DISSERTATION

Titel der Dissertation

„Synthetic Studies Toward the Total Syntheses of the Jatrophone Diterpenes PI-3 and PI-4“

Verfasserin

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<table>
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<th>Definition</th>
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<tr>
<td>(R)-HYTRA</td>
<td>(R)-(+)2-Hydroxy-1,2,2-triphenylethyl acetate</td>
</tr>
<tr>
<td>2,2-DMP</td>
<td>2,2-Dimethoxypropane</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>ABC</td>
<td>ATP-Binding cassette</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BnCl</td>
<td>Benzyl chloride</td>
</tr>
<tr>
<td>BSA</td>
<td>Bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>Da</td>
<td>Dalton</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPA</td>
<td>Diisopropylamine</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyldioxirane</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>DTPS</td>
<td>Diterpene synthase</td>
</tr>
<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ent</td>
<td>enantiomeric</td>
</tr>
<tr>
<td>GGPP</td>
<td>Geranylgeranyl diphosphate</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner Wadsworth Emmons reaction</td>
</tr>
<tr>
<td>IBX</td>
<td>2-Iodoxybenzoic acid</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>Lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>liq.</td>
<td>Liquid</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi drug resistance</td>
</tr>
<tr>
<td>MeLi</td>
<td>Methyllithium</td>
</tr>
</tbody>
</table>

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MEM 2-Methoxyethoxymethyl
MOM Methyl chloromethyl
Ms Mesyl (methanesulfonyl group)
MsCl Methanesulfonyl chloride
$n$-Bu$_2$BOTf Dibutylboron triflate
$n$-BuLi $n$-Butyllithium
NADPH Nicotinamide adenine dinucleotide phosphate
NaHMDS Sodium hexamethyldisilazide
NBD Nucleotide binding domain
NCS $N$-Chlorsuccinimide
NMO $N$-Methylmorpholine $N$-oxide
ox. Oxidation
PDC Pyridinium chlorochromate
Pgp P-glycoprotein
PhNTf$_2$ $N$-Phenyl-bis(trifluoromethanesulphonimide)
$P_i$ Inorganic phosphate
PMB $para$-Methoxybenzyl
PP Diphosphate (pyrophosphate)
PPTS Pyridinium $p$-toluenesulphonate
pyr, Py Pyridine
RCM Ring closing metathesis
rfx Reflux
t-$BuLi$ $tert$-Butyllithium
TASF Tris(dimethylamino)sulphonium difluorotrimethylsilyl
TBAF Tetra-$n$-butylammonium fluoride
TBDPS $tert$-Butyldiphenylsilyl
TBS $tert$-Butyldimethylsilyl
TES Triethylsilyl
Tf Trifluoroacetate (trifluoromethanesulfonate group)
TMD Transmembrane domain
TMG 1,1,3,3-Tetramethylguanidine
TMS Trimethylsilyl
Ts Tosyl ($p$-toluenesulfonyl group)
TsOH $para$-Toluenesulfonic acid
UDP Uridine diphosphate
ABSTRACT

The jatrophane diterpenes Pl-3 and Pl-4, two highly oxygenated and stereochemically demanding natural products were isolated in 2003 from *Euphorbia platyphyllos* by Hohmann *et al.* Jatrophane diterpenes show a wide range of pharmacologically promising properties, including the selective inhibition of the ATP-dependent efflux pump P-glycoprotein (Pgp), which is responsible for multidrug resistance (MDR) in cancer.

Jatrophane diterpenes are characterized by a bicyclo[10.3.0]pentadecane framework; a highly functionalized five-membered ring is annulated to a twelve-membered macrocycle. In most of these terpene-based natural products the two rings are *trans*-fused, as in Pl-3. However, a few compounds were isolated, including Pl-4, which possess a double bond at the ring junction.

The synthetic goal of the first part of this doctoral thesis is the development of a general, diastereoselective synthesis of the eastern part of the jatrophane skeleton (C7-12, jatrophane numbering). Due to the recurring stereochemical substitution pattern of this part of the macrocycle the route is suitable for the preparation of Pl-3, Pl-4 and other jatrophanes. Key step in the synthesis for the eastern segment of both compounds is a samarium diiodide mediated Reformatsky reaction.

The second part of the thesis is devoted to the investigation of an enantioselective route toward Pl-4. The aim of the proposed strategy was to close both rings, present in the natural product, at a very late stage of the synthesis. While the 12-membered macrocycle was envisaged to be elaborated through an RCM-reaction, an internal vinyl halide should serve as key intermediate for the closure of the five-membered ring *via* a nucleophilic, or radical reaction.

The focus of the second part rests on the preparation of an advanced internal vinyl-halide as precursor for the five-membered ring closing reaction. Three strategically different routes were investigated: The initial approach for the preparation of the advanced internal vinyl-halide relied on a late stage, regioselective *syn*-hydrometalation of a sterically demanding ynone. Alternatively, in a more concise manner, the alkyne of the requisite ynone could also be directly employed in a five-*exo*-dig ring closure reaction *via* a ketyl radical as intermediate. A conceptually different strategy for the synthesis of an internal vinyl halide takes advantage of a chelation controlled regioselective lithiation/alkylation reaction of an unsymmetrical terminal vinyl dibromide and the appropriate aldehyde. The method is suitable for the facile access of sterically hindered internal vinyl halides and constitutes a valuable alternative to hydrometalation reactions, as these often give unsatisfying results with sterically demanding substrates.

The mechanistic considerations and synthetic attempts proposing the preparation of highly advanced intermediates toward the natural product Pl-4 are described in detail within this thesis.
ZUSAMMENFASSUNG


1. General Part

1.1. Introduction

The genus *Euphorbia*, member of the Euphorbiaceae plant family, is one of the largest and most diverse genera among flowering plants with more than 2000 species, which are endemic in different climate zones worldwide. The common characteristic of *Euphorbia* species, also known as spurge, is the existence of a milky sap (latex), which has a very high content of mainly terpene-based, biologically active ingredients. These structurally diverse plant metabolites are responsible for the application of spurge in traditional phytotherapy, preferentially used as anticancer agents and for the treatment of swellings and warts.

Although predominantly known as poisonous plants, some members of the genus *Euphorbia* are of great economic importance. To name just a few examples – the latex of *Havea brasiliensis* (Para rubber tree) is the major source of natural rubber, the starch tapioca is obtained from the roots of *Manihot esculenta* (cassava) or *Ricinus communis*, which is the commercial source of castor oil. The latter has a wide field of application ranging from the use as laxative right up to the utilization as a naturally occurring polyol for the preparation of polyurethane plastic.

![Figure 1. Core structures of Euphorbiaceae diterpenes.](image)

Natural products isolated from plants of the Euphorbiaceae plant family show a fascinating diversity in their isoprenoid structures. Diterpenes with different, partially closely related, core frameworks such as jatrophanes, casbanes, lathyranes, tiglianes, ingenanes, myrsinanes, segetanes, pepluanes, paralianes and euphoractines, summarized as Euphorbiaceae diterpenes, were identified.
as major constituents (Figure 1). In addition, tetra- and pentacyclic triterpenes as well as sesquiterpenoids, phloracetophenones, glycerols, cerebrosides, flavonoids and steroids were isolated.¹

Jatrophone (1), the first jatrophane-type diterpene, was isolated by Kupchan and co-workers in 1970 from an alcoholic extract of *Jatropha gossypifolia* L. The mentioned *Euphorbia* species was used for the treatment of neuroplasms in traditional herbal folk medicine. When 1 was identified as a natural product with significant antiproliferative effects against human tumor cell lines, the biological and chemical interest in active ingredients of the jatrophane skeleton increased.⁴,⁵ As a result, a huge number of diterpenes, characterized by the jatrophane framework, was isolated from plant extracts of members of the genus *Euphorbia* in the past decades and biologically evaluated.

![Jatrophone (1)](image)

**Figure 2**

The two title compounds Pl-3 (2) and Pl-4 (3), two highly oxygenated and stereochemically complex diterpenes were isolated from *Euphorbia platyphyllos* L., a glabrous or pubescent annual plant which occurs mainly in southern Europe, by Hohman *et al* in 2003.⁶

![Jatrophone skeleton](image)

![Pl-3 (2)](image)

![Pl-4 (3)](image)

![Altotibetin A (4)](image)

![Esulatin B (5)](image)

![Pepluanin A (6)](image)

![Eser-2 (7)](image)

![8](image)

![Serrulatin B (9)](image)

**Figure 3. Representative jatrophane diterpenes.**

Jatrophane diterpenes are characterized by a *trans*-bicyclo[10.3.0]pentadecane framework. A highly functionalized five-membered ring is annulated to a twelve-membered macrocycle. In most diterpenes the two rings are *trans*-fused as in Pl-3. However, a few compounds were isolated,
including Pl-4, which possess a double bond at the ring junction. Individual members of this class of natural products often only differ in the stereochemical pattern of methyl- and hydroxyl groups, while the regiochemical substitution pattern remains highly similar.\textsuperscript{7,8} The structurally elucidated compounds are substituted with various acyl groups, including acetyl, propanoyl, butanoyl, benzoyl, tigloyl, nicotinoyl, angeloyl, etc. which is why they are often called jatrophane polyesters.\textsuperscript{1} A few representative jatrophane diterpenes (2–9) are outlined in Figure 3.

Numerous jatrophane diterpenes were analyzed in detail within different biological studies, demonstrating a wide range of pharmacologically promising properties including antiproliferation, cytotoxic, antimicrobial, anti-inflammatory as well as antiviral activities.\textsuperscript{1,9} Several of these diterpenes were also identified as highly active inhibitors of the ATP-dependent efflux pump P-glycoprotein (Pgp), which is responsible for multi drug resistance (MDR) in cancer.\textsuperscript{10-14} Summarizing, jatrophane diterpenes represent an interesting target for different scientific areas. Probably, the most important aspect is that these diterpenes could provide potential lead structures for drug development. As the overexpression of Pgp in cancer cells of malignant tumors is a serious problem in cancer therapy the examination of potential novel anticancer drugs that could address this problem is of great importance in modern cancer research. At this point the synthetic influence becomes more and more important. Since natural sources afford insufficient quantities of diterpenes required for biological studies, a synthetic access to target compounds will be inevitable. Simplified unnatural derivatives could play an important role in the elucidation of the physiological mode of action of natural products. The synthesis of simplified substrates for structure-activity relationship (SAR) studies needs the expertise of synthetic chemists and combines the scientific ambitions of biology and chemistry. Nevertheless, the fundamental idea behind this thesis is that jatrophane diterpenes represent stereochemically challenging and fascinating natural products yielding excellent targets in the field of total synthesis.

1.2. BIOSYNTHESIS OF JATROPHANE DITERPENES\textsuperscript{15,16}

The biosynthesis of diterpenes arises from geranylgeranyl diphosphate (GGPP, 10). Carbocation mediated cyclization reactions combined with Wagner-Meerwein rearrangements allow the synthesis of numerous structural variants of compounds belonging to this important class of natural products.

As demonstrated in Figure 4, two mechanistically different biogenetic pathways are possible for the biosynthesis of polycyclic diterpenes, leading either to the phytanes\textsuperscript{16} such as abietanes, kauranes, atisanes, etc. or to the casbene derived diterpenes including casbanes, jatrophanes, tiglianes, etc.\textsuperscript{17} While most of the biosynthesis of polycyclic phytanes has been elucidated in detail, including the enzymes that are catalyzing the formation of intermediates, only little is known about the biogenetic routes toward the synthesis of the casbene derived diterpenes.\textsuperscript{15}
1.2.1. Biosynthesis of polycyclic phytanes

The cyclization sequence is initiated by the protonation of the double bond at the end of the chain of GGPP (10), affording a tertiary carbocation. The concerted process is terminated by the proton loss of a methyl group, leading to (−)-copalyl PP (11), outlined in Scheme 1A.\(^{15}\)

The cyclization-cascade is catalyzed by a single enzyme, called (−)-copalyl diphosphate synthase or ent-kaurene synthase A (E1). The stereochemistry of the product is dependent on the folding of the substrate and its interaction with the enzyme surface. The enantiomeric product, (+)-copalyl PP (12, labdadienyl-PP), is formed by an alternative folding of GGPP (Scheme 1B) catalyzed by (+)-copalyl diphosphate synthase (E2). In natural products the stereochemistry is most often derived from (+)-copalyl diphosphate and derivatives thereof. Natural products that can be deduced from (−)-copalyl diphosphate are often referred to as the enantiomeric (ent-) series.\(^{15}\)

The starting point for the cyclization cascades leading to natural products of the abietane-, pimarane-, atisane-, kaurane-, etc., frameworks is the loss of the diphosphate leaving group of (+)- or (−)-copalyl diphosphate. Associated carbocation formation and additional Wagner-Meerwein rearrangements create numerous possibilities leading to structural variants of diterpenes. Scheme 2 demonstrates a representative, but small cutout, of the diversity of possible frameworks and attributed natural products (13–26).
Scheme 2. An overview of polycyclic phytanes.

(-)-15,20-Dihydroxy-16-atisene-19,20-olide (13)

(-)-Labdanolic acid (14)

Pumiloxide (15)

(+)-(8(14),15-Pimaradiene-3,18-diol (16)

(-)-Labdane skeleton

(-)-Copalyl PP (11)

(-)-16α,17-Dihydroxy-atisane-3-one (26)

(-)-Kahweol (25)

Atisane skeleton

(-)-15-Bromo-9(11)-parguerene-2α,7α-16-triol (17)

Pimarane skeleton

(-)-11β-Hydroxy-12-spongien-16-one (19)

(-)-7,18-Dihydroxy-16-kauren-19,6α-olide (24)

Beyerane skeleton

(-)-Beyerol (23)

Beyerene skeleton

(-)-15-Beyerene (22)

Abietane skeleton

(-)-15,20-Dihydroxy-12-spongien-16-one (19)

Cassane skeleton

(-)-Cassaic acid (18)

Kaurane skeleton

(-)-16α,17-Dihydroxy-atisane-3-one (26)

Beyerol (23)

(+)-15-Beyerene (22)

Carnosol (21)

Abietenol (20)
The cyclization sequence of the kaurane skeleton is outlined in Scheme 3 on the example of the biosynthesis of the tetracyclic diterpene stevioside (33), an important non-calorific sugar substitute, starting from (−)-copalyl PP (11).

The third six-membered ring within the kaurane framework is built by an allylic-cation-mediated cyclization reaction resulting in the formation of the tertiary ent-pimarenlyl cation (27), which is further attacked by the terminal double bond. The resulting secondary cation, namely ent-beyeranyl cation (28) is again converted into the more stable tertiary ent-kauranyl cation (29), by a Wagner-Meerwein 1,2-alkyl migration, affording the ring system present in the natural product. A final proton loss delivers the exocyclic double bond of ent-kaurene (30). All described cyclization reactions as well as the Wagner-Meerwein shift are catalyzed by the same enzyme, the kaurene synthase (E1). The final transformations, stereoselective oxidation followed by hydroxylation and three glycosylation reactions complete the biosynthetic route of the natural product 33.18

![Scheme 3. Biosynthetic pathway of stevioside.](image)

### 1.2.2. Biosynthesis of casbene derived diterpenes

Already in 1970, Robinson et al. demonstrated through intense experimentation in a cell free medium, derived from *Ricinus communis* (castor bean, Euphorbiaceae), that the biosynthesis of casbene (34) starts from geranylgeranyl pyrophosphate (10).19

Casbene is considered as a precursor for different macrocyclic and polycyclic diterpenes including those of the jatrophane-, casbane-, lathyrane-, tigliane-, ingenane- and daphnane-type.20 An overview of representative examples of natural products consisting of the mentioned skeletons is shown in Scheme 4 (34–45).
Scheme 4. An overview of casbene derived natural products.

A proposed biogenetic route for the formation of the structurally related diterpenoid skeletons that represent the frameworks of the casbene derived natural products is outlined in Scheme 5. The cembrene cation (46) is considered as their common intermediate. Based on this reactive species all other frameworks are established through different enzymatic sequences.\textsuperscript{20}
As mentioned above, only a few details are known about the biosynthetic pathways leading to the casbene derived natural products. The biogenetic pathway toward casbene (34) and the proposed formation of the tigliane skeleton, by the example of phorbol (40), is outlined in Scheme 6. Especially the phorbol esters show important biological properties. The identification of these compounds as tumor promotors through the activation of protein kinase C had a major impact on the investigation of central regulatory pathways within cells. Therefore, it is not surprising that the elucidation of the biogenetic route toward the natural products of the tigliane skeleton was of particular scientific interest in the past years.

First, the diphosphate group is cleaved, affording delocalized cation 47, which interacts with the C-(14,15) terminal double bond under the formation of the macrocyclic cembrene cation (46). Finally, the cyclopropane ring is formed via proton loss, delivering casbene (34). The whole sequence is catalyzed by a single enzyme, called casbene synthase (E1). A second ring closure between C-6 and C-10 delivers the precursor of natural products of the lathyrane family (48) and a third ring closure between C-5 and C-14 affords the tigliane skeleton, an intermediate in the hypothetical biogenetic route toward phorbol (40). The enzymes involved in the formation of 40 are not identified yet, except for the above-mentioned casbene synthase.
The casbene synthase was first isolated from *Ricinis communis* (Euphorbiaceae) in 1985 by West et al. and could be identified as the enzyme catalyzing the biosynthesis of casbene starting from GGPP. A divalent cation is probably of crucial importance in the enzymatic cleavage of the allylic pyrophosphate at the beginning of the catalytic cycle but the mechanism could not be elucidated so far. That was the only reported successful isolation and characterization of a diterpene synthase (DTPS) from a plant of the Euphorbiaceae plant family for a long time. (DTPSs catalyze the cyclization reactions leading to the hydrocarbon backbone of diterpenes. Further functionalization typically occurs through oxidation of cytochrome P450 monoxygenases to finalize the biosynthesis of oxygenated diterpenoid natural products.) Only recently Demura and co-workers have succeeded in the isolation of a casbene synthase homolog from *Jatropha curcas* L., also suggesting that the enzyme is involved in the casbene biosynthesis. Furthermore, Keasling et al. reported the isolation and cloning of casbene synthases from five representative Euphorbia species (*H. nutans, E. resinifera, S. sebiferum, E. esula, R. communis*). As the authors could not isolate other diterpene synthases, they suggest that the casbene synthase must indeed be a crucial catalyst in the biosynthetic pathway of casbene-derived natural products, an assumption that also confirms the findings of the above-mentioned groups. Nonetheless, Keasling et al. indicated that despite the isolation of the casbene synthases, not a single functionalized diterpene comprising the unaltered casbene backbone was identified among the analyzed natural products isolated from the above-mentioned Euphorbia species. Therefore, the authors suggest that they could not completely rule out that possibly other DTPSs, which remained undiscovered within their investigations, are involved in the biosynthesis of plant metabolites belonging to the class of casbene derived diterpenes.

However, several compounds possessing a functionalized lathyrane skeleton were isolated from the five Euphorbia species, which in turn could imply that the five-membered ring, present also in the tigliane skeleton, is closed first on the proposed way to the phorbols. Additionally, they were able to characterize a neocembrene synthase in *R. communis*, which catalyzes the biogenetic sequence.
outlined in Scheme 7. This was the first report of the evidence of a neocembrene synthase gene but its role in the biosynthesis of Euphorbia diterpenes has not yet been clarified.\textsuperscript{31}

\begin{align*}
\text{GGPP (10)} & \quad \rightarrow \quad \text{Cembrene cation (46)} \\
& \quad \rightarrow \quad \text{Neocembrene (49)}
\end{align*}

\textbf{Scheme 7. Biosynthesis of neocembrene (49).}

Jatrophane diterpenes, isolated from Euphorbia species, are lacking the cyclopropane ring, which is present in the lathyrane skeleton. Two different biogenetic mechanisms for the formation of the jatrophane framework are mentioned and are already indicated in Scheme 5. The macrocycle could either be formed directly from the cembrene cation (46) via a Wagner-Meerwein shift or, alternatively but more likely, the casbene precursor is formed first, followed by the opening of the cyclopropane ring\textsuperscript{20}. Final closure of the five-membered ring between C-6 and C-10 would accomplish the biogenetic route toward the jatrophane skeleton. Further functionalization leads to a huge class of natural products with different oxygenation states and stereochemical features.

Only a few explanations concerning the biosynthesis of natural products, which are considered to arise from the jatrophane skeleton, have been reported. A proposed biogenetic pathway for the synthesis of the tetracyclic natural product pepluane (53) is shown in Scheme 8. Paraliane (51) is formed through a transannular ring closing reaction of the jatrophane diterpene 50 resulting in a 5/6/5/5-ring system. Introduction of a primary alcohol and an epoxide by enzymatic oxidation, followed by a ring expansion and further acetylation complete the biosynthesis of 53.\textsuperscript{32,33}

\begin{align*}
\text{Paraliane (51)} & \quad \rightarrow \quad \text{Pepluane (53)}
\end{align*}

\textbf{Scheme 8. Proposed biosynthesis of pepluane (53).}

The 1(15\rightarrow 14) \textit{abeo}jatrophane-type skeleton 55 could be formed by a base-induced pinacol rearrangement of 54, demonstrated in Scheme 9. The possibility of 55 being an artifact, generated during the isolation process, could be excluded. Thus, the proposed biosynthetic precursor (54) was treated with acetic acid and sodium acetate which did not alter its structure, suggesting that 55 was formed by means of enzymatic transformations.\textsuperscript{34}
1.3. **BIOLOGICAL ACTIVITY OF JATROPHANE DITERPENES**

Jatrophane diterpenes, isolated from plants of the genus *Euphorbia* show a wide range of biological and pharmacological properties, including skin-irritant and tumor-promoting effects, antimicrobial, anti-inflammatory, antiproliferative, antiviral and cytotoxic activity. Furthermore, several structurally diverse diterpenes of the jatrophane skeleton were identified as highly active multidrug resistant reversal (MDR) candidates, by binding to Pgp. This is probably the most interesting biological activity of this class of natural products and, therefore, subject of numerous scientific investigations in the past years. The ability to inhibit the MDR effect turns those compounds to very promising candidates for the investigation of new chemotherapeutics.

1.3.1. **Multidrug resistant reversal effect**

The development of resistance mechanisms in cancer cells to drugs that combat the growth of tumors is a common reason why chemotherapy can fail. MDR can have different causes but the most important mechanism is the overexpression of active drug efflux pumps in the membrane of cancer cells caused by mutations during chemotherapy. As a result, these transport proteins discharge cytotoxic molecules from the cancer cell and the intracellular drug concentration is always held below a cell-killing threshold.
The efflux pump proteins belong to the ATP-Binding Cassette (ABC) superfamily of proteins that utilize the energy of ATP-hydrolysis to carry out certain transport processes. The 49 members of this protein family, identified in the human genome, organize a variety of transport processes in healthy prokaryotic and eukaryotic cells. The efflux processes include the transport of phospholipids, sterols, bile salts and amphiphatic drugs. 15 ABC proteins were identified to export chemotherapeutics in *in vitro* experiments but only three transporters have been found as major contributors to MDR in human cancer. These are the transmembrane proteins, P-glycoprotein (Pgp also termed as MDR1 or ABCB1), multidrug resistance-associated protein 1 (MRP1 or ABCC1) and ABCG2 (also known as breast cancer resistance protein, BCRP, or mitoxantrone resistance protein, MXR). These drug efflux pumps are “polyspecific” which means that they are able to bind and transport a wide range of structurally diverse compounds. The substrate spectra of the three mentioned transport proteins comprise hundreds of different molecules and are not identical although a partial overlap is observed. Figure 5 shows six structures of current chemotherapeutics (56–61) that are substrates for all three termed transport proteins active in human cancer cells.

In the following, the spectrum of substrates and the mechanism of binding and transport of Pgp are discussed. Pgp is the transport protein for which the most structural information is available and additionally it is the target efflux protein of jatrophane diterpenes.

Pgp-substrates show different chemical characteristics, some of them are amphiphatic or lipophilic, also uncharged binding partners are observed and others possess a positively charged nitrogen atom under physiological conditions. Basically, the interacting substrates are large (200-1900 Da) organic molecules. Among others, Pgp-binding partners are classic chemotherapeutics (such as the *Vinca* alkaloids and taxols), tyrosine kinase inhibitors, HIV protease inhibitors, ionophores, peptides, steroids and cardiac glycosides. It is very difficult to make a generalization of structural features and no common pharmacophore has been found until today.

Through different biochemical and biophysical methods including mutagenesis, cross-linking experiments or electron microscopy, the topology of Pgp could be proposed in the past years as follows: Pgp is a pseudosymmetrical heterodimer in which each monomer comprises a nucleotide binding domain (NBD) as well as a transmembrane domain (TMD). The cytoplasmatically localized NBDs are responsible for the ATP-binding and hydrolysis, and their sequence is highly conserved within the ABC-transporter family. On the other hand, the membrane-embedded TMDs contain the substrate-binding site and they show only low sequence similarity within the protein family. Furthermore, a large and flexible binding region is more likely than one or several discrete binding sites within the substrate-binding domain. This could also explain the broad and polyspecific substrate spectrum.

Cryo-electron microscopy and diverse biochemical experiments demonstrated that Pgp undergoes large conformational changes during its catalytic cycle. The different models used to describe the catalytic cycle share the same feature of an ATP-binding dependent dimerization of the NBDs,
which induces the trans-membrane transport of a substrate: In the ATP switch model the transport cycle is initiated by binding of the substrate to its high affinity site on the TMDs at the inner leaflet of the membrane. The model further proposes that the dimerization of the two NBDs through ATP-binding induces a conformational change in the TMDs. As a result, the drug-binding site is exposed extracellularly and its affinity is reduced, leading to the release of the bound drug. Further ATP-hydrolysis and sequential release of inorganic phosphate (P_i) and ADP restores the transporter to its basal configuration (Figure 6).\(^{38}\)

![Figure 6. ATP-switch model.\(^{39}\)](image)

An alternative theory, based on the ATP switch model, hypothesizes that an additional, asymmetric occlusion of one ATP molecule within the dimerized NBDs is responsible for the conformational change in the TMD and the associated substrate release.\(^{40, 41}\) Although our knowledge of substrate binding and understanding of the mechanism of the catalytic cycle is increasing, so far we can only speculate about these processes within biological systems.

The availability of high-resolution X-ray structures of transmembrane transport proteins is essential to understand their function on a molecular basis and additionally, their structure elucidation will offer striking possibilities toward structure-based drug design. While bacterial ABC importers and exporters have already been investigated in detail and X-ray structures are available,\(^{42-47}\) crystallization of mammalian transporters has proven to be more difficult. Only in 2009, Aller et al. succeeded in describing the X-ray structure (3.8 Å crystal structure) of murine Pgp, which is the highest-resolution structure of a mammalian drug transporter to date.\(^{48}\) The murine transport protein shows 87% sequence identity to human Pgp. The publication describes the structures of apo-Pgp (nucleotide-free structure) and, for the very first time, co-crystal structures of Pgp with cyclic peptide inhibitors providing a deeper understanding of substrate binding. It is remarkable that their results reinforce most of the structural features that were proposed based on biochemical and biophysical experiments in the past years as already mentioned above. Most importantly, Aller and co-workers were able to characterize the substrate-binding region, which is a large cavity of
approximately 6000 Å³. This flexible binding site comprises mostly hydrophobic and aromatic amino acids and only a small number of polar and potentially charged amino acid residues where drugs can bind in different orientations.\(^48, 49\) Although the published murine Pgp crystal structure is just a single snapshot of the protein within its catalytic cycle and lacks the high resolution needed to elucidate the uncertainty about the broad substrate recognition spectrum, it provided useful new insights into the molecular function of mammalian Pgp.\(^49\)

### 1.3.2. Jatropane diterpenes as Pgp-inhibitors

Numerous jatrophane diterpenes isolated over the past years were identified as inhibitors or modulators that reverse MDR in intact cancer cells in \textit{in vitro} experiments. In 2001 Hohmann \textit{et al.} reported the isolation of the diterpene euphosalicin (62), from \textit{Euphorbia salicifolia}. They could identify 62 to be more than twice as active as the reference substance verapamil in inhibiting multidrug resistance in mouse lymphoma cells. By contrast, two additional jatrophane diterpenes (63, 64), isolated from the same \textit{Euphorbia} species as 62, were found to be inactive in reversing MDR. The cells, incubated with the assumed MDR modulators, were analyzed using flow cytometry for their ability to efflux the fluorescent dye Rhodamine 123. Verapamil was used as positive control for those exclusion experiments.\(^10\)

![Figure 7. MDR modulators I.](image)

In 2002, again Hohmann \textit{et al.} published detailed biological investigations of additional 15 jatrophane polyesters isolated from \textit{E. serrulata}, \textit{E. esula}, \textit{E. salicifolia}, and \textit{E. peplus} concerning their MDR reversing activity.\(^50\) These diterpenes, although structurally closely related, differ significantly in their inhibiting effect of Pgp in tumor cells. Unfortunately, a consistent structure-activity relationship trend could not be observed.

![Figure 8. MDR modulators II.](image)

However, a few similarities could be demonstrated: comparison of the pairs 65 and 66 as well as 67 and 68 which vary only in the lipophilicity of one substituent, shows an increase of MDR reversing activity. This link between lipophilicity and the increase of the inhibiting effect is consistent with
the assumption that the effect of drug accumulation in drug-resistant cells is proportional to their hydrophobicity.\textsuperscript{50}

Surprisingly, regarding other pairs such as \textbf{68} and \textbf{69} where also an increase in the overall lipophilicity can be observed the above-mentioned trend could not be confirmed, because \textbf{69}, the more hydrophilic compound, shows higher inhibition of Pgp. The authors mention that this phenomenon could be explained by the high flexibility of the macrocyclic ring and its alignment of different conformers.\textsuperscript{50} These early observations demonstrate that the analysis of the three-dimensional structure of related jatrophane diterpenes will be the crucial point for a more detailed understanding of their structure-activity relationship.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure9.png}
\caption{MDR modulators III.}
\end{figure}

Lanzotti and co-workers published the isolation of ten closely related jatrophane diterpenes from the latex of \textit{E. dendroides}. For the first time, the authors tried to elaborate a definite structure-activity relationship based on the substitution pattern of the south-western fragment (C-2 to C-5) of the newly isolated diterpenes. Finally they identified euphodendroidin D (\textbf{70}) as the most potent inhibitor of MDR within their test series. Euphodendroidin D shows almost double efficiency compared to the internal standard cyclosporine A. They hypothesized that the free hydroxyl group at C-3 as well as the lack of a quarternary center at C-2 possess a crucial role in the MDR inhibiting properties of the jatrophane diterpenes compared in this study.\textsuperscript{12}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure10.png}
\caption{MDR modulators IV.}
\end{figure}

In the following years Hohmann \textit{et al.} as well as Lanzotti and co-workers isolated numerous jatrophane diterpenes from different Euphorbia species and evaluated those structurally complex natural products in respect to their MDR modulating effect.\textsuperscript{13, 51-53} Different jatrophane diterpenes from \textit{E. esula}, \textit{E. peplus}, \textit{E. villosa} and \textit{E. serrulata} were tested for their MDR reversing activity on human colon cancer cell lines. Unfortunately, compared to the results received from mouse lymphoma cell assays, the inhibiting effect of Pgp decreased for all tested compounds. Thus, compound \textbf{71}, isolated from \textit{E. serrulata}, showed highly potent properties as a MDR-inhibitor on mouse lymphoma cells with an almost three fold activity compared to the reference substance
verapamil. Otherwise, in the human colon cancer assay the activity decreased and reached not even the value of the internal standard.\textsuperscript{9}

Ferreira \textit{et al.} published the isolation of related jatropane diterpenes from \textit{E. mellifera} and tested their activity as Pgp modulators. Euphomelliferine (72) and euphomelliferine A (73), two jatropane diterpenes, which are structurally very similar to 71, displayed a significant MDR reversing activity on mouse lymphoma cells in a dose-dependent manner (again about twice as active compared to verapamil). They could also confirm the decrease of activity on human colon cancer cells.\textsuperscript{14}

![Figure 11. MDR modulators VI.](image)

Summarizing, a large number of jatropane diterpenes could be isolated in the past years and evaluated in respect to their MDR-reversing activity. Numerous, partially structurally closely related natural products were identified as highly promising MDR-modulators showing a higher activity than different reference substances such as verapamil or cyclosporine A. Although a vast number of compounds was investigated no definite trend within their substitution pattern, which could explain their structure-activity relationship, was observed. As already mentioned, the conformation of the macrocycle probably plays a crucial role in the interaction of the diterpene within the binding pocket of Pgp. X-ray structures of the substrates combined with the synthesis of systematic compound libraries and expanding knowledge of the Pgp-substrate binding process will be essential for the identification of lead structures as foundation for structure-based drug design.

1.4. \textbf{TOTAL SYNTHESES OF JATROPHONE DITERPENES}

1.4.1. \textbf{Total synthesis of \(\pm\)-normethyljatrophone by Smith \textit{et al.}}\textsuperscript{54}

In 1981 A. B. Smith \textit{et al.} reported the racemic total synthesis of normethyljatrophone (74).\textsuperscript{54} The retrosynthetic analysis is shown in Scheme 10. The macrocyclization should be achieved via a Mukaiyama-aldol reaction\textsuperscript{55, 56} and the conversion of the acetylene functionality to the corresponding \textit{trans}-double bond would complete the synthesis of 74. The key part of the molecule, the spiro-3(2\textit{H})-furanone-moiety, was envisaged to be formed through an acid catalyzed cyclization-dehydration sequence after the connection of ketone 78 and TBS-protected aldehyde 77 through an aldol reaction.
Cyclopentenone 79 was converted to acetal-protected bromide 80 through a two-step procedure. A bromination-elimination sequence was followed by an acid catalyzed protection of the keto-functionality with ethylene glycol. In the next step, first a vinyl anion was formed which was captured with formaldehyde. Further treatment with oxalic acid resulted in deprotection of the acetal group to afford α-(hydroxymethyl)cyclopentenone 81 in 62% yield over four steps. The formation of the silyl-ether was followed by the treatment with lithioethyldithiane 83, delivering racemic tertiary alcohol 82. Next, the dithiane moiety was hydrolyzed and after the cleavage of the TBS-group, both free hydroxyl functionalities were TMS-protected to give ketone 78 in 42% yield over 5 steps (Scheme 11).  

The preparation of aldehyde 77 is outlined in Scheme 12. The dianion, derived from 3,3-dimethyl-4-pentyanoic acid (84) under exposure to LDA/HMPA, was treated with an excess of propanal to afford elongated hydroxy-acid 85. The secondary alcohol was protected as a TBS-ether and a reduction-oxidation sequence completed the synthesis of the desired aldehyde 77 in 55% yield over 4 steps.
Next, aldehyde 77 and ketone 78 were coupled via an aldol reaction to give \( \beta \)-hydroxy ketone 86. Exposure of 86 to an excess of the Collins’ reagent\(^{59} \) resulted in oxidation of the secondary alcohol and concomitant cleavage of the primary TMS-group. The resulting primary alcohol was immediately oxidized within the same step to deliver the corresponding aldehyde. Finally, acid catalyzed deprotection of the remaining silyl-groups followed by an acid induced cyclization-dehydration reaction sequence afforded spirofuranone 87 as a mixture of diastereomers in 68% overall yield. Unfortunately, the direct closure of the macrocycle through an aldol reaction after the oxidation of the free alcohol functionality in 87 was met with failure. An alternative route was found by aspiring a TiCl\(_4\)-promoted Mukaiyama condensation of an acetal with a silyl-enol ether.\(^{50} \) Therefore, the aldehyde functionality in 87 was protected as an acetal with ethylene glycol and the secondary hydroxyl group was oxidized by using the Collins’ reagent to yield ketone 88.

The formation of the macrocycle succeeded under Mukaiyama-aldol reaction conditions and the formation of two diastereomeric products (47%, 2:1). The stereochemistry of the major product 89
was identified by X-ray analysis. Elimination of ethylene glycol initially afforded the trans-fused double bond, but it could be demonstrated that the undesired E-isomer undergoes slow isomerization to the desired cis-double bond (75) after extended exposure (2 weeks) to toluenesulfonic acid. Final cis-hydrogenation of the acetylene moiety followed by isomerization of the double bond completed the total synthesis of ±-normethyljatrophone 74 (Scheme 13). Summarizing, the total synthesis of 74 has been achieved in a convergent manner in 5.6% overall yield, starting from cyclopentenon (79).

1.4.2. Total synthesis of (+)-hydroxyjatrophone A and (+)-hydroxyjatrophone B by Smith et al. 61

In 1989 again A. B. Smith et al. published the first non-racemic total syntheses of (+)-hydroxyjatrophone A (91) and (+)-hydroxyjatrophone B (92). 61 The synthetic strategy (Scheme 14) is in close analogy to the synthesis of normethyljatrophone (74) discussed above. The spirofuranone-part should again be constructed by an acid-promoted cyclization sequence and closure of the macrocycle should be achieved through a Mukaiyama aldol-reaction, as already elaborated for the synthesis of 74. 54 The intermediates 93 and 94 can be attributed to aldehyde 77 and highly substituted five-membered ring fragments 95 and 96, respectively. Aldehyde 77 should be coupled with the respective ketone (95 or 96) via an aldol reaction to give the precursors for the spirofuranone formation reaction.

The synthesis of chiral cyclopentenone 101 started with the esterification of racemic tertiary alcohol 97 with (+)-O-methylmendeloyl chloride (102) to afford the diasteromeric esters 98 and 99. In the following, the total synthesis of (+)-hydroxyjatrophone B (92) is discussed, as the synthesis of (+)-hydroxyjatrophone A (91) essentially differs only in the choice of the diastereomeric ester 98 at the beginning of the synthetic route.

After separation of the two esters 98 and 99 by column chromatography, reduction of 99 was followed by an acid-promoted-hydrolysis rearrangement to give diol 100, before selective protection of the primary alcohol as a silyl-ether completed the sequence with the isolation of cyclopentenone 101 (Scheme 15).
Subsequent reaction of 101 with the lithiated dithiane species 83 afforded intermediate 103 in an 18:1 diastereomeric ratio, favoring the desired isomer (Scheme 16). The resulting syn-diol was TMS-protected after hydrolysis of the thioacetal moiety, delivering 96. Subsequent deprotonation with LDA generated the corresponding enolate, the reactive coupling partner for aldehyde 77. Oxidation of the diastereomeric aldol product 104 using the Collins’ reagent resulted in additional deprotection of the primary TES-group and oxidation of the resulting alcohol to provide enal-dione 105.

Scheme 16. Total synthesis of (+)-hydroxyjatrophone B (92).
Thus, the stage was set for the crucial acid-promoted cyclization of the spiropyranone part. Exposure of 105 to hydrochloric acid promoted the cleavage of all silyl-ethers and concomitant formation of furanone 106 in excellent 90% yield. Conversion of the aldehyde functionality to the acetal and oxidation of the free secondary alcohol in 106 was required as preparation for the Mukaiyama aldol reaction to close the macrocyclic ring. Initial transformation of 94 to the TMS-enolate and following treatment with titanium tetrachloride delivered the macrocyclic intermediate 107 in a 2.5:1 mixture of diastereomers with respect to the α-methyl group. Next, the cis-alkene 108 could be isolated after elimination of ethylene glycol with p-toluenesulfonic acid and DBU and subsequent photoisomerization of the formed undesired trans-double bond. Final palladium catalyzed syn-hydrogenation and isomerization of the double bond to provide the trans-linked product completed the total synthesis of (+)-hydroxyjatrophone B (92).\textsuperscript{61}

1.4.3. Total synthesis of ±-jatrophone and ±-epi-jatrophone by Hegedus et al.\textsuperscript{63}

Racemic syntheses of jatrophone (1) and C2-epi-jatrophone were published by Hegedus et al. in 1990.\textsuperscript{63} They intended to close the macrocycle via a palladium catalyzed carboxylative Stille coupling reaction\textsuperscript{64, 65} of advanced intermediate 109, while the construction of the spiropyranone part was intended to be elaborated in close analogy to the synthesis published by Smith, described above, through a Lewis acid-catalyzed cyclization-dehydration reaction sequence (Scheme 17). The proposed aldol reaction of ketone 110 and aldehyde 111 has already been employed in the syntheses discussed earlier.

\[ \text{Scheme 17. Retro synthesis of ±-jatrophone.} \]

The thiophene derived cuprate 112\textsuperscript{66} was allowed to react with ethyl-3,3-dimethylacrylate 114 in the presence of boron trifluoride etherate in a 1,4-addition. The following reduction afforded aldehyde 111 in overall 78% yield over two steps.

\[ \text{Scheme 18. Synthesis of vinyl-stannane 111.} \]

Starting from racemic cyclopentenone 115, α-bromo-ketal 116 was isolated after an initial bromination/dehydrobromination sequence followed by ketalization with ethylene glycol. Halogen-metal exchange of the vinylic bromide with n-BuLi and further addition of propylene oxide afforded the corresponding secondary alcohol, which was protected as a TBS-ether, to provide 117.
as a mixture of diastereomers. Deprotection of the ketal moiety gave the intermediate $\alpha,\beta$-unsaturated ketone, precursor for the dithiane addition. The attack of lithiated 83 resulted in the formation of 118 as an unseparable mixture of diastereomers. After cleavage of the thioketal with mercury chloride ketones 119 and 120 were obtained as a 9:1 diastereomeric mixture. Thus, the initial dithiane addition proceeded mainly from the opposite side of the methyl group.

Next, the secondary TBS-group was cleaved and the resulting diol was protected with bis(trimethylsilyl)acetamide (BSA), delivering 110. Enolate formation was followed by the addition of aldehyde 111 to afford highly advanced intermediate 121. After oxidation, following the Corey-Kim protocol\textsuperscript{67}, diketone 122 was obtained.

The spirofuranone part could be formed by the exposure to TASF, which served as a weak Lewis acid. Additional deprotection of the secondary TMS-group resulted in the isolation of 123 in

\[ \text{Scheme 19. Preparation of cyclopentene fragments 119 and 120.} \]

\[ \text{Scheme 20. Completion of the total synthesis of ±-jatrophone.} \]
acceptable 64% yield. Oxidation of the free hydroxyl group to the corresponding ketone 124 and installation of the vinyl-triflate (109) paved the way for the final carbonylative Stille coupling to complete the racemic total synthesis of jatrophone (1).

C2-epi-jatrophone was prepared following exactly the same route using 119, the major diastereomer after the dithiane addition (Scheme 19), as the cyclopentene fragment within the natural product.

1.4.4. Total synthesis of (+)-jatrophone by Wiemer et al.68

The first nonracemic total synthesis of (+)-jatrophone (1) was published by Wiemer et al. in 1992.68 The construction of the core of the molecule, the cyclofuranone part, was envisioned to proceed via an intramolecular Horner-Wadsworth-Emmons reaction69, leading to intermediate 125. Cyclopentene fragment 126 and acetylenic acid chloride 127 should be connected via direct esterification to afford the precursor for the HWE reaction. Commercially available (+)-pulegone (129) was chosen as starting material from the chiral pool, which should initially be converted to diester 128 (Scheme 21).

The monoterpene (+)-pulegone (129) was oxidized to the corresponding dicarboxylic acid, which was esterified with methanol to yield chiral diester 128.70 The following Dieckmann condensation71 resulted in the formation of a 2.8:1 mixture of the regioisomers 130 and 131 favoring desired cyclopentanone 130. The introduction of a TMS-enol ether (132) was followed by dihydroxylation with OsO4/NMO, delivering preferentially R-configurated cyclopentanone 133 (in respect to the newly introduced stereocenter) via a substrate-controlled reaction mechanism. TMS-protection of the tertiary alcohol and final triflate-formation concluded the sequence toward the highly substituted cyclopentene fragment 134, the chiral key intermediate in the synthesis of (+)-jatrophone (1, Scheme 22).72
Reaction of TMS-protected triflate 134 with diethyl-ethyl phosphonate provided β-keto phosphonate 127, which was directly esterified with acid chloride 127 under the influence of FeCl₃ to afford 135, the precursor for the spirofuranone constructing HWE-reaction. Treatment with sodium hydride gave 125, which was converted to primary alcohol 136 via palladium catalyzed Stille coupling with vinyl stannane 139, followed by deprotection of the silyl-ether with TBAF. Macrocyclic intermediate 137 was obtained after Swern-oxidation to give the corresponding acteylenic aldehyde and deprotonation of the acetylene moiety with LHMDS. Oxidation of the propargylic alcohol in 137, again under Swern conditions, delivered ynone 138 and final palladium catalyzed hydrogenation followed by isomerization of the undesired cis-double bond completed the total synthesis of optically active (+)-jatrophone (1, Scheme 23).
1.4.5. Total synthesis of the norjatrophane diterpene \((-\)-15-acetyl-3-propionyl-17-norcharaciol by Hiersemann et al.\(^7^4\)

Hiersemann et al. published the total synthesis of the unnatural norjatrophane diterpene, \((-\)-15-acetyl-3-propionyl-17-norcharaciol (140)).\(^7^4,7^5\) The retrosynthetic analysis of the target compound is outlined in Scheme 24. The twelve-membered macrocycle was intended to be closed via a ring closing metathesis (RCM) reaction of diene 141, which could be established from aldehyde 142 and phosphonate 143 through a HWE reaction. The preparation of the highly functionalized five-membered ring fragment 144 was envisioned to proceed via an intramolecular thermal ene-reaction of \(\alpha\)-keto ester 145.

