrahydrocyclohepta[b]indol-9-yl})\text{methanol (}(-)\text{-485})\) (98 mg, \( \text{o2s 75\%} \))

To a solution of the TBDPS-protected cyclohepta[b]indoline (0.264 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise HF-pyr (70% in pyridine, 2 mL) at 0°C. The reaction mixture was stirred for 1h at 0°C and for 2 h at ambient temperature (completion monitored by TLC) before it was diluted with EtOAc (10 mL) and quenched by the addition of sat. aq. NaHCO\textsubscript{3}. The layers were separated and the aqueous layer was extracted twice with EtOAc (2 x 20 mL). The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (PE/EA 3:2) to obtain the product as a mixture of partly rearomatized indole and cyclohepta[b]indoline, which was directly dissolved in anhydrous DCM (3 mL) and pTsOH (0.264 mmol, 1.0 eq.) was added in one portion. The resulting mixture were stirred for 14 h at room temperature (completion monitored by TLC) after which time the solvent was removed \textit{in vacuo} to give the crude product, which was purified by column chromatography (PE/EA 3:2) to yield the desired product as a slightly yellowish foam.

\[ ^1H \text{NMR} \] (400 MHz, CDCl\textsubscript{3}) \( \delta = 8.20 \) (d, \( J = 8.1 \) Hz, 1H), 7.56 (d, \( J = 8.1 \) Hz, 2H), 7.37 (d, \( J = 7.5 \) Hz, 1H), 7.30 – 7.21 (m, 2H), 7.16 (d, \( J = 8.1 \) Hz, 2H), 5.83 (dt, \( J = 10.6, 5.1 \) Hz, 1H), 5.74 (d, \( J = 11.6 \)
Hz, 1H), 4.05 (dd, \( J = 20.5, 6.2 \) Hz, 1H), 3.86 (d, \( J = 20.5 \) Hz, 1H), 3.65 (dd, \( J = 10.4, 5.1 \) Hz, 1H), 3.52 (dd, \( J = 10.2, 6.8 \) Hz, 1H), 2.94 (t, \( J = 10.1 \) Hz, 1H), 2.71 (d, \( J = 11.6 \) Hz, 2H), 2.33 (s, 3H) ppm.

\(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta = 144.7, 136.5, 136.1, 134.1, 132.6, 129.9, 126.6, 126.4, 124.4, 123.7, 120.8, 117.9, 115.4, 66.3, 39.6, 27.2, 25.4, 21.7 \) ppm.

\(^{1}\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta = 7.98 (d, J = 8.3 \) Hz, 1H), 7.72 (d, \( J = 8.2 \) Hz, 2H), 7.54 (d, \( J = 7.7 \) Hz, 1H), 7.46 (s, 1H), 7.32 (t, \( J = 7.7 \) Hz, 1H), 7.22 (t, \( J = 7.9 \) Hz, 3H), 4.28 (dd, \( J = 11.9, 6.7 \) Hz, 1H), 3.2.4 Alcohol-to-Olefin Route

\(((1R,2S,3R)-2-\text{hydroxymethyl})-3-\text{-tosyl}-1\text{-H-indol-3-yl})\text{cyclopropyl)methyl pivalate} \) (493)

Alcohol (1.15 mmol, 1.0 eq.) and DMAP (0.11 mmol, 0.1 eq.) were dissolved in anhydrous DCM (20 mL), and Et\(_3\)N (3.44 mmol, 3.0 eq.) was added in one portion. The mixture was cooled down with ice bath cooling and PivCl (1.72 mmol, 1.5 eq) was added dropwise to the mixture at 0 °C. The reaction mixture was slowly warmed up to the room temperature over 18h. After that time, the mixture was diluted with DCM (20 mL) and water (50 mL). Phases were separated and the aqueous phase were extracted twice with DCM (2x20 mL). The combined organic phases were subsequently washed with 0.1 M HCl (30 mL), sat. NaHCO\(_3\), brine, dried over anhydrous MgSO\(_4\), and the solvent was removed in vacuo to give the crude product, which was used for the next step without purification.

To a solution of the crude cyclopropane (1.15 mmol, 1.0 eq.), which was obtained in the previous step, in anhydrous THF (10 mL) was added dropwise HF-pyr (70% in pyridine, 5 mL) at 0°C. The reaction mixture was stirred 1h at 0 °C and 2h at ambient temperature (completion monitored by TLC) before it was diluted with EtOAc (20 mL) and quenched be the addition of sat. aq. NaHCO\(_3\). The layers were separated and the aqueous layer was extracted twice with EtOAc (2 x 20 mL). The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (PE/EA 3:2) to obtain the desired alcohol as a white foam.
3.91 (dd, $J = 12.0, 8.0$ Hz, 1H), 3.84 – 3.71 (m, 1H), 3.57 (dd, $J = 10.9, 7.9$ Hz, 1H), 2.34 (s, 3H), 2.23 (t, $J = 8.7$ Hz, 1H), 1.84 – 1.64 (m, 3H), 1.22 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 178.5, 144.9, 135.2, 135.1, 131.9, 129.9, 126.7, 125.1, 124.9, 123.4, 119.7, 116.9, 113.9, 61.9, 59.6, 38.8, 27.2, 22.1, 21.6, 18.0, 14.8 ppm.

HRMS (ESI, m/z) not found.

[\alpha]_D^{23}: +34.9 (c 0.22, CHCl$_3$).

((1R,2S,3S)-2-formyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (281 mg, 85%)

To a solution of an alcohol (0.768 mmol, 1.0 eq.) in anhydrous DCM (8 mL), NMO (1.23 mmol, 1.5 eq.) and freshly powdered MS 4A (500 mg/mmole) were added subsequently. To the stirring reaction mixture TPAP (27 mg, 0.08 mmol, 0.1 eq.) was added and the mixture was stirred at room temperature until consumption of the starting material (about 1–2 h). The reaction was diluted with DCM (20 mL) and filtered through a pad of celite, and eluted with another amount of DCM (50 mL). The solvent was removed under reduced pressure and the crude foam was purified by column chromatography (PE/EA 3:1) to obtain the desired aldehyde as a white foam.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 9.07 (d, $J = 6.2$ Hz, 1H), 7.99 (d, $J = 8.3$ Hz, 1H), 7.72 (d, $J = 8.3$ Hz, 2H), 7.50 (s, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.34 (t, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 4H), 4.52 (dd, $J = 12.0, 7.8$ Hz, 1H), 4.26 (dd, $J = 12.1, 7.1$ Hz, 1H), 2.79 (t, $J = 8.5$ Hz, 1H), 2.33 (d, $J = 6.4$ Hz, 5H), 1.23 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 199.2, 178.4, 145.3, 135.3, 135.0, 131.3, 130.2, 126.9, 126.0, 125.6, 123.9, 119.6, 114.6, 114.1, 60.3, 38.9, 30.5, 27.3, 24.7, 21.7, 21.3 ppm.

HRMS (ESI, m/z) calculated for C$_{25}$H$_{27}$NO$_5$ $^+$ [M+H]$^+$: 454.1683; found: 454.1669.

[\alpha]_D^{23}: +3.2 (c 1.12, CHCl$_3$).

((1S,2R,3S)-2-(1-tosyl-1H-indol-3-yl)-3-vinylcyclopropyl)methyl pivalate (494) (210 mg, 86%)

Methyltriphenylphosphonium bromide (1.43 mmol, 2.6 eq.) was suspended in anhydrous THF (80 mL) and stirred for 5 min at room temperature. Then the mixture was cooled down to $-78$ °C and NaHMDS (1 M in THF, 1.1 mmol, 2.0 eq.) was added dropwise at $-78$ °C. Reaction mixture stirred for 20 min at $-78$ °C and 30 min at 0 °C, after which time, was further re-cooled to $-78$ °C. In parallel, an aldehyde (0.551 mmol, 1.0 eq.) was dissolved in anhydrous THF (10 mL)
and added dropwise to the reaction mixture at −78 °C. The resulting mixture was stirred additionally for 20 min at −78 °C and 60 min at 0 °C. After starting material is consumed (monitored by TLC), 40 mL of ice-cold water were added and mixture was extracted with 50 mL of EtOAc (80 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo to give the crude product as a yellowish oil, which was purified by column chromatography (PE/EA 2:1) to obtain the desired alkene as a slightly yellowish foam.