![Scheme 24. Retrosynthetic analysis of \((-\)-15-acetyl-3-propionyl-17-norcharaciol (140).](image)

2-Iodo-ethanol (146) was protected as a TES-ether, alkylated with ethyl isobutyrate and a subsequent reduction/oxidation sequence delivered aldehyde 147 in 78% overall yield. Silylation of the intermediate secondary alcohol, obtained after Grignard reaction with homoallyl iodide, was followed by the exposure to Swern oxidation conditions, which resulted in the isolation of aldehyde 142 via cleavage of the primary TES-group and subsequent oxidation of the alcohol.

![Scheme 25. Synthesis of aldehyde (142).](image)

The preparation of \(\alpha\)-keto ester 145, started with an Evans aldol reaction\(^7^6\) of chiral oxazolidinone 148 and aldehyde 153. Removal of the auxiliary allowed the isolation of methyl ester 149. Next, TBS-protection of the free hydroxyl group was followed by a reduction/oxidation sequence, which resulted in the formation of aldehyde 150. A HWE-reaction using phosphonate 152 and 1,1,3,3-tetramethylguanidin (TMG) as base afforded intermediate 151, which was subsequently converted to the desired \(\alpha\)-keto ester 145 via cleavage of the acetate group.\(^7^5\)

The thermal intramolecular ene-reaction provided the corresponding cyclopentanes 144 and 154 in a 4.5:1 diastereomeric ratio, favoring the desired isomer 144. The exclusive formation of the 4,15-cis configuration (jatrophane numbering) was observed. Protection of the tertiary alcohol with TMS-chloride was followed by a Claisen-type condensation with diethyl ethylphosphonate (158) delivering β-keto ester 143, which was further deprotonated with nBuLi and allowed to react with aldehyde 142 to give α,β-unsaturated ketone 155.

Scheme 27. Total synthesis of 140.

Next, the tertiary TMS- and the secondary TES-ethers were cleaved consecutively followed by oxidation of the resulting secondary alcohol with Dess-Martin periodinane and deprotection of the remaining silyl-ether employing HF.pyridine, to afford diene 156. The synthesis was continued by inversion of the C-3 stereocenter via a Mitsunobu reaction, delivering the corresponding benzoate, which was subsequently saponified to the free alcohol. A final regioselective acylation completed the sequence toward the RCM-precursor 141. The RCM-reaction, using the second
generation Grubbs catalyst\textsuperscript{80} (157), proceeded successfully and supplied exclusively the \textit{E}-
configured double bond isomer. Finally, acetate protection of the free tertiary alcohol functionality completed the synthesis of \((-\)-15-acetyl-3-propionyl-17-norcharaciol (140)).\textsuperscript{75}

\textbf{1.4.6. Total synthesis of \((-\)-15-\textit{O}-acetyl-3-\textit{O}-propionylcharaciol by Hiersemann \textit{et al.}}\textsuperscript{81}

In close analogy to the synthesis of the unnatural norjatrophane 140, described above, Hiersemann \textit{et al.} reported the first enantioselective total synthesis of \((-\)-15-\textit{O}-acetyl-3-\textit{O}-propionylcharaciol (159), a jatrophane diterpene isolated from \textit{Euphorbia characias}.\textsuperscript{81} As outlined in the retrosynthetic analysis given in Scheme 28, the twelve-membered macrocycle will be dissected between C-12 and C-13 and again constructed \textit{via} an RCM-reaction from diene 160. One of the key operations of the synthesis, the fusion of vinyl iodide 161 and alkene 162, will be established through a palladium catalyzed Suzuki-Miyaura cross coupling\textsuperscript{82} reaction.

![Scheme 28. Retrosynthetic analysis of \((-\)-15-\textit{O}-acetyl-3-\textit{O}-propionylcharaciol (159).](image)

An \textit{in situ} generated phenylselenide anion equivalent was allowed to react with dibromide 163, followed by alkylation with deprotonated isobutyronitrile to afford intermediate 164. Subsequent reduction of the nitrile moiety to give the corresponding aldehyde, a Grignard reaction with vinylmagnesium bromide and PMB-protection of the resulting secondary alcohol provided alkene 162 in 55% overall yield (Scheme 29).

![Scheme 29. Synthesis of alkene 162.](image)

The five-membered ring intermediate 144 (the synthesis thereof is described in section 1.4.5) was reduced using lithium aluminum hydride to give the corresponding diol, which was protected as acetonide with 2,2-dimethoxypropane and further oxidative cleavage of the double bond resulted in the formation of aldehyde 165. Following the Corey-Fuchs protocol\textsuperscript{83, 84}, 165 was first converted to the corresponding dibromoolefin with CBr\textsubscript{4} and PPh\textsubscript{3} followed by the treatment with methylthiium to form the terminal alkyne, which was \textit{in situ} alkylated with methyl iodide. Finally, vinyl iodide 161 was synthesized \textit{via} hydrozirconation using the Schwartz reagent\textsuperscript{85, 86} and exposure of the intermediate vinyl zirconium species to iodide.
Scheme 30. Preparation of vinyl iodide 161.

Alkene 162 and vinyl iodide 161 were connected via a Suzuki-Miyaura cross coupling to afford highly advanced intermediate 166 in excellent yield. The synthesis was continued by oxidation of the selenide with hydrogen peroxide and elimination of the resulting selenoxide. Deprotection of the acetonide protection group under mild Lewis acidic conditions to avoid additional cleavage of the TBS-group and additional oxidation using IBX allowed the isolation of α-hydroxy-aldehyde 167. Ketone 160, precursor for the RCM-reaction, was obtained through nucleophilic attack of 167 with isopropenyl lithium followed by the cleavage of the PMB group and oxidation of the free secondary alcohol. The twelve-membered macrocycle was closed via an RCM reaction, mediated by Grubbs’ 2nd generation catalyst, exclusively affording the trans-connected double-bond isomer. Deprotection of the remaining TBS-group delivered diol 168, which already features the complete jatrophane framework. Mitsunobu reaction to introduce the desired stereocenter at C-3, subsequent transesterification and final acylation provided tertiary alcohol 169, which was finally converted to (−)-15-O-acetyl-3-O-propionylcharaciol (159) through the introduction of the missing acetate group.

Scheme 31. Completion of the total synthesis of (−)-15-O-acetyl-3-O-propionylcharaciol (159).
1.5. **PARTIAL SYNTHESES – SYNTHESES OF FIVE-MEMBERED RING INTERMEDIATES**

1.5.1. **Synthesis of a cyclopentane fragment by Yamamura et al.**

The synthesis of the cyclopentane core (171), as found in euphohelioscopin A (170) and euphoscopin A (172), was published by Yamamura *et al.* in 1993 (Scheme 32).  

Cyclopentene 173 was oxidized using OsO₄ and the resulting diol was protected as a benzylidene acetal. Cleavage of the acetate group was followed by a mesylation/elimination sequence resulting in the isolation of intermediate 174. The secondary alcohol, obtained after TBS-deprotection with TBAF, was oxidized under Swern oxidation conditions. The synthesis was continued by 1,4-addition of a methyl-cuprate species, substrate-controlled reduction with L-selectride and benzyl-protection of the intermediate secondary alcohol to afford 175.

![Scheme 32. Retrosynthetic analysis of the cyclopentane fragment 171.](image)

![Scheme 33. Synthesis of the cyclopentane fragment 171.](image)
Next, deprotection of the benzylidene acetal, regioselective TBS-protection of the sterically less hindered hydroxyl group and Swern oxidation allowed the isolation of ketone 176. Petasis methylenation\(^8^8\) of 176, subsequent hydroboration and additional deprotection of the remaining TBS-group delivered diol 177, which was protected as an isopropylidene acetal in the next step. Cleavage of the benzyl group and oxidation of the corresponding secondary alcohol under Swern conditions furnished ketone 178. Substrate controlled addition of propinylmagnesium bromide provided the propinyl-adducts 179 and 180 as a 4.5:1 mixture of diastereomers, in favor of the desired isomer 179. Finally, the introduction of the ethyl-ketone moiety was accomplished via the cyclic carbamate 181, which was subsequently hydrolyzed to the desired five-membered ring fragment 171.

1.5.2. Synthesis of the cyclopentane fragment of euphosalicin and pepluanin A by Mulzer \textit{et al.}\(^8^9\)

Mulzer \textit{et al.} published a highly substrate-controlled synthesis of the cyclopentanyl vinyl triflate 182, an advanced synthetic target toward the total synthesis of euphosalicin and pepluanin A.\(^8^9,\)\(^9^0\)
The authors intended to prepare vinyl triflate 182 from intermediate 183 via stereoselective \(\alpha\)-hydroxylation and opening of the lactone. Cyclopentene 184 was elaborated as a suitable precursor for bicyclic lactone 183 (Scheme 34).

![Scheme 34. Retrosynthetic analysis of cyclopentane fragment 182.](image)

The synthesis started with the conversion of furfuryl alcohol (185) to the racemic secondary alcohol 186 through a three-step procedure. The initial acid mediated furfuryl alcohol rearrangement affording alcohol 195 proceeds through the mechanism outlined in Scheme 35. Protection of the hydroxyl group as a TBS-ether and reduction with lithium aluminum hydride allowed the isolation of the racemic intermediate 186. The kinetic resolution of rac-186 using the enzyme pancreatin and vinyl acetate as the acylating agent delivered acetate 187 and secondary alcohol 188 with excellent enantiomeric purity.\(^9^1\)
Deprotection of the acetate group in 187 and oxidation of the intermediate secondary alcohol resulted in the isolation of ketone 196. Transformation of alcohol 188, obtained as second product after the kinetic resolution, to ketone 196 was accomplished via intermediate 197 in five steps. Finally, substrate-controlled addition of methyl lithium, attacking from the opposite side of the TBS-group provided tertiary alcohol 184 (Scheme 36).

In the following step, an Eschenmoser-Claisen rearrangement provided amide 198 in excellent yield. The treatment with dimethyldioxirane (DMDO) delivered epoxide 199, which was subsequently converted to intermediate 200 via flash chromatography mediated intramolecular epoxide-opening lactonization. Subsequent MOM-protection of the resulting tertiary alcohol afforded lactone 201.

Initially, a five-step sequence was elaborated for the synthesis of secondary alcohol 204 (Scheme 38). The conversion to amide 205 through opening of the lactone with pyrrolidine, was followed by acetate protection of the free hydroxyl functionality and deprotection of the TBS-group with
TBAF. Amide 206 was subsequently utilized in an intramolecular lactonization reaction and final cleavage of the acetate protecting group afforded secondary alcohol 204. The authors could impressively optimize the described sequence by the application of a single-step transformation. The treatment of lactone 201 with TBAF at room temperature induced TBS-deprotection and translactonization in one step. Mechanistically, alkoxide 202, which is formed in the desilylation reaction, adopts the appropriate conformation for the intramolecular lactonization reaction.

![Scheme 38. Synthesis of lactone 204.](image)

The final sequence toward the highly substituted five-membered ring fragment 182 commenced with the protection of the free alcohol functionality in lactone 204 as a MOM-ether. The last missing hydroxyl functionality was introduced from the convex face of the cis-fused bicyclic lactone by α-hydroxylation using the Davis’ reagent (2-benzenesulfonyl-3(3-nitrophenyl)oxaziridine). Further PMB-protection provided intermediate 207 and methyl ketone 209 could be prepared via amide 208 in a three-step sequence. The lactone moiety was opened with pyrrolidine and TES-protection of the resulting secondary alcohol was carried out before addition of methyllithium completed the sequence. Finally, kinetically controlled formation of a vinyl triflate concluded the highly substrate-controlled synthesis of the cyclopentane fragment 182.

![Scheme 39. Total synthesis of cyclopentany vinyl triflate 182.](image)

1.5.3. Synthesis of the cyclopentane fragment of Kansuine A by Uemura et al.

Uemura et al. published the synthesis of the highly functionalized cyclopentane fragment 211 on their route toward the total synthesis of kansuine A (210). They envisaged a samarium diiodide
mediated intramolecular nucleophilic acyl substitution of δ-halo ester 212 as their ring closing reaction (Scheme 40).

Scheme 40. Restrosynthetic analysis of Uemura’s cyclopentane fragment (211).

The sequence was initiated with a Mukaiyama aldol reaction of ethyl-C,O-bis(trimethylsilyl)ketene acetal (219) and benzyl-protected aldehyde 213, followed by TMS-deprotection to give β-hydroxy ester 214. A second aldol reaction using formaldehyde and LDA afforded diol 215 in a 78:22 mixture of diastereomers and further acetal protection provided anti- and syn-216 in excellent yield. Reductive cleavage of the benzyl group and conversion of the resulting primary alcohol to iodide 212 under Appel reaction conditions95 was followed by the crucial samarium diiodide induced ring closing reaction, delivering ketone 217. The next sequence, substrate controlled addition of TMS-ethinylmagnesium bromide, deprotection of the isopropylidene group and protection of the primary alcohol allowed the isolation of intermediate 218. Finally, acetate protection of the remaining free secondary hydroxyl group, cleavage of the TBS-ether and subsequent oxidation with Dess-Martin periodinane concluded the synthesis of the advanced cyclopentane fragment 211.

Scheme 41. Synthesis of cyclopentane fragment 211.
1.5.4. A general access to cyclopentane fragments of jatrophane diterpenes by 
Rinner et al.96

A general approach for the synthesis of the five-membered ring part of jatrophane diterpenes giving access to various natural products such as Pl-3 (2) or altotibetin A (4) was reported by our group in 2009.96 Cyclopentanones 220a and 220b were established as advanced intermediates for further application in the total synthesis of different jatrophane diterpenes (Scheme 42). The approach allows the flexible introduction of the stereocenters at C-2 and C-3 (jatrophane numbering) of the jatrophane skeleton. The decisive idea behind this variable access is, that a methyl group at C-2, present in an either $R$ or $S$ configuration, as well as an oxygen functionality at C-3 are common structural motifs of the cyclopentane fragment of jatrophane diterpenes.

The intended key-step in the synthesis is an RCM-reaction to close the five-membered ring. The intermediates 220a and 220b could be synthesized starting from primary alcohols 222a or 222b via a C-2 elongation.

Scheme 42. Retrosynthetic analysis of cyclopentanones 220a and 220b.

The synthesis of cyclopentanone 220a is outlined in Scheme 43. Stereoselective C-2 elongation using (R)-HYTRA (223) as chiral auxiliary97, 98 was achieved after oxidation of primary alcohol 222a. The cleavage of the auxiliary in 224 and an aldol reaction with formaldehyde delivered diol 225, which was converted to $\alpha,\beta$-unsaturated ester 226 through a tosylation/elimination sequence followed by TBDPS-protection.

Scheme 43. Synthesis of cyclopentanone 220a.
Reduction of the methyl ester and subsequent PMB-protection gave the precursor for the RCM reaction using Grubbs 2nd generation catalyst (157). Cyclopentene containing intermediate 227, formed in excellent yield, was further converted to the corresponding secondary alcohol by a hydroboration/oxidation sequence and, finally, cyclopentanone 220a was provided after IBX oxidation in 12 steps starting from chiral 222a.

2. AIM OF THE SYNTHETIC WORK

The present Ph.D. thesis is divided into two parts. The first part is dealing with a general synthetic access to the eastern part of jatrophane diterpenes while in the second part the synthetic efforts toward the total synthesis of Pl-4 are described.

Due to the recurring stereochemical substitution pattern of the eastern fragment (C7–12) in various jatrophane diterpenes, including Pl-3 and Pl-4 (Figure 12), we have established a general sequence for the synthesis of this part of the macrocycle. The intermediates 230 and 231, precursors within our retrosynthetic considerations, were both synthesized in a diastereoselective manner. The sequence for the preparation of the eastern fragment of Pl-3 is outlined in Scheme 44. Key step in the preparation of 230 is a samarium diiodide mediated Reformatsky reaction, which works exclusively via stereochemical control of the chiral auxiliary. The application of D-ribose (232) as starting material for the preparation of 230 offers the advantage of acquiring stereochemical information from the chiral pool. Individual jatrophane diterpenes often only differ in the stereochemistry of the methyl and hydroxyl groups while the substitution pattern remains highly similar. Therefore, the utilization of different sugars as starting materials and the application of the enantiomeric chiral auxiliary (ent-236) in the Reformatsky reaction grants access to different stereochemical substitution patterns within the eastern fragment of jatrophane diterpenes.
As already mentioned above, the second part of this thesis is focusing on synthetic studies toward the total synthesis of the jatrophane diterpene Pl-4. The aim of our strategies is a late stage closure of both rings, present in the natural product (Scheme 45). The 12-membered macrocycle should be closed via an RCM-reaction in all our approaches. Different ring closing reactions would be conceivable, for the preparation of the cyclopentane ring, leading to highly advanced intermediates 236 and 237. On the one hand, starting from vinyl halide 236 the closure of the five-membered ring could be achieved either by a nucleophilic reaction via lithiation of the vinyl halide, an NHK-coupling reaction or a SmI$_2$-induced radical ring closing reaction. On the other hand, regarding ynone 237 as the cyclization precursor, the five-membered ring could be directly formed through the generation of a ketyl-radical, using SmI$_2$, which attacks the internal alkyne in a five-exo-dig ring closing reaction. 

![Scheme 44. Synthesis of the eastern fragment of Pl-3.](image)

![Scheme 45. Retrosynthetic analysis of Pl-4.](image)

Two general strategies for the preparation of vinyl-bromide 236 were pursued and are outlined in Scheme 46. Either a regioselective syn-hydrometalation of ynone 238 or a lithiation/alkylation sequence of aldehyde 242 and dibromide 243 via a chelating, regioselective transition state, were considered. 

![Scheme 46. General considerations for the synthesis of internal vinyl halide 240.](image)
Unfortunately, despite intense experimentation the hydrometalation as well as the direct cyclization approach via a ketyl species (from 237) were not brought to an end. Therefore, we turned our attention on the dibromide coupling approach. As outlined in Scheme 47, the northern fragment (aldehyde 245) should become accessible via coupling of Roche-ester derived bromide 246 and aldehyde 247. Dibromide 248 was intended to be elaborated from aldehyde 249 and methylisobutyrate (250). Again, D-ribose could be employed as an ideal and inexpensive starting material from the chiral pool for the preparation of intermediate 249.

Scheme 47. Retrosynthesis dibromide coupling approach.

Following the route outlined in Scheme 48, the desired coupling partners, dibromide 252 and aldehyde 245, could be obtained in good overall yield on a multigram scale. The regioselective lithiation/alkylation reaction, key step in the synthesis of 255, is based on a report by Braun and co-workers. They demonstrated that regioselective alkylation of the more hindered position of a vinyl dibromide could be achieved through coordination of the intermediary formed organolithium species to a chelating MEM-group in α-position to the double bond. We were pleased to find that the lithiation of dibromide 252 proceeded exclusively via the anticipated, chelate-controlled transition state and advanced intermediate 254 could be isolated in excellent yield. Unfortunately, the chiral information of the chelating MEM-group in the lithiated species was not transferred to the reaction partner and 254 was obtained in a 1:1 mixture of diastereomers.

Scheme 48. Preparation of vinylbromide 255.
Summarizing, we could demonstrate that the application of the regioselective lithiation/alkylation reaction of the more hindered bromide in geminal vinyl dibromides is a valuable alternative for the preparation of internal vinyl halides. The protocol allows the selective, stepwise introduction of functionalities, and the preparation of highly substituted alkenes. The remaining bromide constitutes an anchor for further functionalization and closure of the cyclopentane moiety. In future studies, strategies toward the closure of the five-membered ring, as well as the completion of the synthesis, will be elaborated.

Our synthetic efforts toward the total synthesis of Pl-4 can be divided into three related approaches:

- The direct alkyne cyclization approach
- The hydrometalation approach
- The dibromide coupling approach.

Detailed discussion of our retrosynthetic analyses, synthetic achievements and setbacks are content of the following three manuscripts, published in the course of this Ph.D. thesis.
3. REFERENCES


4. **LIST OF PUBLICATIONS**

**Peer-reviewed Publications**


**Oral Presentations**

- Towards the First Total Synthesis of Pl-4. 14th Austrian Chemistry Days, Linz, Austria, September 26-29, **2011**.

- Towards the First Total Synthesis of Pl-4 – A Jatrophane Diterpene with Remarkable Multidrug Resistant Reversal (MDR) Effect. 240th National Meeting of the American Chemical Society, Boston, MA, USA, August 22-26, **2010**.

- Synthesis and Biological Evaluation of Novel Combretastatin Analogos. Graz University of Technology, Austria, December 4, **2008**.

- Synthesis of Novel Combretastatin A-4 Analogos. University of Szeged, Hungary, September 16, **2008**.

**Poster Presentations**


• Lentsch, C.; Fürst, R.; Rinner, U., Highlights on the way to the first total synthesis of Pl-3. 240th National Meeting of the American Chemical Society, Boston, MA, USA, August 22-26, 2010.


5. Appendix I

Towards the Total Synthesis of Pl-3: Preparation of the Eastern Fragment through a Diastereoselective SmI$_2$-Mediated Reformatsky Reaction

Rita Fürst,[a] Christoph Lentsch,[a] and Uwe Rinner*,[a]

Keywords: Natural products / Terpenoids / Samarium / Diastereoselectivity / Multidrug resistance

The jatrophane diterpene Pl-3, isolated in 2003 from Euphorbia platyphyllos, is a structurally complex natural product with highly promising biological properties that include pronounced antiproliferative activity and the inhibition of the efflux-pump activity of multidrug resistance p-glycoprotein. Herein, the synthesis of the eastern fragment of Pl-3 is outlined. The target compound is synthesized in nine synthetic operations in good overall yield, starting from readily available D-ribose. The key step in the preparation of the eastern part of Pl-3 is a diastereoselective SmI$_2$-mediated Reformatsky reaction. The proposed route is highly flexible and could also be applied to the synthesis of structurally related jatrophane diterpenes.

Introduction

The genus Euphorbia, a member of the Euphorbiaceae plant family, is one of the largest genera among flowering plants comprising more than 2000 species. Euphorbia plants, also known as spurge, are endemic in tropical and subtropical regions as well as in temperate climate zones. Several members are in cultivation and are of great economic importance. For example, the Pará rubber tree (Hevea brasiliensis) serves as a source of natural rubber, whereas Cassava (Manihot esculenta) is an important annual crop that is rich in carbohydrates. Other members, such as poinsettia (Euphorbia pulcherrima), are cultivated for their appealing nature.

Because of their pronounced biological activities, spurge have been common ingredients in traditional herbal folk medicine, and they are mainly used in the treatment of cancerous conditions, swellings, and warts.[1] The milky sap (latex) is a common attribute of members of the Euphorbiaceae plant family. It contains a large number of structurally diverse diterpenes, which are responsible for the application of spurge in traditional phytotherapy.[2] Several of these diterpenes were also identified as highly active inhibitors of the adenosine-5'-triphosphate (ATP)-dependent efflux pump p-glycoprotein, which is responsible for multidrug resistance in cancer.[3] Given that resistance to prevalent drugs is one of the major drawbacks in the development of cancer therapeutics, progress in the synthetic preparation of Euphorbia diterpenes is also of medicinal importance.

Chemical interest in the biologically active ingredients of the genus Euphorbia started with the isolation of jatrophane by Kupchan in 1970.[4] Since then, numerous diterpenes of the jatrophane, tigliane, ingenane, and lathyrane frameworks have been isolated and, to some extent, evaluated for their biological activity.[5] Despite their challenging structural features, only few synthetic efforts towards these fascinating natural products have been reported to date.[5]

Pl-3 (1) was isolated by Hohmann and co-workers from Euphorbia platyphyllos in 2003.[6] As outlined in Figure 1, jatrophane diterpenes are characterized by a highly functionalized trans-bicyclo[10.3.0]pentadecane framework. Individual diterpenes often only differ in the stereochemical pattern of the methyl and hydroxy groups, whereas the substitution pattern remains highly similar.

Figure 1. Jatrophane skeleton and representative jatrophane diterpenes.
The retrosynthetic analysis is shown in Scheme 1. The final operation in the synthesis of Pl-3 is a metathesis reaction to close the macrocyclic ring, whereas advanced intermediate 4 should become available from cyclopentane 5 and alkene 6 through cross-metathesis. The key step in the preparation of the eastern part of Pl-3 is a diastereoselective SmI2-mediated Reformatsky reaction. In an attempt to take advantage of the chiral pool, d-ribose was identified as an ideal starting material to access alkene 6. The utilization of different sugars and the application of an enantiomeric chiral auxiliary in the Reformatsky reaction should furthermore allow the facile preparation of related fragments for the synthesis of other jatrophane diterpenes.

Scheme 1. Retrosynthetic analysis.

Recently, we reported the synthesis of the cyclopentane moiety of Pl-3 (1). Herein, we will discuss the preparation of the eastern fragment (i.e., 6).

Results and Discussion

The first approach towards alkene 6 started with acetone protection of d-ribose (9) as outlined in Scheme 2. Initially, we intended to install the alkene moiety required for the cross-metathesis reaction by Tebbe olefination of the corresponding methyl ketone, which should be accessible from terminal alkene 14 after Wacker oxidation. Thus, acetone 10 was allowed to react with Wittig salt 11 before periodate cleavage of the formed diol afforded unsaturated aldehyde 12 in excellent yield.

With 12 in hand, the crucial diastereoselective Reformatsky reaction could be attempted. According to literature precedents, the S configuration at the newly generated stereocenter is expected when bromoacyl oxazolidinone 7, readily available on multigram scale upon acylation of oxazolidinone 15 and 2-bromoisoobutyryl bromide (16), is allowed to react with aldehyde 12. Unfortunately, as shown in Table 1, initial attempts with the use of tin[9,10] and zinc[11] for the generation of the nucleophile in the Reformatsky reaction resulted in reisolation of the starting material. The desired product, although only in low yield, was first obtained when chromium salts were employed (Table 1, entries 3–6).[12] Cp2TiCl (Cp = cyclopentadienyl) has been described to promote Reformatsky reactions,[13] but we chose to utilize SmI2 next and were able to isolate oxazolidinone 13 in excellent yield as a single diastereomer (the opposite diastereomer was not observed by NMR spectroscopy), which was further converted into methoxymethyl (MOM)-protected intermediate 14. The high level of selectivity can be explained by the exclusive formation of a pentacoordinate transition state, as described by Thornton and Pridgen.[7a,14] Steric repulsion of the auxiliary and presumably the bulky geminal dimethyl group efficiently prevents $Re$ attack and forces the system to undergo the desired $Si$ attack. The $S$-configured hydroxy group in 13 (Scheme 3) is formed through exclusive stereochemical control of the chiral auxiliary.

Table 1. Reaction conditions in the diastereoselective Reformatsky reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal and solvents</th>
<th>Temp. [°C]</th>
<th>% Yield of 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl2, LiAlH4, THF</td>
<td>0 to r.t.</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Zn, THF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CrCl2, LiI, THF</td>
<td>r.t.</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>CrCl2, THF</td>
<td>r.t.</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>CrCl3, NiCl3, THF</td>
<td>r.t.</td>
<td>&lt;10[9]</td>
</tr>
<tr>
<td>6</td>
<td>CrCl3, LiAlH4, THF</td>
<td>r.t.</td>
<td>&lt;10[9]</td>
</tr>
<tr>
<td>7</td>
<td>SmI2, THF</td>
<td>–78</td>
<td>85</td>
</tr>
</tbody>
</table>

[a] Yield was determined by analysis of the crude product by $^1$H NMR spectroscopy.

Scheme 2. Preparation of alkene 14 (DIPEA = N,N-diisopropyl-ethylamine).

Scheme 3. Transition-state model for the diastereoselective Reformatsky reaction.
Towards the Total Synthesis of Pl-3

Scheme 4. Determination of the stereochemistry.

The proposed configuration of the newly installed hydroxy moiety in 13 was unambiguously confirmed by comparison of the coupling constants between H-4 and H-3 in cyclic intermediates 18 and 20, according to the Karplus correlation and NOESY experiments (Scheme 4). Cleavage of the terminal double bond in 13 and 19, available upon Reformatsky reaction of 12 with ent-7, by ozonolysis was followed by pyridinium chlorochromate (PCC) oxidation of the resulting lactol. Whereas the H-4–H-3 coupling constant in 20, which originated from the alcohol with the R configuration, was 1.0 Hz, a value of 3.7 Hz was measured for cyclic intermediate 18, and thus, the stereochemical configuration of alcohol 13 could be confirmed.

All attempts to convert alkene 14 into methyl ketone 22 through Wacker oxidation failed and only resulted in reisolation of the starting material. As outlined in Scheme 5, dihydroxylation of the terminal double bond with OsO₄ and periodate cleavage of the resulting diol allowed the isolation of highly unstable aldehyde 21. However, the conversion of 21 into methyl ketone 22 proved to be troublesome, as addition of the methyl Grignard reagent and subsequent oxidation of the secondary alcohol delivered the desired compound in low and irreproducible yield.

Scheme 5. Preparation of methyl ketone 22 (NMO = N-methylmorpholine-N-oxide; DMP = Dess–Martin periodinane).

In a modified approach, we intended to install the methyl ketone at an early stage to circumvent the problems discussed above. As shown in Scheme 6, the route started with Lewis acid promoted conversion of α-ribonolactone (23) into acetone 24. Silylation of the primary hydroxy group delivered lactone 25, which was treated with methyllithium to afford lactol 26 as a masked methyl ketone in quantitative yield as a single diastereomer.[15] Next, we intended to install the terminal double bond. Methylenation of 26 with Tebbe’s reagent was unsuccessful, and even at elevated temperature no conversion could be detected (Table 2, entries 1 and 2). Surprisingly, when allowed to react with the methyl Wittig reagent (11) under standard reaction conditions in THF with tBuOK as the base, α-racemization occurred and a diastereomeric mixture of 27/28 in a 5:1 ratio was isolated in moderate 34% yield. When toluene was used as the solvent, the exclusive formation of desired alkene 27 was observed; however, the isolated yield did not exceed 30%. Several other protocols were investigated: potassium hexamethyldisilazane (KHMDs) in THF afforded exclusively undesired diastereomer 28 (Table 2, entry 7), whereas other bases such as NaH and BuLi resulted in reisolation of the starting material. As the yield in the methylenation reaction could not be further improved, another approach was elaborated.


Table 2. Methylenation of lactol 26.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent/solvent</th>
<th>Temp. °C</th>
<th>Time [h]</th>
<th>% Yield (27/28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tebbe reagent/THF</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Tebbe reagent/THF</td>
<td>r.t. to 80</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>iBuOK/THF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0 to r.t.</td>
<td>4</td>
<td>34 (5:1)</td>
</tr>
<tr>
<td>4</td>
<td>NaH/DMSO&lt;sup&gt;b&lt;/sup&gt;</td>
<td>r.t. to 50</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NaH/THF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–20 to r.t.</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>iBuLi/THF&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–78 to r.t.</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>KHMDs/THF&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–78 to r.t.</td>
<td>14</td>
<td>13 (&lt;1:99)</td>
</tr>
<tr>
<td>8</td>
<td>iBuOK/toluene&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–78 to r.t.</td>
<td>4</td>
<td>30 (&gt;99:1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The Wittig salt was deprotonated at 0 °C over 20 min and at r.t. over 1.5 h before 26 was added. <sup>b</sup> NaH was heated in DMSO to 75 °C for 45 min before the Wittig salt was added at 0 °C, and deprotonation was accomplished at r.t. over 20 min. <sup>c</sup> The Wittig salt was deprotonated at r.t. over 2 h. <sup>d</sup> The Wittig salt was deprotonated at –78 °C over 1 h.
In our third approach, protection of d-ribonolactone (23) as its acetone was followed by exposure of the lactone to pyrrolidine at elevated temperature to obtain amide 29 in excellent yield (Scheme 7). Next, silylation of both hydroxyl functionalities was followed by addition of methyl ketone to pyrrolidine at elevated temperature to obtain amide 30 upon reaction with Tebbe’s reagent. Removal of both silyl ethers and substituent oxidative cleavage of the vicinal diol with NaIO₄ with Tebbe’s reagent. Removal of both silyl ethers and subquent oxidative cleavage of the vicinal diol with NaIO₄ delivered aldehyde 31, the precursor for the crucial dia stereoselective Reformatsky reaction. Again, as discussed for the first approach, the desired secondary alcohol was obtained in good yield as a single isomer when a degassed, precooled THF solution of bromide 7 (1.44 g, 4.41 mmol, 1.1 equiv.) and aldehyde 32 (683 mg, 4.01 mmol, 1.0 equiv.) in degassed THF (60 mL, 3 pump-freeze–thaw cycles) at –78 °C by cannula. The reaction mixture was stirred for 1 h at –78 °C before it was quenched by the addition of aqueous saturated solutions of sodium thio sulfate (50 mL) and sodium hydrogen carbonate (50 mL) at –78 °C, and the biphasic system was warmed to room temperature. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic extract was dried with sodium sulfate and filtered, and the organic solvents were removed under reduced pressure to deliver alcohol 33 as a light yellow oil, which was further purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to provide 33 (1.14 g, 68%).

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ¹H NMR and ¹³C NMR spectra of all compounds described in this communication.

Conclusions

We have established a general nine-step sequence for the synthesis of the eastern fragment of Pl-3. The Reformatsky reaction, described in detail within this manuscript, can be employed in the synthesis of jatrophone diterpenes to establish recurring structural motifs within the eastern part. The application of different carbohydrate derivatives as the starting material in combination with the highly diastereoselective SmI₂-mediated Reformatsky reaction grants access to a variety of structurally related Euphorbiaceae diterpenes. Owing to the diastereoselective control of the chiral auxiliary within the SmI₂-mediated Reformatsky reaction, the utilization of this reaction will be of interest for other synthetic applications. The scope of the synthetic route and the completion of the preparation of Pl-3 are currently under investigation in our group.

Experimental Section

Preparation of 33: To a solution of SmI₂ (0.1 m in THF, 100 mL, 10 mmol, 2.5 equiv.) in a 250 mL round bottom Schlenk flask was added a solution of bromide 7 (1.44 g, 4.41 mmol, 1.1 equiv.) and aldehyde 32 (683 mg, 4.01 mmol, 1.0 equiv.) in degassed THF (60 mL, 3 pump-freeze–thaw cycles) at –78 °C by cannula. The reaction mixture was stirred for 1 h at –78 °C before it was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium hydrogen carbonate (50 mL) at –78 °C, and the biphasic system was warmed to room temperature. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic extract was dried with sodium sulfate and filtered, and the organic solvents were removed under reduced pressure to deliver alcohol 33 as a light yellow oil, which was further purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to provide 33 (1.14 g, 68%).

Acknowledgments

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References

Towards the Total Synthesis of PI-3


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Supporting Information

Towards the Total Synthesis of PI-3 – Preparation of the Eastern Fragment via a diastereoselective SmI\textsubscript{2} induced Reformatsky Reaction

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General methods

**Synthetic methods:** All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum) unless noted otherwise.

**Solvents and chemical purification:** THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxycethane, benzene and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DMSO and N,N-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral, activity. Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å). Triethylamine, diethylisopropylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/ethyl acetate or toluene/ethyl acetate. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [H₂SO₄ (conc., 22 mL), phosphormolybdic acid (20 g), Ce(SO₄)₂ (0.5 g), 378 mL H₂O] or silica gel impregnated with iodine.

**Chromatography:** Preparative column chromatography and flash chromatography were performed with silica gel 60 from Merck (0.040-0.063 μm, 240-400 mesh).

For HPLC separations on analytical scale module systems from Jasco (PU-980, UV-975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was Superphere Si 60 (40 μm, Merck) or Nucleosil 50 (4 μm, Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

Solvents were removed by rotary evaporation at 30 °C at the appropriate pressure, unless stated otherwise. Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise.

**Optical rotations:** Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: [α]TD, concentration (g/100 mL), and solvent.

**NMR spectra:** NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl₃ solutions and referenced to the residual CDCl₃ signal (¹H, δ = 7.26, ¹³C, δ = 77.16). All ¹H and ¹³C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy.
IR spectra: IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR spectrometer and are reported in wave numbers (cm\(^{-1}\)). All compounds were measured as a thin film on silicon single crystal plate.

Experimental part

\[(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (10).\] To a suspension of D-ribose (5 g, 33.3 mmol, 1 eq) in acetone (62.5 mL) was added dropwise at room temperature a catalytic amount of concentrated sulfuric acid (150 \(\mu\)L, 0.1 eq). The reaction mixture was stirred for twelve hours at ambient temperature before it was neutralized with solid sodium bicarbonate. The suspension was stirred for additional five hours before the precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 2:1) providing lactole 10 (5.2 g, 81%) as colorless oil.

\[^{1}\text{H NMR (400 MHz, CDCl}_3]: \delta = 1.32 (s, 3H), 1.49 (s, 3H), 3.47 (bs, 1H), 3.62-3.83 (m, 2H), 4.40 (bs, 1H), 4.58 (d, \text{ } J = 5.83 \text{ Hz}, 1H), 4.84 (d, \text{ } J = 5.83 \text{ Hz}, 1H), 5.42 (bs, 1H) \text{ ppm.}\)

\[^{13}\text{C NMR (100 MHz, CDCl}_3]: \delta = 24.9 (\text{CH}_3), 26.5 (\text{CH}_3), 63.9 (\text{CH}_2), 81.9 (\text{CH}), 87.0 (\text{CH}), 88.0 (\text{CH}), 103.2 (\text{CH}), 112.3 (\text{C}) \text{ ppm.}\)

These spectral characteristics are identical to those previously reported.\[^{[1]}\]

\[(R)-1-((4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethane-1,2-diol \text{ (S1).} \] To a stirred suspension of methyltriphenylphosphonium bromide (3.5 g, 9.8 mmol, 3.5 eq) in THF (10 mL) was added potassium tert-butoxide (1.1 g, 9.8 mmol, 3.5 eq) at 0 °C. The reaction mixture was kept at that temperature for 20 min before it was warmed to room temperature and stirred for one additional hour. After recooling to 0 °C, lactole 10 (530 mg, 2.8 mmol, 1.0 eq) was dissolved in 2.5 mL THF and added via syringe. The resulting yellow mixture was stirred for 14 hours at room temperature. The reaction was then quenched by the addition of saturated ammonium chloride solution. The aqueous phase was extracted three times with ethyl acetate, the combined organic extracts were dried over solid sodium sulfate and the solvent was removed under reduced pressure. Afterwards, the crude material was purified by flash chromatography (hexanes/ethyl acetate 1:2) affording the Wittig-product (S1, 470 mg, 89%) as light yellow oil.\[^{[2]}\]
Appendix I

Experimental part

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.37$ (s, 3H), 1.48 (s, 3H, CH$_3$), 2.0-2.08 (bs, 1H), 2.19-2.42 (m, 1H), 3.67-3.87 (m, 3H), 4.11 (dd, $J = 6.6, 8.4$ Hz, 1H), 4.71 (bt, $J = 6.58$ Hz, 1H), 5.33 (dt, $J = 1.2, 10.4$ Hz, 1H), 5.47 (dt, $J = 1.2, 17.3$ Hz, 1H), 6.01 (ddd, $J = 6.6, 10.4, 17.3$ Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 25.4$ (CH$_3$), 27.9 (CH$_3$), 64.5 (CH$_2$), 70.0 (CH), 78.4 (CH), 78.7 (CH), 109.2 (C), 118.8 (CH$_2$), 133.9 (CH) ppm.

IR (thin film) $\nu = 3384, 2987, 2937, 1372, 1216, 1055, 928, 872, 798$ cm$^{-1}$.

HRMS (EI) calcd for C$_9$H$_{16}$O$_4$ [M+Na]$^+$, 211.0947; found 211.0940 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = +25.9°.

(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (12). Diol S1 (3.3 g, 17.5 mmol, 1.0 eq) was dissolved in methylene chloride (60 mL) before sodium periodate (5.6 g, 26.3 mmol, 1.5 eq) dissolved in 40 mL water was added dropwise via syringe. The cooling bath was removed and the reaction mixture was stirred at room temperature for two hours before it was diluted with water. The layers were separated and the aqueous phase was extracted three times with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvent was removed in vacuum (180-250 mbar, 30 °C water bath temperature). The resulting very labile product was filtered through a short plug of silica gel (pentanes/diethyl ether 3:1) delivering aldehyde 12 (2.2 g, 81%) as colorless oil which was immediately used for the next step.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.44$ (s, 3H), 1.62 (s, 3H), 4.41 (dd, $J = 3.0, 7.5$ Hz, 1H), 4.86 (bt, $J = 7.5$ Hz, 1H), 5.33 (dt, $J = 1.3, 10.5$ Hz, 1H), 5.47 (dt, $J = 1.3, 17.1$ Hz, 1H), 5.74 (ddd, $J = 6.8, 10.3, 17.3$ Hz, 1H), 9.56 (d, $J = 3.0$ Hz, 1H) ppm.

These spectral characteristics are identical to those previously reported.$^[1a]$
organic extracts were dried over solid sodium sulfate and afterwards the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 5:1) giving bromide 7 (5.15 g) in 94% yield.

\[^{1}\text{H NMR (400 MHz, CDCl}_3\text{: }\delta = 0.94 (d, J = 6.6 Hz, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 4.81 (quint, J = 6.7 Hz, 1H), 5.73 (d, J = 7.1 Hz, 1H), 7.29-7.46 (m, 5H) ppm.}\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{: }\delta = 14.2 (CH}_3\text{), 30.6 (CH}_3\text{), 31.7 (CH}_3\text{), 57.1 (C), 57.6 (CH), 79.1 (CH), 125.8 (CH) 128.9 (CH), 129.0 (CH), 133.6 (C), 151.2 (C), 171.57 (C) ppm.}\]

IR (thin film) \(\nu = 1788, 1682, 1455, 1339, 1284, 1191, 1122, 1068, 966, 699\) cm\(^{-1}\).

HRMS (EI) calcd for C\(_{14}\)H\(_{16}\)BrNO\(_3\) [M+Na]\(^{+}\), 325.0314; found 325.0318 +/- 5ppm.

Optical Rotation: \([\alpha]^{20}_D (c 0.1, \text{CHCl}_3) = +28.4^\circ\).

\(\text{(4S,5R)-3-(2-Bromo-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (S2).} \)

Bromide S2 was synthesized following the same procedure as described for bromide 7, starting from (4S,5R)-5-methyl-4-phenyloxazolidin-2-one (3 g, 23.4 mmol) in 94% yield.

Optical Rotation: \([\alpha]^{20}_D (c 0.1, \text{CHCl}_3) = -28.4^\circ\).

\(\text{(4R,5S)-3-((S)-3-((4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (13).} \)

\text{SmI\(_2\) method: A solution of SmI\(_2\) (100 mL, 0.1 M in THF, 10.0 mmol, 2.5 eq) was cannulated in a 250 mL round bottom Schlenk flask which was precooled to -78 °C. A solution of bromide 7 (1.44 g, 4.4 mmol, 1.1 eq) and aldehyde 12 (624 mg, 4 mmol, 1.0 eq) in 60 mL degassed THF (3 pump freeze thaw cycles) was added to the SmI\(_2\) solution via cannula. The reaction mixture was stirred for one hour at -78 °C before the reaction was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium bicarbonate (50 mL) at -78 °C and the biphasic mixture was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure delivering alcohol 13 as light oil which was further purified by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) in 85% yield (1.37 g).} \)
Chromium method I: Chromium dichloride (157 mg, 128 mmol, 4.0 eq) and lithium chloride (21 mg, 0.16 mmol, 0.5 eq) were suspended in freshly distilled THF (2 mL) and vigorously stirred at room temperature. Aldehyde 12 was added, followed by bromide 7, each dissolved in THF (1.0 mL). The reaction mixture was stirred for 1.5 h at room temperature, 1 h 20 min at 40 °C and 3 h at 60 °C before it was quenched with brine. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 9/1) delivering alcohol 13 (8.5 mg) in 7% yield.

Chromium method II: Chromium dichloride (98 mg, 0.8 mmol, 2.5 eq) was suspended in freshly distilled THF (1.5 mL). Aldehyde 12 (50 mg, 0.32 mmol, 1.0 eq) and bromide 7 (114 mg, 0.35 mmol, 1.1 eq), dissolved in 1.0 mL THF each, were added consecutively within five minutes at room temperature. The resulting mixture was stirred for seven hours at room temperature before the reaction was quenched with brine. The two layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) delivering alcohol 13 (30 mg) in 23% yield.

Chromium method III: Chromium trichloride (136 mg, 0.86 mmol, 2.7 eq) was suspended in 1.3 mL THF and a solution of lithium aluminum hydride (4.0 M in diethyl ether, 0.113 mL, 0.45 mmol, 1.4 eq) was added at 0 °C under vigorous stirring. The resulting black suspension was stirred for 45 min at 0 °C before aldehyde 12 (50 mg, 0.32 mmol, 1.0 eq) was added, followed by the addition of bromide 7 (147 mg, 0.45 mmol, 1.4 eq) at 0 °C; both dissolved in 0.5 mL THF, respectively. The reaction mixture was allowed to warm to room temperature over a period of 3.5 hours. The reaction was terminated by the addition of brine, the two layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9/1) delivering alcohol 13 (12.5 mg, 10%) as light yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): \( \delta = 0.92 \) (d, \( J = 6.6 \) Hz, 3H, CH$_3$-11), 1.35 (s, 3H, CH$_3$-14 or 15), 1.36 (s, 3H, CH$_3$-16 or 17), 1.44 (s, 3H, CH$_3$-14 or 15), 1.51 (s, 3H, CH$_3$-16 or 17), 3.44 (d, \( J = 10.1 \) Hz, 1H, OH), 4.28 (d, \( J = 7.6 \) Hz, 1H, H-4), 4.35 (d, \( J = 10.1 \) Hz, 1H, H-5), 4.67 (dd, \( J = 7.6, 8.0 \) Hz, 1H, H-3), 4.78 (quint, \( J = 6.6 \) Hz, 1H, H-9), 5.33-5.42 (m, 2H, H-1a,b), 5.66 (d, \( J = 6.8, 1H, H-10 \)), 6.14 (ddd, \( J = 8.1, 10.1, 17.5 \) Hz, 1H, H-2), 7.28-7.33 (m, 2H, CH-phenyl), 7.34-7.45 (m, 3H, CH-phenyl) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 14.0 \) (CH$_3$-11), 20.0 (CH$_3$-14 or 15), 23.3 (CH$_3$-14 or 15), 24.9 (CH$_3$-16 or 17), 27.0 (CH$_3$-16 or 17), 50.7 (C-6), 57.8 (CH-9), 71.5 (CH-5), 76.1 (CH-4), 79.3
(CH-10), 80.4 (CH-3), 108.8 (C-13), 119.8 (CH-2-1), 125.8 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.6 (C-12), 152.7 (C-8), 177.0 (C-7) ppm.

IR (thin film) v 3424, 2987, 2937, 1773, 1687, 1456, 1341, 1255, 1150, 1119, 1045, 939, 889, 768, 701, 657 cm$^{-1}$.

HRMS (EI) calcd for C$_{22}$H$_{29}$NO$_6$ [M+Na]$^+$, 426.1893; found 426.1890 +/- 5 ppm.

Optical Rotation: $[\alpha]^{20}_D (c 1.0, CHCl_3) = +52.8^\circ$.

\[ \text{19} \]

(4R,5S)-3-((R)-3-((4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (19).

Diastereomer 19 was prepared following the same procedures as described above for alcohol 13.

<table>
<thead>
<tr>
<th></th>
<th>Aldehyde (12)</th>
<th>Bromide (S2)</th>
<th>Yield (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmI$_2$ (4.9 eq)</td>
<td>50 mg, 0.32 mmol, 1.0 eq</td>
<td>111 mg, 0.34 mmol, 1.06 eq</td>
<td>56 mg (43%)</td>
</tr>
<tr>
<td>CrCl$_2$ (2.5 eq), Lil (0.1 eq)</td>
<td>50 mg, 0.32 mmol, 1.0 eq</td>
<td>115 mg, 0.35 mmol, 1.1 eq</td>
<td>50 mg (39%)</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.93$ (d, $J = 6.6$ Hz, 3H, CH$_3$-11), 1.35 (s, 3H, CH$_3$-16 or 17), 1.38 (s, 3H, CH$_3$-14 or 15), 1.48 (s, 3H, CH$_3$-16 or 17), 1.49 (s, 3H, CH$_3$-14 or 15), 2.21 (d, $J = 6.1$ Hz, 1H, OH), 4.18 (dd, $J = 6.3$, 9.9 Hz, 1H, H-4), 4.64 (dd, $J = 6.3$, 7.5 Hz, 1H, H-3), 4.70-4.80 (m, 2H, H-5, H-9), 5.29-5.42 (m, 2H, H-1a,b), 5.62 (d, $J = 7.1$ Hz, 1H, H-10), 5.99 (ddd, $J = 7.5$, 10.2, 17.1 Hz, 1H, H-2), 7.27-7.32 (m, 2H, CH-phenyl), 7.33-7.44 (m, 3H, CH-phenyl) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.6$ (CH$_3$-11), 20.0 (CH$_3$-14 or 15), 20.8 (CH$_3$-14 or 15), 25.2 (CH$_3$-16 or 17), 28.0 (CH$_3$-14 or 17), 49.6 (C-6), 57.6 (CH-9), 69.5 (CH-5), 77.9 (CH-4), 79.2 (CH-10), 79.8 (CH-3), 109.1 (C-13), 118.9 (CH$_2$-1), 125.7 (CH-phenyl), 128.8 (CH-phenyl), 133.6 (C-12), 135.0 (CH-2), 152.5 (C-8), 175.9 (C-7) ppm.

IR (thin film) $\nu$ 3424, 2987, 2937, 1773, 1687, 1456, 1341, 1255, 1150, 1119, 1045, 939, 889, 768, 701, 657 cm$^{-1}$.

HRMS (EI) calcd for C$_{22}$H$_{29}$NO$_6$ [M+Na]$^+$, 426.1893; found 426.1890 +/- 5 ppm.

Optical Rotation: $[\alpha]^{20}_D (c 1.0, CHCl_3) = +8.3^\circ$. 

\[ \text{18} \]
Experimental part

(4R,5S)-3-(2-((3aR,4S,6aR)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (18). Alkene 13 (58 mg, 0.14 mmol, 1.0 eq) was dissolved in 5 mL methylene chloride and cooled to −78 °C. A stream of ozone was bubbled through the reaction mixture (for approximately 2 min) until the solution turned characteristically blue. In order to remove excess of ozone from the reaction mixture, oxygen was bubbled through the solution and the reaction mixture turned colorless. Next, the solution was purged with argon for approximately two minutes before the reaction mixture was allowed to warm to room temperature over a period of 14 hours. The solvent was removed under reduced pressure delivering an inseparable mixture of diastereomers of the corresponding lactol (43 mg, 75%) as colorless oil, which was used for the next step without any purification.

To a solution of the crude mixture of lactols from above (20 mg, 0.05 mmol, 1.0 eq) in methylene chloride (1.0 mL) was added sodium acetate (8 mg, 0.1 mmol, 2.0 eq) and PCC (22 mg, 0.1 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at room temperature for twelve hours. The resulting suspension was filtered through a short plug of silica gel and the solvent was removed under reduced pressure delivering the crude lactone as yellow oil. Further purification by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) delivered lactone 18 (13 mg) in 65% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.91 (d, $J$ = 6.6 Hz, 3H, CH$_3$-9), 1.35 (s, 3H, CH$_3$-15), 1.47 (s, 3H, CH$_3$-16), 1.60 (s, 3H, CH$_3$-13 or 14), 1.65 (s, 3H, CH$_3$-13 or 14), 4.82 (d, $J$ = 5.6 Hz, 1H, H-2), 4.83 (quint, $J$ = 4.8 Hz, 1H, H-8) 4.99 (dd, $J$ = 3.7, 5.5 Hz, 1H, H-3), 5.24 (d, $J$ = 3.7 Hz, 1H, H-4), 5.68 (d, $J$ = 7.3 Hz, 1H, H-10), 7.28-7.32 (m, 2H, CH-phenyl), 7.36-7.46 (m, 3H, CH-phenyl) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.5 (CH$_3$-9), 18.6 (CH$_3$-15), 21.0 (CH$_3$-16), 25.7 (CH$_3$-13 or 14), 26.7 (CH$_3$-13 or 14), 48.3 (C-5), 76.6 (CH-2), 77.5 (CH-3), 79.6 (CH-10), 80.3 (CH-4), 114.7 (C-12), 125.9 (CH-phenyl), 128.9 (CH-phenyl), 129.1 (CH-phenyl), 133.5 (C-11), 125.5 (C-7), 173.5 (C-1), 175.8 (C-6) ppm.

IR (thin film): $\nu$ 2990, 2929, 1780, 1675, 1457, 1341, 1191, 1069, 1014, 953, 733, 701 cm$^{-1}$.

HRMS (EI) calcd for C$_{21}$H$_{25}$NO$_7$ [M+Na]$^+$, 426.1529; found 426.1527 +/- 5ppm.

Optical Rotation: $[\alpha]^{\text{20o}}$ (c 1.0, CHCl$_3$) = $-1.9^0$.

NOE-analysis:

![NOE diagram]

62
(4R,5S)-3-((3aR,4R,6aR)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (20). For the preparation of intermediate 20 the same procedure as described above was used starting from diastereomeric alcohol 19 (60 mg, 0.13 mmol). Lactone 20 (14 mg, 27%) was isolated after the two step procedure.

\[
\text{\textit{1H NMR (400 MHz, CDCl}_3\text{): } \delta = 0.83 \text{ (d, } J = 6.7 \text{ Hz, CH}_3-9), 1.40 \text{ (s, 3H, CH}_3-15), 1.49 \text{ (s, 3H, CH}_3-16), 1.57 \text{ (s, 3H, CH}_3-13 \text{ or 14), 1.67 \text{ (s, 3H, CH}_3-13 \text{ or 14), 4.36 \text{ (d, } J = 1.0 \text{ Hz, 1H, H-4), 4.74-4.82 \text{ (m, 2H, H-3, H-8), 4.99 \text{ (d, } J = 6.6 \text{ Hz, 1H, H-2), 5.67 \text{ (d, } J = 7.6 \text{ Hz, 1H, H-10), 7.24-7.45 \text{ (m, 5H, CH-phenyl) ppm.}}}
\]

\[
\text{\textit{13C NMR (100 MHz, CDCl}_3\text{): } \delta = 14.5 \text{ (CH}_3-9), 19.0 \text{ (CH}_3-13 \text{ or 14), 20.7 \text{ (CH}_3-13 \text{ or 14), 25.4 \text{ (CH}_3-15), 26.6 \text{ (CH}_3-16), 47.9 \text{ (C-5), 56.6 \text{ (CH-3), 76.9 \text{ (CH-2), 78.1 \text{ (CH-8), 79.3 \text{ (CH-10), 92.4 \text{ (CH-4), 113.9 \text{ (C-12), 125.8 \text{ (CH-phenyl), 129.0 \text{ (CH-phenyl), 129.1 \text{ (CH-phenyl), 133.3 \text{ (C-11), 151.6 \text{ (C-7), 174.0 \text{ (C-1), 175.5 \text{ (C-6) ppm.}}}}}
\]

IR (thin film) v 2990, 2929, 1780, 1457, 1341, 1191, 1069, 1014, 953, 733, 701 cm\textsuperscript{-1}.

HRMS (EI) calcd for C\textsubscript{21}H\textsubscript{25}NO\textsubscript{7} [M+Na]\textsuperscript{+}, 426.1529; found 426.1527 +/- 5 ppm.

Optical Rotation: [\alpha]\textsuperscript{20}\textsubscript{D} (c 0.5, CHCl\textsubscript{3}) = -3.8°.

**NOE-analysis:**

(4R,5S)-3-((S)-3-((4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (14). To a cooled solution (0 °C) of alcohol 13 (230 mg, 0.57 mmol, 1.0 eq) in methylene chloride (3.0 mL) was added DIPEA (0.49 mL, 2.85 mmol, 5.0 eq), followed by the slow dropwise addition of MOM-Cl (0.13 mL, 1.71 mmol, 3.0 eq). Next, the cooling bath was removed and the reaction mixture was stirred for twelve hours at room temperature and additional 2.5 hours at 50 °C until no more starting material could be detected by TLC. The reaction mixture was quenched with water and diluted with methylene chloride. The layers were separated and the aqueous phase was extracted three times.
with methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The resulting crude MOM-protected product was purified by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) providing intermediate 14 (237 mg, 93%) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.90$ (d, $J = 6.6$ Hz, 3H, CH$_3$-13), 1.38 (s, 3H, CH$_3$-14 or 15), 1.44 (s, 3H, CH$_3$-16 or 17), 1.48 (s, 3H, CH$_3$-16 or 17), 1.53 (s, 3H, CH$_3$-14 or 15), 3.36 (s, 3H, OCH$_3$-MOM), 4.32 (dd, $J = 3.7, 6.2$ Hz, 1H, H-4), 4.57 (dd, $J = 6.2, 7.5$ Hz, 1H, H-3), 4.62 (d, $J = 6.6$ Hz, 1H, CH$_2$-MOM), 4.68 (d, $J = 6.6$ Hz, 1H, CH$_2$-MOM), 4.77 (quint, $J = 6.7$ Hz, 1H, H-9), 4.78 (d, $J = 3.7$ Hz, 1H, H-5), 5.28-5.39 (m, 2H, CH$_2$-1), 5.63 (d, $J = 7.1$ Hz, 1H, H-10), 6.09 (ddd, $J = 7.5, 10.1, 17.4$ Hz, 1H, H-2), 7.27-7.32 (m, 2H, CH-phenyl), 7.34-7.44 (m, 3H, CH-phenyl) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.4$ (CH$_3$-13) 21.3 (CH$_3$-14 or 15), 21.9 (CH$_3$-14 or 15), 25.8 (CH$_3$-16 or 17), 27.5 (CH$_3$-16 or 17), 50.5 (C-6), 56.7 (OCH$_3$-MOM), 57.3 (CH-5), 76.6 (CH-9), 78.3 (CH-4), 79.3 (CH-10), 79.9 (CH-3), 98.5 (CH$_2$-MOM), 108.5 (C-12), 118.8 (CH$_2$-1), 125.9 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.7 (C-11), 134.9 (CH-2), 152.6 (C-8), 176.6 (C-7) ppm.

IR (thin film) $\nu$ 2985, 2937, 1776, 1690, 1456, 1369, 1339, 1247, 1191, 1121, 1068, 1032, 882, 769, 700 cm$^{-1}$.

HRMS (EI) calcd for C$_{24}$H$_{33}$NO$_7$ [M+Na]$^+$, 470.2155; found 470.2160 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = $-11.5^\circ$.

![24]

(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethylidihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (24).

D-Ribonolactone (10.0 g, 67.5 mmol) was dissolved in acetone (50 mL) and boron trifluoride etherate (0.855 mL, 6.75 mmol, 0.1 eq) was added to the solution at room temperature, followed by 2,2-dimethoxypropane (10.0 mL). The reaction mixture was stirred for one hour before the solvent was removed under reduced pressure to afford a light brown solid, which was dissolved in ethyl acetate. The resulting solution was extracted with water twice, with brine once, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure delivering crude lactone 24 (10.93 g, 86%) as light yellow crystals. The product was used without any further purification for the following step.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.38$ (s, 3H), 1.48 (s, 3H), 2.29 (t, $J = 5.4$ Hz, 1H, OH), 3.81 (ddd, $J = 1.8, 5.6, 12.1$ Hz, 1H), 4.0 (ddd, $J = 2.5, 5.6, 12.1$ Hz, 1H), 4.63 (bt, $J = 2.0$ Hz, 1H), 4.78 (d, $J = 5.8$ Hz, 1H), 4.83 (d, $J = 5.8$ Hz, 1H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 25.6 (CH$_3$), 26.9 (CH$_3$), 62.2 (CH$_2$), 75.8 (CH), 78.4 (CH), 82.7 (CH), 113.3 (C), 174.9 (C) ppm.

IR (thin film) $\nu$ 3469, 2991, 1767, 1379, 1273, 1222, 1200, 1154, 1093, 975, 856, 810, 774 cm$^{-1}$.

HRMS (EI) calcd for C$_8$H$_{12}$O$_5$ [M+Na]$^+$, 211.0583; found 211.0583 $\pm$ 0.5 ppm.

Optical Rotation: [\alpha]$_{20}^D$ (c 1.0, CHCl$_3$) = $-66.9^\circ$.

$^{(3aR,6R,6aR)}$-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethylidihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (25). Imidazole (2.17 g, 31.9 mmol, 1.2 eq) and TBS-Cl (4.08 g, 27.1 mmol, 1.02 eq) were added to a solution of lactone 24 (5.0 g, 26.6 mmol, 1.0 eq) in DMF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours before the reaction was quenched by the addition of water. After separating the two layers the aqueous phase was extracted with diethyl ether three times. The combined organic extracts were dried over magnesium sulfate, filtered and the organic solvents were removed under reduced pressure to afford the crude fully protected ribonolactone (25), which was further purified by flash chromatography (hexanes/ethyl acetate 5:1) to give 25 in 93% yield (7.5 g).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.39 (s, 3H), 1.47 (s, 3H), 3.80 (dd, $J$ = 1.5, 11.3 Hz, 1H), 3.90 (dd, $J$ = 1.5, 11.3 Hz, 1H), 4.58-4.61 (m, 1H), 4.70 (d, $J$ = 5.8 Hz, 1H), 4.73 (d, $J$ = 5.8 Hz, 1H), 4.73 (d, $J$ = 5.8 Hz, 1H) ppm.

These spectral characteristics are identical to those previously reported.$^{[3]}$

$^{(3aR,4S,6R,6aR)}$-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (26). A solution of methyllithium (0.68 mL, 1.6 M in Et$_2$O, 1.1 mmol, 1.1 eq) was added dropwise to a solution of lactone 25 (300 mg, 0.99 mmol, 1.0 eq) in dry THF (3.5 mL). The reaction mixture was stirred for 3.5 hours at $-78$ °C before it was quenched with water at $-78$ °C and warmed to room temperature. The product was extracted with ethyl acetate, the combined organic extracts were washed with brine and dried over sodium sulfate. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude lactole 26 (312 mg, 99%) was used for the following step without any further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.14 (s, 3H), 0.15 (s, 3H), 0.93 (s, 9H), 1.34 (s, 3H), 1.50 (s, 3H), 1.52 (d, 3H, $J$ = 1.0 Hz), 3.75 (dd, $J$ = 2.0, 11.1 Hz, 1H), 3.78 (dd, $J$ = 2.0, 11.1 Hz, 1H), 4.25 (dd,
J = 2.0, 3.5 Hz, 1H), 4.43 (d, J = 5.8 Hz, 1H), 4.80 (dd, J = 1.5, 5.8 Hz, 1H), 5.11 (bd, J = 1.0 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -5.6$ (CH$_3$), $-5.5$ (CH$_3$), 18.4 (C), 21.4 (CH$_3$), 25.3 (CH$_3$), 25.9 (CH$_3$), 26.8 (CH$_3$), 65.1 (CH$_2$), 82.2 (CH), 86.0 (CH), 88.2 (CH), 106.7 (C), 112.6 (C) ppm.

These spectral characteristics are identical to those reported.$^{[4]}$

Most conditions applied for the installation of the double bond resulted in $\alpha$-racemization. Depending on reaction conditions, mixtures containing diastereomeric alkenes 27 and 28 were obtained.

The following procedure allowed the isolation of pure diastereomer 27 in moderate yield.

(R)-2-((tert-Butyldimethylsilyl)oxy)-1-((4R,5S)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)ethanol (27). Methyltriphenylphosphonium bromide (789 mg, 2.2 mmol, 2.2 eq) was dissolved in toluene (6.5 mL) and cooled to 0 °C. t-BuOK (248 mg, 2.2 mmol, 2.2 eq) was added in one portion and the resulting yellow reaction mixture was stirred for 30 min at 0 °C and additional three hours at room temperature. The yellow suspension was cooled to $-78$ °C, lactole 26 (200 mg, 1.0 mmol, 1.0 eq) was added and the reaction mixture was allowed to come to room temperature over twelve hours. The reaction was terminated by the addition of saturated ammonium chloride solution, the layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 19:1) delivering alcohol 27 (58 mg) in 30% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.08$ (s, 3H, Si-CH$_3$), 0.081 (s, 3H, Si-CH$_3$), 0.90 (s, 9H, CH$_3$-tBu), 1.36 (s, 3H, CH$_3$-9), 1.47 (s, 3H, CH$_3$-8), 1.85 (s, 3H, CH$_3$-3), 2.47 (d, $J = 4.8$ Hz, 1H, OH), 3.56-3.64 (m, 1H, H-6), 3.67 (dd, $J = 6.3$, 9.9 Hz, 1H, H-7), 3.80 (dd, $J = 3.0$, 9.9 Hz, 1H, H-7), 4.07 (dd, $J = 6.3$, 8.8 Hz, 1H, H-5), 6.06 (d, $J = 6.3$ Hz, 1H, H-4), 5.0-5.04 (m, 1H, H-1a), 5.16-5.19 (m, 1H, H-1b) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -5.2$ (Si-CH$_3$), $-5.24$ (Si-CH$_3$), 18.5 (C-tBu), 20.8 (CH$_3$-3), 25.3 (CH$_3$-9), 26.1 (CH$_3$-tBu), 27.4 (CH$_3$-8), 64.6 (CH$_3$-7), 69.7 (CH-6), 77.9 (CH-5), 80.4 (CH-4), 108.2 (C-10), 112.5 (CH$_2$-1), 141.5 (C-2) ppm.

IR (thin film) $\nu$ 3565, 2929, 2857, 1463, 1380, 1253, 1165, 1115, 1078, 1057, 899, 833 cm$^{-1}$.

HRMS (EI) calcd for C$_{16}$H$_{32}$O$_4$Si $[M+Na]^+$, 339.1968; found 339.1970 +/- 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl$_3$) = +40.8°.
NOE-analysis:

Experimental data for diastereomer 28 (undesired):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.08$ (s, 3H, Si-CH$_3$), 0.081 (s, 3H, Si-CH$_3$), 0.90 (s, 9H, CH$_3$-tBu), 1.41 (s, 3H, CH$_3$-8), 1.43 (s, 3H, CH$_3$-9), 1.81 (s, 3H, CH$_3$-3), 3.63-3.71 (m, 1H, H-7), 3.71-3.80 (m, 2H, H-7, H-6), 3.83-3.89 (m, 1H, H-5), 4.48 (d, $J = 7.8$ Hz, 1H, H-4), 4.98-5.02 (m, 1H, H-1a), 5.13-5.16 (m, 1H, H-1b) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -5.29$ (Si-CH$_3$), -5.23 (Si-CH$_3$), 17.7 (CH$_3$-3), 18.4 (C-tBu), 26.0 (CH$_3$-tBu), 27.2 (CH$_3$-9), 27.3 (CH$_3$-8), 64.1 (CH$_2$-7), 73.0 (CH-5), 78.3 (CH-6), 82.9 (CH-4), 109.2 (C-10), 115.1 (CH$_2$-1), 142.6 (C-2) ppm.

IR (thin film) $\nu$ 3487, 2930, 2859, 1463, 1370, 1253, 1167, 1060, 902, 836, 778 cm$^{-1}$.

HRMS (EI) calcd for C$_{16}$H$_{32}$O$_4$Si [M+Na]$^+$, 339.1968; found 339.1967 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]^{20}_D$(c 0.5, CHCl$_3$) = $-3.4^\circ$.

NOE-analysis:

(4R,5R)-5-((R)-1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (29). Protected ribonolactone 24 (500 mg, 2.7 mmol, 1.0 eq) was dissolved in toluene (11 mL). After the addition of pyrrolidine (1.1 mL, 13.5 mmol, 5.0 eq) the reaction mixture was heated to reflux for twelve hours. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (methylene chloride/methanol 19/1) to give amide 29 (610 mg) in 87% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.37$ (s, 3H), 1.52 (s, 3H), 1.79-2.03 (m, 4H), 2.35 (bs, 1H, OH), 3.43-3.59 (m, 2H), 3.60-3.72 (m, 3H), 3.77-3.89 (m, 2H), 4.27 (dd, $J = 6.3, 8.8$ Hz, 1H), 4.59 (bs, 1H, OH), 4.84 (d, $J = 6.3$ Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 23.8$ (CH$_2$), 25.3 (CH$_3$), 26.5 (CH$_2$), 27.2 (CH$_3$), 47.02 (CH$_2$), 47.14 (CH$_2$), 64.5 (CH$_2$), 70.0 (CH), 76.7 (CH), 78.3 (CH), 109.9 (C), 167.8 (C) ppm.

IR (thin film) $\nu$ 3335, 2981, 2876, 1781, 1630, 1454, 1372, 1214, 1164, 1053, 907, 726 cm$^{-1}$. 
Appendix I  Experimental part

HRMS (EI) calcd for C_{12}H_{21}O_{5}NH [M+H]^+, 260.1498; found 260.1492 +/- 5ppm.

Optical Rotation: \([\alpha]^{20}_D(c 1.0, CHCl_3) = +16.2^\circ\).

\[
\text{((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (30). To a solution of diol 29 (250 mg, 0.96 mmol, 1.0 eq) in methylene chloride (2 mL) were sequentially added 2,6-lutidine (0.335 mL, 2.88 mmol, 3.0 eq) and TBS-triflate (0.706 mL, 3.07 mmol, 3.2 eq) at 0 \text{ °C. The cooling bath was removed after the addition and the reaction mixture was allowed to stir at room temperature for 15 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over solid sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) delivering 30 (375 mg) in 80% yield.}
\]

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{: } \delta &= 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.74-2.0 (m, 4H), 3.36-3.55 (m, 3H), 3.60-3.69 (m, 1H), 3.74-3.77 (m, 2H), 4.37-4.41 (m, 2H), 4.67-4.70 (m, 1H) ppm.} \\
\text{13C NMR (100 MHz, CDCl}_3\text{: } \delta &= -5.4 (CH_3), -5.2 (CH_3), -4.5 (CH_3), -3.7 (CH_3), 18.3 (C), 18.6 (C), 24.2 (CH_2), 26.0 (CH_3), 26.05 (CH_3), 26.1 (CH_3), 26.4 (CH_2), 27.0 (CH_3), 46.1 (CH_2), 46.6 (CH_2), 64.7 (CH_2), 72.4 (CH), 74.6 (CH), 77.6 (CH), 110.4 (C), 167.3 (C) ppm.} \\
\text{IR (thin film) v 2953, 2929, 2856, 1655, 1442, 1368, 1342, 1250, 1223, 1090, 992, 938, 831, 774, 675 cm}^{-1}. \\
\text{HRMS (EI) calcd for C}_{24}H_{49}NO_5Si_2 [M+Na]^+, 510.3047; found 510.3048 +/- 5ppm.} \\
\text{Optical Rotation: } [\alpha]^{20}_D(c 1.0, CHCl_3) = -46.7^\circ.
\end{align*}\]

\[
\text{1-((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)ethanone (S3). A solution of methyllithium (1.6 M, 12.8 mL, 20.4 mmol, 2.0 eq) was added to amide 30 (5 g, 10.2 mmol, 1.0 eq) in THF (50 mL) at −78 \text{ °C. The reaction mixture was stirred for 15 min when TLC-control showed total consumption of the starting material. The reaction was then terminated by the addition of water. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. Further purification of crude}
\]


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**Appendix I  Experimental part**

**S3** by flash chromatography (hexanes/ethyl acetate 40:1) delivered ketone **S3** (4.23 g) in 95% yield.

**1H NMR (400 MHz, CDCl₃):** δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.36 (s, 3H), 1.60 (s, 3H), 2.31 (s, 3H), 3.57 (dd, J = 5.1, 10.4 Hz, 1H), 3.74 (dd, J = 7.3, 10.4 Hz, 1H), 4.05 (ddd, J = 3.5, 5.1, 7.3 Hz, 1H), 4.38 (d, J = 7.8 Hz, 1H), 4.57 (dd, J = 3.4, 7.8 Hz, 1H) ppm.

**13C NMR (100 MHz, CDCl₃):** δ = −5.3 (CH₃), −4.8 (CH₃), −4.1 (CH₃), 18.4 (C), 18.6 (C), 24.7 (CH₃), 26.1 (CH₃), 26.15 (CH₃), 26.7 (CH₃), 29.2 (CH₃), 63.9 (CH₂), 72.6 (CH), 79.8 (CH), 80.6 (CH), 109.1 (C), 209.3 (C) ppm.

**IR (thin film)** ν 2930, 2887, 2858, 1717, 1473, 1361, 1253, 1214, 1150, 1082, 939, 832, 776, 669 cm⁻¹.

**HRMS (EI)** calcld for C₂₁H₄₄O₅Si₂ [M+Na]+, 455.2625; found 455.2620 +/- 5ppm.

**Optical Rotation:** [α]²⁰_D(c 1.0, CHCl₃) = −20.2°.

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(R)-5-((4S,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (31). Ketone **S3** (2.8 g, 6.5 mmol, 1.0 eq) was dissolved in freshly distilled THF (40 mL) and cooled to 0 °C. A solution of Tebbe-reagent (15.6 mL, 0.5 M in toluene, 7.8 mmol, 1.2 eq) was slowly added via syringe. The reaction mixture was stirred for one hour at 0 °C before it was quenched by the addition of a saturated sodium bicarbonate solution. After the separation of the two layers, the aqueous phase was extracted with ethyl acetate three times. The combined organic extracts were dried over solid sodium sulfate, filtered and the solvent was removed under reduced pressure. Crude alkene **31** was further purified by flash chromatography (hexanes/ethyl acetate 40:1) delivering 2.32 g (83%) of the desired intermediate as light yellow oil.

**1H NMR (400 MHz, CDCl₃):** δ = 0.04 (s, 6H), 0.041 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.78 (s, 3H), 3.64-3.75 (m, 3H), 4.28 (dd, J = 4.8, 7.1 Hz, 1H), 4.61 (d, J = 7.1 Hz, 1H), 4.95-4.98 (m, 1H), 5.07-5.10 (m, 1H) ppm.

**13C NMR (100 MHz, CDCl₃):** δ = −5.3 (CH₃), −4.3 (CH₃), −3.7 (CH₃), 18.50 (C), 18.59 (C), 20.4 (CH₃), 25.1 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 26.6 (CH₃), 65.4 (CH₂), 73.2 (CH), 79.4 (CH), 80.5 (CH), 107.9 (C), 113.9 (CH₂), 141.0 (C) ppm.

**IR (thin film)** ν 2954, 2857, 1492, 1463, 1368, 1252, 1211, 1143, 1087, 1040, 1002, 986, 965, 947, 830, 773, 665 cm⁻¹.

**HRMS (EI)** calcld for C₂₂H₄₆O₄Si₂ [M+Na]+, 453.2833; found 453.2834 +/- 5ppm.

**Optical Rotation:** [α]²⁰_D(c 1.0, CHCl₃) = +30.1°.
(R)-1-((4R,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)ethane-1,2-diol (S4). TBAF (1.59 mL, 1 M in THF, 1.59 mmol, 3.0 eq) was added to a solution of TBS-protected diol 31 (230 mg, 0.53 mmol, 1.0 eq) in THF (3 mL) at 0 °C. After the addition the cooling bath was removed and the reaction mixture was stirred for 3.5 hours at room temperature. The reaction was then quenched by the addition of saturated ammonium chloride solution. The two layers were separated and the aqueous layer was extracted with ethyl acetate three times. The organic extracts were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude diol was purified by flash chromatography (hexanes/ethyl acetate 5:1 to 1:1) providing S4 (107 mg) in quantitative yield.

1H NMR (400 MHz, CDCl₃): δ = 1.37 (s, 3H), 1.49 (s, 3H), 1.87 (s, 3H), 2.06 (dd, J = 5.3, 6.8 Hz, OH), 2.14 (d, J = 4.8 Hz, OH), 3.65-3.74 (m, 2H), 3.76-3.86 (m, 1H), 4.08-4.16 (m, 1H), 4.66 (d, J = 6.1 Hz, 1H), 5.06-5.09 (m, 1H), 5.24-5.27 (m, 1H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 20.9 (CH₃), 25.4 (CH₃), 27.5 (CH₃), 64.5 (CH₂), 69.9 (CH), 78.2 (CH), 80.0 (CH), 108.4 (C), 112.9 (CH₂), 141.7 (C) ppm.

IR (thin film) ν 3369, 2986, 2935, 1652, 1380, 1234, 1212, 1164, 1038, 900, 875, 799 cm⁻¹.

HRMS (EI) calcd for C₁₀H₁₈O₄ [M+Na]⁺, 225.1103; found 225.1100 ± 5 ppm.

Optical Rotation: [α]²⁰_D(c 1.0, CHCl₃) = +80.4°.

(4S,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane-4-carbaldehyde (32). To a solution of diol S4 (900 mg, 4.44 mmol, 1.0 eq) in methylene chloride (24 mL) was added a solution of sodium periodate (1.42 g, 6.66 mmol, 1.5 eq) in water (12 mL) at 0 °C. The reaction was stirred for two hours at 0 °C before it was diluted with methylene chloride and water. The layers were separated and the aqueous phase was extracted with methylene chloride three times. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed in vacuo.

The crude aldehyde was further purified by flash chromatography (pentanes/diethyl ether 5:1) giving 32 (683 mg) in 90% yield.

1H NMR (400 MHz, CDCl₃): δ = 1.44 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 4.37 (dd, J = 3.5, 7.6 Hz, 1H), 4.79 (d, J = 7.6 Hz, 1H), 4.98-5.01 (m, 1H), 5.19-5.22 (m, 1H), 9.44 (d, J = 3.5 Hz, 1H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 19.7 (CH₃), 25.3 (CH₃), 27.2 (CH₃), 80.9 (CH), 81.6 (CH), 111.3 (C), 113.7 (CH₂), 138.1 (C), 199.9 (CHO) ppm.
Appendix I

Experimental part

IR (thin film) ν 2989, 2939, 1732, 1655, 1450, 1381, 1255, 1215, 1159, 1078, 907, 858, 795, 744 cm⁻¹.


Optical Rotation: [α]²⁰ₒₒ = +55.0°.

(4R,5S)-3-(((S)-3-((4R,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (33). A solution of SmI₂ (100 mL, 0.1 M in THF, 10 mmol, 2.5 eq) was cannulated into a 250 mL round bottom Schlenk flask which was pre-cooled to −78 °C. A solution of bromide 7 (1.44 g, 4.41 mmol, 1.1 eq) and aldehyde 32 (683 mg, 4.01 mmol, 1.0 eq) in 60 mL degassed THF (3 pump freeze thaw cycles) was added to the SmI₂ solution via cannula. The reaction mixture was stirred for one hour at −78 °C before it was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium bicarbonate (50 mL) at −78 °C. The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure delivering alcohol 33 as light yellow oil which was further purified by flash chromatography (hexanes/ethyl acetate 9:1) providing 33 (1.14 g) in 68% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.91 (d, J = 6.6 Hz, 3H, CH₃-11), 1.36 (s, 3H, CH₃-12 or 13), 1.39 (s, 3H, CH₃-17), 1.43 (s, 3H, CH₃-12 or 13), 1.56 (s, 3H, CH₃-18), 1.87 (s, 3H, CH₃-16), 2.93 (d, J = 8.6 Hz, 1H, OH), 4.29 (d, J = 7.6 Hz, 1H, H-4), 4.42 (d, J = 8.6 Hz, 1H, H-5), 4.71 (d, J = 7.6 Hz, 1H, H-3), 4.79 (quint, J = 6.6 Hz, 1H, H-9), 5.08-5.12 (m, 1H, H-1a), 5.16-5.20 (m, 1H, H-1b), 5.64 (d, J = 7.1 Hz, 1H, H-10), 7.28-7.33 (m, 2H, phenyl), 7.33-7.46 (m, 3H, phenyl) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃-11), 19.9 (CH₃-12 or 13), 20.0 (CH₃-16), 22.4 (CH₃-12 or 13), 25.0 (CH₃-17), 26.4 (CH₃-18), 50.8 (C-6), 57.6 (CH-9), 70.5 (CH-5), 76.0 (CH-4), 79.3 (CH-10), 81.2 (CH-3), 108.8 (C-15), 112.9 (CH₂-1), 125.9 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.7 (C-14), 141.3 (C-2), 152.6 (C-8), 176.7 (C-7) ppm.

IR (thin film) n 3330, 2987, 2937, 1777, 1689, 1456, 1340, 1254, 1214, 1191, 1152, 1120, 972, 950, 905, 768, 700 cm⁻¹.

HRMS (EI) calcd for C₂₃H₃₁O₆N [M+Na]⁺, 440.2049; found 440.2039 +/- 5ppm.

Optical Rotation: [α]²⁰ₒₒ = +55.6°.
NOE-analysis:

\[
\begin{align*}
\text{NOE-} & -\text{analysis:} \\
\text{(4R,SS)-3-((S)-3-((4R,SS)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-3-}
\text{(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (34).}
\end{align*}
\]

Alcohol 33 (1.0 g, 2.4 mmol, 1.0 eq) was dissolved in methylene chloride (8 mL) and cooled to 0 °C. DIPEA (2.1 mL, 12.0 mmol, 5.0 eq) and MOM-Cl (0.54 mL, 7.2 mmol, 3.0 eq) were added sequentially. After the addition, the ice bath was removed, the reaction mixture was heated to 50 °C and the yellow solution was stirred for 48 hours. The reaction was quenched by the addition of water. After separating the two layers the aqueous phase was extracted with methylene chloride three times. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) 879 mg (79%) of the MOM protected alkene (34) could be isolated as colorless oil.

\[\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{: } & \delta = 0.91 \text{ (d, } J = 6.8 \text{ Hz, 3H), 1.40 \text{ (s, 3H), 1.46 \text{ (s, 3H), 1.48 \text{ (s, 3H), 1.58 \text{ (s, 3H), 1.86 \text{ (s, 3H), 3.26 \text{ (s, 3H), 4.46 (dd, } J = 1.5, 6.8 \text{ Hz, 1H), 4.48 (d, } J = 6.4 \text{ Hz, 1H), 4.57 (d, } J = 6.4 \text{ Hz, 1H), 4.62 (d, } J = 6.8 \text{ Hz, 1H), 4.68 (d, } J = 1.5 \text{ Hz, 1H), 4.77 (quint, } J = 6.8 \text{ Hz, 1H), 5.0-5.02 (m, 1H), 5.15-5.17 (m, 1H), 5.65 (d, } J = 7.2 \text{ Hz, 1H), 7.28-7.33 (m, 2H), 7.34-7.44 (m, 3H) ppm.}
\end{align*}\]

\[\begin{align*}
\text{C NMR (100 MHz, CDCl}_3\text{: } & \delta = 14.3 \text{ (CH}_3\text{), 20.4 \text{ (CH}_3\text{), 21.9 \text{ (CH}_3\text{), 22.2 \text{ (CH}_3\text{), 26.0 \text{ (CH}_3\text{), 26.3 \text{ (CH}_3\text{), 50.8 \text{ (C), 56.3 \text{ (OCH}_3\text{), 57.7 \text{ (CH), 77.5 \text{ (CH), 77.9 \text{ (CH), 79.4 \text{ (CH), 81.0 \text{ (CH), 99.3 \text{ (CH), 108.2 \text{ (C), 112.6 \text{ (CH}_2\text{), 125.8 \text{ (CH), 128.8 \text{ (CH), 128.82 \text{ (CH), 133.7 \text{ (C), 140.6 \text{ (C), 152.6 \text{ (C), 176.6 \text{ (C) ppm.}}}
\end{align*}\]

IR (thin film) ν 2985, 2939, 1776, 1693, 1455, 1367, 1340, 1247, 1192, 1158, 1121, 1083, 1033, 948, 904 cm\textsuperscript{-1}.

HRMS (EI) calcd for C\textsubscript{25}H\textsubscript{35}O\textsubscript{7}N [M+Na]\textsuperscript{+}, 484.2311; found 484.2309 +/- 5 ppm.

Optical Rotation: \([\alpha]^{20}_D\text{ (c 1.0, CHCl}_3\text{) } = -0.9^\circ.\]
References


Selected NMR-spectra

Solvent: CDCl$_3$

Instrument frequency: $^1$H: 400 MHz

$^{13}$C: 100 MHz
Appendix I  NMR-spectra
Appendix I  NMR-spectra
Appendix I

NMR-spectra
Synthesis of an Advanced Intermediate of the Jatrophane Diterpene Pl-4: A Dibromide Coupling Approach

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ABSTRACT: The preparation of an advanced intermediate toward the synthesis of the jatrophane diterpene Pl-4 is described. The key step is a regioselective chelation-controlled lithiation of the (Z)-configured bromide in the corresponding vinyl dibromide precursor. The method outlined within this Article is suitable for the facile access of sterically hindered internal vinyl halides for further coupling reactions.

INTRODUCTION

A general characteristic of members of the Euphorbiaceae plant family, commonly referred to as spurge, is the milky latex that has been identified as a rich source of structurally complex and intriguing terpene-based natural products. Over the past decades, phytochemists have shown great interest in the active ingredients of the Euphorbia species, and a vast number of diterpenes of the jatrophane, tigliane, ingenane, and lathyrane frameworks have been isolated.1

Some of these complex natural products show promising biological properties, including cytotoxic, antiviral, multidrug-resistance reversing (MDR), and antitumor activities,2–5 and recently, an ingenol ester has been approved for the topical treatment of precancerous skin conditions.6,7 Thus, it is not surprising that several Euphorbia species have been employed in traditional herbal folk medicines, mainly to treat cancerous conditions, swellings, and warts.8 In particular, the MDR-reversing properties, more precisely, the selective inhibition of the ATP-dependent efflux pump p-glycoprotein, are of great interest to modern cancer research. The overexpression of p-glycoprotein in the cancer cells of malignant tumors is a serious problem in chemotherapy. The elaboration of synthetic routes to jatrophane diterpenes is of importance for the development of novel anticancer drugs that could potentially address this problem.

In 2003, Pl-4 (1) was isolated by Hohmann et al. from Euphorbia platypyllos, an annual herbaceous plant that is found in different climate regions.9 Pl-4 belongs to the family of jatrophane diterpenes and is characterized by a highly functionalized five-membered ring that is annulated to a 12-membered macrocycle. Despite the challenging structural properties, only a few approaches to jatrophane diterpenes have been reported.10–24

RESULTS AND DISCUSSION

Herein, we present a concise route to a highly advanced intermediate of Pl-4 via a regioselective lithiation/alkylation sequence of geminal dibromide 3 as a key step, which is retrosynthetically outlined in Scheme 1. The synthetic approach is based on a report by Braun and co-workers who showed that selective alkylation of the more hindered bromide can be achieved through coordination of the intermediate organolithium species to a chelating functionality in the α-position to the vinyl dibromide.25 Furthermore, Braun demonstrated that the chiral information of the chelating MEM group in the lithium species is transferred to the reaction partner to deliver the corresponding secondary alcohol in a diastereoselective manner.

Surprisingly, this protocol has not yet been applied to total synthesis, especially because this reaction sequence provides access to sterically hindered vinyl halides that could serve as
reaction of PPh₃ and CBr₄ for the in situ generation of the ylide resulted in no reaction. Also, the addition of activated zinc dust or 2,6-lutidine did not lead to any detectable amounts of dibromide 14 with the preformed Wittig salt and t-BuOK as base allowed the isolation of dibromide 14 in low yield (Scheme 2). Presumably, the steric hindrance of the MEM transformation. Further elaboration of the alkyl chain and the

As outlined in Scheme 1, a ring-closing metathesis (RCM) reaction was envisaged to be the final operation to establish the jatrophane framework. The cyclopentane ring would be closed via an NHK-coupling reaction of key intermediate 2, which is available through the previously mentioned selective lithiation/alkylation sequence of dibromide 3 and aldehyde 4. The northern fragment (aldehyde 4) should become accessible via the coupling of Roche ester-derived bromide 6 and aldehyde 5. Dibromide 3 would be elaborated from aldehyde 8 and methyl isobutylate (7). t-Ribose could be employed as an ideal and inexpensive starting material from the chiral pool for the preparation of intermediate 8.