**¹H NMR** (400 MHz, CDCl₃) δ = 7.97 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.21 (dd, J = 7.5, 4.1 Hz, 3H), 5.36 – 5.21 (m, 2H), 5.01 (dd, J = 9.4, 2.7 Hz, 1H), 4.11 (dd, J = 11.9, 7.0 Hz, 1H), 3.99 (dd, J = 11.9, 8.8 Hz, 1H), 2.33 (s, 3H), 2.32 – 2.27 (m, 1H), 2.17 (q, J = 8.8 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.21 (s, 9H) ppm.

**¹³C NMR** (101 MHz, CDCl₃) δ = 178.5, 144.9, 135.2, 135.1, 133.6, 131.9, 129.9, 126.7, 125.4, 124.9, 123.2, 120.4, 117.4, 116.9, 113.8, 62.1, 38.7, 27.2, 23.8, 21.6, 20.6, 17.2 ppm.

**HRMS** (ESI, m/z) calculated for C₂₆H₂₉NO₄S⁺ [M+H]⁺: 452.1890; found: 452.1883.

**[(αR,βS)-5-tosyl-5,6,9-tetrahydrocyclohepta[b]indol-9-yl)methyl pivalate (495)]** (195 mg, 97%)

To perform divinylcyclopropane-cycloheptadiene rearrangement, the corresponding vinylcyclopropane (0.442 mmol) was dissolved in anhydrous toluene (6 mL), placed in a sealed tube and heated at 125 °C for 2 h. After starting material is consumed (monitored by NMR), the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (PE/EA 2:1) to obtain the desired cyclohepta[b]indoline as a white foam.

**¹H NMR** (400 MHz, CDCl₃) δ = 7.71 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.24 (dd, J = 7.6, 5.0 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 5.95 (dd, J = 6.5, 2.1 Hz, 1H), 5.89 (ddt, J = 10.7, 8.3, 2.3 Hz, 1H), 5.60 (dt, J = 12.3, 3.4 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.07 (dd, J = 10.4, 6.8 Hz, 1H), 3.95 (dd, J = 10.5, 7.3 Hz, 1H), 3.36 – 3.25 (m, 1H), 3.04 (ddd, J = 15.9, 8.3, 3.0 Hz, 1H), 2.49 (ddd, J = 16.0, 11.1, 2.8 Hz, 1H), 2.34 (s, 3H), 1.16 (s, 9H) ppm.

**¹³C NMR** (101 MHz, CDCl₃) δ = 178.2, 144.2, 142.9, 141.1, 133.9, 129.8, 129.7, 129.3, 128.5, 127.7, 127.3, 124.4, 120.2, 116.4, 115.6, 66.6, 64.5, 40.1, 38.8, 34.5, 27.2, 21.5 ppm.

**HRMS** (ESI, m/z) calculated for C₂₆H₂₉NO₄S⁺ [M+H]⁺: 452.1890; found: 452.1882.
(R)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl)methanol ((+) -485) (102 mg, 0.2 s 64%)

To a solution of the Piv-protected cyclohepta[b]indoline (0.432 mmol, 1.0 eq.) in anhydrous DCM (2 mL) was added pTsOH monohydrate (0.432 mmol, 1.0 eq.) at room temperature and the resulting mixture was stirred for 16 h at ambient temperature (monitored by TLC), after which time the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (PE/EA 3:1) to yield the desired product, which was subjected to further step without characterization.

Corresponding crude pivalate (0.21 mmol) was dissolved in anhydrous DCM (2.1 mL) and the solution was cooled to −78 °C in an acetone/dry ice bath. DIBAL-H (1 M in toluene, 0.44 mmol, 2.2 eq.) was added dropwise and the reaction was stirred for 1 h. 1 M HCl (5 mL) was added and the reaction was warmed up to room temperature. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered off and concentrated in vacuo to give the crude product, which was purified by column chromatography (PE/EA 1:1) to yield the desired product as a white foam.

^1H NMR (400 MHz, CDCl₃) δ = 8.20 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.31 – 7.21 (m, 2H), 7.15 (d, J = 8.1 Hz, 2H), 5.83 (dt, J = 10.6, 5.2 Hz, 1H), 5.74 (d, J = 9.5 Hz, 1H), 4.05 (dd, J = 20.5, 6.2 Hz, 1H), 3.86 (d, J = 20.4 Hz, 1H), 3.65 (dd, J = 10.3, 5.0 Hz, 1H), 3.51 (dd, J = 14.8, 4.4 Hz, 1H), 2.94 (t, J = 10.7 Hz, 1H), 2.70 (d, J = 12.1 Hz, 2H), 2.32 (s, 3H) ppm.