The first approach toward dibromide 3 started with methyl ketone 10, readily available from t-ribose in 60% yield, via a five-step procedure. The addition of vinylimagnesium bromide to methyl ketone 10 afforded terminal alkene 11 in excellent yield as the only detectable isomer after MEM protection of the newly formed tertiary alcohol. Deprotection of the vicinal silyl ethers and subsequent peridate cleavage delivered aldehyde 8, which served as a substrate for the aldol reaction with methyl isobutylate to give alcohol 12 in 78% yield as a 3:1 mixture of diastereomers. Protection of the hydroxy group and subsequent ozonolysis delivered aldehyde 13, the precursor for the installation of the dibromide, in good overall yield. With aldehyde 13 in hand, the installation of the dibromooolen was pursued as outlined in Table 1, the

Table 1. Reagents and Conditions for the Formation of Dibromide 14

<table>
<thead>
<tr>
<th>reagents</th>
<th>temperature</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh₃, CBr₄</td>
<td>0 °C to rt</td>
<td>CH₂Cl₂</td>
<td>0</td>
</tr>
<tr>
<td>PPh₃, CBr₄, 2,6-lutidine</td>
<td>0 to 50 °C</td>
<td>CH₂Cl₂</td>
<td>0</td>
</tr>
<tr>
<td>PPh₃, CBr₄, Zn</td>
<td>0 °C to rt</td>
<td>CH₂Cl₂</td>
<td>0</td>
</tr>
<tr>
<td>PPh₃, CHBr₃, t-BuOK, Zn</td>
<td>reflux</td>
<td>dioxane</td>
<td>0</td>
</tr>
<tr>
<td>PPh₃, CHBr₃, t-BuOK</td>
<td>0 °C to rt</td>
<td>THF</td>
<td>12</td>
</tr>
<tr>
<td>PPh₃, CHBr₃, t-BuOK</td>
<td>0 °C to rt</td>
<td>toluene</td>
<td>17</td>
</tr>
</tbody>
</table>

installation of the geminal dimethyl group were postponed until after the closure of the cyclopentane ring.

Conditions for the crucial, regioselective lithiation/alkylation of dibromide 16 were first elaborated using known aldehyde 17. In accordance with Braun’s publication, we found that the temperature is of crucial importance for the selective lithiation and the reaction mixture has to be kept between −105 and −110 °C to prevent the formation of the terminal alkyne, the product of the competing Corey–Fuchs reaction. We were pleased to learn that lithiation of dibromide 16 and subsequent addition of aldehyde 17 at −110 °C delivered the desired adduct 19. Although the product was obtained as a 1:1 diastereomeric mixture with respect to the newly formed hydroxy moiety, we showed that lithiation of the (Z)-configured bromide occurs preferentially, which can be explained via the formation of chelated intermediate 18. The selective attack and formation of the trans double bond in vinyl halide 19 was confirmed by termination of the lithiation reaction after 30 min at −108 °C with methanol. The resulting H NMR spectroscopic analysis showed unreacted starting material, the terminal alkyne, and the exclusive formation of the trans-vinyl bromide. The double-bond geometry could be easily identified by the assignment of the coupling constant, which

Scheme 2. Preparation of Dibromide 14

Scheme 3. Preparation of Dibromide 16

\[ \text{Conditions for the crucial, regioselective lithiation/alkylation of dibromide 16 were first elaborated using known aldehyde 17 (Scheme 4).} \]
amounts to 14 Hz. As a consequence, the electrophile was introduced at the more hindered position, and the diastereomeric mixture of alcohol 19 was isolated in 40% overall yield.

With these promising results in hand, the synthesis of the northern fragment of Pl-4 was launched. The sequence started with Roush crotylation of aldehyde 5, the coupling partner for aldehyde 5, was synthesized from a commercially available Roche ester (Scheme 4). The route features a regioselective lithiation of the more sterically hindered side of an unsymmetrical vinyl dibromide; thus, the diastereomers of unprotected bromide 5 were easily separated by silica gel chromatography, and the respective stereochemistries were determined by the modified Mosher ester analysis. Advanced intermediate 25 was obtained as a 1:1 mixture of diastereomers, which is in contrast to Braun’s findings, who reported excellent diastereoselectivity with two structurally complex chiral substrates. We were hoping to observe similar preferences and, in accordance with Braun’s results, the predominant formation of the desired diastereomer. However, with two structurally complex chiral substrates, the reaction of a mismatched pair is possible. Inversion of the undesired stereoisomer is envisaged to increase the overall efficiency of the route.

**EXPERIMENTAL SECTION**

**General Methods.** All nonaqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum), unless noted otherwise.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon.

**CONCLUSIONS**

We have established a concise route to a highly advanced intermediate toward the synthesis of Pl-4. Strategies toward the closure of the cyclopentane moiety of the diterpene have to be elaborated, which will take place at a later point because we are currently experiencing extenuating circumstances and the project is on hold until the relocation of the group.

The route features a regioselective lithiation of the more hindered side of an unsymmetrical vinyl dibromide; thus, generating a species that can be used in a further coupling reaction to establish the cyclopentane motif in the jatrophone diterpene. This method constitutes a valuable alternative to the preparation of internal vinyl halides via hydrometalation chemistry. This method constitutes a valuable alternative to the preparation of internal vinyl halides via hydrometalation reactions and allows the selective, stepwise introduction of functionalities and the preparation of highly substituted alkenes.

——

*Reagents and conditions: (a) n-BuLi, Et₂O, −116 to −108 °C; then 17, 40%, dr 1:1.*

*Reagents and conditions: (a) PMB-trichloroacetimidate, CSA, rt; (b) DBAL-H, THF, −78 °C; (c) CBr₄, PPh₃, 70% (over three steps); (d) 22, toluene, −78 °C, 71% (70% ee); (e) MOMCl, DIPEA, DCM, 0 °C to rt, 95%; (f) TBAF, THF, 0 °C to rt, 80%; (g) NMO, TPAP, DCM, 78%; (h) 6, t-BuLi, Et₂O, −78 °C; MgBr₂·5 H₂O, 96%, dr 9:1; and (k) SO₃/py, NEt₃, DMSO, DCM, 0 °C, 93%.

*Reagents and conditions: (a) a, 16, n-BuLi, −112 to −108 °C, Et₂O; then 4, 74%, dr 1:1 and (b) BzCl, DMAP, NEt₃, DCM, 71%.*

**Scheme 4. Coupling Reaction with Dibromide 16**

**Scheme 5. Preparation of Northern Fragment 4**

**Scheme 6. Coupling of Dibromide 16 and Completion of Advanced Fragment 26**
DMSO and N,N-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide (neutral activity). Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to storage under an argon atmosphere over molecular sieves (4 Å). Unless the compound was colored, the solvent was removed under reduced pressure. After purification, the crude product was dissolved in DCM (5 mL) and cooled to 0 °C before it was added to DCM (22 mL) and cooled to 0 °C, and a solution of NaOAc (1.44 g, 6.75 mmol, 1.5 equiv) in water (15 mL) was added. The solution was warmed to room temperature and stirred for 2 h at 25 °C. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/DCM 1:1) on silica gel 60-230 mesh.
Methyl-3-(4R,5R)-5-(1-oxo-2,2-dimethylpropanoate (S3). For proof of the stereochemistry of alcohol 12. Alkene S2 (the major diastereomer from above), 78 mg, 0.18 mmol, 1.0 equiv) was dissolved in DCM (7.0 mL) and cooled to −78 °C before a stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of dimethylsulfide (15 μL, 0.23 mmol, 1.3 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the crude product was purified by filtration over a short plug of silica gel (hexanes/EtOAc 5:1), affording a diastereomeric, inseparable mixture of the corresponding lactols (24 mg) in 34% yield. The diastereomeric mixture of lactols was dissolved in DCM (1 mL) and cooled to 0 °C. NaHCO3 (11 mg, 0.134 mmol, 2.2 equiv) and Dess–Martin periodinane (52 mg, 0.122 mmol, 2.0 equiv) were added sequentially. The reaction was quenched by the addition of a saturated aqueous solution of Na2S2O3 (5 mL). The organic extracts were dried over Na2SO4 and filtered, and the solvent was removed under reduced pressure. The crude lactone was further purified by flash column chromatography (hexanes/EtOAc 3:2 to 1:1) to afford S3 (16 mg) in 67% yield as a colorless oil. [α]D 22° +3.0 (c 0.8, CHCl3). 1H NMR (400 MHz, CDCl3): δ 1.19 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.32 (s, 3H), 1.43 (s, 3H), 3.37 (s, 3H), 3.50–3.59 (m, 3H), 3.62 (s, 3H), 3.76–3.83 (m, 1H), 4.03 (d, J = 5.8 Hz, 1H), 4.10 (d, J = 8.9, 5.8 Hz, 1H), 4.64 (d, J = 8.9 Hz, 2H), 4.62 (d, J = 7.8 Hz, 1H), 4.76 (d, J = 6.0 Hz, 2H), 4.80 (d, J = 6.0 Hz, 1H), 4.88 (d, J = 6.0 Hz, 1H), 5.24–5.35 (m, 2H), 10.68 (s, 1H). HRMS (ESI) calcd for C13H16O9Na [M + Na]+, 437.2316; found, 437.2316.

S-Methyl-3-(4R,5R)-5-(2-(2-methoxyethoxy)ethoxymethyl)-1-o xo-o- propan-2-yl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethyl)-2,2-dimethy lpropanoate (13). Alkene S2 (200 mg, 0.46 mmol, 1.0 equiv) was dissolved in DCM (12 mL) and cooled to −78 °C. A stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of PPh3 (181 mg, 0.69 mmol, 1.5 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the cold crude product was further purified by flash column chromatography (hexanes/EtOAc 3:1 to 1:1) to afford S3 (23 mg, 0.05 mmol, 11% yield) in 86% yield as a colorless oil. [α]D 22° −81.5° (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 1.124 (s, 3H), 1.23 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 3.37 (s, 3H), 3.37, 3.51–3.56 (m, 2H), 3.58–3.64 (m, 1H), 3.67 (s, 3H), 3.79–3.85 (m, 1H), 4.00 (d, J = 5.8 Hz, 1H), 4.10 (d, J = 6.8, 5.8 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 7.3 Hz, 1H), 4.72 (d, J = 6.1 Hz, 1H), 4.87 (d, J = 6.6 Hz, 1H), 4.89 (d, J = 7.3 Hz, 1H), 5.24–5.34 (m, 2H), 1.67 (d, J = 17.6 Hz, 1H). HRMS (ESI) calcd for C24H24O14Na [M + Na]+, 547.2416; found, 547.2416. Minor diastereomer: [α]D 22° +3.74 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 1.174 (s, 3H), 2.15 (CH), 24.72 (CH3), 25.13 (CH3), 26.7 (CH), 46.9 (C), 51.3 (CH3), 56.3 (CH3), 59.1 (CH3), 67.1 (CH3), 71.9 (CH), 77.9 (CH), 79.3 (CH), 80.4 (C), 82.3 (CH), 90.4 (CH3), 99.0 (CH), 107.2 (C), 118.7 (C), 138.7 (CH), 176.7 (C). IR (ATR) ν 2986, 2878, 2855, 2366, 1746, 1724, 1472, 1415, 1368, 1295, 1217, 1193, 1101, 1036, 945, 873, 833 cm⁻¹. HRMS (ESI) calcd for C24H24O14Na [M + Na]+, 547.2416; found, 547.2414.

Methyl-2-(3ar45,75,76)-7-(2-(methoxymethyl)-2,2 trimethyl-6-oxetetrahydro-3A+1-[3dioxalo(4,5-c)pyran-4-y1]-2 methyl-propanoate. For the preparation of the Wittig salt (dimethylbromophosphinylphosphine) (S4), tetrabromomethane (16.4 g, 49.4 mmol, 1.0 equiv) was added to a solution of trimethylphosphine (26 g, 99.1 mmol, 2.0 equiv) in 240 mL of methylene chloride at 0 °C. The resulting red reaction mixture was stirred for 30 min. Water (8 mL) was added, and the resulting yellow mixture was stirred vigorously for 15 min at 0 °C. The two
To a suspension of Wittig-salt S4 (180 mg, 0.35 mmol, 5.0 equiv) in THF (2.5 mL) was added f-BuOK (39 mg, 0.35 mmol, 5.0 equiv) in one portion at 0°C. The resulting brown suspension was stirred for 30 min before a solution of aldehyde 13 (30 mg, 0.07 mmol, 1.0 equiv) in THF (0.5 mL) was added. The resulting reaction mixture was then stirred for 1 h at room temperature. The reaction was terminated by the addition of brine (5 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na2SO4 and filtered, and the solvent was removed under vacuum. Further purification by flash column chromatography (hexanes/EtOA 19:1) afforded dibromide S6 (183 mg, 87%) as a light-yellow oil. [α]20 −170 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.84 (s, 6H), 0.04 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.52–1.59 (m, 2H), 1.73–1.80 (m, 2H), 2.30 (s, 3H), 2.45–2.47 (m, 2H), 4.26 (d, J = 6.0, 8.9 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ −5.2 (CH3), −5.1 (CH3), −4.3 (CH3), −3.8 (CH3), 18.5 (CH3), 16.8 (CH3), 21.5 (CH), 26.1 (CH2), 26.2 (CH), 26.6 (CH3). IR (ATR): ν 3415, 2930, 2886, 1598, 1471, 1383, 1256, 1213, 1142, 1062, 980, 935, 885, 812, 780 cm−1. HRMS (ESI) calcd for C9H18Br2O2SiNa [M + Na]+: 561.1128; found, 561.1133.

(R)-5-[(4R,5S)-5-[(R)-4,4-Dibromo-2-((4R,5S)-2,2-dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-diaza[1,6-c][1,2,4]diazol-5-yl)-1,3-dioxolan-4-yl)-2-methylbutan-1-ol ([α]20 +19.1 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.08 (s, 6H), 0.90 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.52–1.59 (m, 2H), 1.73–1.80 (m, 2H), 2.30 (s, 3H), 2.45–2.47 (m, 2H), 4.26 (d, J = 6.0, 8.9 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ −5.2 (CH3), −5.1 (CH3), −4.3 (CH3), −3.8 (CH3), 18.5 (CH3), 16.8 (CH3), 21.5 (CH), 26.1 (CH2), 26.2 (CH), 26.6 (CH3). IR (ATR): ν 3415, 2930, 2886, 1598, 1471, 1383, 1256, 1213, 1142, 1062, 980, 935, 885, 812, 780 cm−1. HRMS (ESI) calcd for C9H18Br2O2SiNa [M + Na]+: 561.1128; found, 561.1133.
μM in hexanes, 48 mL, 1.03 mg, 0.96 equiv) at −108 °C (Liquid nitrogen/ethanol cooling bath) dropwise over 3 min. The reaction mixture was stirred for 1 h with the temperature kept between −116 and −108 °C. A solution of aldehyde 17 (46 mg, 0.214 mmol, 2.0 equiv) in Et2O (0.5 mL) was added over 5 min, and the colorless solution was stirred for 2 h in the same temperature range. The reaction was terminated by the addition of a saturated NH4Cl solution (2 mL) at −108 °C. After warming to room temperature (10 °C), 1H NMR (400 MHz, CDCl3): δ 1.67 (m, 3H), 1.80 (dd, J = 6.8, 1.5 Hz, 3H), 2.25 (s, 3H), 2.57 (s, 3H), 2.73–2.86 (m, 2H), 3.10–3.16 (m, 2H), 3.81–3.90 (m, 2H), 4.42 (d, J = 9.3, 3H, CH-9), 4.73 (d, J = 7.3 Hz, 1H, CH-8), 5.03 (d, J = 7.2 Hz, 1H, CH-7), 5.32 (s, 6H), 1.62–1.67 (m, 3H), 1.80–1.86 (m, 2H), 4.76 (s, 2H), 5.07–5.17 (m, 2H), 5.45–5.51 (m, 2H). These spectral characteristics are identical to those previously reported.35

A suspension of S8 and (R,R)-disopropyraltantrate (5.37 g, 63.5 mmol, 1.0 equiv) in EtO (150 mL) was treated with brine (150 mL) and treated with diethanolamine (11.2 mL, 0.8 mmol, 0.08 equiv). The solution was stirred under reduced pressure, and the resulting white solid was recrystallized from a mixture of EtO and DCM (the solid was suspended and heated to reflux in EtO (20 mL) and DCM was added dropwise until the solid was dissolved), afforded S8 (4.0 g) in 75% yield. mp 121–122 °C. 1H NMR (400 MHz, CDCl3): δ 1.37 (d, J = 7.8 Hz, 2H), 1.63 (dd, J = 6.3, 1.5 Hz, 2H), 2.73–2.86 (m, 2H), 3.10–3.16 (m, 2H), 3.81–3.90 (m, 2H), 4.42 (d, J = 9.3 Hz, 3H), 4.73 (d, J = 7.3 Hz, 1H), 5.03 (d, J = 7.2 Hz, 1H), 5.32 (s, 6H), 1.62–1.67 (m, 3H), 1.80–1.86 (m, 2H), 4.76 (s, 2H), 5.07–5.17 (m, 2H), 5.45–5.51 (m, 2H). These spectral characteristics are identical to those previously reported.35

A solution of crude (R)-crotylboronate (22, 9.41 g, 31.6 mmol, 1.2 equiv) in toluene (165 mL) was cooled to −78 °C and aldehyde 21 (4.83 mg, 26.3 mmol, 1.0 equiv) dissolved in toluene (20 mL) was added dropwise over 5 min. The reaction mixture was stirred for 4 h at −78 °C. After quenching by the addition of an aqueous NaOH solution (30 mL, 2 M) at −78 °C, the reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for 20 min before it was filtered over a pad of Celite. The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic fractions were dried over K2CO3 and filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/EtOAc 40:1 to 19:1) to give secondary alcohol 23 (4.28 g in 71% yield as a colorless oil. The enantiomeric excess (70% ee) of the product was determined by Mosher ester analysis. [α]D 20 = −1.4 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 2.25–2.36 (m, 1H), 3.37 (d, J = 3.0 Hz, 1H), 3.48–3.54 (m, 2H), 3.61–3.69 (m, 1H), 5.03–5.07 (m, 1H), 5.07–5.10 (m, 1H), 5.81–5.92 (m, 1H). 13C NMR (100 MHz, CDCl3): δ −5.24 (CH3), −5.18 (CH3), 1.63 (CH3), 18.4 (C), 26.0 (CH3), 40.6 (CH3), 65.4 (CH3), 75.0 (CH3), 115.2 (CH2), 140.5 (CH). IR (ATR) v 3630, 3076, 2882, 2360, 2342, 1471, 1389, 1254, 1103, 1005, 913, 836 cm−1. HRMS (ESI) calced for C17H22O4SiNa [M + Na]+, 371.1502; found, 371.1506.

(S)-5-(3-But-3-enyl)-8,8,9,9-tetramethyl-2,4,7-tri-oxa-8-siladecane (59). A solution of secondary alcohol 23 (2.46 g, 10.7 mmol, 1.0 equiv) in DCM (100 mL) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 25 min until it was recooled to −78 °C. Triisopropylborane (34 mL, 146 mmol, 1.0 equiv) was added slowly over 15 min, and the internal temperature did not rise above −65 °C. After complete addition, the resulting mixture was stirred for 10 min at −78 °C. The reaction was quenched by pouring the mixture into a separatory funnel containing HCl (300 mL, 1 M). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried over Na2SO4, filtered, and treated with diethanolamine (11.2 mL, 116.8 mmol, 0.8 equiv). The solution was stirred under reduced pressure, and the resulting white solid was recrystallized from a mixture of EtO and DCM (the solid was suspended and heated to reflux in EtO (20 mL) and DCM was added dropwise until the solid was dissolved), afforded S8 (14.0 g) in 57% yield. A white crystalline solid mp 121–122 °C (Found: 81BrO9Si3Na [M + Na]+, 867.4093; found, 867.4099.

HRMS (ESI) calced for C38H79BrO9Si3Na [M + Na]+, 867.4093; found, 867.4087.
The layers were separated, and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic extracts were dried over Na2SO4 and filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexanes/ EtOAc 9:1) affording S6 (2.79 g) in 95% yield as a colorless oil. [α]D20 +49.2° (c 1.0, CHCl3).

1H NMR (400 MHz, CDCl3): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.07 (d, J = 7.0 Hz, 3H), 2.45–2.55 (m, 1H), 3.39 (s, 3H), 3.48–3.54 (m, 1H), 3.58–3.64 (m, 2H), 4.65 (d, J = 6.7 Hz, 1H), 4.79 (d, J = 6.7 Hz, 1H), 5.01–5.03 (m, 1H), 5.04–5.08 (m, 1H), 5.77–5.89 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 29.2 (CH3), 54.0 (CH2), 75.3 (CH2), 110.5 (CH), 140.3 (CH). IR (ATR) ν 2925, 2855, 2360, 2341, 1513, 1462, 1372, 1249, 1148, 1095, 1036, 836 cm⁻¹. HRMS (ESI) calcd for C19H34O2SiNa [M + Na]+, 297.1862; found, 297.1851.

(25S)-3-Methylpropyl-4-en-1-ol (S10). To a solution of alkene S9 (4.62 g, 16.5 mmol, 1.0 equiv) in THF (85 mL) was added a solution of TBAF (1.0 M in THF, 25.2 mL, 25.2 mmol, 1.5 equiv) at 0°C. After the addition, the cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. TLC showed the total consumption of the starting material, and the reaction was quenched by the addition of saturated aqueous NH4Cl solution (30 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried over Na2SO4 and filtered, and the solvents were removed in vacuo. The crude material was purified by flash column chromatography (hexanes/EtOAc 9:1) delivering S10 (2.15 g, 80%) as a colorless oil. [α]D20 +46.8° (c 1.0, CHCl3).

1H NMR (400 MHz, CDCl3): δ 1.05 (s, 3H), 2.38–2.49 (m, 1H), 2.95 (dd, J = 8.7, 4.0 Hz, 1H), 3.43 (s, 3H), 3.43–3.47 (m, 1H), 3.52–3.64 (m, 2H), 4.67 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 5.0–5.03 (m, 1H), 5.03–5.08 (m, 1H), 5.81 (dd, J = 17.3, 10.7, 5.5 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ 16.3 (CH3), 40.4 (CH), 55.9 (CH2), 72.1 (CH2), 73.1 (CH2), 76.7 (CH2), 80.4 (CH), 84.6 (CH), 84.9 (CH). IR (ATR) ν 3424, 2360, 2340, 1514, 1462, 1417, 1251, 1213, 1149, 1102, 1036, 915 cm⁻¹. HRMS (ESI) calcd for C19H32O2Na [M + Na]+, 264.2097; found, 264.2092.

(25S,35S)-3-Methylpropyl-4-en-4-ol (S11). To a solution of alcohol S10 (2.0 g, 12.5 mmol, 1.0 equiv) in DCM (125 mL) were added N-methylmorpholine-N-oxide (2.2 g, 18.8 mmol, 1.5 equiv) and 4 A molecular sieves (8 g) at room temperature. After the addition of tetrapropylammonium peroxinitrate (220 mg, 0.63 mmol, 0.05 equiv), the reaction mixture was stirred for 2 h at room temperature. The suspension was filtered through a plug of silica (silica packed with DCM), and the product was eluted with a mixture of pentane and Et2O (9:1). The solvents were removed under reduced pressure. Because of the volatility of the product, the pressure was maintained by a dry-ice/acetone bath, and after cooling, S11 (2.18 g) was isolated in 78% yield as a colorless oil. [α]D20 +21.6° (c 1.0, CHCl3).

1H NMR (400 MHz, CDCl3): δ 1.05 (s, 3H), 2.38–2.49 (m, 1H), 2.95 (dd, J = 8.7, 4.0 Hz, 1H), 3.43 (s, 3H), 3.43–3.47 (m, 1H), 3.52–3.64 (m, 2H), 4.67 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 5.0–5.03 (m, 1H), 5.03–5.08 (m, 1H), 5.81 (dd, J = 17.3, 10.7, 5.5 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ 16.3 (CH3), 40.4 (CH), 55.9 (CH2), 72.1 (CH2), 73.1 (CH2), 76.7 (CH2), 80.4 (CH), 84.6 (CH), 84.9 (CH). IR (ATR) ν 3424, 2360, 2340, 1514, 1462, 1417, 1251, 1213, 1149, 1102, 1036, 915 cm⁻¹. HRMS (ESI) calcd for C19H32O2Na [M + Na]+, 264.2097; found, 264.2092.
crude product was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford primary alcohol S12 (481 mg) in 90% yield as a colorless oil. [α]D 25 = −27.9 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.63 (quad, J = 7.9 Hz, 6H), 0.94 (d, J = 6.7 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 1.10 (d, J = 7.0 Hz, 1H), 1.35 (dd, J = 13.8, 9.0, 2.7 Hz, 1H), 1.50–1.62 (m, 2H), 1.74–1.85 (m, 1H), 2.46–2.58 (m, 1H), 3.31 (bt, J = 5.1 Hz, 1H), 3.38 (s, 3H), 3.46 (bt, J = 5.9 Hz, 2H), 3.91 (dd, J = 9.0, 5.1, 2.7 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.95–5.06 (m, 2H), 5.88 (ddd, J = 17.3, 10.3, 8.3 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ 5.4 (CH3), 7.1 (CH1), 16.9 (CH9), 19.0 (CH10), 32.6 (CH3), 36.3 (CH2), 38.9 (CH6), 69.2 (CH7), 72.5 (CH8), 84.9 (CH11), 114.4 (CH14), 141.8 (CH15), 1377, 1301, 1245, 1147, 1008, 934, 725 cm−1. HRMS (ESI) calcd for C18H38O4SiNa [M + Na]+, 369.2437; found, 369.2430.

To a solution of the mixture of lactols (30 mg, 0.085 mmol, 1.0 equiv) in dry Et2O (0.25 mL) was added over a period of 4 h at 0 °C. The absorbed product was puriﬁed by flash column chromatography (hexanes/EtOAc 3:1), and diol S13 (27 mg) was obtained in 90% yield as a light-yellow oil. [α]D 25 = −25.6 (c 0.75, CHCl3). 1H NMR (400 MHz, CDCl3): δ 1.0 (d, J = 6.6 Hz, 3H, CH−15), 1.26 (d, J = 7.1 Hz, 3H, CH−14), 1.47 (ddd, J = 14.1, 8.5, 4.0 Hz, 1H, CH−15b), 1.92–2.15 (m, 2H, CH−3a, CH−3b), 2.71 (dt, q, J = 7.1, 5.3 Hz, 1H, CH−2), 3.32 (ddd, J = 9.2, 6.2 Hz, 1H, CH−7a), 3.36 (dd, J = 9.2, 6.2 Hz, 1H, CH−7b), 3.41 (ddd, J = 5.3, 3.3 Hz, 1H, CH−3a), 4.43–4.48 (m, 1H, CH−4), 4.63 (s, 2H, CH−1b, 15a), 6.84–6.89 (m, 2H, CH−2, CH−11a), 7.21–7.26 (m, 2H, CH−10, 10a). 13C NMR (100 MHz, CDCl3): δ 9.3 (CH−14), 17.2 (CH−15), 30.5 (CH−6), 33.7 (CH−3b, 4a) (CH−2), 55.7 (OCH3−16), 56.8 (OCH3−17), 72.9 (CH−8), 78.8 (CH−7b), 80.7 (CH−3b), 97.7 (CH−16), 114.1 (CH−11, 11a), 129.5 (CH−10, 10a), 131.1 (C−9), 159.2 (C−12), 178.2 (C−1). IR (ATR) ν 2973, 2853, 2365, 2339, 1773, 1513, 1462, 1376, 1302, 1247, 1171, 1145, 1125, 1089, 997, 964, 882, 820 cm−1. HRMS (ESI) calcd for C8H19O4SiNa [M + Na]+, 375.1784; found, 375.1784.

Bromide (25). Di bromide 16 (80 mg, 0.114 mmol, 2.0 equiv) was dissolved in dry Et2O (0.57 mL) and cooled to −115 °C (liquid nitrogen/ethanol cooling bath), and a solution of n-BuLi (2.0 M in hexanes, 60 μL, 0.114 mmol, 2.0 equiv) was added dropwise over 3 min. The reaction mixture was stirred for 1 h 15 min with the temperature kept between −112 and −108 °C. Aldehyde 4 (20 mg, 0.057 mmol, 1.0 equiv) in Et2O (0.25 mL) was added over a period of 20 min via syringe pump, and the colorless solution was stirred for 1 h between −112 and −108 °C and for 90 min between −100 and −105 °C. The reaction was terminated by the addition of saturated, aqueous sodium bicarbonate and −100 °C was cooled to room temperature, the layers were separated, and the organic phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na2SO4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by preparative flash column chromatography (hexanes/EtOAc 19:1 to 9:1), and diastereomers 25 (20 mg, 0.028 mmol, 2.0 equiv) were obtained in 77.4% overall yield as colorless oils. Diastereomer 25a: [α]D 25 = −21.1 (c 0.9, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.06 (s, 3H, CH3−TES), 0.08 (s, 3H, CH3−TBS), 0.11 (s, 6H, CH3−TES), 0.58–0.66 (m, 6H, CH3−TES), 0.90 (s, 9H, CH2−Bu−TBS), 0.91 (s, 9H, CH2−Bu−TBS), 0.97 (s, J = 8.0 Hz, 9H, CH3−TES), 1.02 (−1.09 mg, 1H, CH−9), 1.07 (d, J = 6.6 Hz, 3H, CH−17), 1.10 (d, J = 6.6 Hz, 3H, CH−16), 1.32 (s, 3H, CH3−21 or 22), 1.46 (s, 3H, CH3−21 or 22), 1.47–1.54 (m, 1H, CH−1a), 1.55 (s, 3H, CH−19), 1.92–2.0 (m, 2H, CH−7), 2.45–2.52 (m, 1H, CH−3), 3.11 (dd, J = 5.3, 5.1 Hz, CH−4), 3.36 (s, 3H, OCH3−MEM), 3.38 (s, 3H, OCH3−MEM), 3.48–3.55 (m, 3H, CH3−MEM, OH−18), 3.62–3.68 (m, 2H, CH2−MEM, CH−15b), 3.83 (ddd, J = 10.5, 1.5 Hz, CH−15a), 3.88–3.92 (m, 2H, CH2−MEM, CH−5), 4.09 (d, J = 10.5 Hz, 1H, CH−15a), 4.12 (s, 1H, CH−22), 4.22 (m, 2H, CH−14), 4.24 (d, J = 7.2, 6.6 Hz, 1H, CH−13), 4.41 (dd, J = 9.2, 3.0 Hz, 1H, CH−16), 6.85 (d, J = 6.8 Hz, 1H, CH−15MOM), 6.90 (s, J = 6.8 Hz, 1H, CH−15MOM), 7.26 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.29 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.32 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.72 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.26 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.72 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.32 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.72 (d, J = 6.8 Hz, 1H, CH−15MOM), 7.26 (d, J = 6.8 Hz, 1H, CH−15MOM).
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CH3-21 or 22), 1.54 (s, 3H, CH3-19), 1.85−1.93 (m 1H, CH2-6a),
2.03−2.10 (m 1H, CH-7), 2.47−2.55 (m, 1H, CH-3), 2.79−2.91 (bs,
1H, OH-18), 3.32 (dd, J = 5.5, 5.3 Hz, 1H, CH-4), 3.37 (s, 3H, OCH3MEM), 3.38 (s, 3H, OCH3-MOM), 3.52−3.54 (m, 2H, CH2-MEM),
3.62 (dd, J = 10.9, 7.2 Hz, 1H, CH2-15b), 3.69−3.74 (m, 1H, CH2MEM), 3.77−3.82 (m, 2H, CH2-MEM, CH2-15a), 3.88−3.92 (m, 1H,
CH-5), 4.03−4.07 (m, 1H, CH-14), 4.17 (d, J = 7.0 Hz, 1H, CH-12),
4.20 (dd, J = 7.0, 2.0 Hz, 1H, CH-13), 4.41 (dd, J = 9.4, 6.6 Hz, 1H,
CH-8), 4.62 (d, J = 7.0 Hz, 1H, CH2-MOM), 4.71 (d, J = 7.0 Hz, 1H,
CH2-MOM), 4.87 (d, J = 7.2 Hz, 1H, CH2-MEM), 4.94 (d, J = 7.2 Hz,
1H, CH2-MEM), 4.96−5.0 (m, 2H, CH2-1a, b), 5.83−5.91 (m, 1H,
CH-2), 6.18 (s, 1H, CH-10). 13C NMR (100 MHz, CDCl3): δ −5.3
(CH3-TBS), −5.1 (CH3-TBS), −4.3 (CH3-TBS), −3.8 (CH3-TBS),
5.32 (CH2-TES), 7.2 (CH3-TES), 16.7 (CH3-17), 18.4 (C-tBu-TBS),
18.5 (C-tBu-TBS), 18.9 (CH3-16), 23.2 (CH3-19), 25.0 (CH3-21 or
22), 26.2 (CH3-tBu-TBS), 26.25 (CH3-tBu-TBS), 26.3 (CH3-21 or
22), 35.2 (CH-7), 35.4 (CH2-6), 39.0 (CH-3), 56.0 (OCH3-MOM),
59.2 (OCH3-MEM), 66.7 (CH2-15), 68.0 (CH2-MEM), 71.9 (CH2MEM), 72.5 (CH-5), 74.3 (CH-14), 74.6 (CH-8), 79.9 (C-11), 81.3
(CH-13), 82.3 (CH-12), 85.1 (CH-4), 91.6 (CH2-MEM), 98.2 (CH2MOM), 107.7 (C-20), 114.4 (CH2-1), 135.9 (CH-10), 136.7 (C-9),
141.7 (CH-2). IR (ATR) ν 3462, 2954, 2929, 2856, 1461, 1380, 1252,
1211, 1101, 1067, 1036, 1005, 911, 834, 776 cm−1. HRMS (ESI) calcd
for C45H9181BrO11Si3Na [M + Na]+, 995.4930; found, 995.4936.
Mosher Ester S14. To a solution of secondary alcohol 25a (5 mg,
0.005 mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt3 (9 μL,
0.06 mmol, 12.0 equiv), DMAP (0.6 mg, 0.005 mmol, 1.0 equiv), and
S-(+)-Mosher’s acid chloride (2 μL, 0.01 mmol, 2.0 equiv) sequently
at room temperature. The reaction mixture was stirred for 14 h at
room temperature. As TLC control showed total consumption of the
starting material, the reaction was terminated by the addition of a
saturated, aqueous solution of NH4Cl (1 mL), and the resulting
mixture was diluted with DCM (3 mL). The layers were separated,
and the aqueous phase was extracted with DCM (3 × 5 mL). The
combined organic fractions were dried over Na2SO4 and ﬁltered, and
the solvent was removed under reduced pressure. The crude material
was puriﬁed by ﬂash column chromatography (hexanes/EtOAc 19:1 to
9:1) to aﬀord Mosher ester S14 (5 mg) in 85% yield as a colorless oil.
1
[α]20
D +2.0 (c 0.2, CHCl3). H NMR (400 MHz, CDCl3): δ 0.05 (s,
3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.60 (quart, J = 7.9 Hz,
6H), 0.90 (s, 18H), 0.95 (t, J = 7.9 Hz, 9H), 1.0 (d, J = 7.0 Hz, 3H),
1.07 (d, J = 7.0 Hz, 3H), 1.22−1.29 (m, 1H), 1.31 (s, 3H), 1.46 (s,
3H), 1.70 (s, 3H), 1.66−1.74 (m, 1H), 2.21−2.30 (m, 1H), 2.41−2.49
(m, 1H), 3.27 (t, J = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.49−
3.58 (m, 5H), 3.64 (dd, J = 10.5, 7.3 Hz, 1H), 3.70−3.75 (m, 1H),
3.77 (dd, J = 10.5, 1.9 Hz, 1H), 3.80−3.85 (m, 1H), 3.87−3.91 (m,
1H), 4.16−4.19 (m, 1H), 4.26 (dd, J = 7.3, 1.8 Hz, 1H), 4.30 (d, J =
7.3 Hz, 1H), 4.62 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 4.88−
4.96 (m, 3H), 5.06 (d, J = 7.3 Hz, 1H), 5.83 (ddd, J = 17.3, 10.3, 8.3
Hz, 1H), 5.90 (d, J = 9.8 Hz, 1H), 6.54 (s, 1H), 7.36−7.42 (m, 3H),
7.51−7.55 (m, 2H). 13C NMR (100 MHz, CDCl3): δ −5.1 (CH3),
−5.0 (CH3), −4.2 (CH3), −3.6 (CH3), 5.2 (CH2), 7.1 (CH3), 15.7
(CH3), 18.4 (C), 18.6 (C), 19.2 (CH3), 23.8 (CH3), 24.8 (CH3), 26.2
(CH3), 26.3 (CH3), 26.4 (CH3), 32.8 (CH), 35.0 (CH2), 38.8 (CH),
55.9 (CH3), 56.0 (CH3), 59.2 (CH3), 66.9 (CH2), 68.1 (CH2), 71.7
(CH), 72.0 (CH2), 73.6 (CH), 78.1 (CH), 80.1 (C), 82.0 (CH), 82.5
(CH), 85.2 (CH), 91.6 (CH2), 98.2 (CH2), 107.7 (C), 114.5 (CH2),
122.5 (C), 124.4 (C), 125.3 (C), 127.8 (CH), 128.5 (CH), 129.7
(CH), 131.8 (C), 140.1 (CH), 141.5 (CH), 166.3 (C). 19F NMR (565
MHz, CDCl3): δ −72.13 (s). IR (ATR) ν 2956, 2929, 2855, 2366,
1746, 1707, 1472, 1461, 1415, 1386, 1293, 1252, 1170, 1100, 1065,
1004, 916, 859, 811, 743 cm −1 . HRMS (ESI) calcd for
C55H9881BrF3O13Si3Na [M + Na]+, 1211.5328; found, 1211.5350.
Mosher Ester S15. Mosher ester S15 was prepared following the
same procedure as described above. Using enantiomeric R(−)-Mosher’s acid chloride, S15 (5 mg) was aﬀorded in 85% yield
1
as a colorless oil. [α]20
D −31.0 (c 0.3, CHCl3). H NMR (400 MHz,
CDCl3): δ 0.06 (s, 3H), 0.065 (s, 3H), 0.07 (s, 3H), 0.072 (s, 3H),
0.56 (quart, J = 8.0 Hz, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 0.93 (t, J = 8.0
Hz, 9H), 0.99 (d, J = 4.5 Hz, 3H), 1.0 (d, J = 4.5 Hz, 3H), 1.18 (dd, J

= 12.0, 12.0 Hz, 1H), 1.25 (s, 3H), 1.45 (s, 3H), 1.43−1.49 (m, 1H),
1.62 (s, 3H), 2.20−2.27 (m, 1H), 2.27−2.33 (m, 1H), 3.17 (t, J = 5.6
Hz, 1H), 3.37 (s, 3H), 3.371 (s, 3H), 3.49−3.57 (m, 2H), 3.58 (s,
3H), 3.64 (dd, J = 10.5, 7.5 Hz, 1H), 3.67−3.72 (m, 1H), 3.76 (dd, J =
10.5, 1.5 Hz, 1H), 3.79−3.85 (m, 2H), 4.15−4.19 (m, 1H), 4.23−4.27
(m, 2H), 4.58 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 4.89 (d, J
= 7.2 Hz, 1H), 4.92−4.94 (m, 1H), 4.95 (bs, 1H), 5.07 (d, J = 7.2 Hz,
1H), 5.80 (ddd, J = 16.7, 10.8, 8.1 Hz, 1H), 5.96 (d, J = 9.8 Hz, 1H),
6.58 (s, 1H), 7.36−7.40 (m, 3H), 7.56−7.60 (m, 2H). 13C NMR (100
MHz, CDCl3): δ −5.1 (CH3), −5.0 (CH3), −4.3 (CH3), −3.6 (CH3),
5.2 (CH2), 7.0 (CH3), 15.6 (CH3), 18.4 (C), 18.5 (CH3), 18.7 (C),
23.8 (CH3), 24.7 (CH3), 26.2 (CH3), 26.3 (CH3), 26.4 (CH3), 32.8
(CH), 34.7 (CH2), 39.1 (CH), 55.8 (CH3), 56.0 (CH3), 59.2 (CH3),
67.0 (CH2), 68.0 (CH2), 71.5 (CH), 71.9 (CH2), 73.6 (CH), 77.9
(CH), 80.2 (C), 82.0 (CH), 82.5 (CH), 85.0 (CH), 91.6 (CH2), 98.1
(CH2), 107.7 (C), 114.3 (CH2), 122.5 (C), 124.4 (C), 125.3 (C),
127.5 (CH), 128.5 (CH), 129.7 (CH), 132.3 (C), 140.4 (CH), 141.7
(CH), 166.4 (C). 19F NMR (565 MHz, CDCl3): δ −70.93 (s). IR
(ATR) ν 2956, 2929, 2855, 2366, 1746, 1707, 1472, 1461, 1415, 1386,
1293, 1252, 1170, 1100, 1065, 1004, 916, 859, 811, 743 cm−1. HRMS
(ESI) calcd for C55H9881BrF3O13Si3Na [M + Na]+, 1211.5328; found,
1211.5338.
Bromide 26. To a solution of secondary alcohol 25 (12 mg, 0.012
mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt3 (22 μL, 0.144
mmol, 12.0 equiv), DMAP (1.5 mg, 0.012 mmol, 1.0 equiv), and
benzoyl chloride (2.8 μL, 0.024 mmol, 2.0 equiv) at 0 °C. After the
addition, the cooling bath was removed, and the reaction mixture was
allowed to stir at room temperature for 5 h. As TLC control showed
remaining starting material, 2 equiv of benzoyl chloride (2.8 μL, 0.024
mmol) were added at room temperature, and the reaction mixture was
stirred for 5 h. The reaction was quenched by the addition of a
saturated, aqueous solution of NH4Cl (1 mL), and the resulting
mixture was diluted with DCM (5 mL). The layers were separated,
and the aqueous phase was extracted with DCM (3 × 10 mL). The
combined organic fractions were dried over Na2SO4 and ﬁltered, and
the solvent was removed under reduced pressure. The crude material
was puriﬁed by ﬂash column chromatography (hexanes/EtOAc 9:1) to
aﬀord bromide 26 (9 mg) in 71% yield as a colorless oil. [α]20
D −15.8
(c 0.46, CHCl3). 1H NMR (400 MHz, CDCl3): δ −0.01 (s, 3H), 0.00
(s, 6H), 0.01 (s, 3H), 0.64 (q, J = 7.9 Hz, 6H), 0.77 (s, 9H), 0.86 (s,
9H), 0.99 (t, J = 7.9 Hz, 9H), 1.01 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.0
Hz, 3H), 1.27−1.36 (m, 1H), 1.41 (s, 3H), 1.44 (s, 3H), 1.58 (s, 3H),
1.64−1.75 (m, 1H), 2.26−2.39 (m, 1H), 2.47−2.56 (m, 1H), 3.33 (bt,
J = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.52−3.60 (m, 3H), 3.67−
3.71 (m, 1H), 3.73−3.81 (m, 2H), 3.82−3.86 (m, 1H), 3.88−3.95 (m,
1H), 4.00 (dd, J = 6.8, 1.8 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.70 (d, J
= 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.93−5.04 (m, 3H), 5.11 (d, J
= 7.3 Hz, 1H), 5.87 (ddd, J = 17.5, 10.2, 8.4 Hz, 1H), 6.18 (d, J = 9.3
Hz, 1H), 6.35 (s, 1H). 7.41−7.48 (m, 2H), 7.53−7.60 (m, 1H), 8.04−
8.11 (m, 2H). 13C NMR (100 MHz, CDCl3): δ −5.4 (CH3), −5.2
(CH3), −4.5 (CH3), −3.9 (CH3), 5.4 (CH2), 7.2 (CH3), 15.6 (CH3),
18.4 (C), 18.5 (C), 19.1 (CH3), 22.4 (CH3), 25.1 (CH3), 26.2 (CH3),
33.6 (CH), 34.6 (CH2), 39.1 (CH), 56.0 (CH3), 59.1 (CH3), 67.1
(CH2), 67.7 (CH2), 71.6 (CH), 72.0 (CH2), 74.9 (CH), 76.9 (CH),
79.6 (C), 81.6 (CH), 82.4 (CH), 84.7 (CH), 91.7 (CH2), 98.2 (CH2),
107.9 (C), 114.4 (CH2), 128.5 (CH), 129.2 (C), 130.1 (CH), 130.2
(C), 133.2 (CH), 139.5 (CH), 141.7 (CH), 165.5 (C). IR (ATR) ν
2957, 2927, 2877, 2854, 1718, 1471, 1452, 1381, 1300, 1250, 1213,
1176, 1111, 1067, 1006, 989, 968, 889, 834, 777, 711 cm−1. HRMS
(ESI) calcd for C52H9581BrO12Si3Na [M + Na]+, 1099.5192; found,
1099.5210.

■

ASSOCIATED CONTENT

S Supporting Information
*

NMR spectra of all compounds, NOE analysis of S3 and S13,
and Mosher ester analysis of S14 and S15. This material is
available free of charge via the Internet at http://pubs.acs.org.
8757

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REFERENCES

(28) The Grignard addition selectively proceeds via the Cram-chelate transition state; for proof of stereochemistry, see the Supporting Information.
(30) Proof of stereochemistry was performed via NOE correlation studies (see the Supporting Information).

(36) The ee of the product was determined by Mosher ester analysis.
Supporting Information

Synthesis of an Advanced Intermediate of the Jatrophane Diterpene Pl-4
– A Dibromide Coupling Approach

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uwe.rinner@univie.ac.at
NMR-spectra

Solvent: CDCl₃

Instrument frequency: $^1\text{H}$: 400 MHz

$^{13}\text{C}$: 100 MHz
Appendix II

NMR-spectra
Appendix II

NMR-spectra

[Diagram of NMR spectrum with chemical shifts and peaks labeled]

[Diagram of another NMR spectrum with chemical shifts and peaks labeled]

[Diagram of a third NMR spectrum with chemical shifts and peaks labeled]
Appendix II  NMR-spectra

109
Appendix II

NMR-spectra
Appendix II  NMR-spectra

S10

119
Appendix II  
NMR-spectra
Appendix II

NMR-spectra
Appendix II  NMR-spectra

126
Appendix II  NMR-spectra
Appendix II

NMR-spectra

S2 (major diastereomer)
Appendix II

NMR-spectra

S2 (minor diastereomer)

S2 (minor diastereomer)
Appendix II  NMR-spectra

134
**NOE-Analysis**

**NOE-analysis S3:**

![Diagram of NOE-analysis S3]

**NOE-analysis S13:**

![Diagram of NOE-analysis S13]

**Mosher-ester Analysis**

**Mosher-ester Analysis:**

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<th>Proton</th>
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<th>S14 (R-configurated) ppm</th>
<th>Diff. (dS-dR)</th>
<th>S15–S14</th>
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<td>2a</td>
<td>1.46</td>
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<td>2b</td>
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<td>5</td>
<td>6.58</td>
<td>6.54</td>
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7. APPENDIX III

Abstract: Jatrophane diterpenes, isolated from members of the Euphorbiaceae plant family, constitute a class of biologically and structurally intriguing natural products. Herein, different strategies for the preparation of an advanced intermediate towards the total synthesis of the jatrophane diterpene Pl-4 are described. Key strategies for the elaboration of the jatrophane precursors include hydrometalation, and radical reactions.

Key words: Euphorbiaceae, jatrophane diterpene, hydrometalation, samarium diiodide, Reformatsky reaction.

When Juba II of Mauretania, one of the most loyal client kings of the Roman Empire and contemporary of Emperor Augustus, was troubled by a swollen belly, Euphorbus applied herbal remedies to cure his ailments. In appreciation of his healing and relief, and in honor of his Greek physician, Juba named the succulent and strongly laxative plant, which helped to improve his conditions, Euphorbia. Much later, Carl Linnaeus, one of the most important botanists in the 18th century, assigned the name Euphorbia to the entire genus.

The application of spurges, as members of the Euphorbiaceae plant family are commonly referred to, in the treatment of cancerous conditions, swellings and warts in traditional herbal folk medicine is historically documented from different cultures around the globe. Since the isolation of jatrophone by Kupchan in 1970, phytochemists showed increasing interest in the isolation of active ingredients from plants of the Euphorbiaceae family. To date, numerous natural products, possessing different core frameworks, such as the tigliane, ingenane, daphnane, and jatrophane skeleton were isolated. These terpene-based natural products were explored within extensive biological studies demonstrating a wide range of pharmacologically promising properties, including antiproliferation, cytotoxic, antimicrobial, anti-inflammatory as well as antiviral activities. Additionally, jatrophane diterpenes were identified to bind and selectively inhibit the ATP-dependent efflux pump P-glycoprotein (Pgp). This is probably the most interesting biological activity of this class of natural products, as overexpression of Pgp and the resulting multi-drug resistance (MDR) are commonly observed in cancer cells. Therefore, jatrophane diterpenes might serve as lead compounds in the development of co-therapeutics for cancer chemotherapy. Despite these promising biological properties and the challenging structural features, only few synthetic routes to jatrophane diterpenes have been reported.

Figure 1. Jatrophane skeleton and representative jatrophane diterpenes.

Pl-4 (1) was isolated in 2003 from a Hungarian sample of Euphorbia platyphyllos, an annual herbaceaous plant. The natural product belongs to the jatrophane-type family of diterpenes. As shown in Figure 1, jatrophanes are characterized by a highly functionalized cyclopentane ring, which is annulated to a twelve-membered macrocycle. In most jatrophanes, the two rings are trans-fused, however, a few derivatives, such as Pl-4, were isolated which possess a double bond at the ring junction. In addition to its promising biological properties, Pl-4 represents an exciting target for a synthetic chemist, which inspired us to develop a strategy towards this terpenoid natural product.

Recently, we reported the preparation of an advanced intermediate towards the synthesis of Pl-4 (1). The key strategy of this approach relied on a regioselective chelation-controlled lithiation/alkylation sequence of the more hindered bromide in the requisite vinyl dibromide as outlined in Scheme 1. However, before the preparation of vinyl bromide 5 was achieved via the
aforementioned dibromide coupling approach, several routes were investigated. With the intrinsic potential of jatrophone diterpene as co-therapeutics for modern cancer chemotherapy, we also wish to describe unsuccessful approaches to accelerate the development of future synthetic routes towards members of the jatrophone family. The following section summarizes unsuccessful attempts to access 5 via different strategies, such as hydrometalation reactions and radical protocols.

The initial retrosynthetic considerations towards the jatrophone diterpene Pl-4 are outlined in Scheme 1. We envisaged a late stage closure of the cyclopentane ring and intended the preparation of vinyl halide 5 as a precursor for the key cyclization reaction. The initial strategy (Path A) relied on a regioselective syn-hydrometalation of ynone 6. Alternatively, in a more concise manner, the alkyne in intermediate 6 could also be directly employed in a five-exo-dig ring closure reaction via an initially formed ketyl radical (Path B). Attempts towards the preparation of the highly advanced intermediate 5 via Path A and Path B are described in detail. The eventually successful regioselective lithiation/alkylation sequence (Path C) has already been described as pointed out above.5o

Results and Discussion

Hydrometalation Approach: The initial retrosynthetic analysis towards Pl-4 (1) is outlined in Scheme 2. As mentioned above, we intended to close the twelve-membered macrocycle as well as the cyclopentane ring at a very late stage of the synthesis via a ring-closing-metathesis (RCM), and a Nozaki-Hiyama-Kishi (NHK) or a radical reaction, respectively. The precursor for the ring closing reactions, intermediate 14, should become accessible from alkyne 15 through a syn-selective hydrometalation reaction. The sterical influence of the quaternary center adjacent to the alkyne should govern the metal to the more accessible, desired position. Alkyne 15 was envisaged to be elaborated from aldehyde 17 and terminal alkyne 16 by a lithiation/alkylation sequence. While 17 can be prepared from aldehyde 18 and literature known bromide 19, alkyne 16 is accessible via a route featuring a diastereoselective SmI 2-mediated Reformatsky reaction as key step.5k,8 D-Ribose was chosen as inexpensive and readily available starting material for aldehyde 21.

Scheme 2. Retrosynthetic analysis – hydrometalation approach.
protection of the secondary alcohol and a desilylation/oxidation sequence allowed the isolation of aldehyde 27.

Scheme 3. First attempt for the synthesis of the northern fragment of Pl-4.

The synthesis of the coupling partners for aldehyde 27, bromides 31 and 32, is outlined in Scheme 4. Protection of the hydroxyl moiety in commercially available R-(–)-Roche ester (28) as TES- or TBS-ether was followed by DIBALH reduction of the methyl ester. Then, the bromide was introduced either by mesylation of the primary alcohol, followed by nucleophilic displacement with tetrabutyl-ammonium bromide 12, or alternatively under Appel conditions. All attempts to accomplish the coupling of bromide 31 or 32 with aldehyde 27 failed. Lithiation of 31 with n-BuLi or t-BuLi in different solvents resulted in decomposition of the lithiated species. The instability of silyl ethers towards organolithium species is well documented and we hoped to solve the problem by exchanging the labile TES-ether for a more stable TBS-group (32). Unfortunately, lithiation of halide 32 using n-BuLi or t-BuLi also failed to deliver the desired product. Addition of MgBr₂·OEt₂ and LiBr to the lithiated species for the in situ formation of the transmetalated Grignard species resulted in decomposition of the starting material. Direct formation of the Grignard species, reaction with indium (activated under sonication), or NHK coupling conditions only allowed the re-isolation of 32.

Scheme 4. Completion of the northern fragment of Pl-4.

Because of the instability of the silyl-ethers, we decided to introduce a PMB protecting group. Reaction of Roche ester (28) with PMB-trichloroacetimidate followed by LAH reduction allowed the isolation of alcohol 35 (Scheme 5). The bromide was installed applying the Appel protocol and 19 could be obtained in good overall yield. With bromide 19 in hand, the crucial coupling reaction could be approached. Lithiation of 19 with t-BuLi at –78 °C and subsequent addition of MgBr₂·OEt₂ afforded the intermediate Grignard species, which readily reacted with aldehyde 27 to deliver the desired adduct 36 in excellent 96% yield, as a 9:1 diastereomeric mixture. The expected, predominant formation of the S-configured alcohol through this chelation-controlled addition reaction could be confirmed by NMR studies. However, as the hydroxyl moiety is oxidized at a later stage of the synthesis, the stereocchemical outcome of the reaction is inconsequential to the overall efficiency and both diastereomers could be employed for all successive steps. Next, the corresponding secondary hydroxyl group was protected as TES-ether. The following steps were devoted to mask the terminal alkene as a primary TBS-ether to prevent potential side reactions in the hydrometalation reaction later in the synthesis. Dihydroxylation of the terminal alkene with catalytic amounts of OsO₄ and NMO, was followed by addition of sodium periodate to deliver the desired aldehyde in a one-pot-procedure, which was instantly reduced with NaBH₄ to give the corresponding alcohol. Next, the primary hydroxyl group was TBS-protected to afford fully protected intermediate 37 which was then converted to aldehyde 17 via a DDQ-mediated debenzylization and oxidation of the primary alcohol under Parikh-Doehring conditions.

Scheme 5. Second attempt towards the northern fragment of Pl-4.

For the preparation of the southern part of the natural product D-ribose (22) was selected as inexpensive and readily available starting material (Scheme 6). Oxidation of the lactol with bromine and sodium bicarbonate delivered d-ribonolactone, which was converted to acetone 38. Exposure of the lactone
to pyrrolidine at elevated temperature afforded amide 39 in excellent yield. Both hydroxyl functionalities in 39 were silylated before addition of methyllithium at –78 °C allowed the isolation of methyl ketone 40. The synthesis of alkyne 41 was accomplished after Grignard reaction with ethynylmagnesium bromide,18 which afforded the terminal alkyne as single isomer,19 and MOM-protection of the newly generated tertiary alcohol. Alkyne 41 was used in the further course of the synthesis as a simplified model-system for the southern fragment of Pl-4.

As summarized in Table 1, various conditions for the coupling of alkyne 41 and aldehyde 17 (Scheme 7) were evaluated. Unfortunately, a chiral alkylation reaction, following the Carreira protocol,20 with (–)-N-methylephedrine, Zn(OTf)2, and NEt3 only resulted in reisolation of the starting materials. When n-BuLi was used for the lithiation of alkyne 41, the desired coupling products 42 and 42a could be obtained, however, the yield of the reaction was non-reproducible on a larger scale. Unfortunately, further addition of HMPA or CeCl3 resulted in decreasing yield.21 Non-nucleophilic bases proved to be advantageous for the coupling reaction and the desired products 42 and 42a could be isolated in 71% yield when LHMDS was employed in THF at –78 °C. In this case, transmetalation using CeCl3 helped to further improve the overall yield of the coupling reaction to excellent 84%. The only drawback was the stereochemical outcome of the alkyne/aldehyde coupling reaction as under all reaction conditions, the desired intermediates 42 and 42a were isolated as a 1:2 mixture of diastereomers, favoring the undesired isomer.22 However, at this point we decided to proceed with the synthesis before improving the diastereoselectivity or developing methods for the inversion of the stereocenter in the undesired isomer.

With internal alkyne 42 in hand, the stage was set to explore the key hydrometalation reaction. We expected that reaction of alkyne 42 with an organometallic species should result in an attack of the metal at the less hindered position with concomitant syn-hydrogenation which should establish the desired double bond geometry. Subsequent metal-halogen exchange would further provide a synthetic anchor for the closure of the cyclopentane ring, either via a radical process, or a NHK coupling reaction.

As outlined in Table 2, reaction of alkyne 42 with tributyltin hydride and a catalytic amount of Pd(PPh3)2Cl2 (Table 2, entry 1)23 or palladium acetate and tricyclohexylphosphine (entry 2)24 only resulted in isolation of the starting material, even when the reaction was carried out at elevated temperatures. Next, we decided to apply hydrozirconation conditions.25 However, no product formation was observed when the Schwartz reagent26 was added to a solution of alkyne 42 in toluene (entry 3);27 the same outcome was observed after addition of MeLi and ZnCl2 (entry 4).27 Our final attempt was a nickel mediated hydrometalation reaction,28 which resulted in decomposition of the starting material (entry 5).
Either sterical hindrance, or the free hydroxyl moiety in alkyne 42 might be responsible for the unsatisfying outcome of the hydrometalation reaction. Thus, secondary alcohol 42 was allowed to react with NaH and PMBCl, which resulted in PMB-protection of the secondary hydroxyl moiety adjacent to the alkyne, with concomitant cleavage of the TES-group. The fully protected substrate was obtained after exposure of PMB-ether 44 to TBS-triflate and 2,6-lutidine, as shown in Scheme 9. With alkyne 45 in hand, the hydrometalation conditions, outlined in Table 2, were re-evaluated. Also, since PMB-ether 44 was available, this compound was included in this study. Unfortunately, all experiments carried out with either 44 or 45, confirmed our previous results and the desired vinyl halide was not obtained.

We could rule out that the free hydroxyl moiety in 42 was responsible for the unfavorable outcome of the intended hydrometalation reaction and we concluded that the sterical hindrance of the internal alkyne might be the limiting factor. These results are in agreement with literature examples, as in most cases, hydrometalation reactions are carried out on unsubstituted or sterically less demanding substrates. As the only remaining option, the cleavage of the MOM-group on the quaternary center next to the internal alkyne, seemed unfeasible with respect to the protecting group strategy and overall efficiency of the synthesis, the hydrometalation route was abandoned.

Table 2  Hydrometalation reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynes</th>
<th>Reagents</th>
<th>Temp.</th>
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</thead>
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<td>1</td>
<td>42, 44, 45</td>
<td>Pd(PPh₃)₂Cl₂, SnBu₃H, H₂O</td>
<td>rt to 60 °C reisolation of s.m.</td>
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<tr>
<td>2</td>
<td>42, 44, 45</td>
<td>Pd(OAc)₂, PCy₃, Bu₃SnH, H₂O</td>
<td>rt to 60 °C reisolation of s.m.</td>
</tr>
<tr>
<td>3</td>
<td>42, 44, 45</td>
<td>Cp₂Zr(HCl), I₂</td>
<td>60 °C reisolation of s.m.</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>Cp₂Zr(HCl), MeLi, ZnCl₂, I₂ quench</td>
<td>–78 °C to rt reisolation of s.m.</td>
</tr>
<tr>
<td>5</td>
<td>42, 45</td>
<td>Ni(PPh₃)₂Cl₂, DIBAL-H, NBS</td>
<td>0 °C to rt decomp.</td>
</tr>
</tbody>
</table>

Alkyne cyclization approach: Several methods describing the direct intramolecular cyclization reaction of aldehydes or ketones with internal or terminal alkynes have been published: Nickel-mediated intramolecular ring-closing reactions between internal alkynes and ketones as well as cyclization reactions via low-valent titanium complexes can be used for the preparation of five-membered cycloalkanols. Samarium diiodide is a useful reagent for the formation of ketyl radicals, which triggers cyclization reactions of alkynes. According to these promising literature precedents, an alternative approach was launched, based on the direct utilization of internal alkynes without the foregoing installation of a vinyl halide, as pursued in the hydrometalation approach. Additionally, this idea seemed even more appealing, as the protection of the terminal double bond within the northern fragment, originating from the enantioselective crotylation reaction, is not required, and can be directly employed in the final RCM reaction later.

As outlined in Scheme 10, we started our endeavors from previously prepared alkene 36. Silylation of the secondary alcohol was followed by cleavage of the benzyl ether and Parikh-Doehring oxidation of the primary hydroxyl group (48). Next, the lithiation/alkylation reaction of aldehyde 48 and alkyne 41 was pursued. We were pleased to find that the previously established cerium-mediated coupling reaction delivered the desired diastereomeric adducts 49 and 49a in excellent 90% overall yield. Again, the stereochemical outcome of the coupling reaction was not perfectly satisfying, as a 1:2 mixture of diastereomers, favoring the undesired isomer, was obtained. We again decided to proceed with the synthesis using the desired diastereomer 49 without any optimization or correction of the stereocenter in 49a. PMB-protection of the secondary alcohol resulted in simultaneous cleavage of the TES-group. Exposure of the resulting alcohol to Dess-Martin
periodinane allowed the isolation of the substrate for the crucial radical ring closure reaction (50).

Scheme 10. Preparation of the cyclization precursor.

With alkyne 50 in hand, conditions for the cyclopentane formation were investigated. As pointed out above, addition of SmI2 to the cyclization precursor (50) should initiate the formation of a ketyl radical which should further attack the internal alkyne and establish the five-membered ring via a five-exo-dig ring closing reaction (Scheme 11). Unfortunately, the SmI2-mediated reaction only resulted in the reisolation of the starting material when carried out at 78 °C, and partial formation of the reduced intermediate 51 at elevated temperature. The isolation of the reduced species (51) gives evidence that a ketyl radical is formed during the course of the reaction. However, the second step, the formation of the cyclopentane ring system, did not occur. We hoped that the addition of t-BuOH, MeOH, HMPA, LiCl, or NiI2 would facilitate the ring closure, but the desired cyclized product could not be isolated.

Scheme 11. Cyclization reaction.

At this point we reasoned that again the sterical hindrance of the internal alkyne might be responsible for the lack of reactivity, as the ketyl formation was observed under the SmI2-mediated cyclization conditions. We expected that a closer spatial arrangement of the two reacting functionalities would enhance the reactivity and trigger the formation of the cyclopentane ring. Thus, we decided to slightly modify the route towards the natural product and intended to close the macrocycle via a RCM reaction prior to establishing the five-membered ring.

The synthesis of the RCM-precursor is outlined in Scheme 12. The modified sequence started with readily available D-isoascorbic acid (53) which was converted to acetonide protected lactone 54 via a literature known two-step procedure.34 Alcohol 55 became available after reaction of lactone 54 with pyrrolidine. The resulting primary hydroxyl group was protected as PMB-ether before treatment with methylolithium allowed the isolation of methyl ketone 56 in excellent yield. Next, C2-elongation with ethynylmagnesium bromide delivered the corresponding tertiary alcohols in a 3:1 diastereomeric ratio, favoring the desired R-configurated isomer, which was protected as its TBS-ether (57).35

Table 3 Cyclization reaction conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SmI2</td>
<td>–78 °C</td>
<td>reisolation of s.m.</td>
</tr>
<tr>
<td>2</td>
<td>SmI2</td>
<td>rt</td>
<td>51 + s.m.</td>
</tr>
<tr>
<td>3</td>
<td>SmI2, t-BuOH</td>
<td>–78 °C</td>
<td>51 + s.m.</td>
</tr>
<tr>
<td>4</td>
<td>SmI2, t-BuOH, HMPA</td>
<td>–78 °C</td>
<td>51 + s.m.</td>
</tr>
<tr>
<td>5</td>
<td>SmI2, t-BuOH, HMPA</td>
<td>0 °C</td>
<td>51[b]</td>
</tr>
<tr>
<td>6</td>
<td>SmI2, HMPA</td>
<td>rt</td>
<td>51[b]</td>
</tr>
<tr>
<td>7</td>
<td>SmI2, MeOH</td>
<td>0 °C to rt</td>
<td>51[b]</td>
</tr>
<tr>
<td>8</td>
<td>SmI2, NiI2</td>
<td>rt</td>
<td>51[b]</td>
</tr>
<tr>
<td>9</td>
<td>SmI2, LiCl</td>
<td>rt</td>
<td>51[b]</td>
</tr>
<tr>
<td>10</td>
<td>Ni(cod)2, IPr.HCl, Et3SiH, t-BuOK</td>
<td>0 °C to rt</td>
<td>reisolation of s.m.</td>
</tr>
<tr>
<td>11</td>
<td>Ni(cod)2, PBu3, Et3SiH</td>
<td>0 °C to rt</td>
<td>reisolation of s.m.</td>
</tr>
<tr>
<td>12</td>
<td>Ni(cod)2, PBu3, BEt3</td>
<td>rt</td>
<td>reisolation of s.m.</td>
</tr>
</tbody>
</table>

[a] 51 was isolated in less than 10% yield under all given reaction conditions. [b] Slow decomposition of the starting material.
Then, the PMB group was removed with DDQ and the primary alcohol was oxidized with Dess-Martin periodinane to give aldehyde 58. The installation of the geminal dimethyl group was accomplished via a diastereo-selective SmI₂-mediated Reformatsky reaction of aldehyde 58 and chiral bromide 20, and advanced alcohol 59 was obtained as single isomer. MOM-protection of the secondary alcohol was followed by reductive cleavage of the chiral auxiliary with LiBH₄ and primary alcohol 60 was isolated in good yield. Alkene 61 was obtained after IBX-oxidation of the primary alcohol functionality, followed by installation of the terminal alkyne moiety in 61 with t-BuLi, and subsequent reaction with aldehyde 48 afforded the RCM precursor in 80% yield, again as a 1:2 mixture of diastereomers.

With diene 62 in hand, the closure of the 15-membered ring was attempted. As outlined in Table 4 (Entry 1-6), different reaction conditions and RCM catalysts were evaluated. Unfortunately, we were not able to achieve the desired macrocyclization using either diene 62 or fully protected substrate 64, available after PBM-protection of the hydroxyl group with concomitant cleavage of the TES-ether and subsequent oxidation of the secondary alcohol, were met with failure (Scheme 13). All attempts resulted in re-isolation of the starting material, along with minor amounts (up to 10%) of the thermodynamically more stable double bond isomer (66).

As the outcome of RCM reactions strongly depends on the steric environment of the double bonds, we reasoned that the geminal dimethyl moiety in 62 and 64 prevents the formation of the 15-membered macrocycle. The influence of the sterial effects might even be more pronounced as the alkyne functionality adds additional rigidity to the system. We decided to prepare a structurally simplified model compound lacking the geminal dimethyl group. As only little information on the structural requirements for MDR-reversal activity of jatrophanes is available, the synthesis and biological evaluation of derivatives is of essential importance.

The synthesis of the sterically less demanding RCM-precursor is outlined in Scheme 14. The addition of allylmagnesium bromide to aldehyde 58 allowed the isolation of the corresponding allylic alcohols in a 1:1.5 diastereomeric ratio, favoring the undesired exemplarily shown for the reaction starting from diene 64).
isomer. Although we were not concerned with the stereochemical outcome of the Grignard reaction, we decided to alter the reaction conditions only after successful closure of the macrocycle. The diastereomers were separated and the desired compound converted to MOM-ether 69 in 82% yield. With 69 in hand, the RCM-precursor (70) became accessible after lithiation of the alkyne and subsequent reaction with aldehyde 48. Unfortunately, all attempts to close the macrocycle via a RCM-reaction (conditions as described in Table 4, Entry 1-6) remained unsuccessful and the desired product 71 could not be isolated.


At this point it became obvious that the rigidity provoked by the internal alkyne, was obstructive for the formation of the desired macrocycle. We decided to further investigate our initial idea which envisaged the closure of the cyclopentane ring prior to the macrocyclization.

As outlined in Scheme 15, we intended to prepare aldehyde 76 as precursor for a SmI₂- or Ni-mediated ring closure reaction. Thus, we could take advantage of the higher reactivity of aldehydes versus ketones. Additionally, the undesired reductive removal of the MOM-ether as observed in the SmI₂-mediated reaction of 62 and 64 would be avoided. The resulting cyclopentanol could later be oxidized to the corresponding ketone and used for further functionalization.

The sequence started with Myer’s alkylation using TBS-protected iodide 78 and pseudoephedrine propionamide 72 (Scheme 15). Cleavage of the chiral auxiliary with BH₃·NH₃, and oxidation of the primary alcohol with IBX resulted in the isolation of aldehyde 74. The following reaction of aldehyde 74 with deprotonated alkyne 57 delivered the corresponding secondary alcohols as an inseparable 1:2 mixture of diastereomers (as previously observed for similar substrates but the stereochemistry was not proven at this point). The alcohol functionality was protected as a PMB-ether before the compound was treated with camphorsulfonic acid (CSA) to cleave the primary TBS-group (75a,b). Final oxidation of the primary alcohol with IBX afforded aldehydes 76a and 76b which served as substrates for the intended ring closing reaction. Unfortunately, neither reaction of aldehyde 76a nor 76b afforded the desired products. An overview of different reaction conditions applied to aldehydes 76a and 76b is presented in Table 5. Because of these disappointing findings the approach was abandoned. The inability to access the desired intermediate led to the development of the ultimately successful dibromide coupling approach (Path C in Scheme 1) which has been published elsewhere.

Table 5  Cyclization reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temperature</th>
<th>Conditions (Table 5)</th>
<th>Reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SmI₂, LDA, LiCl</td>
<td>–78 to –40 °C</td>
<td>reisolation of s.m.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SmI₂, LDA, Bu₄NI</td>
<td>0 to 50 °C</td>
<td>decomposition [a]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SmI₂, HMPA, t-BuOH</td>
<td>–78 °C</td>
<td>mixture of undefined products</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>SmI₂, HMPA, t-BuOH</td>
<td>–78 °C</td>
<td>1:2 mixture</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SmI₂, HMPA, MeOH</td>
<td>–78 to 0 °C</td>
<td>decomposition [a]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ni(cod)₂, IPr-HCl, EtSiH, t-BuOK</td>
<td>rt to 50 °C</td>
<td>reisolation of s.m. [a]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ni(cod)₂, PBu₃, EtSiH</td>
<td>rt</td>
<td>reisolation of s.m.</td>
<td></td>
</tr>
</tbody>
</table>

[a] Partial reduction of the aldehyde to the corresponding alcohol.

Conclusions

Herein, we describe two approaches towards a highly advanced intermediate in the synthesis of the jatrophane diterpene PI-4 (1). These routes feature a syn-selective hydrometalation reaction, and a radical approach, respectively. Although the desired advanced intermediate (5) could not be accessed, we
were able to elaborate efficient protocols for the preparation of structural motifs present in this fascinating class of natural products. Jatrophane diterpenes are synthetically challenging targets, mainly because of the complex stereochemoanaly substitution pattern. Additionally, the high level of oxygenation necessitates sophisticated protecting group strategies and facilitates undesired side reactions and modified reactivity. We are positive that results and strategies discussed within this manuscript, as well as problems and synthetic drawbacks will be of importance for the design of future routes to structurally related jatrophane diterpenes.

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware. Solvents were purified and dried by standard procedures. The reactions were monitored by thin layer chromatography using silica gel 60-F254 glass plates. Flash column chromatography was performed with silica gel 60-240 mesh. Optical rotations were measured using a single reflection monolithic diamond ATR mode and a UHR-TOF (Qq-TOF) mass analyzer. Positive pressure of argon using oven-dried (100 °C) solutions and referenced to the residual CD 3 Cl signal (1H, δ = 7.26, 13C, δ = 77.16). IR spectra are reported in wave numbers (cm\(^{-1}\)). All compounds were measured using a single reflection monolithic diamond ATR module. High resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer.

(2S,5S,6S)-1-((4-Methoxybenzyl)oxy)-7-en-4-ol (36). A solution of bromide 19 (590 mg, 2.16 mmol, 2.0 eq) in Et 2O (17 mL) was cooled to −78 °C and a solution of t-BuLi (1.6 M, 2.84 mL, 4.54 mmol, 4.2 eq) was added dropwise over 3 minutes. The reaction mixture was stirred for 10 minutes at that temperature before a freshly prepared MgBr 2 solution (1 M, 2.48 mL, 2.48 mmol, 2.3 eq) was added. After 10 minutes at −78 °C aldehyde 27 (171 mg, 1.08 mmol, 1.0 eq), dissolved in Et 2O (6.8 mL) was added dropwise via syringe over 3 minutes. The reaction mixture was allowed to stir at −78 °C for 90 minutes until TLC-control showed total consumption of aldehyde 5. The reaction was terminated by the addition of a saturated, aqueous solution of NH 4 Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na 2SO 4, filtered and the solvent was removed under reduced pressure. The resulting crude mixture of secondary alcohols was purified by flash column chromatography (hexane/EtOAc 9:1 to 5:1) providing 36 (342 mg) and 36a (38 mg) as colorless oils, in a 9:1 diastereomeric ratio and 96% overall yield.

Major diastereomer (36): [α] 20\(^{D}\) +6.3 (c 1.0, CHCl 3).

IR (ATR): 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl 3): δ = 0.93 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.22-1.31 (m, 1H), 1.52 (dd, J = 4.3, 10.5, 13.8 Hz, 1H), 2.08-2.16 (m, 1H), 2.43-2.56 (m, 1H), 3.18 (dd, J = 3.9, 5.9 Hz, 1H), 3.23 (d, J = 3.9 Hz, 1H), 3.27-3.31 (m, 2H), 3.42 (s, 3H), 3.62-3.69 (m, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 4.67 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.99-5.02 (m, 1H), 5.02-5.06 (m, 1H), 5.76-5.88 (m, 1H), 6.84-6.90 (m, 2H), 7.22-7.28 (m, 2H) ppm.

\(^1\)C NMR (100 MHz, CDCl 3): δ = 16.9 (CH 3), 17.7 (CH 3), 30.4 (CH), 37.9 (CH 3), 40.0 (CH), 55.4 (CH3), 69.8 (CH), 72.6 (CH2), 76.3 (CH2), 88.7 (CH), 98.9 (CH2), 113.6 (CH), 115.3 (CH2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C) ppm.

HRMS (ESI) m/z [M+Na]\(^{+}\) calcd for C 20H32O5: 375.2148; found: 375.2141.

(4R,5S)-3-((S)-3-((4R,5R)-5-((Tert-butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (59). A solution of SmI 2 (0.1 M in THF, 31.3 mL, 3.13 mmol, 2.5 eq) was transferred into a 250 mL round bottom Schlenk flask which was precooled to −78 °C. A solution of bromide 20 (449 mg, 1.38 mmol, 1.1 eq) and aldehyde 58 (390 mg, 1.25 mmol, 1.0 eq) in 20 mL degassed THF (3 pump-freeze-thaw cycles) was added to the SmI 2 solution via a cannula over a period of 5 minutes. The reaction mixture was stirred for 1 hour at −78 °C before it was quenched by the addition of aqueous saturated solutions of Na 2SO 4 (20 mL) and NaHCO 3 (20 mL) at −78 °C. The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na 2SO 4, filtered and the organic solvents were removed under reduced pressure delivering the crude secondary alcohol as a light yellow oil which was purified by flash chromatography (hexane/EtOAc 9:1) providing 59 (420 mg) as single diastereomer in 60% (94% brsm) yield.

[a] 20\(^{D}\) +34.4 (c 1.0, CHCl 3).

IR (ATR): 3511, 3264, 2933, 2858, 2361, 2341, 1773, 1688, 1457, 1338, 1248, 1151, 1086, 1028, 987, 835, 768 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl 3): δ = 0.23 (s, 3H), 0.30 (s, 3H), 0.90 (s, 9H), 0.91 (d, J = 6.6 Hz, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.71 (s, 3H), 2.58 (s, 1H), 3.32 (d, J = 4.8 Hz, 1H), 4.08 (d, J = 6.3 Hz, 1H), 4.27 (d, J = 6.3 Hz, 1H), 4.81
(m, 1H), 4.93 (d, J = 4.8 Hz, 1H), 5.66 (d, J = 6.8 Hz, 1H), 7.27-7.31 (m, 2H), 7.33-7.44 (m, 3H) ppm.

13C NMR (100 MHz, CDCl3): d = -2.9 (CH3), -2.2 (CH3), 14.4 (CH3), 18.5 (C), 20.2 (CH3), 22.4 (CH3), 25.7 (CH3), 26.1 (CH3), 26.4 (CH3), 28.2 (CH3), 50.6 (C), 57.7 (CH3), 69.1 (CH), 69.5 (C), 74.0 (CH), 75.7 (CH), 79.2 (CH), 84.5 (CH), 86.9 (C), 108.5 (C), 125.8 (CH), 128.8 (CH), 128.9 (CH), 133.8 (C), 152.6 (C), 177.0 (C) ppm.

HRMS (ESI) m/z [M+Na]+ calcd for C30H45NO7Si: 582.2863; found: 582.2859 +/- 5ppm.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. The experimental procedures and analytical data of all intermediates, described within this manuscript, can be found in the supporting information.

Acknowledgment

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References

(8) For practical reasons, all subsequent steps were carried out using the major S-configured alcohol.
(12) For stereochemical assignment by NMR spectroscopy see Supporting Information (S17). After the Grignard reaction with ethynylmagnesium bromide the two vicinal TBS-groups were deprotected with TBAF and the resulting diol was cleaved with NaOAc to afford a mixture of the corresponding lactols which were further oxidized with PCC to give lactone S17.
(15) The stereochemistry of the newly installed hydroxyl moiety was proven by advanced Mosher-ester analysis, see Supporting Information (S7, S8). All subsequent steps were carried out with the desired S-configured isomer.

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(33) The stereochemistry of the newly installed hydroxyl moiety was proven by advanced Mosher-ester analysis, see Supporting information (S9, S10). All subsequent steps were carried out with the desired S-configurated isomer.


(35) For stereochemical assignment by NMR spectroscopy see Supporting Information (S16, S17).


(37) Stereochemistry of the major diastereomer (S20a) could be proven by X-ray analysis.

Supporting Information

Synthetic Studies Towards an Advanced Precursor of the Jatrophae Diterpene Pl-4

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General methods

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum), unless noted otherwise. THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DMSO and N,N-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral activity. Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diisopropylethylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/EtOAc or toluene/EtOAc. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [H₂SO₄ (conc., 22 mL), phosphormolybdic acid (20 g), Ce(SO₄)₂ (0.5 g), 378 mL H₂O)] or silica gel impregnated with iodine.

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

Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: [α]ₜₜ, concentration (g/100 mL), and solvent.

NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl₃ solutions and referenced to the residual CDCl₃ signal (1H, δ = 7.26, 13C, δ = 77.16). All 1H and 13C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY).

IR spectra are reported in wave numbers (cm⁻¹). All compounds were measured using a single reflection monolithic diamond ATR module.

High resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer (acetonitrile/Methanol 1:1, +1% H₂O).
**Experimental part**

(R)-Methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (S1). To a solution of R-(−)-Roche ester (2.0 g, 16.9 mmol, 1.0 eq) in DCM (10 mL) were added a solution of p-methoxybenzyl trichloroacetimidate (1.1 M in hexanes, 23 mL, 23.35 mmol, 1.5 eq) and camphorsulfonic acid (314 mg, 1.35 mmol, 0.08 eq) successively. The reaction mixture was stirred for 12 hours at room temperature until TLC-control showed total consumption of the starting material. The reaction was quenched by the addition of saturated NaHCO₃ solution (15 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After flash column chromatography (hexane/EtOAc 19:1) S1 (3.86 g) was isolated in 96% yield as a light yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 1.17 (d, J = 7.0 Hz, 3H), 2.72-2.81 (m, 1H), 3.46 (dd, J = 5.0, 11.8 Hz, 1H), 3.63 (dd, J = 7.3, 9.0 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 4.44 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 6.84-6.90 (m, 2H), 7.21-7.25 (m, 2H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃), 40.4 (CH), 51.9 (CH₃), 55.4 (CH₃), 71.8 (CH₂), 72.9 (CH₂), 113.9 (CH), 129.4 (CH), 130.4 (C), 159.4 (C), 175.5 (C) ppm.

These spectral characteristics are identical to those previously reported.[1]

(S)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol (35). To a suspension of LiAlH₄ (603 mg, 15.9 mmol, 1.0 eq) in Et₂O (16 mL) was added a solution of S1 (3.8 g, 15.9 mmol, 1.0 eq) in Et₂O (11 mL) at 0 °C. The reaction mixture was allowed to stir for 1 hour at 0 °C and additional 90 minutes at room temperature before it was quenched by the addition of H₂O (3 mL) and aqueous 15% NaOH (1.5 mL). After stirring for 15 min, MgSO₄ (heaped spoon) was added and the mixture was stirred for 30 minutes at room temperature. Afterwards the suspension was filtered over a plug of Celite and the filtrate was concentrated in vacuo. The crude material was purified by flash column chromatography (hexanes/EtOAc 5:1) delivering 35 (2.94 g) in 88% yield as a light yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 0.87 (d, J = 7.0 Hz, 3H), 1.99-2.12 (m, 1H), 2.51 (dd, J = 4.5, 6.8 Hz, 1H), 3.39 (dd, J = 8.3, 9.0 Hz, 1H), 3.53 (dd, J = 4.5, 9.0 Hz, 1H), 3.56-3.67 (m, 2H), 3.81 (s, 3H), 4.43 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 6.85-6.90 (m, 2H), 7.22-7.27 (m, 2H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 13.6 (CH₃), 35.7 (CH), 55.4 (CH₃), 68.2 (CH₂), 73.2 (CH₂), 75.4 (CH₂), 114.0 (CH), 129.4 (CH), 130.3 (C), 159.4 (C) ppm.

These spectral characteristics are identical to those previously reported.[1]
**Appendix III**

**Experimental part**

(R)-1-((3-Bromo-2-methylpropoxy)methyl)-4-methoxybenzene (19). A mixture of alcohol 35 (2.9 g, 14.2 mmol, 1.0 eq), CBr₄ (10.36 g, 31.24 mmol, 2.2 eq), pyridine (4.6 mL, 56.8 mmol, 4.0 eq) and PPh₃ (8.57 g, 32.66 mmol, 2.3 eq) in DCM (44 mL) was stirred at room temperature for 3 hours. The reaction mixture was transferred to a separatory funnel and washed once with aqueous 10% CuSO₄ solution (30 mL), saturated NaHCO₃ solution (30 mL) and H₂O (30 mL). Silica gel was added to the organic fraction and the solvent was removed under reduced pressure. The crude bromide, applied on silica gel, was transferred to a chromatography column and eluated with hexane/EtOAc 40:1 affording 19 (3.27 g) in 84% yield as a colorless oil.

**1H NMR** (400 MHz, CDCl₃): \( \delta = 1.02 \) (d, \( J = 6.8 \) Hz, 3H), 2.07-2.18 (m, 1H), 3.34-3.42 (m, 2H), 3.44-3.53 (m, 2H), 3.81 (s, 3H), 4.45 (s, 2H), 6.86-6.91 (m, 2H), 7.23-7.28 (m, 2H) ppm.

**13C NMR** (100 MHz, CDCl₃): \( \delta = 16.0 \) (CH₃), 35.8 (CH), 38.4 (CH₂), 55.4 (CH₃), 72.7 (CH₂), 73.0 (CH₂), 114.0 (CH), 129.3 (CH), 130.6 (C), 159.4 (C) ppm.

These spectral characteristics are identical to those previously reported.[1]

**OMOM**

(2S,5S,6S)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (36). A solution of bromide 19 (590 mg, 2.16 mmol, 2.0 eq) in Et₂O (17 mL) was cooled to \(-78 \) °C and a solution of \( t \)-BuLi (1.6 M, 2.84 mL, 4.54 mmol, 4.2 eq) was added dropwise over 3 minutes. The reaction mixture was stirred for 10 minutes at that temperature before a freshly prepared MgBr₂ solution (1 M, 2.48 mL, 2.48 mmol, 2.3 eq) was added. After 10 minutes of stirring at \(-78 \) °C aldehyde 27 (171 mg, 1.08 mmol, 1.0 eq), dissolved in Et₂O (6.8 mL) was added dropwise via syringe over 3 minutes. The reaction mixture was allowed to stir at \(-78 \) °C for 90 minutes until TLC-control showed total consumption of aldehyde 5. The reaction was terminated by the addition of a saturated, aqueous solution of NH₄Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting crude mixture of secondary alcohols was purified by flash column chromatography (hexane/EtOAc 9:1 to 5:1) providing 36 (342 mg) and 36a (38 mg) as colorless oils, in a 9:1 diastereomeric ratio and 96% overall yield.

**Major diastereomer (36):**

**1H NMR** (400 MHz, CDCl₃): \( \delta = 0.93 \) (d, \( J = 6.6 \) Hz, 3H), 1.07 (d, \( J = 6.8 \) Hz, 3H), 1.22-1.31 (m, 1H), 1.52 (ddd, \( J = 4.3, 10.5, 13.8 \) Hz, 1H), 2.08-2.16 (m, 1H), 2.43-2.56 (m, 1H), 3.18 (dd, \( J = 3.9, 5.9 \) Hz, 1H), 3.23 (d, \( J = 3.9 \) Hz, 1H), 3.27-3.31 (m, 2H), 3.42 (s, 3H), 3.62-3.69 (m, 1H), 3.80
Experimental part

(5S)-5-((S)-But-3-en-2-yl)-8,8-diethyl-6-((S)-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,4,7-trioxa-8-siladecane (S2). To a solution of secondary alcohol 36 (660 mg, 1.9 mmol, 1.0 eq), imidazole (259 mg, 3.8 mmol, 2.0 eq) and DMAP (4 mg, 0.03 mmol, 0.02 eq) in DCM (9.5 mL) was added chlorotriethylsilane (0.64 mL, 3.8 mmol, 2.0 eq) at 0 °C. The mixture was stirred for 12 hours at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of NaHCO₃ (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic fractions were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 9:1) affording S2 (0.82 g) in 93% yield as a colorless oil.

1H NMR (400 MHz, CDCl₃): δ = 0.61 (quart, J = 7.9 Hz, 6H), 0.93 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 1.08 (d, J = 7.1 Hz, 3H), 1.29 (ddd, J = 3.2, 9.7, 13.7 Hz, 1H), 1.58 (ddd, J = 3.2, 8.9, 13.7 Hz, 1H), 1.88-2.01 (m, 1H), 2.44-2.56 (m, 1H), 3.22 (dd, J = 7.0, 9.3 Hz, 1H), 3.27-3.32 (m,
Appendix III

1H NMR (400 MHz, CDCl 3): δ = 0.62 (quart, J = 7.9 Hz, 6H), 0.94 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 1.03 (d, J = 7.0 Hz, 3H), 1.35 (ddd, J = 3.8, 9.1, 13.6 Hz, 1H), 1.53-1.62 (m, 1H), 1.88-2.0 (m, 2H), 2.73 (bt, J = 6.4 Hz, 1H), 3.23 (dd, J = 6.7, 9.1 Hz, 1H), 3.31 (dd, J = 5.7, 9.1 Hz, 1H), 3.41 (s, 3H), 3.43 (dd, J = 7.6, 3.9 Hz, 1H), 3.49-3.57 (m, 1H), 3.71-3.78 (m, 1H), 3.93-4.0 (m, 1H), 4.42 (s, 2H), 4.66 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 6.84-6.91 (m, 2H), 7.21-7.28 (m, 2H) ppm.

The compound was further purified by flash column chromatography (hexane/EtOAc 9:1 to 5:1) affording S3 (439 mg) in 87% yield as a colorless oil.
Appendix III  Experimental part

13C NMR (100 MHz, CDCl3): \( \delta = 5.3 \) (CH2), 7.1 (CH3), 15.2 (CH3), 17.3 (CH3), 29.9 (CH), 36.0 (CH), 37.0 (CH2), 55.4 (CH3), 56.3 (CH3), 66.3 (CH2), 71.3 (CH), 72.7 (CH2), 76.2 (CH2), 85.0 (CH), 97.9 (CH2), 113.9 (CH), 129.3 (CH), 131.0 (C), 159.2 (C) ppm.