^13C NMR (101 MHz, CDCl₃) δ = 144.7, 136.5, 136.1, 134.1, 132.6, 131.4, 129.9, 126.6, 126.4, 124.4, 123.7, 120.8, 117.9, 115.4, 66.3, 39.6, 27.2, 25.4, 21.7 ppm.

HRMS (ESI, m/z) calculated for C₂₁H₂₁NO₃S⁺ [M+H]⁺: 368.1315; found: 368.1309.

[α]D₂₃: +12.6 (c 0.19, CHCl₃).

3.2.5 Phosphonates as Olefination Reagents (Protocol A) / DVCPR
The corresponding phosphonate (1.04 mmol, 3.0 eq.) was dissolved in anhydrous THF (3 mL), the solution was cooled down to –78 °C and nBuLi (2.5 M in THF, 0.642 mmol, 1.8 eq.) was added dropwise at –78 °C and the resulting mixture were stirred at the same temperature for an additional 1 hour. After which time a solution of an aldehyde (0.347 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise to the reaction mixture at –78 °C. The resulting mixture was stirred additionally for 20 min at –78 °C and slowly warmed up to the room temperature over 4 hours. After starting material is consumed (monitored by TLC), 5 mL of ice-cold water were added and mixture was extracted with EtOAc (25 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo to give the crude product as a yellowish oil, which was purified by column chromatography (PE/EA 3:1) to obtain the desired alkene as a yellowish oil.

3-((1S,2R,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-1-tosyl-1H-indole (497b) (110 mg, 75%).

Used in the further step immediately without full characterization.

1H NMR (400 MHz, CDCl₃) δ = 8.00 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H), 7.68 (dd, J = 7.2, 4.9 Hz, 4H), 7.61 (d, J = 6.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.36 (d, J = 8.3 Hz, 4H), 7.30 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 6.21 (dd, J = 15.0, 10.5 Hz, 1H), 5.98 (dt, J = 16.9, 10.3 Hz, 1H), 5.05 – 4.92 (m, 2H), 4.84 (d, J = 10.2 Hz, 1H), 3.81 (dd, J = 11.3, 5.8 Hz, 1H), 3.73 – 3.65 (m, 1H), 2.31 (s, 4H), 2.05 (q, J = 9.2 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.09 (s, 9H) ppm.

HRMS (ESI, m/z) calculated for C₃₉H₄₁NO₃SSi [M+H]+: 632.2649; found: 632.2642.

[α]D²³: +7.3 (c 0.43 CHCl₃).

3-((1S,2R,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3-((E)-styryl)cyclopropyl)-1-tosyl-1H-indole (497c) (185 mg, 87%).

1H NMR (400 MHz, CDCl₃) δ = 8.02 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 1.3 Hz, 1H), 7.67 (dd, J = 7.3, 4.7 Hz, 3H), 7.62 (d, J = 6.7 Hz, 2H), 7.53 (dd, J = 7.6, 3.5 Hz, 2H), 7.44 – 7.37 (m, 3H), 7.32 (dd, J = 15.7, 8.4 Hz, 5H), 7.15 (d, J = 7.5 Hz, 3H), 7.09 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 6.8 Hz, 2H), 6.55 (d, J = 15.6 Hz, 1H), 5.48 (dd, J = 15.7, 10.0 Hz, 1H), 3.86 (dd, J = 11.4, 6.1 Hz, 1H), 3.83 – 3.72 (m, 1H), 2.32 (d, J = 24.9 Hz, 4H), 2.20 (q, J = 9.1 Hz, 1H), 1.79 (qd, J = 8.9, 6.1 Hz, 1H), 1.09 (s, 9H) ppm.
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 144.7, 137.7, 135.8, 135.8, 134.9, 133.9, 133.8, 132.4, 131.4, 129.8, 129.8, 128.8, 128.5, 127.9, 127.8, 126.8, 126.7, 125.9, 125.8, 124.9, 123.4, 120.6, 118.1, 113.8, 61.4, 27.1, 25.5, 23.7, 21.7, 19.3, 18.0 ppm.