IR (ATR) \( \nu = 3525, 2954, 2876, 1785, 1612, 1586, 1513, 1458, 1415, 1376, 1301, 1243, 1148, 1093, 1031, 938, 822, 725 \) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{25}\)H\(_{46}\)O\(_6\)Si \([\text{M+Na}]^+\), 493.2962; found 493.2954 +/- 5ppm.

Optical Rotation: \([\alpha]^{20}_D(c 1.0, \text{CHCl}_3) = -32.7^\circ\).

\((6S,7S,8S)-10,10-\text{Diethyl}-8-((S)-3-((4-\text{methoxy benzyl})oxy)-2-\text{methylpropyl})-7-(\text{methoxymethoxy})-2,2,3,3,6-\text{pentamethyl}-4,9-\text{dioxa}-3,10-\text{disiladodecane (37)}\). To a solution of alcohol S3 (390 mg, 0.83 mmol, 1.0 eq) in DMF (3.5 mL) were added imidazole (68 mg, 1 mmol, 1.2 eq) and TBS-chloride (128 mg, 0.85 mmol, 1.02 eq) at room temperature. The mixture was stirred for 14 hours before the reaction was quenched by the addition of a saturated solution of NH\(_4\)Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and the solvent was removed under vacuum. Purification of the crude material by flash column chromatography (hexane/EtOAc 19:1) delivered 37 (444 mg) in 91% yield as a colorless oil.

1H NMR (400 MHz, CDCl\(_3\)):
\( \delta = 0.03 \) (s, 3H), 0.032 (s, 3H), 0.61 (quart, \( J = 7.8 \) Hz, 6H), 0.89 (s, 9H), 0.95 (d, \( J = 6.4 \) Hz, 3H), 0.96 (t, \( J = 7.8 \) Hz, 9H), 1.01 (d, \( J = 7.0 \) Hz, 3H), 1.33 (ddd, \( J = 3.3, 9.4, 13.5 \) Hz, 1H), 1.54-1.61 (m, 1H), 1.76-1.87 (m, 1H), 1.92-2.03 (m, 1H), 2.32 (dd, \( J = 6.9, 9.2 \) Hz, 1H), 3.33 (dd, \( J = 5.7, 9.2 \) Hz, 1H), 3.37 (s, 3H), 3.39-3.44 (m, 1H), 3.56 (dd, \( J = 3.1, 9.4 \) Hz, 1H), 3.64 (dd, \( J = 5.1, 9.4 \) Hz, 1H), 3.81 (s, 3H), 3.96-4.01 (m, 1H), 4.43 (s, 2H), 4.64 (d, \( J = 6.7 \) Hz, 1H), 4.70 (d, \( J = 6.7 \) Hz, 1H), 6.84-6.89 (m, 2H), 7.23-7.29 (m, 2H) ppm.

13C NMR (100 MHz, CDCl\(_3\)):
\( \delta = -5.3 \) (CH3), 5.3 (CH2), 5.3 (CH3), 7.2 (CH3), 15.0 (CH3), 17.3 (CH3), 18.4 (C), 26.1 (CH2), 29.7 (CH), 36.2 (CH2), 36.9 (CH), 55.4 (CH3), 55.9 (CH3), 65.3 (CH2), 71.7 (CH), 72.6 (CH2), 76.4 (CH2), 82.8 (CH), 98.3 (CH2), 113.9 (CH), 129.3 (CH), 131.1 (C), 159.2 (C) ppm.

IR (ATR) \( \nu = 2954, 2877, 2361, 1789, 1513, 1416, 1247, 1148, 1095, 1033, 836 \) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{31}\)H\(_{60}\)O\(_6\)Si\(_2\) \([\text{M+Na}]^+\), 607.3826; found 607.3810 +/- 5ppm.

Optical Rotation: \([\alpha]^{20}_D(c 1.0, \text{CHCl}_3) = +0.3^\circ\).

\((2S,4S,5S,6S)-7-((\text{tert-Butyldimethylsilyl})oxy)-5-(\text{methoxymethoxy})-2,6-\text{dimethyl}-4-(\text{triethylsilyl})oxy)heptan-1-ol (S4). To a solution of 37 (870 mg, 1.49 mmol, 1.0 eq) in DCM (74 mL) were added phosphate buffer (pH 7, 0.87 mL) and DDQ (507 mg, 2.24 mmol, 1.5 eq) at
0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and for 2 hours at room temperature when TLC-control showed total conversion of the starting material. The reaction was terminated by the addition of a saturated solution of NaHCO₃ (30 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was concentrated under vacuum. After purification by flash column chromatography (hexane/EtOAc 9:1), primary alcohol \( \text{S4} \) (596 mg) was isolated in 86% yield as a colorless oil.

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 0.03 \text{ (s, 3H), 0.04 (s, 3H), 0.64 (quart, } J = 8.0 \text{ Hz, 6H), 0.90 (s, 9H), 0.96 (d, } J = 6.7 \text{ Hz, 3H), 0.97 (t, } J = 8.0 \text{ Hz, 9H), 1.04 (d, } J = 6.8 \text{ Hz, 3H), 1.40 (dd, } J = 2.9, 8.5, 13.8 \text{ Hz, 1H), 1.53-1.64 (m, 2H), 1.76-1.88 (m, 2H), 3.37 (s, 3H), 3.42-3.51 (m, 3H), 3.55 (dd, } J = 3.1, 9.5 \text{ Hz, 1H), 3.66 (dd, } J = 4.9, 9.5 \text{ Hz, 1H), 3.97-4.04 (m, 1H), 4.65 (d, } J = 6.6 \text{ Hz, 1H), 4.71 (d, } J = 6.6 \text{ Hz, 1H) ppm.} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = -5.3 \text{ (CH}_3\text{), 5.3 (CH}_2\text{), 7.1 (CH}_3\text{), 15.0 (CH}_3\text{), 17.1 (CH}_3\text{), 18.4 (C), 26.1 (CH}_3\text{), 32.7 (CH), 35.7 (CH}_2\text{), 36.9 (CH), 55.9 (CH}_3\text{), 65.3 (CH}_2\text{), 69.2 (CH}_2\text{), 72.4 (CH), 82.6 (CH), 98.3 (CH}_2\text{) ppm.} \]

IR (ATR) \( \nu = 2953, 2929, 2879, 2360, 2341, 1462, 1252, 1215, 1149, 1102, 1036, 940, 915 \text{ cm}^{-1}. \)

HRMS (ESI) calcd for C\text{23}H\text{52}O\text{5}Si\text{2} [M+Na]\text{]+, } 487.3251; found 487.3252 +/- 5ppm.

Optical Rotation: \( [\alpha]_{D}^{20} \text{ (c 1.2, CHCl}_3\text{) = } -3.9^\circ. \)

(2\text{S,4S,5S,6S})-7-((tert-Butyldimethylsilyl)oxy)-5-(methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)oxy)heptanal (17). To a mixture of alcohol \( \text{S4} \) (150 mg, 0.32 mmol, 1.0 eq) and DMSO (250 \( \mu \text{L}, 3.9 \text{ mmol, 12.0 eq) in DCM (2 mL) were added triethylamine (270 \( \mu \text{L}, 1.94 \text{ mmol, 6.0 eq) and SO}_3\cdot\text{pyridine (155 mg, 0.97 mmol, 3.0 eq) at 0 °C. After the addition the cooling bath was removed and the reaction mixture was stirred for 3 hours at room temperature. The reaction was terminated by the addition of H\text{2O} (2 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na\text{2SO}_4, filtered and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexane/EtOAc 19:1) delivering aldehyde \( 17 \) (137 mg) in 91% yield as a colorless oil.

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 0.03 \text{ (s, 3H), 0.04 (s, 3H), 0.63 (quart, } J = 7.7 \text{ Hz, 6H), 0.90 (s, 9H), 0.97 (t, } J = 7.7 \text{ Hz, 9H), 1.04 (d, } J = 7.1 \text{ Hz, 3H), 1.11 (d, } J = 7.1 \text{ Hz, 3H), 1.50-1.57 (m, 1H), 1.76-1.88 (m, 1H), 1.96 (dd, } J = 6.0, 9.3, 14.0 \text{ Hz, 1H), 2.46-2.57 (m, 1H), 3.36 (s, 3H), 3.46 (dd, } J = 3.8, 8.8 \text{ Hz, 1H), 3.55 (dd, } J = 3.0, 9.6 \text{ Hz, 1H), 3.68 (dd, } J = 4.7, 9.6 \text{ Hz, 1H), 3.98-4.03 (m, 1H), 4.64 (d, } J = 6.8 \text{ Hz, 1H), 4.70 (d, } J = 6.8 \text{ Hz, 1H), 9.64 (d, } J = 2.0 \text{Hz, 1H) ppm.} \]
13C NMR (100 MHz, CDCl3): δ = −5.3 (CH3), 5.2 (CH2), 7.1 (CH3), 13.9 (CH3), 14.9 (CH3), 18.4 (C), 26.0 (CH3), 33.0 (CH3), 36.9 (CH), 43.5 (CH), 55.9 (CH), 65.2 (CH2), 72.0 (CH), 82.3 (CH), 98.4 (CH2), 205.2 (CH) ppm.

IR (ATR) ν 2955, 2930, 2856, 1728, 1707, 1472, 1460, 1415, 1252, 1148, 1100, 1066, 1032, 1004, 946, 916, 834, 775 cm−1.


Optical Rotation: [α]20 D (c 1.0, CHCl3) = +13.2°.

(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (38).2 A vigorously stirred solution of D-ribose (15 g, 100 mmol, 1.0 eq) and NaHCO3 (16.8 g, 200 mmol, 2.0 eq) in H2O (90 mL) was cooled to 0 °C and bromine (5.4 mL, 104 mmol, 1.04 eq) was added slowly (20 min) via an additional funnel. During the addition the temperature of the reaction mixture was controlled by an internal thermometer and did not exceed 5 °C. When the addition was completed the orange solution was stirred for an additional hour. Solid NaHSO3 (1.26 g, 10 mmol, 0.1 eq) was added to destroy the excess of bromine. The water in the colorless reaction mixture was removed on a rotary evaporator (bath temperature 60 °C) until a yellow wet slurry remained. Afterwards EtOH (60 mL) and toluene (30 mL) were added to give a cloudy suspension and the solvent was removed under reduced pressure to give a damp solid. Again EtOH (60 mL) was added and the crude product mixture was heated to reflux on an oil bath for 30 minutes. The hot ethanolic suspension was filtered and the solids were rinsed once with hot EtOH (15 mL). The filtrate was cooled and stored in the refrigerator for 16 hours. The crystalline product was filtered, washed first with cold EtOH (10 mL), then with Et2O (10 mL) and dried under vacuum to yield 20 g of crude product (the major contaminant is NaBr) The crude material was used without any further purification for the acetonide protection.

To a suspension of crude D-ribonolactone (20 g) in acetone (120 mL) was added boron trifluoride etherate (1.71 mL, 13.5 mmol, 0.1 eq) followed by 2,2-dimethoxypropane (24 mL, 19.6 mmol, 1.3 eq) at room temperature and the reaction mixture was stirred for 3 hours. The resulting yellow suspension was filtered through a pad of Celite, the solids were washed with acetone (15 mL) and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (50 mL), extracted with H2O (40 mL) and brine (40 mL), respectively. The organic extract was dried over Na2SO4 and the solvent was removed under reduced pressure delivering protected D-ribonolactone (38, 12.4 g) in 66% yield over two steps as a light yellow oil, which was used without any further purification for the next step.
1H NMR (400 MHz, CDCl3): δ = 1.38 (s, 3H), 1.48 (s, 3H), 2.29 (t, J = 5.4 Hz, 1H, OH), 3.81 (ddd, J = 1.8, 5.6, 12.1 Hz, 1H), 4.0 (ddd, J = 2.5, 5.6, 12.1 Hz, 1H), 4.63 (bt, J = 2.0 Hz, 1H), 4.78 (d, J = 5.8 Hz, 1H), 4.83 (d, J = 5.8 Hz, 1H) ppm.

13C NMR (100 MHz, CDCl3): δ = 25.6 (CH3), 26.9 (CH3), 62.2 (CH2), 75.8 (CH), 78.4 (CH), 82.7 (CH), 113.3 (C), 174.9 (C) ppm.

IR (ATR) ν 3469, 2991, 1767, 1379, 1273, 1222, 1200, 1154, 975, 856, 810, 774 cm⁻¹.

HRMS (ESI) calcd for C₈H₁₂O₅ [M+Na]+, 211.0583; found 211.0585 ± 5 ppm.

Optical Rotation: [α]ºD(c 1.0, CHCl3) = −66.9°.

((4R,5R)-5-((R)-1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (39). Protected D-ribonolactone 38 (500 mg, 2.7 mmol, 1.0 eq) was dissolved in toluene (11 mL). After the addition of pyrrolidine (1.1 mL, 13.5 mmol, 5.0 eq) the mixture was heated to reflux for 12 hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (DCM/MeOH 19:1) to afford amide 39 (610 mg) in 87% yield as a light yellow oil.

1H NMR (400 MHz, CDCl3): δ = 1.37 (s, 3H), 1.52 (s, 3H), 1.79 - 2.03 (m, 4H), 2.35 (bs, 1H, OH), 3.43 - 3.59 (m, 2H), 3.60 - 3.72 (m, 3H), 3.77 - 3.89 (m, 2H), 4.27 (dd, J = 6.3, 8.8 Hz, 1H), 4.59 (bs, 1H, OH), 4.84 (d, J = 6.3 Hz, 1H) ppm.

13C NMR (100 MHz, CDCl3): δ = 23.8 (CH2), 25.3 (CH3), 26.5 (CH2), 27.2 (CH3), 47.02 (CH2), 47.14 (CH2), 64.5 (CH), 70.0 (CH), 76.7 (CH), 78.3 (CH), 109.9 (C), 167.8 (C) ppm.

IR (ATR) ν 3335, 2981, 2876, 1781, 1630, 1454, 1372, 1214, 1164, 1053, 907, 726 cm⁻¹.

HRMS (ESI) calcd for C₁₂H₂₁NO₅ [M+Na]+, 282.1318; found 282.1321 ± 5 ppm.

Optical Rotation: [α]ºD(c 1.0, CHCl3) = +16.2°.

((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (S5). To a solution of diol 39 (250 mg, 0.96 mmol, 1.0 eq) in DCM (2 mL) were added 2,6-lutidine (0.335 mL, 2.88 mmol, 3.0 eq) and TBS-triflate (0.706 mL, 3.07 mmol, 3.2 eq) at 0 °C. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 15 hours. The reaction was quenched by the addition of a saturated solution of NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered
Appendix III  Experimental part

and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) to deliver **S5** (375 mg) in 80% yield as a slightly yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.74-2.0 (m, 4H), 3.36-3.55 (m, 3H), 3.60-3.69 (m, 1H), 3.74-3.77 (m, 2H), 4.37-4.41 (m, 2H), 4.67-4.70 (m, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = −5.4 (CH$_3$), −5.2 (CH$_3$), −4.5 (CH$_3$), −3.7 (CH$_3$), 18.3 (C), 18.6 (C), 24.2 (CH$_2$), 26.0 (CH$_3$), 26.05 (CH$_3$), 26.1 (CH$_3$), 26.4 (CH$_2$), 27.0 (CH$_3$), 46.1 (CH$_2$), 46.6 (CH$_2$), 64.7 (CH$_2$), 72.4 (CH), 74.6 (CH), 77.6 (CH), 110.4 (C), 167.3 (C) ppm.

IR (ATR) ν 2953, 2929, 2856, 1655, 1442, 1368, 1342, 1250, 1223, 1090, 992, 938, 831, 774 cm$^{-1}$.

HRMS (ESI) calcd for C$_{24}$H$_{49}$NO$_5$Si$_2$ [M+Na]$^+$, 510.3047; found 510.3048 +/- 5ppm.

Optical Rotation: [α]$^D_{20}$ (c 1.0, CHCl$_3$) = −46.7°.

1-((4$^R$,5$^S$)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)ethanone (**40**). A solution of MeLi (1.6 M in Et$_2$O, 6.4 mL, 20.5 mmol, 2.0 eq) was added to amide **S5** dissolved in THF (50 mL) at −78 °C. The reaction mixture was stirred for 15 minutes when TLC-control showed total consumption of the starting material. The reaction was terminated by the addition of H$_2$O (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). Further purification of crude ketone by flash column chromatography (hexane/EtOAc 40:1) delivered **40** (4.23 g) in 95% yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.36 (s, 3H), 1.60 (s, 3H), 2.31 (s, 3H), 3.57 (dd, $J = 5.1, 10.4$ Hz, 1H), 3.74 (dd, $J = 7.3$ Hz, 10.4, 1H), 4.05 (dd, $J = 3.4, 5.1, 7.3$ Hz, 1H), 4.38 (d, $J = 7.8$ Hz, 1H), 4.57 (dd, $J = 3.4, 7.8$ Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = −5.3 (CH$_3$), −4.8 (CH$_3$), −4.1 (CH$_3$), 18.4 (CH$_3$), 18.6 (CH$_3$), 24.7 (CH$_3$), 26.1 (CH$_3$), 26.15 (CH$_3$), 26.7 (CH$_3$), 29.2 (CH$_3$), 63.9 (CH$_2$), 72.6 (CH), 79.8 (CH), 80.6 (CH), 109.1 (C), 209.3 (C) ppm.

IR (ATR) ν 2930, 2887, 2858, 1717, 1473, 1361, 1253,1214, 1150, 1082, 939, 832, 776, 669 cm$^{-1}$.

HRMS (ESI) calcd for C$_{21}$H$_{44}$O$_5$Si$_2$ [M+Na]$^+$, 455.2625; found 455.2620 +/- 5ppm.

Optical Rotation: [α]$^D_{20}$ (c 1.0, CHCl$_3$) = −20.2°.
(R)-2-((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxoa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-yn-2-ol (S6). To a solution of methyl ketone 40 (5.0 g, 11.6 mmol, 1.0 eq) in THF (220 mL) was added a solution of ethynyl magnesium bromide (0.5 M in THF, 69 mL, 34.7 mmol, 3.0 eq) at 0 °C via a syringe. The reaction mixture was stirred for 2 hours at 0 °C and 90 minutes at room temperature. After TLC-analysis indicated complete consumption of the starting material, the reaction was quenched by the addition of H2O (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na2SO4, filtered and the solvent was removed under reduced pressure. After purification of the crude material by flash column chromatography (hexane/EtOAc 19:1 to 9:1) tertiary alcohol S6 (5.13 g) was isolated as single diastereomer in 97% yield as a colorless oil.

1H NMR (400 MHz, CDCl3): δ = 0.08 (s, 6H), 0.22 (s, 3H), 0.23 (s, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 1.34 (s, 3H), 1.52 (s, 3H), 1.56 (d, J = 0.98 Hz, 3H), 2.41 (s, 1H), 3.86 (dd, J = 3.4, 11.6 Hz, 1H), 3.92 (dd, J = 2.9, 11.6 Hz, 1H), 3.97 (d, J = 6.2 Hz, 1H), 4.37 (dd, J = 6.2, 8.5 Hz, 1H), 4.76-4.81 (m, 1H), 4.98 (d, J = 0.98 Hz, 1H) ppm.

13C NMR (100 MHz, CDCl3): δ = −5.4 (CH3), −5.2 (CH3), −3.4 (CH3), −3.2 (CH3), 18.6 (C), 18.7 (C), 25.4 (CH3), 26.1 (CH3), 26.3 (CH3), 27.3 (CH3), 29.6 (CH3), 64.0 (CH2), 67.8 (C), 73.1 (CH), 73.3 (CH), 76.6 (CH), 82.9 (CH), 87.4 (C), 108.4 (C) ppm.

IR (ATR) ν 3312, 2986, 2930, 2885, 1472, 1410, 1254, 1172, 1084, 1053, 980, 895, 834, 779 cm⁻¹.

HRMS (ESI) calcd for C23H46O5Si2 [M+Na]⁺, 481.2782; found 481.2793 +/- 5ppm.

Optical Rotation: [α]D(c 1.0, CHCl3) = −1.6°.

(Methoxymethoxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxoa-3,8-disiladecane (41). To a solution of tertiary alcohol S6 (2.5 g, 5.46 mmol, 1.0 eq) in DCM (27 mL) were added DIPEA (5.68 mL, 32.8 mmol, 6.0 eq) and MOM-Cl (1.25 mL, 16.4 mmol, 3.0 eq) at 0 °C. The reaction mixture was warmed to 50 °C and was stirred for 24 hours before it was quenched by the addition of H2O (15 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na2SO4, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane/EtOAc 19:1) affording 41 (2.47 g) in 90% yield as a colorless oil.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.04 (s, 6H), 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.34 (s, 3H), 1.50 (s, 3H), 1.64 (s, 3H), 2.57 (s, 1H), 3.38 (s, 3H), 3.64 (dd, $J$ = 6.8, 10.7 Hz, 1H), 3.94 (dd, $J$ = 1.8, 10.7 Hz, 1H), 4.09 (d, $J$ = 6.6 Hz, 1H), 4.24 (dd, $J$ = 4.2, 6.6 Hz, 1H), 4.44 (dd, $J$ = 1.8, 4.3, 6.8 Hz, 1H), 4.71 (d, $J$ = 7.5 Hz, 1H), 5.22 (d, $J$ = 7.5 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = −5.2 (CH$_3$), −5.1 (CH$_3$), −4.6 (CH$_3$), −3.7 (CH$_3$), 18.5 (C), 18.6 (C), 25.1 (CH$_3$), 26.1 (CH$_3$), 26.2 (CH$_3$), 26.7 (CH$_3$), 27.2 (CH$_3$), 55.9 (CH$_3$), 66.4 (CH$_2$), 72.3 (CH), 74.6 (C), 77.2 (CH), 81.7 (CH), 81.8 (CH), 82.7 (C), 92.8 (CH$_2$), 108.1 (C) ppm.

IR (ATR) $\nu$ 2929, 2887, 2856, 1463, 1380, 1371, 1251, 1135, 1092, 1056, 991, 833 cm$^{-1}$.

HRMS (ESI) calcd for C$_{25}$H$_{50}$O$_6$Si$_2$ [M+Na$^+$], 525.3044; found 525.3033 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{20}^{20}$D(c 1.0, CHCl$_3$) = −35.3°.

Alcohol 42.

**LHMDS-method:**

**Preparation of a 0.5 M solution of LHMDS:** To a solution of freshly distilled hexamethyldisilazane (0.22 mL, 1.04 mmol, 1.04 eq) in THF (1.4 mL) was added a solution of $n$-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol, 1.0 eq) at 0 °C. After the addition the reaction mixture was allowed to warm to room temperature and was stirred for 20 minutes.

A solution of freshly prepared LHMDS (0.5 M in THF, 0.73 mL, 0.36 mmol, 1.1 eq) was added to a solution of alkyne 41 (166 mg, 0.33 mmol, 1.0 eq) in dry THF (2.5 mL) at −78 °C. The reaction mixture was stirred for 2 h 30 min before it was warmed to −40 °C and dry CeCl$_3$ (81 mg, 0.33 mmol, 1.0 eq) was added. After stirring for an additional hour at 40 °C a solution of aldehyde 17 (91 mg, 0.2 mmol, 0.6 eq) in THF (1.3 mL) was added and the colorless solution was warmed to 0 °C and stirred for 20 minutes when TLC-analysis indicated total conversion of the aldehyde. The reaction was terminated by the addition of a saturated, aqueous solution of NH$_4$Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude secondary alcohols were purified by flash column chromatography (hexane/EtOAc 19:1) to obtain 42 (60 mg, less polar, minor diastereomer) and 42a (100 mg, more polar, major diastereomer) in a 2:1 diastereomeric ratio and 84% overall yield as a colorless oils.

**t-BuLi method:**

To a solution of alkyne 41 (171 mg, 0.34 mmol, 2.0 eq) and HMPA (106 μL, 0.612 mmol, 3.6 eq) in THF (2.8 mL) was added $t$-BuLi (1.7 M in pentane, 200 μL, 0.34 mmol, 2.0 eq) at −78 °C. After
stirring for 30 minutes at that temperature, 30 μL of the reaction mixture were removed via a syringe and quenched by the addition of D₂O (mini-quench). According to the following ¹H-NMR-experiment, which indicated a 50% lithiation of the alkyne, two additional equivalents of t-BuLi (200 μL) were added. After 25 minutes, complete lithiation was indicated by another mini-quench experiment, and a solution of aldehyde 17 (80 mg, 0.17 mmol, 1.0 eq) in THF (1.0 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 2:1 diastereomeric ratio (42, less polar, minor diastereomer, 54 mg, and 42a, more polar, major diastereomer, 108 mg) and 80% overall yield as colorless oils.

Alcohol 42a (major diastereomer):

¹H NMR (400 MHz, CDCl₃): δ = 0.03 (s, 3H), 0.031 (s, 3H), 0.06 (s, 3H), 0.08 (s, 6H), 0.10 (s, 3H), 0.63 (quart, J = 7.8 Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.96 (t, J = 7.8 Hz, 6H), 1.02 (d, J = 5.1 Hz, 3H), 1.04 (d, J = 5.3 Hz, 3H), 1.33 (s, 3H), 1.37-1.46 (m, 1H), 1.50 (s, 3H), 1.62 (s, 3H), 1.73-1.83 (m, 2H), 1.85-1.93 (m, 1H), 2.75 (bd, J = 5.3 Hz, OH), 3.36 (s, 3H), 3.37 (s, 3H), 3.45 (dd, J = 3.8, 8.8 Hz, 1H), 3.53 (dd, J = 3.2, 9.7 Hz, 1H), 3.67 (dd, J = 4.6, 9.7 Hz, 1H), 3.71 (dd, J = 6.3, 10.8 Hz, 1H), 3.92 (dd, J = 1.8, 10.8 Hz, 1H), 3.96-4.01 (m, 1H), 4.05 (d, J = 6.3 Hz, 1H), 4.21-4.28 (m, 2H), 4.42-4.48 (m, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 6.6 Hz, 1H), 5.21 (d, J = 7.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = −5.3 (CH₃), −5.1 (CH₃), −5.0 (CH₃), −4.5 (CH₃), −3.6 (CH₃), 5.3 (CH₃), 7.1 (CH₃), 14.9 (CH₃), 15.5 (CH₃), 18.4 (C), 18.5 (C), 18.7 (C), 25.2 (CH₃), 26.0 (CH₃), 26.2 (CH₃), 26.3 (CH₃), 26.7 (CH₃), 27.4 (CH₃), 34.5 (CH₂), 36.2 (CH), 37.0 (CH), 55.81 (OCH₃), 55.84 (OCH₃), 65.3 (CH₂), 66.4 (CH₂), 67.3 (CH), 72.0 (CH), 72.2 (CH), 74.7 (C), 81.3 (CH), 81.9 (CH), 82.5 (CH), 84.6 (C), 89.4 (C), 92.6 (C), 98.3 (C), 108.0 (C) ppm.

IR (ATR) ν 3409, 2953, 2929, 2856, 1462, 1380, 1252, 1216, 1144, 1097, 1032, 986, 919, 833, 775, 667 cm⁻¹.

HRMS (ESI) calcd for C₄₇H₁₀₀O₁₁Si₄ [M+Na]⁺, 987.6241; found 987.6235 +/- 5 ppm.

Optical Rotation: [α]₀²⁰ d (c 1.0, CHCl₃) = −27.9°.
Alcohol 42 (minor diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.03 (s, 3H), 0.032 (s, 3H), 0.08 (s, 3H), 0.084 (s, 6H), 0.13 (s, 3H), 0.62 (quart, $J$ = 7.9 Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.96 (t, $J$ = 7.9 Hz, 9H), 1.03 (d, $J$ = 6.8 Hz, 3H), 1.04 (d, $J$ = 6.6 Hz, 3H), 1.35 (s, 3H), 1.40-1.48 (m, 1H), 1.50 (s, 3H), 1.63 (s, 3H), 1.64-1.70 (m, 1H), 1.76-1.87 (m, 1H), 1.90-2.0 (m, 1H), 3.35 (s, 3H), 3.37 (s, 3H), 3.42 (dd, $J$ = 3.8, 8.6 Hz, 1H), 3.53-3.58 (m, 2H), 3.66 (dd, $J$ = 5.1, 9.6 Hz, 1H), 3.73 (dd, $J$ = 7.1, 10.9 Hz, 1H), 3.94-4.04 (m, 2H), 4.08 (d, $J$ = 6.6 Hz, 1H), 4.25-4.31 (m, 2H), 4.43-4.48 (m, 1H), 4.63 (d, $J$ = 7.3 Hz, 1H), 4.64 (d, $J$ = 6.6 Hz, 1H), 4.70 (d, $J$ = 6.6 Hz, 1H), 5.27 (d, $J$ = 7.3 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = $-5.3$ (CH$_3$), $-5.2$ (CH$_3$), $-4.6$ (CH$_3$), $-3.7$ (CH$_3$), 5.3 (CH$_2$), 7.2 (CH$_3$), 15.0 (CH$_3$), 15.1 (CH$_3$), 18.41 (C), 18.43 (C), 19.0 (C), 25.2 (CH$_3$), 26.1 (CH$_3$), 26.2 (CH$_3$), 26.3 (CH$_3$), 26.4 (CH$_3$), 27.9 (CH$_3$), 35.2 (CH), 35.3 (CH$_2$), 36.9 (CH), 55.87 (CH$_3$), 55.90 (CH$_3$), 65.3 (CH$_2$), 67.0 (CH), 67.5 (CH$_2$), 71.9 (CH), 72.3 (CH), 74.3 (C), 82.0 (CH), 82.2 (CH), 82.7 (CH), 84.4 (C), 89.8 (C), 92.5 (CH$_2$), 98.3 (CH$_2$), 108.2 (C) ppm.

IR (ATR) $\nu$ 3409, 2953, 2929, 2856, 1462, 1380, 1252, 1216, 1144, 1097, 1032, 986, 919, 833, 775, 667 cm$^{-1}$.

HRMS (ESI) calcd for C$_{48}$H$_{100}$O$_{11}$Si$_4$ [M+Na]$^+$, 987.6241; found 987.6260 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = $-19.9^\circ$.

Mosher ester S7. To a solution of secondary alcohol 42 (minor diastereomer, 10 mg, 0.01 mmol, 1.0 eq) in DCM (0.3 mL) were added NEt$_3$ (17 $\mu$L, 0.12 mmol, 12.0 eq), DMAP (1.2 mg, 0.01 mmol, 1.0 eq) and S-(-)-Mosher’s acid chloride (3.7 $\mu$L, 0.02 mmol, 2.0 eq) sequentially at room temperature. The reaction mixture was stirred for 4 hours at room temperature. As TLC-control showed total conversion of the starting material the reaction was terminated by the addition of a saturated, aqueous solution of NH$_4$Cl (5 mL) and the resulting mixture was diluted with DCM.
(5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1) to afford Mosher-ester S7 (12 mg) in quantitative yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.02$ (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.041 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.57-0.63 (m, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.94 (t, $J = 7.9$ Hz, 9H), 1.01 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 1.30 (s, 3H), 1.36-1.40 (m, 1H), 1.41 (s, 3H), 1.58 (s, 3H), 1.62-1.73 (m, 2H), 2.08-2.16 (m, 1H), 3.34 (s, 3H), 3.342 (s, 3H), 3.43 (dd, $J = 3.6$, 9.2 Hz, 1H), 3.50 (dd, $J = 3.0$, 9.4 Hz, 1H), 3.53 (s, 3H), 3.67 (dd, $J = 4.5$, 9.4 Hz, 1H), 3.76 (dd, $J = 4.2$, 10.6 Hz, 1H), 3.79 (dd, $J = 2.0$, 10.6 Hz, 1H), 3.94-3.98 (m, 1H), 3.98 (d, $J = 5.3$ Hz, 1H), 4.23 (dd, $J = 4.1$, 9.5 Hz, 1H), 4.35-4.39 (m, 1H), 4.59 (d, $J = 7.5$ Hz, 1H), 4.61 (d, $J = 6.6$ Hz, 1H), 4.69 (d, $J = 6.6$ Hz, 1H), 5.17 (d, $J = 7.5$ Hz, 1H), 5.51 (d, $J = 5.6$ Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -5.37$ (CH$_3$), $-5.36$ (CH$_3$), $-5.30$ (CH$_3$), $-5.28$ (CH$_3$), $-4.2$ (CH$_3$), $-3.6$ (CH$_3$), 5.2 (CH$_2$), 7.0 (CH$_3$), 14.7 (CH$_3$), 14.8 (CH$_3$), 18.4 (C), 18.48 (C), 18.5 (C), 25.3 (CH$_3$), 26.0 (CH$_3$), 26.1 (CH$_3$), 26.2 (CH$_3$), 26.8 (CH$_3$), 26.9 (CH$_3$), 33.8 (CH), 34.5 (CH$_2$), 36.9 (CH), 55.5 (CH$_3$), 55.8 (CH$_3$), 55.81 (CH$_3$), 65.2 (CH$_2$), 65.5 (CH$_2$), 71.3 (CH), 71.7 (CH), 71.8 (CH), 74.9 (C), 79.6 (CH), 81.9 (CH), 82.3 (CH), 83.2 (C), 87.0 (C), 92.9 (CH$_2$), 98.3 (CH$_2$), 107.7 (C), 122.0 (C), 124.8 (C), 127.7 (CH), 128.5 (CH), 129.7 (CH) 132.2 (C), 165.5 (C) ppm.

HRMS (ESI) calcd for C$_{58}$H$_{107}$F$_3$O$_{13}$Si$_4$ [M+Na]$^+$, 1203.6639; found 1203.6633 +/- 5ppm.

Mosher-ester S8. Mosher-ester S8 was prepared following the same procedure as described above. Starting from diastereomeric alcohol 42a (major diastereomer, 10 mg, 0.01 mmol, 1.0 eq) and S-(+)-Mosher’s acid chloride, S8 (12 mg) was afforded in quantitative yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.02$ (s, 3H), 0.024 (s, 3H), 0.027 (s, 3H), 0.03 (s, 3H), 0.08 (s, 3H), 0.1 (s, 3H), 0.55-0.63 (m, 6H), 0.88 (s, 9H), 0.89 (s, 18H), 0.94 (t, $J = 8.1$ Hz, 9H), 0.97 (d, $J = 7.3$ Hz, 3H), 1.03 (d, $J = 7.2$ Hz, 3H), 1.31 (s, 3H), 1.34-1.42 (m, 1H), 1.46 (s, 3H), 1.57-1.61 (m, 1H), 1.62 (s, 3H), 1.63-1.68 (m, 1H), 2.06-2.13 (m, 1H), 3.31 (s, 3H), 3.34 (s, 3H), 3.38 (dd, $J = 4.0$, 8.8 Hz, 1H), 3.49 (dd, $J = 2.8$, 9.6 Hz, 1H), 3.56 (s, 3H), 3.64 (dd, $J = 4.6$, 9.6 Hz, 1H), 3.74 (dd, $J = 4.3$, 10.7 Hz, 1H), 3.81 (dd, $J = 2.0$, 10.7 Hz, 1H), 3.91-3.96 (m, 1H), 4.0 (d, $J = 5.8$ Hz, 1H), 4.24 (dd, $J = 5.8$, 6.3 Hz, 1H), 4.38-4.42 (m, 1H), 4.59 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 7.5$ Hz, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 5.28 (d, $J = 7.5$ Hz, 1H), 5.60 (d, $J = 4.0$ Hz, 1H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): δ = −5.4 (CH$_3$), −5.28 (CH$_3$), −5.27 (CH$_3$), −4.2 (CH$_3$), −3.5 (CH$_3$), 5.2 (CH$_2$), 7.1 (CH$_3$), 14.4 (CH$_3$), 14.7 (CH$_3$), 18.4 (C), 18.5 (C), 18.6 (C), 25.4 (CH$_3$), 26.0 (CH$_3$), 26.1 (CH$_3$), 26.2 (CH$_3$), 26.9 (CH$_3$), 27.0 (CH$_3$), 33.9 (CH$_2$), 34.2 (CH), 36.8 (CH), 55.6 (CH$_3$), 55.7 (CH$_3$), 55.8 (CH$_3$), 65.2 (CH$_2$), 65.4 (CH$_2$), 71.0 (CH), 71.6 (CH), 71.9 (CH), 75.1 (C), 79.6 (CH), 81.9 (CH), 82.5 (CH), 84.1 (C), 87.0 (C), 92.8 (CH$_2$), 98.3 (CH$_2$), 107.9 (C), 122.0 (C), 124.8 (C), 127.6 (CH), 128.6 (CH), 129.7 (CH), 132.5 (C), 165.6 (C) ppm.

HRMS (ESI) calcd for C$_{58}$H$_{107}$F$_3$O$_{13}$Si$_4$ [M+Na]$^+$, 1203.6639; found 1203.6638 +/− 5ppm.

**Mosher-ester Analysis:**

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<th>Proton</th>
<th>S7 (S-configurated) ppm</th>
<th>S8 (R-configurated) ppm</th>
<th>Diff. S7-S8 (dSdR) ppm</th>
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<tr>
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<td>1.62</td>
<td>−0.04</td>
</tr>
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</table>

**Alcohol 44.** To a solution of alcohol 42 (110 mg, 0.11 mmol, 1.0 eq) in DMF (2 mL) was added NaH (60% dispersion in mineral oil, 9.1 mg, 0.22 mmol, 2 eq) at 0 °C. After 30 minutes, PMB-Cl (28 μL, 0.21 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for 2 hours at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO$_3$ (3 mL). After dilution with Et$_2$O (5 mL) the layers were separated and the aqueous phase was extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were washed with H$_2$O once (10 mL), dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. The
crude product was further purified by flash column chromatography (hexane/EtOAc 19:1 to 5:1) to provide 44 (65 mg) in 59% yield as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.00 \) (s, 6H), 0.04 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 0.96 (d, \(J = 7.1\) Hz, 3H), 1.06 (d, \(J = 6.6\) Hz, 3H), 1.20-1.29 (m, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 1.64 (s, 3H), 1.79 (ddd, \(J = 4.0, 10.9, 13.6\) Hz, 1H), 1.90-2.01 (m, 1H), 2.11-2.22 (m, 1H), 2.82 (d, \(J = 6.6\) Hz, 1H), 3.26 (ddd, \(J = 3.5, 5.6\) Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.54 (dd, \(J = 5.8, 9.9\) Hz, 1H), 3.63 (dd, \(J = 5.6, 9.9\) Hz, 1H), 3.68-3.76 (m, 1H), 3.73 (dd, \(J = 4.2, 10.5\) Hz, 1H), 3.76-3.81 (m, 4H), 3.99 (d, \(J = 6.1\) Hz, 1H), 4.05 (d, \(J = 6.1\) Hz, 1H), 4.26 (dd, \(J = 6.1, 5.9\) Hz, 1H), 4.40 (d, \(J = 11.6\) Hz, 1H), 4.42-4.47 (m, 1H), 4.66 (d, \(J = 7.5\) Hz, 1H), 4.67 (d, \(J = 6.5\) Hz, 1H), 4.70 (d, \(J = 6.5\) Hz, 1H), 4.73 (d, \(J = 11.6\) Hz, 1H), 5.30 (d, \(J = 7.3\) Hz, 1H), 6.83-6.88 (m, 2H), 7.22-7.28 (m, 2H) ppm.

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -5.3\) (CH\(_3\)), -4.2 (CH\(_3\)), -3.5 (CH\(_3\)), 14.7 (CH\(_3\)), 15.8 (CH\(_3\)), 18.45 (C), 18.50 (CH), 18.54 (C), 25.5 (CH\(_3\)), 26.0 (CH\(_3\)), 26.1 (CH\(_3\)), 26.2 (CH\(_3\)), 27.1 (CH\(_3\)), 27.5 (CH\(_3\)), 35.0 (CH), 38.0 (CH\(_2\)), 38.1 (CH), 55.4 (CH\(_3\)), 55.8 (CH\(_3\)), 56.2 (CH\(_3\)), 64.4 (CH\(_2\)), 65.6 (CH\(_2\)), 69.2 (CH), 70.2 (CH\(_2\)), 71.7 (CH), 73.7 (CH), 75.1 (C), 79.8 (CH), 82.1 (CH), 85.7 (CH), 85.9 (C), 87.3 (C), 92.8 (CH\(_2\)), 98.6 (CH\(_2\)), 107.8 (C), 113.9 (CH), 129.5 (CH), 130.4 (C), 159.3 (C) ppm.

IR (ATR) \(\nu = 3467, 2929, 2856, 2360, 2340, 1614, 1514, 1463, 1379, 1250, 1142, 1054, 833, 775\) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{50}\)H\(_{94}\)O\(_{12}\)Si\(_3\) \([M+Na]^+\), 993.5951; found 993.5960 +/- 5ppm.

Optical Rotation: \([\alpha]^{20}_D(c 1.0, \text{CHCl}_3) = -100.1^\circ\).

**Alkyne 45.** To a solution of secondary alcohol 44 (60 mg, 0.062 mmol, 1.0 eq) and 2,6-lutidine (44 \(\mu\)L, 0.372 mmol, 6.0 eq) in DCM (1.0 mL) was added TBS-triflate (42 \(\mu\)L, 0.186 mmol, 3.0 eq) at 0\(^\circ\)C. The reaction mixture was allowed to stir for 48 hours at room temperature before it was quenched by the addition of a saturated, aqueous solution of NaHCO\(_3\) (5 mL). After dilution with DCM (5 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) 45 (30 mg) was isolated in 45% yield (85% brsm) as a light yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.02$ (s, 9H), 0.03 (s, 3H), 0.05 (s, 3H), 0.09 (s, 6H), 0.11 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 1.00 (d, $J = 7.1$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.33 (s, 3H), 1.39-1.49 (m, 1H), 1.50 (s, 3H), 1.64 (s, 3H), 1.71-1.81 (m, 2H), 1.94-2.07 (m, 1H), 3.36 (s, 6H), 3.43 (dd, $J = 3.5$, 9.1 Hz, 1H), 3.53 (dd, $J = 3.0$, 9.3 Hz, 1H), 3.66 (dd, $J = 4.7$, 9.3 Hz, 1H), 3.76 (dd, $J = 4.5$, 10.6 Hz, 1H), 3.80 (s, 3H), 3.84 (dd, $J = 2.0$, 10.6 Hz, 1H), 3.92-3.97 (m, 1H), 3.98 (d, $J = 4.8$ Hz, 1H), 4.04 (d, $J = 6.1$ Hz, 1H), 4.26 (dd, $J = 6.1$, 6.3 Hz, 1H), 4.38 (d, $J = 11.6$ Hz, 1H), 4.44-4.49 (m, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.65 (d, $J = 7.3$ Hz, 1H), 4.69 (d, $J = 6.6$ Hz, 1H), 4.71 (d, $J = 11.6$ Hz, 1H), 5.24 (d, $J = 7.3$ Hz, 1H), 6.83-6.88 (m, 2H), 7.22-7.26 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ −5.1 (CH$_3$), −5.0 (CH$_3$), −4.5 (CH$_3$), −4.0 (CH$_3$), −3.4 (CH$_3$), −3.3 (CH$_3$), 15.2 (CH$_3$), 15.5 (CH$_3$), 18.4 (C), 18.6 (C), 18.7 (C), 18.8 (C), 25.7 (CH$_3$), 26.2 (CH$_3$), 26.3 (CH$_3$), 26.4 (CH$_3$), 26.45 (CH$_3$), 27.3 (CH$_3$), 27.7 (CH$_3$), 34.7 (CH), 34.9 (CH$_2$), 37.2 (CH), 55.6 (CH$_3$), 56.01 (CH$_3$), 56.03 (CH$_3$), 65.5 (CH$_2$), 65.9 (CH$_2$), 70.5 (CH$_2$), 71.9 (CH), 72.3 (CH), 74.0 (CH), 75.3 (C), 80.2 (CH), 82.2 (CH), 82.6 (CH), 86.0 (C), 87.5 (C), 93.0 (CH$_2$), 98.5 (CH$_2$), 108.0 (C), 114.0 (CH), 129.7 (CH), 130.8 (C), 159.5 (C) ppm.

IR (ATR) $\nu$ 2927, 2856, 2365, 1614, 1519, 1475, 1379, 1250, 1140, 1078, 1035, 837, 779 cm$^{-1}$.

HRMS (ESI) calcd for $\text{C}_{56}\text{H}_{108}\text{O}_{12}\text{Si}_3$ [M+Na]$^+$, 1107.6816; found 1107.6810 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 0.88, CHCl$_3$) = −6.3°.

**Alcohol 49.** Alcohol 49 was prepared following the same procedures as described for alcohol 42 above.

<table>
<thead>
<tr>
<th>Method</th>
<th>Alkyne (41)</th>
<th>Aldehyde (48)</th>
<th>Yield</th>
<th>$dr$ 49:49a</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHMDS (0.5 M in THF), 1.1 eq CeCl$_3$, 1 eq</td>
<td>241 mg, 0.48 mmol, 1.0 eq</td>
<td>100 mg, 0.29 mmol, 0.6 eq</td>
<td>90%</td>
<td>1:2</td>
</tr>
<tr>
<td>t-BuLi (1.7 M in pentane), 2.0 eq, HMPA, 3.6 eq</td>
<td>231 mg, 0.46 mmol, 2.0 eq</td>
<td>80 mg, 0.23 mmol, 1.0 eq</td>
<td>60%</td>
<td>1:2</td>
</tr>
</tbody>
</table>
Alcohol 49a (major diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): δ = 0.07 (s, 3H), 0.09 (s, 6H), 0.10 (s, 3H), 0.62 (quart, $J = 7.9$ Hz, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 0.97 (t, $J = 7.9$ Hz, 9H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.34 (s, 3H), 1.36-1.44 (m, 1H), 1.50 (s, 3H), 1.62 (s, 3H), 1.72-1.81 (m, 1H), 1.82-1.92 (m, 1H), 2.41-2.56 (m, 1H), 2.70 (d, $J = 5.8$ Hz, 1H), 3.29 (dd, $J = 5.1$, 5.3 Hz, 1H), 3.36 (s, 3H), 3.38 (s, 3H), 3.70 (dd, $J = 6.4$, 11.0 Hz, 1H), 3.84-3.90 (m, 1H), 3.92 (dd, $J = 1.5$, 11.0 Hz, 1H), 4.05 (d, $J = 6.3$ Hz, 1H), 4.21-4.27 (m, 2H), 4.42-4.48 (m, 1H), 4.61 (d, $J = 7.1$ Hz, 1H), 4.65 (d, $J = 7.3$ Hz, 1H), 4.70 (d, $J = 7.1$ Hz, 1H), 4.95-5.04 (m, 2H), 5.22 (d, $J = 7.3$ Hz, 1H), 5.87 (ddd, $J = 8.2$, 10.0, 17.3 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = −5.1 (CH$_3$), −4.9 (CH$_3$), −4.5 (CH$_3$), −3.6 (CH$_3$), 5.3 (CH$_3$), 7.1 (CH$_3$), 15.5 (CH$_3$), 18.5 (C), 18.7 (C), 19.0 (CH$_3$), 25.2 (CH$_3$), 26.2 (CH$_3$) 26.4 (CH$_3$), 26.7 (CH$_3$), 27.5 (CH$_3$), 35.2 (CH$_2$), 36.1 (CH), 39.0 (CH), 55.8 (CH$_3$), 56.0 (CH$_3$), 66.4 (CH$_2$), 67.2 (CH), 72.0 (CH), 72.4 (CH), 74.7 (C), 81.4 (CH), 81.9 (CH), 84.6 (C), 84.9 (CH), 89.2 (C), 92.6 (CH$_2$), 98.2 (CH$_3$), 108.0 (C), 114.5 (CH$_2$), 141.6 (CH) ppm.

IR (ATR) ν 3372, 2954, 2883, 2363, 2340, 1462, 1379, 1251, 1141, 1096, 1036, 833, 775 cm$^{-1}$.

HRMS (ESI) calcd for C$_{43}$H$_{86}$O$_{10}$Si$_3$ [M+Na]$^+$, 869.5427; found 869.5428 ±5ppm.

Optical Rotation: $[\alpha]^{20}_D$ (c 1.15, CHCl$_3$) = −50.1°.

Alcohol 49 (minor diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): δ = 0.08 (s, 3H), 0.09 (s, 6H), 0.13 (s, 3H), 0.62 (quart, $J = 8.0$ Hz, 6H), 0.91 (s, 9H), 0.92 (s, 9H), 0.97 (t, $J = 8.0$ Hz, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 7.1$ Hz, 3H), 1.35 (s, 3H), 1.36-1.44 (m, 1H), 1.50 (s, 3H), 1.64 (s, 3H), 1.64-1.70 (m, 1H), 1.86-1.98 (m, 1H), 2.44-2.56 (m, 1H), 3.29 (dd, $J = 5.3$, 5.5 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.57 (d, $J = 3.0$ Hz, 1H), 3.73 (dd, $J = 7.2$, 11.0 Hz, 1H), 3.86 (ddd, $J = 2.9$, 5.3, 8.7 Hz, 1H), 4.01 (dd, $J = 1.8$, 11.0 Hz, 1H), 4.08 (d, $J = 6.8$ Hz, 1H), 4.24 (dd, $J = 3.0$, 5.2 Hz, 1H), 4.28 (dd, $J = 6.8$, 2.8 Hz, 1H).
Appendix III

Experimental part

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.04$ (s, 6H), 0.08 (s, 3H), 0.11 (s, 3H), 0.59 (quart, $J = 7.6$ Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.96 (t, $J = 7.6$ Hz, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.30 (s, 3H), 1.32-1.41 (m, 1H), 1.42 (s, 3H), 1.58 (s, 3H), 1.60-1.69 (m, 1H), 2.02-2.15 (m, 1H), 2.39-2.49 (m, 1H), 3.27 (dd, $J = 5.1, 5.3$ Hz, 1H), 3.34 (s, 3H), 3.36 (s, 3H), 3.53 (s, 3H), 3.76 (dd, $J = 4.0, 10.6$ Hz, 1H), 3.80 (dd, $J = 2.3, 10.6$ Hz, 1H), 3.85 (ddd, $J = 1.8, 5.3, 9.6$ Hz, 1H), 3.99 (d, $J = 5.8$ Hz, 1H), 4.23 (dd, $J = 5.8, 6.2$ Hz, 1H), 4.34-4.40 (m, 1H), 4.59 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 7.6$ Hz, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 4.92-5.01 (m, 2H), 5.17 (d, $J = 7.6$ Hz, 1H), 5.48 (d, $J = 5.6$ Hz, 1H), 5.85 (ddd, $J = 8.4, 10.2, 17.3$ Hz, 1H), 7.37-7.42 (m, 3H), 7.51-7.55 (m, 2H) ppm.

Mosher-ester S9. To a solution of secondary alcohol 49 (minor diastereomer, 10 mg, 0.012 mmol, 1.0 eq) in DCM (0.15 mL) were added NEt$_3$ (22 $\mu$L, 0.144 mmol, 12.0 eq), DMAP (1.5 mg, 0.012 mmol, 1.0 eq) and S-(+)-Mosher’s acid chloride (4.7 $\mu$L, 0.024 mmol, 2.0 eq) sequentially at room temperature. The reaction mixture was stirred for 14 hours at room temperature. As TLC-control showed total consumption of the starting material the reaction was terminated by the addition of a saturated, aqueous solution of NH$_4$Cl (5 mL) and the resulting mixture was diluted with DCM (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexane/EtOAc 19:1) to afford Mosher-ester S9 (12.8 mg) in quantitative yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = -5.2$ (CH$_3$), $-4.7$ (CH$_3$), $-4.6$ (CH$_3$), $-3.7$ (CH$_3$), 5.4 (CH$_2$), 7.1 (CH$_3$), 15.2 (CH$_3$), 18.4 (C), 18.8 (CH$_3$), 19.0 (C), 25.2 (CH$_3$), 26.2 (CH$_3$), 26.3 (CH$_3$), 26.4 (CH$_3$), 28.0 (CH$_3$), 35.2 (CH), 36.0 (CH$_3$), 39.0 (CH), 55.9 (CH$_3$), 56.0 (CH$_3$), 67.0 (CH), 67.4 (CH$_2$), 72.2 (CH), 72.3 (CH), 74.3 (C), 82.0 (CH), 82.2 (CH), 84.3 (C), 85.0 (CH), 90.0 (C), 92.5 (CH$_2$), 98.2 (CH$_2$), 108.2 (C), 114.4 (CH$_2$), 141.6 (CH) ppm.

HRMS (ESI) calcld for C$_{43}$H$_{86}$O$_{10}$Si$_3$ [M+Na]$^+$, 869.5427; found 869.5416 +/- 5ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.8, CHCl$_3$) = $-31.0^\circ$.
Appendix III

Experimental part

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -5.3\) (CH\(_3\)), \(-5.2\) (CH\(_3\)), \(-4.2\) (CH\(_3\)), \(-3.5\) (CH\(_3\)), 5.3 (CH\(_2\)), 7.1 (CH\(_3\)), 14.8 (CH\(_3\)), 18.4 (C), 18.5 (C), 19.1 (CH\(_3\)), 25.3 (CH\(_3\)), 26.1 (CH\(_3\)), 26.2 (CH\(_3\)), 26.8 (CH\(_3\)), 26.9 (CH\(_3\)), 33.9 (CH), 35.3 (CH\(_2\)), 38.8 (CH), 55.4 (CH\(_3\)), 55.8 (CH\(_3\)), 55.9 (CH\(_3\)), 65.5 (CH\(_2\)), 71.2 (CH), 71.7 (CH), 71.9 (CH), 74.9 (C), 79.7 (CH), 81.9 (CH), 83.2 (C), 84.9 (CH), 87.1 (C), 92.9 (CH\(_3\)), 98.1 (CH\(_3\)), 107.8 (C), 114.5 (CH\(_2\)), 122.0 (C), 124.8 (C), 127.8 (CH), 128.5 (CH), 129.7 (CH), 132.2 (C), 141.5 (CH), 165.5 (C) ppm.

IR (ATR) \(\nu = 2956, 2878, 2361, 1754, 1719, 1462, 1251, 1171, 1106, 1015, 834, 777\) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{53}\)H\(_{93}\)F\(_3\)O\(_{12}\)Si\(_3\) \([\text{M+Na}]+\), 1085.5825; found 1085.5834 +/- 5 ppm.

Optical Rotation: \([\alpha]_{20}^{20}D(c 0.63, \text{CHCl}_3) = -44.3^\circ\).

\[ \text{Mosher-ester S10.} \]

Mosher-ester S10 was prepared following the same procedure as described above. Starting from diastereomeric alcohol 49a (major diastereomer, 10 mg, 0.01 mmol, 1.0 eq) and \(S\)-(+) Mosher’s acid chloride, S10 (12.4 mg) was afforded in 97% yield as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.03\) (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 1.58 (quart, \(J = 8.0\) Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.95 (t, \(J = 8.0\) Hz, 9H), 1.01 (d, \(J = 6.8\) Hz, 3H), 1.04 (d, \(J = 7.1\) Hz, 3H), 1.31 (s, 3H), 1.31-1.38 (m, 1H), 1.45 (s, 3H), 1.56-1.64 (m, 1H), 1.62 (s, 3H), 1.99-2.11 (m, 1H), 2.28-2.41 (m, 1H), 3.22 (dd, \(J = 5.1, 5.1\) Hz, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 3.57 (s, 3H), 3.74 (dd, \(J = 4.6, 10.6\) Hz, 1H), 3.78-3.82 (m, 1H), 3.82 (dd, \(J = 2.0, 10.6\) Hz, 1H), 4.0 (d, \(J = 5.8\) Hz, 1H), 4.24 (dd, \(J = 5.8, 6.4\) Hz, 1H), 4.40 (ddd, \(J = 2.0, 4.5, 6.4\) Hz, 1H), 4.58 (d, \(J = 6.8\) Hz, 1H), 4.61 (d, \(J = 7.6\) Hz, 1H), 4.65 (d, \(J = 6.8\) Hz, 1H), 4.58-4.91 (m, 1H), 4.91-4.94 (m, 1H), 5.19 (d, \(J = 7.6\) Hz, 1H), 5.56 (d, \(J = 4.0\) Hz, 1H), 5.81 (ddd, \(J = 8.3, 10.4, 17.2\) Hz, 1H), 7.37-7.42 (m, 3H), 7.52-7.57 (m, 2H) ppm.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -5.3\) (CH\(_3\)), \(-4.2\) (CH\(_3\)), \(-3.4\) (CH\(_3\)), 5.3 (CH\(_2\)), 7.07 (CH\(_3\)), 14.4 (CH\(_3\)), 18.5 (C), 18.6 (C), 19.3 (CH\(_3\)), 25.4 (CH\(_3\)), 26.1 (CH\(_3\)), 26.2 (CH\(_3\)), 26.9 (CH\(_3\)), 27.1 (CH\(_3\)), 34.1 (CH\(_3\)), 34.9 (CH\(_2\)), 38.7 (CH\(_3\)), 55.6 (CH\(_3\)), 55.8 (CH\(_3\)), 55.9 (CH\(_3\)), 65.5 (CH\(_2\)), 71.0 (CH), 71.7 (CH), 72.0 (CH), 75.1 (C), 79.7 (CH), 81.9 (CH), 84.0 (C), 85.0 (CH), 87.0 (C), 92.8 (CH\(_2\)), 98.2 (CH\(_3\)), 107.9 (C), 114.5 (CH\(_2\)), 122.0 (C), 124.9 (C), 127.6 (CH), 128.6 (CH), 129.7 (CH), 132.5 (C), 141.3 (CH), 165.6 (C) ppm.

IR (ATR) \(\nu = 2956, 2878, 2361, 1754, 1719, 1462, 1251, 1171, 1106, 1015, 834, 777\) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{53}\)H\(_{93}\)F\(_3\)O\(_{12}\)Si\(_3\) \([\text{M+Na}]+\), 1085.5825; found 1085.5834 +/- 5 ppm.

Optical Rotation: \([\alpha]_{20}^{20}D(c 0.62, \text{CHCl}_3) = -22.9^\circ\).
Mosher-ester analysis:

<table>
<thead>
<tr>
<th>Proton</th>
<th>S9 (S-configurated) ppm</th>
<th>S10 (R-configurated) ppm</th>
<th>Diff. S9S10 (dS-dR) Ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH-1</td>
<td>2.09</td>
<td>2.06</td>
<td>+0.03</td>
</tr>
<tr>
<td>CH$_2$-2a</td>
<td>1.65</td>
<td>1.60</td>
<td>+0.05</td>
</tr>
<tr>
<td>CH$_2$-2b</td>
<td>1.37</td>
<td>1.35</td>
<td>+0.02</td>
</tr>
<tr>
<td>CH-3</td>
<td>3.85</td>
<td>3.80</td>
<td>+0.05</td>
</tr>
<tr>
<td>CH-4</td>
<td>3.27</td>
<td>3.22</td>
<td>+0.05</td>
</tr>
<tr>
<td>CH$_3$-5</td>
<td>1.03</td>
<td>1.01</td>
<td>+0.02</td>
</tr>
<tr>
<td>CH$_3$-3’</td>
<td>1.58</td>
<td>1.62</td>
<td>−0.04</td>
</tr>
<tr>
<td>CH-4’</td>
<td>3.99</td>
<td>4.00</td>
<td>−0.01</td>
</tr>
</tbody>
</table>

Alcohol S11. To a solution of alcohol 49 (268 mg, 0.32 mmol, 1.0 eq) in DMF (5.7 mL) was added NaH (60% dispersion in mineral oil, 26 mg, 0.64 mmol, 2 eq) at 0 °C. After 30 minutes PMB-Cl (78 μL, 0.58 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for 90 minutes at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO$_3$ (5 mL). After dilution with Et$_2$O (10 mL) the layers were separated and the aqueous phase was extracted with Et$_2$O (3 x 10 mL). The combined organic extracts were washed once with H$_2$O (10 mL) and brine (10 mL), dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) to provide S11 (178 mg) in 65% yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ = 0.00 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.23-1.32 (m, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 1.54-1.62 (m, 1H), 1.64 (s, 3H), 2.13-2.24 (m, 1H), 2.40-2.50 (m, 1H), 3.02 (d, $J = 4.5$ Hz, 1H), 3.14 (dd, $J = 3.8$, 6.3 Hz, 1H), 3.37 (s, 3H), 3.41 (s, 3H), 3.56-3.65 (m, 1H), 3.73 (dd, $J = 4.3$, 10.6 Hz, 1H), 3.76-3.81 (m, 4H), 3.97 (d, $J = 5.8$ Hz, 1H), 4.05 (d, $J = 6.1$ Hz, 1H), 4.27 (dd, $J = 6.1$, 6.1 Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 4.42-4.46 (m, 1H), 4.65 (d, $J = 6.8$ Hz, 1H), 4.66 (d, $J = 7.6$ Hz, 1H), 173
1H), 4.73 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.98-5.04 (m, 2H), 5.29 (d, J = 7.6 Hz, 1H), 5.74-5.85 (m, 1H), 6.83-6.89 (m, 2H), 7.22-7.28 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = −5.3 (CH$_3$), −4.2 (CH$_3$), −3.5 (CH$_3$), 15.3 (CH$_3$), 17.7 (CH$_3$), 18.4 (C), 25.5 (CH$_3$), 26.1 (CH$_3$), 26.2 (CH$_3$), 27.1 (CH$_3$), 27.5 (CH$_3$), 34.7 (CH), 36.6 (CH$_2$), 40.0 (CH), 55.4 (CH$_3$), 55.8 (CH$_3$), 56.2 (CH$_3$), 65.6 (CH$_2$), 69.5 (CH), 70.2 (CH$_2$), 71.7 (CH), 73.7 (CH), 75.1 (C), 79.8 (CH), 82.0 (CH), 85.8 (C), 87.2 (C), 89.0 (CH), 92.8 (CH$_2$), 98.9 (CH$_2$), 107.8 (C), 113.9 (CH), 115.4 (CH$_2$), 129.5 (CH), 130.4 (C), 139.6 (CH), 159.3 (C) ppm.

IR (ATR) $\nu$ 3415, 2952, 2856, 2357, 2341, 1780, 1613, 1514, 1463, 1301, 1173, 1142, 1089, 1034, 874 811, 776 cm$^{-1}$.

HRMS (ESI) calcd for C$_{45}$H$_{80}$O$_{11}$Si$_2$ [M+Na]$^+$, 875.5137; found 875.5129 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = $-74.9^\circ$.

Ketone 50. To a solution of secondary alcohol S11 (158 mg, 0.19 mmol, 1.0 eq) and pyridine (92 $\mu$L, 1.14 mmol, 6.0 eq) in DCM (6.0 mL), was added Dess-Martin periodinane (161 mg, 0.38 mmol, 2.0 eq) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2 hours before the reaction was quenched by the addition of saturated, aqueous solutions of Na$_2$S$_2$O$_3$ (5 mL) and NaHCO$_3$ (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) delivering 50 (126 mg) in 78% yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = −0.02 (s, 3H, CH$_3$-TBS), 0.00 (s, 3H, CH$_3$-TBS), 0.09 (s, 3H, CH$_3$-TBS), 0.11 (s, 3H, CH$_3$-TBS), 0.88 (s, 9H, tBu-TBS), 0.89 (s, 9H, tBu-TBS), 1.01 (d, J = 6.6 Hz, 3H, CH$_3$-IX), 1.06 (d, J = 7.1 Hz, 3H, CH$_3$-VIII), 1.34 (s, 3H, CH$_3$-VI), 1.51 (s, 3H, CH$_3$-III), 1.64 (s, 3H, CH$_3$-II), 2.37-2.49 (m, 2H, CH$_2$-X$_2$, CH-Z), 2.55-2.72 (m, 2H, CH$_2$-X$_1$, CH-Y), 3.34 (s, 3H, OCH$_3$-U), 3.37 (s, 3H, OCH$_3$-V), 3.72 (dd, J = 4.5, 10.6 Hz, 1H, CH$_2$-T$_2$), 3.77-3.82 (m, 4H, CH$_2$-T$_1$, OCH$_3$-W), 3.88 (d, J = 5.1 Hz, 1H, CH-M), 3.98 (d, J = 5.8 Hz, 1H, CH-Q), 4.04 (d, J = 5.8 Hz, 1H, CH-N), 4.26 (dd, J = 5.8, 6.2 Hz, 1H, CH-O), 4.38 (d, J = 11.4 Hz, 1H, CH$_2$-S$_2$), 4.43 (ddd, J = 2.0, 4.5, 6.2 Hz, 1H, CH-R), 4.56 (d, J = 6.8 Hz, 1H, CH$_2$-I$_2$), 4.60 (d, J = 6.8 Hz, 1H, CH$_2$-I$_1$), 4.66 (d, J = 7.3 Hz, 1H, CH$_2$-J$_2$), 4.71 (d, J = 11.4 Hz, 1H, CH$_2$-S$_1$), 4.97-5.01 (m, 1H, CH$_2$-F$_2$), 5.02-5.04 (m, 1H, CH$_2$-F$_1$), 5.27 (d, J = 7.3 Hz, 1H, CH$_2$-J$_1$), 5.76 (ddd, J = 8.0, 10.9, 16.6 Hz, 1H, CH-C), 6.84-6.89 (m, 2H, CH-phenyl), 7.22-7.27 (m, 2H, CH-phenyl) ppm.
13C NMR (100 MHz, CDCl3): δ = −5.3 (CH3-TBS), −5.2 (CH3-TBS), −4.2 (CH3-TBS), −3.5 (CH3, TBS), 16.3 (CH2-IX), 17.0 (CH2-VIII), 18.50 (C-TBS), 18.53 (C-TBS), 25.4 (CH2-VI), 26.1 (CH3- tBu-TBS), 26.2 (CH3-tBu-TBS), 27.1 (CH3-III), 27.4 (CH3-II), 33.7 (CH-Z), 40.6 (CH-Y), 42.7 (CH2-X), 55.4 (CH2-W), 55.8 (CH2-V), 56.2 (CH2-U), 65.6 (CH2-T), 70.4 (CH2-S), 71.7 (CH-R), 72.4 (CH-Q), 75.1 (C-P), 79.9 (CH-O), 82.0 (CH-N), 86.2 (CH-M), 86.3 (C-L), 86.6 (C-K), 92.8 (CH2-J), 96.8 (CH2-I), 107.8 (C-H), 113.9 (CH-G), 115.9 (CH2-F), 129.6 (CH-E), 130.1 (C-D), 138.9 (CH-C), 159.4 (C-B), 209.6 (C-A) ppm.

IR (ATR) ν 2929, 2855, 2363, 2341, 1794, 1719, 1612, 1514, 1462, 1248, 1139, 1090, 1054, 1033, 873, 777 cm−1.

HRMS (ESI) calcd for C45H78O11Si2 [M+Na]+, 873.4981; found 873.4974 +/− 5ppm.

Optical Rotation: [α]20D(c 1.0, CHCl3) = −107°.

**Ketone 51:**

1H NMR (400 MHz, CDCl3): δ = 0.02 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.34 (s, 3H), 1.50 (s, 3H), 1.66 (s, 3H), 2.22-2.33 (m, 2H), 2.35-2.45 (m, 2H), 2.64-2.74 (m, 2H), 3.37 (s, 3H), 3.75 (dd, J = 4.5, 10.6 Hz, 1H), 3.80 (s, 3H), 3.83 (dd, J = 2.0, 10.6 Hz, 1H), 4.04 (d, J = 6.1 Hz, 1H), 4.05 (d, J = 4.0 Hz, 1H), 4.26 (dd, J = 6.1, 6.3 Hz, 1H), 4.35 (d, J = 11.4 Hz, 1H), 4.46 (dd, J = 2.0, 4.5, 6.3 Hz, 1H), 4.68 (d, J = 7.3 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 4.88-4.93 (m, 1H), 4.93-4.99 (m, 1H), 5.25 (d, J = 7.3 Hz, 1H), 5.71 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 6.83-6.89 (m, 2H), 7.19-7.26 (m, 2H) ppm.

13C NMR (100 MHz, CDCl3): δ = −5.2 (CH3), −4.2 (CH3), −3.5 (CH3), 16.1 (CH3), 18.5 (C), 18.6 (C), 19.9 (CH3), 25.4 (CH3), 26.1 (CH3), 26.2 (CH3), 27.1 (CH3), 27.5 (CH3), 33.3 (CH3), 34.0 (CH3), 45.9 (CH2), 50.2 (CH2), 55.4 (CH3), 55.8 (CH3), 65.6 (CH2), 70.4 (CH2), 71.6 (CH), 72.1 (CH), 75.2 (C), 79.9 (CH), 82.0 (CH), 86.3 (C), 86.4 (C), 92.8 (CH2), 107.8 (C), 113.1 (CH2), 113.9 (CH), 129.6 (CH), 130.2 (C), 143.7 (CH), 159.4 (C), 209.1 (C) ppm.

IR (ATR) ν 2928, 2855, 1715, 1514, 1463, 1370, 1251, 1150, 1041, 834, 778 cm−1.

HRMS (ESI) calcd for C43H74O9Si2 [M+Na]+, 813.4769; found 813.4770 +/− 5ppm.

Optical Rotation: [α]20D(c 0.5, CHCl3) = −9.3°.
(3aR,6aR)-2,2-Dimethylidihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (54). A 250 mL, three-necked, round bottom flask equipped with and internal thermometer and an addition funnel was charged with erythorbic acid (3.52 g, 20.0 mmol) and 50 mL H₂O. The solution was cooled to 0°C and Na₂CO₃ (4.24 g, 40.0 mmol) was added slowly in small portions because vigorous evolution of CO₂ was observed. The resulting yellow reaction mixture was stirred with ice-bath cooling while a solution of H₂O₂ (4.6 mL, 30%) was added over a period of 10 minutes during that, the internal temperature has risen to 10 °C. Stirring was continued for 5 minutes at 0 °C and then for 30 minutes at 42 °C. Active charcoal (1 g) was added in portions to decompose the excess of peroxide and the mixture was heated to 75 °C for 30 minutes while gas evolution has stopped and a negative starch-iodide test was observed. The hot reaction mixture was filtered over a pad of Celite and the solids were washed with H₂O (30 mL). The combined filtrates were acidified to pH 1 by the cautious addition of HCl (6 M, 15 mL). The acidic solution was evaporated under reduced pressure and was dried for further three hours at 50 °C on the vacuum pump (0.2 mm) to give a pale yellow solid containing D-erythronolactone, oxalic acid and NaCl. To this crude mixture were added first acetone (17.5 mL) and anhydrous MgSO₄ (5 g) followed by the addition of 2,2-dimethoxypropane (35 mL, 0.285 mol) and p-toluenesulfonic acid monohydrate (42 mg, 0.22 mmol) at room temperature. The suspension was stirred for 18 hours at room temperature before it was poured into a 5 °C cooled mixture of Et₂O (50 mL) and NEt₃ (6 mL). After being stirred for 5 minutes the mixture was filtered and the solids were washed thoroughly with Et₂O. The combined filtrates were concentrated in vacuo and the resulting solid material was purified by flash chromatography (hexane/EtOAc 1:1) delivering protected lactone 54 (2.28 g) in 72% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.40 (s, 3H), 1.49 (s, 3H), 4.40 (dd, J = 3.8, 11.0 Hz, 1H), 4.47 (bd, J = 11.0 Hz, 1H), 4.74 (d, J = 5.6 Hz, 1H), 4.88 (ddd, J = 0.6, 3.8, 5.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 26.8 (CH₃), 26.9 (CH₃), 70.4 (CH₂), 74.8 (CH), 75.6 (CH), 114.2 (C), 174.1 (C) ppm.

These spectral characteristics are identical to those previously reported.[³]

((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (55). Protected lactone 54 (22.1 g, 140 mmol, 1.0 eq) was dissolved in toluene (750 mL). After the addition of pyrrolidine (57.4 mL, 698 mmol, 5.0 eq) the reaction mixture was heated to reflux for 18 hours. The resulting brown solution was cooled to room temperature and the solvent was
Appendix III
Experimental part

removed under reduced pressure. The crude material was purified by flash column chromatography
(DCM/MeOH 19:1 to 9:1) to give amide 55 (31.4g) in 98% yield as a light yellow oil.

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 1.38 \text{ (s, 3H), 1.55 (s, 3H), 1.81-2.03 (m, 4H), 3.38-3.44 (m, 1H),} \\
3.44-3.75 \text{ (m, 6H), 4.41 (ddd, } J = 6.4, 6.4, 4.3 \text{ Hz, 1H), 4.83 (d, } J = 6.4 \text{ Hz, 1H) ppm.} \\
\]

\[ \text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 23.8 \text{ (CH}_2\text{), 25.3 \text{ (CH}_3\text{), 26.5 \text{ (CH}_2\text{), 27.1 \text{ (CH}_3\text{), 46.8 \text{ (CH}_2\text{),} } \\
47.0 \text{ (CH}_2\text{), 62.5 \text{ (CH}_2\text{), 76.5 \text{ (CH), 78.0 \text{ (CH), 109.9 \text{ (C), 167.2 (C) ppm.}} \\
\]

IR (ATR) \( \nu = 3348, 2977, 2877, 2361, 2342, 1637, 1456, 1371, 1242, 1164, 1093, 1052 \text{ cm}^{-1} \).

HRMS (ESI) calcd for C\text{11H19NO}_4 \text{ [M+Na]^+}, 252.1212; found 252.1206 +/- 5ppm.

Optical Rotation: \([\alpha]_{D}(c 1.0, \text{ CHCl}_3) = +21.7^\circ.\]

\[ \text{(4R,5R)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl}(pyrrolidin-1-yl)methanone (S12). \text{ To a solution of alcohol 55 (15.7 g, 68.5 mmol, 1.0 eq) in DCM (115 mL) were added } p- \text{methoxybenzyl trichloroacetimidate (29.7 g, 105 mmol, 1.53 eq), dissolved in DCM (30 mL), and camphorsulfonic acid (1.27 g, 5.48 mmol, 0.08 eq) at room temperature. The reaction mixture was stirred for 12 hours at room temperature and 3 hours at 50 °C when TLC-control showed total conversion of the starting material. The reaction was quenched by the addition of saturated NaHCO}_3 \text{ solution, the layers were separated and the aqueous phase was extracted with DCM (3 x 80 mL). The combined organic extracts were dried over Na}_2\text{SO}_4, \text{ filtered and the solvent was removed under reduced pressure. After flash column chromatography (hexane/EtOAc 1:1) S12 (20.4 g) was isolated in 85% yield as a colorless oil.} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 1.38 \text{ (s, 3H), 1.58 (s, 3H), 1.60-1.85 (m, 4H), 3.30-3.50 (m, 4H),} \\
3.55 \text{ (d, } J = 6.7 \text{ Hz, 1H), 3.56 (d, } J = 5.5 \text{ Hz, 1H), 3.80 (s, 3H), 4.38 (d, } J = 11.6 \text{ Hz, 1H), 4.41 (d, } J = 11.6 \text{ Hz, 1H), 4.53 (ddd, } J = 5.5, 6.7, 6.7 \text{ Hz, 1H), 4.82 (d, } J = 6.7 \text{ Hz, 1H), 6.83-6.87 (m, 2H),} \\
7.18-7.23 \text{ (m, 2H) ppm.} \\
\]

\[ \text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 23.8 \text{ (CH}_2\text{), 25.5 \text{ (CH}_3\text{), 26.2 \text{ (CH}_2\text{), 27.3 \text{ (CH}_3\text{), 46.1 \text{ (CH}_2\text{),} } \\
46.4 \text{ (CH}_2\text{), 55.4 \text{ (CH}_3\text{), 69.2 \text{ (CH}_2\text{), 73.3 \text{ (CH}_3\text{), 75.9 \text{ (CH), 76.1 \text{ (CH), 110.3 \text{ (C), 113.9 (CH),} } \\
129.5 \text{ (CH), 130.2 (C), 159.4 (C), 169.5 (C) ppm.}} \\
\]

IR (ATR) \( \nu = 2980, 2874, 2361, 2341, 1655, 1514, 1449, 1302, 1248, 1091, 1034, 822 \text{ cm}^{-1} \).

HRMS (ESI) calcd for C\text{19H27NO}_5 \text{ [M+Na]^+}, 372.1787; found 372.1782 +/- 5ppm.

Optical Rotation: \([\alpha]_{D}(c 1.0, \text{ CHCl}_3) = +24.7^\circ.\]
1-((4R,5R)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (56). A solution of MeLi (1.6 M in Et₂O, 33.2 mL, 53.1 mmol, 2.0 eq) was added to amide S12 (9.3 g, 26.6 mmol, 1.0 eq), dissolved in THF (133 mL), at −78 °C. The reaction mixture was stirred for 10 minutes when TLC-control showed total consumption of the starting material. The reaction was terminated by the addition of H₂O (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under vacuum. Further purification of crude ketone by flash column chromatography (hexane/EtOAc 9:1 to 5:1) delivered 56 (7.3 g) in 94% yield as a colorless oil.

1H NMR (400 MHz, CDCl₃): δ = 1.37 (s, 3H), 1.59 (s, 3H), 2.16 (s, 3H), 3.40 (dd, J = 4.5, 10.5 Hz, 1H), 3.57 (dd, J = 3.9, 10.5 Hz, 1H), 3.80 (s, 3H), 4.36 (s, 2H), 4.47 (d, J = 8.0 Hz, 1H), 4.50-4.55 (m, 1H), 6.83-6.89 (m, 2H), 7.19-7.25 (m, 2H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 25.0 (CH₃), 27.0 (CH₃), 28.4 (CH₃), 55.4 (CH₃), 67.9 (CH₂), 73.2 (CH₂), 77.6 (CH), 81.1 (CH), 110.3 (C), 113.9 (CH), 129.6 (CH), 129.9 (C), 159.4 (C), 208.6 (C) ppm.

IR (ATR) ν 2935, 2360, 1711, 1613, 1514, 1459, 1380, 1302, 1245, 1211, 1135, 1060, 1034, 858, 820 cm⁻¹.

HRMS (ESI) calcd for C₁₆H₂₂O₅ [M+Na]+, 317.1365; found 317.1360 +/- 5ppm.

Optical Rotation: [α]²⁰D (c 1.0, CHCl₃) = +43.2°.

(R)-2-((4R,5R)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S13). To a solution of methyl ketone 56 (14.7 g, 50.0 mmol, 1.0 eq) in THF (880 mL) was added a solution of ethynylmagnesium bromide (0.5 M in THF, 300 mL, 150.0 mmol, 3.0 eq) at 0 °C via a cannula. The reaction mixture was stirred for 1 hour at 0 °C and 90 minutes at room temperature. After TLC-analysis indicated complete conversion of the starting material the reaction was quenched by the addition of H₂O (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude mixture of the corresponding tertiary alcohols was purified by flash column chromatography (hexane/EtOAc 9:1 to 3:1) affording S13 (11.6 g) and S13a (3.9 g) as colorless oils in a 3:1 diastereomeric ratio and 97% overall yield.
Appendix III  Experimental part

Major diastereomer S13:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.36 (s, 3H), 1.48 (s, 3H), 1.60 (d, $J$ = 1.0 Hz, 3H), 2.49 (s, 1H), 3.56 (dd, $J$ = 4.3, 8.8 Hz, 1H), 3.80 (s, 3H), 4.03 (d, $J$ = 5.8 Hz, 1H), 4.32 (dd, $J$ = 8.8, 10.3 Hz, 1H), 4.38-4.45 (m, 1H), 4.42 (d, $J$ = 11.0 Hz, 1H), 4.60 (d, $J$ = 11.0 Hz, 1H), 4.80 (d, $J$ = 1.0 Hz, 1H), 6.85-6.91 (m, 2H), 7.27-7.31 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 25.4 (CH$_3$), 27.8 (CH$_3$), 29.8 (CH$_3$), 55.4 (CH$_3$), 67.3 (C), 67.7 (CH$_2$), 72.8 (CH), 73.4 (CH$_2$), 75.7 (CH), 82.9 (CH), 86.5 (C), 109.1 (C), 114.1 (CH), 128.8 (C), 130.2 (CH), 159.8 (C) ppm.

IR (ATR) $\nu$ 3399, 3285, 2968, 2936, 2360, 2342, 1613, 1514, 1457, 1371, 1303, 1248, 1060 cm$^{-1}$.

HRMS (ESI) calcd for C$_{18}$H$_{24}$O$_5$ [M+Na]$^+$, 343.1522; found 343.1520 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = +0.4°.

Minor diastereomer S13a:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.37 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.43 (s, 1H), 3.79 (s, 3H), 3.97 (dd, $J$ = 4.0, 11.1 Hz, 1H), 4.03 (dd, $J$ = 3.2, 11.1 Hz, 1H), 4.09 (d, $J$ = 6.6 Hz, 1H), 4.36 (ddd, $J$ = 3.2, 4.0, 6.6 Hz, 1H), 4.50 (d, $J$ = 11.1 Hz, 1H), 4.59 (d, $J$ = 11.1 Hz, 1H), 4.60 (d, $J$ = 11.1 Hz, 1H), 6.84-6.90 (m, 2H), 7.27-7.33 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 25.4 (CH$_3$), 26.9 (CH$_3$), 27.8 (CH$_3$), 55.4 (CH$_3$), 67.0 (C), 67.5 (CH$_2$), 72.4 (CH), 73.5 (CH$_2$), 76.5 (CH), 82.5 (CH), 86.5 (C), 108.5 (C), 114.0 (CH), 129.1 (C), 130.1 (CH), 159.6 (C) ppm.

IR (ATR) $\nu$ 3399, 3285, 2968, 2936, 2360, 2342, 1613, 1514, 1457, 1371, 1303, 1248, 1060 cm$^{-1}$.

HRMS (ESI) calcd for C$_{18}$H$_{24}$O$_5$ [M+Na]$^+$, 343.1522; found 343.1523 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = +26.6°.

(S)-2-((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S14). To a solution of tertiary alcohol S13a (300 mg, 0.94 mmol, 1.0 eq) in acetonitrile (23.5 mL) was added phosphate buffer (1.0 M, pH 7-8, 2.3 mL) at room temperature. The reaction mixture was cooled to
0 °C and ceric ammonium nitrate (1.03 g, 1.88 mmol, 2.0 eq) was added in 3 portions. After stirring for 90 minutes at 0 °C TLC-control showed only partial deprotection of the starting material. 2 equivalents of ceric ammonium nitrate (1.03 g) were added and the reaction mixture was stirred for additional 30 minutes at 0 °C. TLC-analysis showed total conversion of the starting material and the reaction was terminated by the addition of a saturated solution of NaHCO₃ (15 mL). The resulting suspension was filtered through a plug of Celite. The filtrate was transferred to a separatory funnel and diluted with DCM (20 mL). The layers were separated and the aqueous phase was extracted with DCM (10 mL). The combined organic fractions were dried over Na₂SO₄, filtered and the solvents were removed under reduced pressure. The crude diol was further purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) affording S14 (145 mg) in 77% yield as a colorless oil.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta = 1.40 (s, 3H), 1.54 (s, 3H), 1.61 (s, 3H), 2.51 (s, 1H), 4.02 (dd, } J = 4.0, 12.3 \text{ Hz, 1H), 4.15 (d, } J = 7.0 \text{ Hz, 1H), 4.27 (dd, } J = 3.6, 12.3 \text{ Hz, 1H), 4.32 (ddd, } J = 3.6, 4.0, 7.0 \text{ Hz, 1H) ppm.} \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3): \delta = 25.1 (CH}_3, 27.0 (CH}_3, 28.5 (CH}_3, 60.7 (CH}_2, 66.9 (C), 73.4 (CH), 77.6 (CH), 82.2 (CH), 85.6 (C), 108.4 (C) ppm.} \]

IR (ATR) \( \nu = 3280, 2987, 2361, 2341, 1380, 1218, 1063 \text{ cm}^{-1}. \)

HRMS (ESI) calcd for C₁₀H₁₆O₄ [M+Na]⁺, 223.0947; found 223.0950 +/- 5ppm.

Optical Rotation: \( [\alpha]^{20}_D (c 1.0, \text{ CHCl}_3) = +16.9°. \)

(R)-2-((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S15). Diol S15 was prepared following the same procedure as described above for diol S14. Starting from tertiary alcohol S13 (300 mg, 0.94 mmol), diol S15 (116 mg) was isolated in 62% yield as a colorless oil.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta = 1.38 (s, 3H), 1.53 (s, 3H), 1.62 (s, 3H), 2.53 (s, 1H), 2.68 (bs, 1H), 3.61 (bs, 1H), 3.87 (dd, } J = 3.6, 9.9 \text{ Hz, 1H), 4.04 (d, } J = 5.8 \text{ Hz, 1H), 4.30-4.41 (m, 2H) ppm.} \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3): \delta = 25.4 (CH}_3, 27.5 (CH}_3, 29.4 (CH}_3, 60.7 (CH}_2, 68.1 (C), 73.7 (CH), 77.7 (CH), 82.5 (CH), 86.1 (C), 109.0 (C) ppm.} \]

IR (ATR) \( \nu = 3280, 2987, 2361, 2341, 1380, 1218, 1063 \text{ cm}^{-1}. \)

HRMS (ESI) calcd for C₁₀H₁₆O₄ [M+Na]⁺, 223.0947; found 223.0948 +/- 5ppm.

Optical Rotation: \( [\alpha]^{20}_D (c 1.0, \text{ CHCl}_3) = +3.6°. \)
(3aS,6S,6aR)-6-Ethynyl-2,2,6-trimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (S16). A solution of diol S14 (115 mg, 0.57 mmol, 1.0 eq) in DCM (8.8 mL) was treated with PCC (638 mg, 2.30 mmol, 4.0 eq) at room temperature. The reaction mixture was warmed to 40 °C (stoppered round bottom flask) and stirred for 12 hours at that temperature. As TLC-control indicated total conversion of the starting material silica gel was added and the solvent was removed under reduced pressure. The absorbed product was transferred to a chromatography column and was eluated with hexane/EtOAc 5:1 to afford lactone S16 (60 mg) in 54% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.41 (s, 3H), 1.47 (s, 3H), 1.73 (s, 3H), 2.70 (s, 1H), 4.71 (d, $J =$ 5.1 Hz, 1H), 4.97 (d, $J =$ 5.1 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 21.8 (CH$_3$), 26.4 (CH$_3$), 27.0 (CH$_3$), 76.6 (CH), 76.8 (CH), 80.6 (C), 81.4 (C), 81.8 (CH), 115.0 (C), 173.3 (C) ppm.

IR (ATR) $\nu$ 3282, 3244, 2999, 2360, 1787, 1375, 1230, 1107, 1091, 981, 835 cm$^{-1}$.

HRMS (ESI) calcd for C$_{10}$H$_{12}$O$_4$ [M+Na]$^+$, 219.0634; found 219.0629 +/- 5ppm.

Optical Rotation: $[\alpha]_{D}^{20}$ (c 1.0, CHCl$_3$) = +50.8°.

NOE-analysis:

(3aS,6R,6aR)-6-Ethynyl-2,2,6-trimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (S17). Lactone S17 was prepared following the same procedure as described above for lactone S16. Starting from diol S15 (90 mg, 0.45 mmol), lactone S17 (45 mg) was isolated in 51% yield as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.44 (s, 3H), 1.53 (s, 3H), 1.66 (s, 3H), 2.77 (s, 1H), 4.58 (d, $J =$ 5.6 Hz, 1H), 4.85 (d, $J =$ 5.6 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 26.3 (CH$_3$), 27.0 (CH$_3$), 27.9 (CH$_3$), 75.7 (CH), 77.1 (CH), 78.8 (C), 78.9 (C), 81.5 (CH), 115.2 (C), 172.4 (C) ppm.

IR (ATR) $\nu$ 3282, 3244, 2999, 2360, 1787, 1375, 1230, 1107, 1091, 981, 835 cm$^{-1}$.

HRMS (ESI) calcd for C$_{10}$H$_{12}$O$_4$ [M+Na]$^+$, 219.0634; found 219.0629 +/- 5ppm.
Optical Rotation: $[\alpha]^{{20}}_{D}(c \ 1.0, \ \text{CHCl}_3) = +53.8^\circ$.