HRMS (ESI, m/z) calculated for C$_{43}$H$_{43}$NO$_3$SSi$^+$ [M+H]$^+$: 682.2806; found: 682.2793.

$[\alpha]_D^{23}$: $-$13.6 (c 0.73, CHCl$_3$).

To perform divinylcyclopropane-cycloheptadiene rearrangement, the corresponding vinyl-cyclopropane (0.709 mmol) was dissolved in anhydrous toluene (10 mL), placed in a sealed tube and heated at 120 °C for 3 h. After starting material is consumed (monitored by TLC), the solvent was removed $\textit{in vacuo}$ to give the crude product, which was purified by column chromatography (PE/EA 3:1) to obtain the desired cyclohepta[b]indoline as a slightly yellowish foam.

(5a$R$,6$R$,9$R$)-9-((((tert-butyldiphenylsilyl)oxy)methyl)-5-tosyl-6-vinyl-5,5a,6,9-tetrahydrocyclohepta[b]indole (80 mg, 73%)

1H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.68 (d, $J$ = 7.9 Hz, 3H), 7.63 (d, $J$ = 7.0 Hz, 2H), 7.41 (dd, $J$ = 14.3, 7.6 Hz, 6H), 7.29 (t, $J$ = 7.5 Hz, 2H), 7.23 – 7.14 (m, 2H), 6.98 (t, $J$ = 7.5 Hz, 1H), 6.89 (d, $J$ = 8.1 Hz, 2H), 5.98 (dd, $J$ = 6.9, 2.5 Hz, 1H), 5.88 (d, $J$ = 4.6 Hz, 2H), 5.64 (ddd, $J$ = 17.1, 10.1, 7.1 Hz, 1H), 5.15 (d, $J$ = 17.1 Hz, 1H), 4.97 (d, $J$ = 10.4 Hz, 1H), 4.92 (s, 1H), 3.83 – 3.70 (m, 1H), 3.63 (dd, $J$ = 9.4, 6.4 Hz, 1H), 3.58 – 3.50 (m, 1H), 3.20 (q, $J$ = 7.3, 6.9 Hz, 1H), 2.20 (s, 3H), 1.24 (s, 9H) ppm.

HRMS (ESI, m/z) calculated for C$_{40}$H$_{38}$NO$_3$SSi$^+$ [M+H]$^+$: 632.2649; found: 632.2639.

$[\alpha]_D^{23}$: $-$101.9 (c 0.91 CHCl$_3$).
(5aR,6S,9R)-9-(((tert-butyldiphenylsilyl)oxy)methyl)-6-phenyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indole (156 mg, 84 %)

^1^H NMR (400 MHz, CDCl_3) δ = 7.77 – 7.72 (m, 2H), 7.71 – 7.64 (m, 2H), 7.56 – 7.51 (m, 1H), 7.50 – 7.45 (m, 3H), 7.44 – 7.38 (m, 2H), 7.35 – 7.31 (m, 5H), 7.06 (d, J = 7.2 Hz, 2H), 7.04 – 6.96 (m, 2H), 7.19 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.6 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.10 (dd, J = 12.4, 5.1 Hz, 1H), 6.07 – 5.91 (m, 2H), 5.21 – 5.06 (m, 1H), 4.39 (dd, J = 7.2, 3.8 Hz, 1H), 3.68 (dd, J = 9.4, 6.3 Hz, 1H), 3.61 (t, J = 8.8 Hz, 1H), 3.37 (p, J = 6.8 Hz, 1H), 2.17 ppm.

^1^C NMR (101 MHz, CDCl_3) δ = 143.9, 143.3, 137.7, 136.5, 135.8, 135.6, 134.9, 133.9, 130.5, 130.0, 129.9, 129.6, 129.2, 128.8, 127.9, 127.8, 127.3, 126.9, 126.7, 124.1, 119.6, 116.9, 116.3, 116.0, 114.7, 113.8, 109.2, 67.7, 66.7, 47.9, 43.8, 26.9, 21.6, 19.4 ppm.

HRMS (ESI, m/z) calculated for C_{43}H_{43}NO_{3}SSi^+ [M+H]^+: 682.2806; found: 682.2794.

[α]_D^{23}: −84.0 (c 1.00, CHCl_3).

3.2.6 Stabilized Ylides as Olefination Reagents (Protocol B) / DVCPR

To perform Wittig reaction - divinylcyclopropane-cycloheptadiene rearrangement cascade, the corresponding aldehyde (0.197 mmol, 1 eq.) and the respective stabilized ylide (0.592 mmol, 3.0 eq.) were dissolved in anhydrous toluene (3 mL) and heated at 110 °C for 2–6 h. After starting material is consumed (monitored by TLC), the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (PE/EA 3:1) to obtain the desired cyclohepta[b]indoline as a yellowish foam.

methyl(5aR,6R,9R)-9-(((tert-butyldiphenylsilyl)oxy)methyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indole-6-carboxylate (90 mg, 65%).

^1^H NMR (400 MHz, CDCl_3) δ = 7.69 (d, J = 8.3 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.61 (d, J = 6.8 Hz, 2H), 7.39 (q, J = 7.5, 6.8 Hz, 6H), 7.29 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.91 ppm.
(d, J = 8.1 Hz, 2H), 6.00 (d, J = 4.9 Hz, 2H), 5.95 (dd, J = 6.6, 2.7 Hz, 1H), 4.82 (s, 1H), 4.28 – 4.22 (m, 1H), 3.66 (dd, J = 9.1, 5.8 Hz, 1H), 3.53 (dd, J = 9.2, 7.8 Hz, 1H), 3.49 (s, 3H), 3.27 (q, J = 7.7, 7.1 Hz, 1H), 2.20 (s, 3H), 1.03 (s, 9H) ppm.

\[13^C\text{ NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 170.4, 144.3, 143.6, 137.9, 135.8, 135.7, 133.7, 133.3, 131.1, 130.1, 130.0, 129.8, 129.5, 128.0, 127.9, 127.5, 124.6, 124.5, 120.0, 116.5, 116.4, 66.8, 64.8, 51.9, 49.1, 44.2, 26.9, 21.6, 19.4 \text{ ppm.}\]

HRMS (ESI, m/z) calculated for C_{39}H_{41}NO_5SSi^+ [M+H]^+: 664.2547; found: 664.2540.

\([\alpha]^D_{23} = -139.4 \text{ (c 0.23, CHCl}_3).\]

\[1-(5aR,6R,9R)-9-(((\text{tert-butyldiphenylsilyl})\text{oxy})\text{methyl})-5-\text{tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-6-yl})\text{ethan-1-one} \ (110 \text{ mg, 73\%}).\]

\[1^H \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \delta = 7.71 \text{ (d, J = 8.1 Hz, 1H), 7.64 (d, J = 6.8 Hz, 2H), 7.61 (d, J = 7.0 Hz, 2H), 7.40 (dd, J = 18.4, 7.9 Hz, 6H), 7.29 (t, J = 7.6 Hz, 2H), 7.23 – 7.17 \text{ (m, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.2 Hz, 2H), 6.02 (d, J = 5.8 Hz, 2H), 5.88 (dd, J = 6.1, 2.8 Hz, 1H), 4.83 – 4.74 \text{ (m, 1H), 4.45 – 4.36 \text{ (m, 1H), 3.66 (dd, J = 9.3, 6.1 Hz, 1H), 3.52 (dd, J = 9.2, 7.5 Hz, 1H), 3.26 (q, J = 6.4 Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.02 \text{ (s, 9H}) ppm.}\]

\[13^C \text{ NMR} \ (101 \text{ MHz, CDCl}_3) \delta = 204.0, 144.3, 143.1, 137.0, 135.7, 135.6, 133.9, 133.6, 133.2, 129.9, 129.9, 129.7, 129.4, 127.9, 127.9, 127.5, 124.7, 124.3, 120.1, 116.4, 116.3, 66.9, 65.1, 57.0, 44.4, 30.8, 26.9, 21.6, 19.4 \text{ ppm.}\]

HRMS (ESI, m/z) calculated for C_{38}H_{40}NO_4SSi^+ [M+H]^+: 648.2598; found: 648.2584.

\([\alpha]^D_{23} = -107.7 \text{ (c 0.75, CHCl}_3).\]

3.2.7 Deprotection/Aromatization Sequence

\[
\begin{array}{c}
\text{R} = \text{Vinyl, Phenyl, CO}_2\text{Me, C(O)Me} \\
\end{array}
\]

To a solution of the TBDDS-protected cyclohepta[b]indoline (0.264 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise HF-pyr (70% in pyridine, 2 mL) at 0 °C. The reaction mixture was stirred for 1h at 0 °C and for 2h at ambient temperature (completion monitored by TLC) before
it was diluted with EtOAc (10 mL) and quenched be the addition of sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted twice with EtOAc (2 x 20 mL). The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (PE/EA 3:2) to obtain the product as a mixture of partly rearomatized indole and cyclohepta[b]indoline, which was directly dissolved in anhydrous DCM (3 mL) and pTsOH (0.264 mmol, 1.0 eq.) was added in one portion. The resulting mixture were stirred for 14h at room temperature (completion monitored by TLC) after which time the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (PE/EA 3:2) to yield the desired product as a slightly yellowish foam.

**methyl(6R,9S)-9-(hydroxymethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indole-6-carboxylate (501)** (38 mg, o2s 73%)

**1H NMR** (400 MHz, CDCl₃) δ = 8.02 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 7.4 Hz, 1H), 7.24 (dt, J = 17.9, 7.8 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.01 (t, J = 10.0 Hz, 1H), 5.88 (dd, J = 11.2, 5.8 Hz, 1H), 5.44 (d, J = 8.7 Hz, 1H), 3.71 (s, 3H), 3.57 (dd, J = 10.4, 5.6 Hz, 1H), 3.39 – 3.30 (m, 1H), 3.10 (dd, J = 15.6, 2.9 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.79 (dd, J = 15.6, 8.8 Hz, 1H), 2.31 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 171.3, 144.8, 136.3, 135.9, 135.1, 131.7, 131.1, 129.7, 126.8, 125.4, 125.0, 123.7, 122.8, 118.7, 115.2, 65.2, 52.7, 43.9, 38.1, 24.8, 21.7 ppm.

**HRMS** (ESI, m/z) calculated for C$_{23}$H$_{23}$NO$_5$S$^+$ [M+H]$^+$: 426.1370; found: 426.1360.

[α]$^2_2$: –2.3 (c 0.18, CHCl₃).

**((6R,9S)-5-tosyl-6-vinyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl)methanol (499)** (25 mg, o2s 58%)

**1H NMR** (400 MHz, CDCl₃) δ = 8.19 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 7.4 Hz, 1H), 7.26 (p, J = 7.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.98 (ddd, J = 16.1, 10.0, 5.5 Hz, 1H), 5.84 (dd, J = 11.8, 7.6 Hz, 1H), 5.76 (dd, J = 11.8, 5.8 Hz, 1H), 5.22 (t, J = 6.4 Hz, 1H), 5.12 – 4.99 (m, 2H), 3.39 (dd, J = 10.4, 5.3 Hz, 1H), 3.06 (t, J = 9.5 Hz, 1H), 3.00 (dd, J = 15.2, 3.3 Hz, 1H), 2.91 (dd, J = 15.1, 6.0 Hz, 1H), 2.82 – 2.69 (m, 1H), 2.31 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 145.0, 137.1, 137.1, 136.9, 136.2, 132.4, 131.9, 130.0, 129.1, 126.8, 124.9, 124.2, 121.2, 118.5, 116.2, 114.8, 64.9, 41.2, 39.2, 23.5, 21.9 ppm.
HRMS (ESI, m/z) calculated for \( \text{C}_{23}\text{H}_{23}\text{NO}_{3}\text{S}^- \) [M+H]⁺: 394.1471; found: 394.1462.

\([\alpha]_D^{23}: -1.3 \text{ (c 0.28, CHCl}_3\text{}).\]

1-((6R,9S)-9-(hydroxymethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-6-yl)ethan-1-one (502) (22 mg, o2s 79%)

\(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta = 7.94 \text{ (d, } J = 7.5 \text{ Hz, } 1\text{H}), 7.57 \text{ (d, } J = 8.3 \text{ Hz, } 2\text{H}), 7.39 \text{ (d, } J = 6.8 \text{ Hz, } 1\text{H}), 7.22 \text{ (p, } J = 7.3, 6.6 \text{ Hz, } 2\text{H}), 7.14 \text{ (d, } J = 8.2 \text{ Hz, } 2\text{H}), 6.05 \text{ (t, } J = 9.9 \text{ Hz, } 1\text{H}), 5.96 \text{ (dd, } J = 11.0, 5.6 \text{ Hz, } 1\text{H}), 5.52 \text{ (d, } J = 8.8 \text{ Hz, } 1\text{H}), 3.59 \text{ (dd, } J = 10.4, 5.8 \text{ Hz, } 1\text{H}), 3.42 \text{ (dd, } J = 10.4, 7.1 \text{ Hz, } 1\text{H}), 3.06 \text{ – 2.91 (m, } 2\text{H}), 2.77 \text{ – 2.63 (m, } 1\text{H}), 2.35 \text{ (s, } 3\text{H}), 2.30 \text{ (s, } 3\text{H}) \text{ ppm.}

\(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta = 203.0, 144.8, 136.9, 136.1, 135.8, 131.8, 131.3, 129.7, 126.8, 124.9, 124.7, 123.7, 123.1, 118.5, 115.1, 65.6, 52.3, 37.8, 29.0, 25.4, 21.7 \text{ ppm.}

HRMS (ESI, m/z) calculated for \( \text{C}_{23}\text{H}_{23}\text{NO}_3\text{S}^- \) [M+H]⁺: 410.1421; found: 410.1409.

\([\alpha]_D^{23}: +25.8 \text{ (c 0.19, CHCl}_3\text{}).\]

((6S,9S)-6-phenyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl)methanol (500) (36 mg, o2s 75%)

\(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta = 8.23 \text{ (d, } J = 7.9 \text{ Hz, } 1\text{H}), 7.45 \text{ (d, } J = 7.8 \text{ Hz, } 1\text{H}), 7.34 \text{ (d, } J = 8.4 \text{ Hz, } 2\text{H}), 7.27 \text{ (d, } J = 7.5 \text{ Hz, } 4\text{H}), 7.18 \text{ (dt, } J = 21.2, 7.0 \text{ Hz, } 3\text{H}), 7.00 \text{ (d, } J = 8.1 \text{ Hz, } 2\text{H}), 6.06 \text{ (ddd, } J = 11.7, 7.8, 1.1 \text{ Hz, } 1\text{H}), 5.94 \text{ (d, } J = 7.8 \text{ Hz, } 1\text{H}), 5.75 \text{ (dd, } J = 11.8, 6.2 \text{ Hz, } 1\text{H}), 3.38 \text{ (dd, } J = 10.4, 5.2 \text{ Hz, } 1\text{H}), 3.13 \text{ – 2.99 (m, } 2\text{H}), 2.96 \text{ (dd, } J = 15.3, 5.7 \text{ Hz, } 1\text{H}), 2.79 \text{ – 2.61 (m, } 1\text{H}), 2.27 \text{ (s, } 3\text{H}) \text{ ppm.}

\(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta = 144.5, 141.7, 137.5, 136.9, 135.5, 131.6, 130.8, 130.8, 129.5, 128.6, 127.8, 126.5, 126.4, 124.7, 123.9, 121.3, 118.2, 116.1, 64.5, 42.5, 38.8, 23.5, 21.6 \text{ ppm.}

HRMS (ESI, m/z) calculated for \( \text{C}_{27}\text{H}_{25}\text{NO}_3\text{S}^- \) [M+H]⁺: 444.1628; found: 444.1620.

\([\alpha]_D^{23}: -89.2 \text{ (c 0.37, CHCl}_3\text{)}.\)
Chiral HPLC Chromatograms

![Chiral HPLC Chromatogram Image]

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Use Multiplier & Dilution Factor with ISTDs

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Use Multiplier & Dilution Factor with ISTDs

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3.3 NMR Spectra
References


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Моя дорога родина, папа Микола, мама Віта, мій рідний брате Сашко, і моя наречена Софія, я безмежно вдячний вам за вашу щиру підтримку, допомогу і просто за те, що ви в мене є. Знавачи що ви за моєю спиною, мені завжди було, є і буде легко досягати будь-яких цілей. Я вас дуже люблю. Дякую вам, мої рідні!