**NOE analysis:**

\[
\text{NOE analysis:}
\]

\[
\begin{array}{c}
\text{H} & \text{H} \\
\text{CH}_3 & \\
\end{array}
\]

**tert-Butyl(((R)-2-(((4R,5R)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (57).** To a solution of tertiary alcohol S13 (3.0 g, 9.36 mmol, 1.0 eq) and 2,6-lutidine (2.17 mL, 18.7 mmol, 2.0 eq) in DCM (18 mL) was added TBS-triflate (2.15 mL, 9.36 mmol, 1.0 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature before it was stirred for 5 hours at 50 °C (stoppered round bottom flask). TLC-analysis showed partial conversion of the starting material and additional 0.2 eq (0.43 mL) of TBS-triflate and 0.4 eq (0.43 mL) of 2,6-lutidine were added. The reaction mixture was stirred for 90 minutes before it was quenched by the addition of a saturated, aqueous solution of NaHCO$_3$ (15 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1) alkyne 57 (3.8 g) was isolated in 93% yield as a colorless oil.

\[
\begin{align*}
{^1}H \text{ NMR (400 MHz, CDCl}_3): & \delta = 0.10 (s, 3H), 0.17 (s, 3H), 0.77 (s, 9H), 1.38 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.48 (s, 1H), 3.80 (s, 3H), 3.81 (d, J = 6.5 Hz, 1H), 3.93 (dd, J = 2.3, 10.5 Hz, 1H), 4.06 (dd, J = 9.7, 10.5 Hz, 1H), 4.44-4.50 (m, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 6.84-6.88 (m, 2H), 7.27-7.31 (m, 2H) ppm. \\
{^{13}}C \text{ NMR (100 MHz, CDCl}_3): & \delta = -3.0 (\text{CH}_3), -2.3 (\text{CH}_3), 18.1 (\text{C}), 25.4 (\text{CH}_3), 25.8 (\text{CH}_3), 27.5 (\text{CH}_3), 30.3 (\text{CH}_3), 55.5 (\text{CH}_3), 68.6 (\text{CH}_2), 69.9 (\text{C}), 73.0 (\text{CH}_2), 74.9 (\text{CH}), 77.8 (\text{CH}), 83.2 (\text{CH}), 85.9 (\text{C}), 109.0 (\text{C}), 113.9 (\text{CH}), 129.4 (\text{CH}), 130.8 (\text{C}), 159.3 (\text{C}) ppm. \\
\text{IR (ATR)}: & \nu 2934, 2857, 2361, 2341, 1514, 1463, 1249, 1171, 1091, 838, 778 \text{ cm}^{-1}. \\
\text{HRMS (ESI)}: & \text{calcd for C}_{24}\text{H}_{38}\text{O}_5\text{Si} [\text{M+Na}]^+, 457.2387; \text{found 457.2383 +/− 5ppm.}
\end{align*}
\]

Optical Rotation: $[\alpha]^{{20}}_{D}(c \ 1.0, \ \text{CHCl}_3) = -35.4^\circ$.

**S18**

**((4R,5R)-5-(((R)-2-(((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (S18).** To a solution of 57 (4.05 g, 9.32 mmol, 1.0 eq) in DCM (450 mL) were added...
phosphate buffer (1.0 M, pH 7-8, 5.5 mL) and DDQ (3.17 g, 14.0 mmol, 1.5 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 14 hours when TLC-control showed total conversion of the starting material. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO₃ (150 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was concentrated under vacuum. After purification by flash column chromatography (hexane/EtOAc 9:1) primary alcohol S₁₈ (5.59 g) was isolated in 95% yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.24 (s, 3H), 0.25 (s, 3H), 0.88 (s, 9H), 1.38 (s, 3H), 1.54 (s, 3H), 1.58 (s, 3H), 2.19 (dd, J = 5.8, 7.8 Hz, 1H), 2.55 (s, 1H), 3.91 (d, J = 6.3 Hz, 1H), 4.03-4.15 (m, 2H), 4.38 (ddd, J = 5.5, 6.3, 7.5 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = −3.0 (CH₃), −2.2 (CH₃), 18.2 (C), 25.6 (CH₃), 25.9 (CH₃), 27.5 (CH₃), 30.4 (CH₃), 61.4 (CH₂), 70.2 (C), 75.1 (CH), 78.9 (CH), 83.3 (CH), 85.8 (C), 108.9 (C) ppm.

IR (ATR) ν 3503, 3310, 2932, 2858, 2362, 2341, 1463, 1371, 1253, 1216, 1143, 1085, 1060, 991, 836, 778 cm⁻¹.

HRMS (ESI) calcd for C₁₆H₃₀O₄Si [M+Na]+, 337.1811; found 337.1806 +/- 5ppm.

Optical Rotation: [α]²⁰D(c 1.0, CHCl₃) = +0.5°.

(4S,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (58). To a solution of primary alcohol S₁₈ (500 mg, 1.59 mmol, 1.0 eq) and pyridine (755 μL, 9.36 mmol, 6.0 eq) in DCM (10.6 mL), was added Dess-Martin periodinane (1.01 g, 2.39 mmol, 1.5 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solutions of Na₂S₂O₃ (5 mL) and NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) delivering 58 (486 mg) in 98% yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.21 (s, 3H), 0.22 (s, 3H), 0.87 (s, 9H), 1.41 (s, 3H), 1.59 (s, 3H), 1.62 (s, 3H), 2.57 (s, 1H), 4.27 (d, J = 7.3 Hz, 1H), 4.44 (dd, J = 3.0, 7.3 Hz, 1H), 9.84 (d, J = 3.0 Hz, 1H) ppm.
13C NMR (100 MHz, CDCl3): δ = −3.1 (CH3), −2.4 (CH3), 18.2 (C), 25.6 (CH3), 25.8 (CH3), 27.2 (CH3), 29.4 (CH3), 69.8 (C), 75.4 (CH), 81.8 (CH), 85.4 (C), 86.2 (CH), 111.4 (C), 197.9 (CH) ppm.

IR (ATR) ν 2932, 2858, 1734, 1473, 1374, 1253, 1217, 1151, 1083, 995, 837, 780 cm\(^{-1}\).

HRMS (ESI) calcd for C16H28O4Si [M+Na]\(^+\), 335.1655; found 335.1658 +/- 5ppm.

Optical Rotation: [\(\alpha\)]\(^{20}\)D(c 1.0, CHCl3) = +0.2°.

(\(4R,5S\))-3-((\(S\))-3-((\(4R,5R\))-2-((Tert-butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (59). A solution of SmI\(_2\) (0.1 M in THF, 31.3 mL, 3.13 mmol, 2.5 eq) was transferred into a 250 mL round bottom Schlenk flask which was precooled to −78 °C. A solution of bromide 20 (449 mg, 1.38 mmol, 1.1 eq) and aldehyde 58 (390 mg, 1.25 mmol, 1.0 eq) in 20 mL degassed THF (3 pump-freeze-thaw cycles) was added to the SmI\(_2\) solution via a cannula over a period of 5 minutes. The reaction mixture was stirred for 1 hour at −78 °C before it was quenched by the addition of aqueous saturated solutions of Na\(_2\)S\(_2\)O\(_3\) (20 mL) and NaHCO\(_3\) (20 mL) at −78 °C. The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and the organic solvents were removed under reduced pressure delivering the crude secondary alcohol as a light yellow oil which was purified by flash chromatography (hexane/EtOAc 9:1) providing 59 (420 mg) as single diastereomer in 60% (94% brsm) yield.

1H NMR (400 MHz, CDCl3): δ = 0.23 (s, 3H), 0.30 (s, 3H), 0.90 (s, 9H), 0.91 (d, J = 6.6 Hz, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.71 (s, 3H), 2.58 (s, 1H), 3.32 (d, J = 4.8 Hz, 1H), 4.08 (d, J = 6.3 Hz, 1H), 4.27 (d, J = 6.3 Hz, 1H), 4.81 (m, 1H), 4.93 (d, J = 4.8 Hz, 1H), 5.66 (d, J = 6.8 Hz, 1H), 7.27-7.31 (m, 2H), 7.33-7.44 (m, 3H) ppm.

13C NMR (100 MHz, CDCl3): δ = −2.9 (CH3), −2.2 (CH3), 14.4 (CH3), 18.5 (C), 20.2 (CH3), 22.4 (CH3), 25.7 (CH3), 26.1 (CH3), 26.4 (CH3), 28.2 (CH3), 50.6 (C), 57.7 (CH3), 69.1 (CH), 69.5 (C), 74.0 (CH), 75.7 (CH), 79.2 (CH), 84.5 (CH), 86.9 (C), 108.5 (C), 125.8 (CH), 128.8 (CH), 128.9 (CH), 133.8 (C), 152.6 (C), 177.0 (C) ppm.

IR (ATR) ν 3511, 3264, 2933, 2858, 2361, 2341, 1773, 1688, 1457, 1338, 1248, 1151, 1086, 1028, 987, 835, 768 cm\(^{-1}\).

HRMS (ESI) calcd for C30H45NO7Si [M+Na]\(^+\), 582.2863; found 582.2859 +/- 5ppm.

Optical Rotation: [\(\alpha\)]\(^{20}\)D(c 1.0, CHCl3) = +34.4°.
Appendix III  Experimental part

(4R,5S)-3-((S)-3-((4R,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (S19). Alcohol 59 (540 mg, 0.97 mmol, 1.0 eq) was dissolved in 1,2-dichloroethane (4.5 mL) and cooled to 0 °C. DIPEA (3 mL, 17.4 mmol, 18.0 eq) and MOM-Cl (0.88 mL, 11.6 mmol, 12.0 eq) were added sequentially. After the addition, the ice bath was removed, the reaction mixture was heated to 100 °C (sealed round bottom flask) and the yellow solution was stirred for 14 hours. The reaction was quenched by the addition of H₂O (5 mL). After separation of the two layers the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (hexane/EtOAc 9:1) 500 mg (86%) of the MOM protected alkyne (S19) could be isolated as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.25 (s, 3H), 0.29 (s, 3H), 0.85 (s, 9H), 0.94 (d, J = 6.3 Hz, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.58 (s, 6H), 1.64 (s, 3H), 2.58 (s, 1H), 3.39 (s, 3H), 3.88 (d, J = 5.8 Hz, 1H), 4.40 (dd, J = 5.3, 5.8 Hz, 1H), 4.65-4.74 (m, 1H), 4.87 (d, J= 5.6 Hz, 1H), 5.0 (d, J = 5.6 Hz, 1H), 5.02 (d, J = 5.3 Hz, 1H), 5.64 (d, J = 6.8 Hz, 1H), 7.29-7.33 (m, 2H), 7.35-7.44 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = −2.2 (CH₃), −1.9 (CH₃), 14.4 (CH₃), 17.8 (CH₃), 18.4 (C), 20.5 (CH₃), 25.5 (CH₃), 26.2 (CH₃), 26.9 (CH₃), 30.7 (CH₃), 50.3 (C), 56.7 (CH₃), 58.1 (CH), 70.2 (C), 75.8 (CH), 76.3 (CH), 76.5 (CH), 79.4 (CH), 84.6 (CH), 86.6 (C), 98.5 (CH₂), 107.8 (C), 125.8 (CH), 128.7 (CH), 128.8 (CH), 133.7 (C), 152.3 (C), 177.0 (C) ppm.

IR (ATR) ν 2936, 2361, 2341, 1782, 1689, 1458, 1340, 1255, 1216, 1189, 1069, 986, 836 cm⁻¹.

HRMS (ESI) calcd for C₃₂H₄₉NO₈Si [M+Na]⁺, 626.3125; found 626.3137 +/- 5ppm.

Optical Rotation: [α]²₀D(c 1.0, CHCl₃) = −44.4°.

(O)-3-((4R,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropan-1-ol (60). To a solution of S19 (107 mg, 0.18 mmol, 1.0 eq) in THF (4.5 mL) were added MeOH (7 μL, 0.18 mmol, 1.0 eq) and a solution of lithium borohydride (2.0 M in THF, 0.35 mL, 0.71 mmol, 4.0 eq) at 0 °C. After the addition the reaction mixture was allowed to warm to room temperature and stirring was continued for 3 hours before the reaction was terminated by the addition of a saturated aqueous solution of NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL).
The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexane/EtOAc 5:1 to 3:1) afforded primary alcohol \( \text{60} \) (66 mg) in 87% yield as a colorless oil.

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 0.25 \) (s, 3H), 0.33 (s, 3H), 0.88 (s, 9H), 0.92 (s, 3H), 1.05 (s, 3H), 1.38 (s, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 2.59 (s, 1H), 3.13 (dd, \( J = 5.8, 7.8 \) Hz, 1H), 3.34 (dd, \( J = 7.8, 11.4 \) Hz, 1H), 3.44 (s, 3H), 3.64 (dd, \( J = 5.8, 11.4 \) Hz, 1H), 3.76-3.81 (m, 1H), 4.38-4.41 (m, 2H), 4.71 (d, \( J = 6.5 \) Hz, 1H), 5.30 (d, \( J = 6.5 \) Hz, 1H) ppm.

\(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta = -2.0 \) (CH₃), -1.8 (CH₃), 18.5 (C), 19.7 (CH₃), 23.1 (CH₃), 25.4 (CH₃), 26.3 (CH₃), 27.0 (CH₃), 31.3 (CH₃), 39.9 (C), 56.5 (CH₃), 69.9 (CH₂), 70.3 (C), 76.2 (CH), 76.3 (CH), 77.6 (CH), 84.3 (CH), 86.7 (C), 98.2 (CH₂), 107.7 (C) ppm.

IR (ATR) \( \nu = 3512, 3241, 2932, 2858, 2360, 2342, 1473, 1370, 1252, 1097, 1068, 979, 835, 779 \) cm\(^{-1}\).

HRMS (ESI) calcd for C\(_{22}\)H\(_{42}\)O\(_6\)Si \([\text{M+Na}]^+\), 453.2649; found 453.2652 +/-5 ppm.

Optical Rotation: \([\alpha]^{20}_{D}(c 1.0, \text{CHCl}_3) = -78.2^\circ\).

**Tert-Butyl(((R)-2-(((4R,5R)-5-((S)-1-(methoxymethoxy)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (61).** To a solution of IBX (162 mg, 0.58 mmol, 1.5 eq) in DMSO (10 mL) was added alcohol \( \text{60} \) (166 mg, 0.39 mmol, 1.0 eq) in DMSO (1.5 mL) and the reaction mixture was stirred for 3 hours at room temperature. As TLC-control indicated total consumption of the starting material the reaction was terminated by the addition of H\(_2\)O (5 mL) at 0 °C. The resulting suspension was filtered over a plug of Celite and the filtrate was diluted with Et\(_2\)O (10 mL). The layers were separated and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic fractions were washed with H\(_2\)O (15 mL) and brine (15 mL) and dried over MgSO₄. After filtration the solvent was removed under reduced pressure (25 °C bath temperature). The crude material was purified by flash column chromatography (hexane/EtOAc 40:1 to 19:1) delivering the corresponding instable aldehyde (143 mg) in 87% yield, which was used immediately for the next step.

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 0.25 \) (s, 3H), 0.35 (s, 3H), 0.87 (s, 9H), 1.13 (s, 3H), 1.20 (s, 3H), 1.36 (s, 3H), 1.56 (s, 3H), 1.62 (s, 3H), 2.61 (s, 1H), 3.35 (s, 3H), 3.77 (d, \( J = 5.8 \) Hz, 1H), 4.33 (dd, \( J = 5.8, 6.8 \) Hz, 1H), 4.64 (d, \( J = 6.8 \) Hz, 1H), 4.71 (d, \( J = 6.8 \) Hz, 1H), 5.24 (d, \( J = 6.8 \) Hz, 1H), 9.71 (s, 1H) ppm.

The aldehyde from above (143 mg, 0.33 mmol, 1.0 eq) was dissolved in freshly distilled THF (2.4 mL) and cooled to 0 °C. A solution of Tebbe-reagent (0.5 M in toluene, 0.8 mL, 0.4 mmol, 1.2 eq) was slowly added via a syringe. The reaction mixture was stirred for 15 minutes at 0 °C before it was quenched by the addition of a saturated solution of NaHCO₃ (3 mL). After the
separation of the two layers, the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. Crude alkene 61 was purified by flash column chromatography (hexane/EtOAc 40:1 to 19:1) delivering 125 mg (88%) of the desired intermediate as a light yellow oil.

\(^1\)H NMR (400 MHz, CDCl₃): \(\delta = 0.26 (s, 3H), 0.37 (s, 3H), 0.89 (s, 9H), 1.11 (s, 3H), 1.13 (s, 3H), 1.33 (s, 3H), 1.54 (s, 3H), 1.58 (s, 3H), 2.58 (s, 1H), 3.44 (s, 3H), 3.68 (d, \(J = 5.6\) Hz, 1H), 4.18 (dd, \(J = 5.6, 8.1\) Hz, 1H), 4.36 (d, \(J = 8.1\) Hz, 1H), 4.70 (d, \(J = 6.6\) Hz, 1H), 5.0-5.03 (m, 1H), 5.04-5.06 (m, 1H), 5.32 (d, \(J = 6.6\) Hz, 1H), 6.13 (dd, \(J = 10.4, 18.0\) Hz, 1H) ppm.

\(^1^3\)C NMR (100 MHz, CDCl₃): \(\delta = -1.9 (CH₃), -1.8 (CH₃), 18.5 (C), 21.9 (CH₃), 24.2 (CH₃), 25.3 (CH₃), 26.4 (CH₃), 27.2 (CH₃), 31.2 (CH₃), 41.9 (C), 56.4 (CH₃), 70.5 (C), 76.0 (CH), 76.3 (CH), 77.3 (CH), 84.2 (CH), 86.6 (C), 97.3 (CH₂), 107.2 (C), 112.5 (CH₂), 145.0 (CH) ppm.

IR (ATR) \(\nu = 3241, 2930, 2858, 2361, 2342, 1463, 1369, 1252, 1134, 1069, 1035, 938, 835\) cm\(^{-1}\).

HRMS (ESI) calcd for C₂₂H₄₂O₅Si [M+Na]\(^+\), 449.2700; found 449.2703 +/- 5 ppm.

Optical Rotation: \([\alpha]_{D}^{17.0} (c 1.0, CHCl₃) = -92.2°\).

**Alcohol 62.** To a solution of alkyne 61 (82 mg, 0.192 mmol, 2.0 eq) and HMPA (60 \(\mu\)L, 0.346 mmol, 3.6 eq) in THF (1.5 mL) was added \(t\)-BuLi (1.9 M in pentane, 101 \(\mu\)L, 0.192 mmol, 2.0 eq) at –78 °C. After stirring for 30 minutes at that temperature 30 \(\mu\)L of the reaction mixture were removed via a syringe and quenched by the addition of D₂O (mini-quench). After \(^1\)H-NMR analysis, which indicated a 50% lithiation of the alkyne, two additional equivalents of \(t\)-BuLi (101 \(\mu\)L) were added. After 25 minutes another sample for an NMR was taken and the analysis indicated complete lithiation of the alkyne. A solution of aldehyde 48 (33 mg, 0.096 mmol, 1.0 eq) in THF (0.5 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 2:1 diastereomeric ratio (62a, less polar diastereomer, 41 mg, and 62, more polar diastereomer, 21 mg) in 80% overall yield as colorless oils.
Alcohol 62a (major diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.26 (s, 3H), 0.40 (s, 3H), 0.61 (quart, $J = 7.9$ Hz, 6H), 0.90 (s, 9H), 0.97 (t, $J = 7.9$ Hz, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.27-1.36 (m, 1H), 1.33 (s, 3H), 1.49 (s, 3H), 1.55 (s, 3H), 1.65-1.74 (m, 1H), 1.87-1.99 (m, 1H), 2.41-2.53 (m, 1H), 3.27 (dd, $J = 5.1$, 5.6 Hz, 1H), 3.38 (s, 3H), 3.48 (s, 3H), 3.69 (d, $J = 5.6$ Hz, 1H), 3.88 (ddd, $J = 1.8$, 5.6, 9.7 Hz, 1H), 4.11 (dd, $J = 1.8$, 6.1 Hz, 1H), 4.21 (dd, $J = 5.6$, 8.3 Hz, 1H), 4.26 (d, $J = 1.8$ Hz, 1H), 4.51 (d, $J = 8.3$ Hz, 1H), 4.56 (d, $J = 7.3$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.70 (d, $J = 6.8$ Hz, 1H), 4.93-5.08 (m, 4H), 5.71 (d, $J = 7.3$ Hz, 1H), 5.86 (ddd, $J = 8.2$, 10.2, 17.3 Hz, 1H), 6.15 (dd, $J = 10.2$, 18.1 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = −1.9 (CH$_3$), −1.6 (CH$_3$), 5.4 (CH$_3$), 7.2 (CH$_3$), 15.3 (CH$_3$), 18.5 (C), 19.0 (CH$_3$), 22.2 (CH$_3$), 24.2 (CH$_3$), 25.2 (CH$_3$), 26.5 (CH$_3$), 27.1 (CH$_3$), 31.1 (CH$_3$), 35.0 (CH), 35.8 (CH$_2$), 39.0 (CH), 41.7 (C), 56.0 (CH$_3$), 56.4 (CH$_3$), 67.4 (CH), 70.6 (C), 72.2 (CH), 72.7 (CH), 77.5 (CH), 84.5 (CH), 85.2 (CH), 87.1 (C), 87.5 (C), 99.5 (CH$_2$), 98.2 (CH$_2$), 107.2 (C), 112.7 (CH$_2$), 114.3 (CH$_2$), 141.6 (CH), 144.9 (CH) ppm.

IR (ATR) ν 3442, 2956, 2879, 2360, 2339, 1719, 1638, 1462, 1416, 1369, 1218, 1251, 1037, 910, 835 cm$^{-1}$.

HRMS (ESI) calcd for C$_4$I$_{78}$O$_{66}$Si$_2$ [M+Na]$^+$, 793.5082; found 793.5075 +/- 5ppm.

Optical Rotation: $[\alpha]^{20}_D$(c 1.0, CHCl$_3$) = −79.5°.

Alcohol 62 (minor diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.25 (s, 3H, CH$_3$-TBS), 0.34 (s, 3H, CH$_3$-TBS), 0.60 (quart, $J = 7.9$ Hz, 6H, TES-CH$_2$-VIII), 0.89 (s, 9H, tBu-TBS), 0.96 (t, $J = 7.9$ Hz, 9H, TES-CH$_3$-VII), 0.99 (d, $J = 6.6$ Hz, 3H, CH$_3$-VI), 1.09 (d, $J = 7.6$ Hz, 3H, CH$_3$-IV), 1.11 (s, 3H, CH$_3$-II), 1.13 (s, 3H, CH$_3$-III), 1.31-1.40 (m, 1H, CH$_2$-U$_2$), 1.32 (s, 3H, CH$_3$-Z), 1.54 (s, 3H, CH$_3$-X), 1.57 (s, 3H, CH$_3$-V), 1.171-1.81 (m, 1H, CH$_2$-U$_1$), 1.82-1.94 (m, 1H, CH-T), 2.41-2.52 (m, 1H, CH-S), 3.26 (dd, $J = 5.3$, 5.3 Hz, 1H, CH-J), 3.37 (s, 3H, OCH$_3$-Q), 3.48 (s, 3H, OCH$_3$-P), 3.70 (d, $J = 5.6$ Hz, 1H, CH-
Appendix III  Experimental part

K), 3.86 (ddd, $J = 1.8, 5.3, 9.6$ Hz, 1H, CH-M), 4.19 (dd, $J = 5.6, 8.8$ Hz, 1H, CH-XII), 4.25 (d, $J = 4.3$ Hz, 1H, CH-O), 4.28-4.32 (m, 1H, CH-O), 4.41 (d, $J = 8.2$ Hz, 1H, CH-L), 4.53 (d, $J = 7.3$ Hz, 1H, CH$_2$-G$_2$), 4.60 (d, $J = 7.1$ Hz, 1H, CH$_2$-F$_3$), 4.69 (d, $J = 7.1$ Hz, 1H, CH$_2$-F$_1$), 4.94-5.08 (m, 4H, CH$_2$-D$_1$, CH$_2$-C$_1$), 5.68 (d, $J = 7.3$ Hz, 1H, CH$_2$-G$_1$), 5.86 (ddd, $J = 8.1, 10.2, 17.3$ Hz, 1H, CH-B), 6.14 (dd, $J = 10.4, 17.9$ Hz, 1H, CH-A) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -1.9$ (CH$_3$-TBS), 5.4 (CH$_2$-VIII), 7.1 (CH$_3$-VII), 15.0 (CH$_3$-VI), 18.4 (C-V), 18.9 (CH$_3$-IV), 22.2 (CH$_3$-III), 24.2 (CH$_3$-II), 25.0 (CH$_3$-Z), 26.4 (CH$_3$-Y), 27.6 (CH$_3$-X), 31.7 (CH$_3$-V), 35.4 (CH$_2$-U), 35.5 (CH-T), 38.9 (CH-S), 41.7 (C-R), 56.0 (CH$_3$-Q), 56.3 (CH$_3$-P), 67.3 (CH-O), 71.0 (C-N), 72.2 (CH-M), 73.6 (CH-L), 76.8 (CH-XII), 84.1 (CH-K), 85.1 (CH-J), 87.8 (C-I), 89.3 (C-H), 95.6 (CH$_2$-G), 98.2 (CH$_2$-H), 107.1 (C-E), 112.7 (CH$_2$-D), 114.4 (CH$_2$-C), 141.6 (C-B), 144.9 (C-A) ppm.

IR (ATR) $\nu = 3442$, 2956, 2879, 2360, 2339, 1719, 1638, 1462, 1416, 1369, 1218, 1251, 910 cm$^{-1}$.

HRMS (ESI) calcd for C$_{41}$H$_{78}$O$_9$Si$_2$ [M+Na]$^+$, 793.5082; found 793.5076 $\pm$ 5ppm.

Optical Rotation: $[\alpha]^{20}_D$(c 0.35, CHCl$_3$) = $-78.2^\circ$.

Ketone 66:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.25$ (s, 3H), 0.36 (s, 3H), 0.90 (s, 9H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.34 (s, 3H), 1.50 (m, 3H), 1.55 (s, 3H), 1.63 (s, 3H), 1.67 (d, $J = 6.8$ Hz, 3H), 2.43 (dd, $J = 8.1, 17.1$ Hz, 1H), 2.47-2.55 (m, 1H), 2.69 (dd, $J = 5.0, 17.1$ Hz, 1H), 3.31 (s, 3H), 3.40 (s, 3H), 3.71 (d, $J = 5.6$ Hz, 1H), 3.80 (s, 3H), 4.07 (d, $J = 4.3$ Hz, 1H), 4.18 (dd, $J = 5.6, 7.9$ Hz, 1H), 4.32 (d, $J = 11.3$ Hz, 1H), 4.34 (d, $J = 7.9$ Hz, 1H), 4.47 (s, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.64-4.68 (m, 2H), 5.01-5.06 (m, 2H), 5.30 (d, $J = 6.8$ Hz, 1H), 5.65-5.72 (m, 1H), 6.12 (dd, $J = 10.4, 18.0$ Hz, 1H), 6.83-6.87 (m, 2H), 7.19-7.23 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -1.7$ (CH$_3$), 11.6 (CH$_3$), 13.7 (CH$_3$), 15.8 (CH$_3$), 18.5 (C), 21.9 (CH$_3$), 24.3 (CH$_3$), 25.2 (CH$_3$), 26.4 (CH$_3$), 27.4 (CH$_3$), 31.9 (CH$_3$), 33.4 (CH$_3$), 41.7 (C), 55.4 (CH$_3$), 55.8 (CH$_3$), 56.4 (CH$_3$), 70.8 (CH$_2$), 71.0 (C), 72.6 (CH), 76.3 (CH), 77.1 (CH), 84.5 (CH), 85.5 (C), 86.6 (CH), 89.5 (C), 93.8 (CH$_3$), 97.6 (CH$_2$), 107.2 (C), 112.6 (CH$_2$), 113.8 (CH), 128.0 (CH), 129.4 (CH), 130.3 (C), 130.6 (C), 145.0 (CH), 159.3 (C), 207.1 (C) ppm.

IR (ATR) $\nu = 2928$, 2856, 1724, 1370, 1252, 1150, 1039, 835, 779 cm$^{-1}$.

HRMS (ESI) calcd for C$_{41}$H$_{70}$O$_9$Si$_2$ [M+Na]$^+$, 797.4636; found 797.4641 $\pm$ 5ppm.

Optical Rotation: $[\alpha]^{20}_D$(c 1.0, CHCl$_3$) = $+15.1^\circ$. 
(S)-1-((4R,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-y)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (S20). A solution of aldehyde 58 (921 mg, 2.95 mmol, 1.0 eq) in Et₂O (100 mL) was treated with a solution of allylmagnesium bromide (1.0 M in Et₂O, 8.85 mL, 8.85 mmol, 3.0 eq) at −78 °C. The mixture was allowed to stir for 90 minutes before the reaction was terminated by the addition of a saturated, aqueous solution of NH₄Cl (50 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 30 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent was removed under vacuum. The crude material was further purified by flash column chromatography (hexane/EtOAc 19:1) affording a 1:1.5 diastereomeric mixture of the corresponding secondary alcohols (S20, desired, minor diastereomer, 329 mg and S20a, undesired, major diastereomer, 521 mg) in 82% overall yield.

Major diastereomer S20a:

¹H NMR (400 MHz, CDCl₃): δ = 0.27 (s, 3H), 0.35 (s, 3H), 0.90 (s, 9H), 1.33 (s, 3H), 1.53 (s, 3H), 1.61 (s, 3H), 2.21-2.32 (m, 1H), 2.54-2.62 (m, 1H), 2.59 (s, 1H), 3.49-3.54 (m, 1H), 3.90 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 5.8, 9.7 Hz, 1H), 4.46-4.58 (m, 1H), 5.06-5.11 (m, 1H), 5.12-5.20 (m, 1H), 5.98 (dddd, J = 6.9, 6.9, 10.2, 17.1 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = −3.1 (CH₃), −2.3 (CH₃), 18.3 (C), 25.3 (CH₃), 25.9 (CH₃), 27.3 (CH₃), 29.9 (CH₃), 38.0 (CH₂), 67.2 (CH), 71.2 (C), 75.8 (CH), 80.8 (CH), 83.4 (CH), 85.7 (C), 108.8 (C), 117.0 (CH₂), 134.8 (CH) ppm.

IR (ATR) ν 3489, 3254, 2930, 2858, 2360, 1463, 1368, 1304, 1254, 1133, 1065, 967, 830, 784 cm⁻¹.

HRMS (ESI) calcd for C₁₉H₃₄O₄Si [M+Na]⁺, 377.2124; found 377.2127 +/− 5ppm.

Optical Rotation: [α]²⁰D(c 1.0, CHCl₃) = −13.8°.

Minor diastereomer S20:

¹H NMR (400 MHz, CDCl₃): δ = 0.24 (s, 3H), 0.25 (s, 3H), 0.88 (s, 9H), 1.39 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 2.35-2.42 (m, 2H), 2.67 (s, 1H), 2.82 (d, J = 2.5 Hz, 1H), 3.97 (d, J = 6.0 Hz, 1H),
4.04 (dd, J = 2.8, 6.0 Hz, 1H), 4.19-4.24 (m, 1H), 5.04-5.18 (m, 2H), 5.88 (dddd, J = 7.0, 7.0, 10.2, 17.2 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -2.8$ (CH$_3$), $-2.2$ (CH$_3$), 18.3 (C), 25.8 (CH$_3$), 25.9 (CH$_3$), 26.7 (CH$_3$), 30.7 (CH$_3$), 38.8 (CH$_3$), 68.0 (CH), 69.5 (C), 75.4 (CH), 79.2 (CH), 83.8 (CH), 86.0 (C), 108.9 (C), 117.2 (CH$_2$), 135.5 (CH) ppm.

IR (ATR) $\nu$ 3489, 3254, 2930, 2858, 2360, 1463, 1368, 1304, 1254, 1133, 1065, 967, 830 cm$^{-1}$.

HRMS (ESI) calcd for C$_{19}$H$_{34}$O$_4$Si [M+Na]$^+$, 377.2124; found 377.2128 +/- 5 ppm.

Optical Rotation: $[\alpha]_{20}^{D}$ (c 1.0, CHCl$_3$) = +12.3°.

**tert-Butyl((R)-2-((4R,5R)-5-((S)-1-(methoxymethoxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (69).** To a solution of secondary alcohol S20 (329 mg, 0.93 mmol, 1.0 eq) in 1,2-dichloroethane (4.6 mL) were added DIPEA (807 µL, 4.65 mmol, 5.0 eq) and MOM-Cl (212 µL, 2.79 mmol, 3.0 eq) at 0 °C. The mixture was warmed to 50 °C (stoppered round bottom flask) and was stirred for 14 hours before the reaction was quenched by the addition of H$_2$O (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) affording 69 (336 mg) in 91% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.20$ (s, 3H), 0.32 (s, 3H), 0.88 (s, 9H), 1.34 (s, 3H), 1.54 (s, 3H), 1.55 (s, 3H), 2.39-2.48 (m, 1H), 2.59 (s, 1H), 2.60-2.69 (m, 1H), 3.41 (s, 3H), 3.72 (d, $J = 5.5$ Hz, 1H), 4.27 (dd, $J = 5.5$, 10.0 Hz, 1H), 4.65-4.72 (m, 1H), 4.70 (d, $J = 6.8$ Hz, 1H), 5.0 (d, $J = 6.8$ Hz, 1H), 5.05-5.10 (m, 1H), 5.10-5.13 (m, 1H), 5.98 (dddd, $J = 4.9$, 9.0, 10.9, 16.4 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -2.7$ (CH$_3$), $-2.1$ (CH$_3$), 18.3 (C), 25.5 (CH$_3$), 26.1 (CH$_3$), 27.4 (CH$_3$), 30.1 (CH$_3$), 37.5 (CH$_3$), 55.7 (CH$_3$), 70.3 (C), 71.5 (CH), 75.8 (CH), 80.0 (CH), 82.8 (CH), 86.2 (C), 96.6 (CH$_2$), 108.2 (C), 117.6 (CH$_2$), 134.6 (CH) ppm.

IR (ATR) $\nu$ 2931, 2858, 2361, 2341, 1473, 1380, 1252, 1211, 1141, 1092, 1038, 916, 836 cm$^{-1}$.

HRMS (ESI) calcd for C$_{21}$H$_{38}$O$_5$Si [M+Na]$^+$, 421.2387; found 421.2392 +/- 5 ppm.

Optical Rotation: $[\alpha]_{20}^{D}$ (c 1.0, CHCl$_3$) = −34.1°.
Appendix III  Experimental part

Alcohol 70. To a solution of alkyne 69 (207 mg, 0.52 mmol, 2.0 eq) and HMPA (163 μL, 0.94 mmol, 3.6 eq) in THF (4.3 mL) was added t-BuLi (1.7 M in pentane, 306 μL, 0.52 mmol, 2.0 eq) at −78 °C. After 30 minutes at this temperature 30 μL of the reaction mixture were removed via a syringe and quenched by the addition of D₂O (mini-quench). ¹H-NMR-analysis indicated complete lithiation of the alkyne and a solution of aldehyde 48 (90 mg, 0.26 mmol, 1.0 eq) in THF (1 mL) was added to the reaction mixture. The mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (3 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 1.5:1 diastereomeric ratio (70a, less polar diastereomer, 75 mg, and 70, more polar diastereomer, 46 mg) in 63% overall yield as colorless oils.

Alcohol 70a (major diastereomer):
¹H NMR (400 MHz, CDCl₃): δ = 0.23 (s, 3H), 0.33 (s, 3H), 0.62 (quart, J = 7.9 Hz, 6H), 0.87 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.04 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.33 (s, 3H), 1.33-1.39 (m, 1H), 1.50 (s, 3H), 1.51 (s, 3H), 1.67 (ddd, J = 3.0, 9.6, 13.9 Hz, 1H), 1.87-1.99 (m, 1H), 2.34-2.62 (m, 3H), 3.27 (ddd, J = 4.9, 5.7 Hz, 1H), 3.38 (s, 3H), 3.44 (s, 3H), 3.73 (d, J = 5.6 Hz, 1H), 3.88 (ddd, J = 2.0, 5.7, 9.6 Hz, 1H), 4.17 (d, J = 3.0 Hz, 1H), 4.21 (dd, J = 3.0, 5.6 Hz, 1H), 4.30 (dd, J = 5.6, 10.4 Hz, 1H), 4.58 (d, J = 7.1 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.85 (ddd, J = 4.3, 5.4, 10.4 Hz, 1H), 4.93-5.02 (m, 2H), 5.05-5.13 (m, 2H), 5.24 (d, J = 7.1 Hz, 1H), 5.87 (ddd, J = 8.1, 10.4, 17.2 Hz, 1H), 5.91-6.02 (m, 1H) ppm.
¹³C NMR (100 MHz, CDCl₃): δ = −2.7 (CH₃), −1.9 (CH₃), 5.4 (CH₃), 7.1 (CH₃), 15.1 (CH₃), 18.3 (C), 19.0 (CH₃), 25.5 (CH₃), 26.1 (CH₃), 27.3 (CH₃), 29.4 (CH₃), 35.2 (CH), 36.0 (CH₂), 38.0 (CH₂), 39.0 (CH), 55.6 (CH₃), 56.0 (CH₃), 67.3 (CH), 68.9 (CH), 70.3 (C), 72.2 (CH), 80.4 (CH), 192
Appendix III  Experimental part

83.3 (CH), 85.2 (CH), 87.3 (C), 87.4 (C), 95.7 (CH₂), 98.2 (CH₂), 108.2 (C), 114.4 (CH₂), 117.9 (CH₂), 134.4 (CH), 141.6 (CH) ppm.

IR (ATR) ν 3447, 2956, 2878, 1639, 1369, 1253, 1217, 1146, 1038, 1003, 982, 834, 779 cm⁻¹.

HRMS (ESI) calcd for C₃₀H₇₄O₉Si₂ [M+Na⁺]⁺, 765.4769; found 765.4771 +/- 5ppm.

Optical Rotation: [α]20D(c 1.0, CHCl₃) = −31.1°.

Alcohol 70 (minor diastereomer):

¹H NMR (400 MHz, CDCl₃): δ = 0.20 (s, 3H), 0.29 (s, 3H), 0.61 (quart, J = 7.9 Hz, 6H), 0.88 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.00 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.39 (ddd, J = 2.0, 10.9, 13.6 Hz, 1H), 1.51 (s, 3H), 1.56 (s, 3H), 1.78 (ddd, J = 2.8, 9.6, 13.6 Hz, 1H), 1.83-1.94 (m, 1H), 2.36-2.53 (m, 2H), 2.54-2.63 (m, 1H), 3.27 (dd, J = 5.3, 5.6 Hz, 1H), 3.38 (s, 3H), 3.43 (s, 3H), 3.72 (d, J = 5.6 Hz, 1H), 3.83-3.92 (m, 2H), 4.25-4.31 (m, 2H), 4.55 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.84 (ddd, J = 4.3, 5.6, 10.1 Hz, 1H), 4.95-5.03 (m, 2H), 5.06-5.13 (m, 2H), 5.29 (d, J = 7.1 Hz, 1H), 5.86 (ddd, J = 8.1, 10.2, 17.3 Hz, 1H), 5.91-6.03 (m, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = −2.7 (CH₃), −2.1 (CH₃), 5.3 (CH₂), 7.1 (CH₃), 15.1 (CH₃), 18.3 (C), 18.8 (CH₃), 25.4 (CH₃), 26.1 (CH₃), 27.8 (CH₃), 29.7 (CH₃), 35.3 (CH₂), 35.5 (CH), 38.0 (CH₂), 39.1 (CH), 55.6 (CH₃), 56.0 (CH₃), 67.4 (CH), 68.7 (CH), 70.6 (C), 72.3 (CH), 80.6 (CH), 82.9 (CH), 85.0 (CH), 87.7 (C), 88.6 (C), 95.7 (CH₂), 98.1 (CH₂), 108.2 (C), 114.4 (CH₂), 117.8 (CH₂), 134.4 (CH), 141.7 (CH) ppm.

IR (ATR) ν 3447, 2956, 2878, 1639, 1369, 1253, 1217, 1146, 1038, 1003, 982, 834, 779 cm⁻¹.

HRMS (ESI) calcd for C₃₀H₇₄O₉Si₂ [M+Na⁺]⁺, 765.4769; found 765.4758 +/- 5ppm.

Optical Rotation: [α]20D(c 0.7, CHCl₃) = −44.4°.

Alcohol S21. To a solution of alkyne 57 (565 mg, 1.3 mmol, 2.0 eq) and HMPA (407 μL, 2.34 mmol, 3.6 eq) in THF (11 mL) was added t-BuLi (1.7 M in pentane, 0.75 mL, 1.3 mmol, 2.0 eq) at −78 °C. After stirring for 30 minutes at that temperature 30 μL of the reaction mixture were removed via a syringe and quenched by the addition of D₂O (mini-quench). ¹H-NMR-analysis
indicated a 40% lithiation of the alkyne, and 1 equivalent of t-BuLi (375 μL) was added. After 25 minutes another mini-quench showed complete lithiation of the alkyne and a solution of aldehyde 74 (150 mg, 0.65 mmol, 1.0 eq) in THF (1.5 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 9:1 to 5:1) the secondary alcohol S21 (323 mg) was isolated as an inseparable 2:1 diastereomeric mixture in 76% overall yield.

Alkyne 75. To a solution of the diastereomeric mixture of alcohol S21 (380 mg, 0.58 mmol, 1.0 eq) in DMF (5.8 mL) was added NaH (60% dispersion in mineral oil, 46 mg, 1.16 mmol, 2.0 eq) at 0 °C. After 30 minutes PMB-Cl (141 μL, 1.04 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for additional 8 hours at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO₃ (5 mL). After dilution with Et₂O the layers were separated and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with H₂O (20 mL) and brine (20 mL) once, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude products were further purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) to provide the inseparable mixture of diastereomers 75 (311 mg) in 70% yield.

Alcohol S22. A solution of 75 (456 mg, 0.59 mmol, 1.0 eq) dissolved in MeOH (12.8 mL) was treated with camphorsulfonic acid (27 mg, 0.12 mmol, 0.2 eq) at 0 °C and was allowed to stir for 90 minutes before it was quenched by the addition of a saturated, aqueous solution of NaHCO₃ (8 mL). After dilution with EtOAc (10 mL), the layers were separated and the aqueous phase was extracted with (EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude mixture of primary alcohols was purified by HPLC (hexane/EtOAc 7:1) affording S22a (less polar diastereomer, 238 mg) and S22b (more polar diastereomer, 119 mg) as colorless oils in a 2:1 diastereomeric ratio and 92% overall yield.
Appendix III

Experimental part

**S22a** (major diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.13$ (s, 3H), 0.19 (s, 3H), 0.79 (s, 9H), 1.02 (d, $J = 7.1$ Hz, 3H), 1.38 (s, 3H), 1.48-1.54 (m, 1H), 1.53 (s, 3H), 1.57 (s, 3H), 1.90 (ddd, $J = 6.5$, 13.1, 13.4 Hz, 1H), 2.0 (ddd, $J = 5.2$, 6.7 13.1 Hz, 1H), 2.12 (bs, 1H), 3.54-3.64 (m, 1H), 3.68-3.76 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.85 (d, $J = 6.6$ Hz, 1H), 3.96 (dd, $J = 1.9$, 10.2 Hz, 1H), 3.98 (d, $J = 5.2$ Hz, 1H), 4.11 (dd, $J = 10.2$, 10.2 Hz, 1H), 4.37 (d, $J = 11.4$ Hz, 1H), 4.46 (d, $J = 12.1$ Hz, 1H), 4.48-4.53 (m, 1H), 4.64 (d, $J = 12.1$ Hz, 1H), 4.77 (d, $J = 11.4$ Hz, 1H), 6.80-6.85 (m, 2H), 6.85-6.90 (m, 2H), 7.22-7.30 (m, 4H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = −2.8$ (CH$_3$), −2.1 (CH$_3$), 16.8 (CH$_3$), 18.1 (C), 25.3 (CH$_3$), 25.8 (CH$_3$), 27.5 (CH$_3$), 30.7 (CH$_3$), 35.6 (CH$_3$), 36.2 (CH$_2$), 55.4 (CH$_3$), 55.43 (CH$_3$), 61.0 (CH$_2$), 68.7 (CH$_2$), 70.1 (C), 70.7 (CH$_2$), 73.1 (CH$_2$), 73.4 (CH), 77.7 (CH), 83.3 (CH), 83.8 (C), 89.2 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.8 (CH), 129.9 (C), 130.6 (C), 159.3 (C), 159.4 (C) ppm.

IR (ATR) $\nu$ 3437, 2929, 2856, 1514, 1302, 1249, 1090, 1037, 836, 779 cm$^{-1}$.

HRMS (ESI) calcd for C$_{37}$H$_{56}$O$_8$Si [M+Na]$^+$, 679.3642; found 679.3641 +/- 5ppm.

Optical Rotation: $[\alpha]^{20}_D(c 1.0, \text{CHCl}_3) = +14.8^\circ$.

**S22b** (minor diastereomer):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.12$ (s, 3H), 0.19 (s, 3H), 0.78 (s, 9H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.39 (s, 3H), 1.50-1.54 (m, 1H), 1.54 (s, 3H), 1.56 (s, 3H), 1.76-1.87 (m, 2H), 1.93-2.02 (m, 1H), 3.55-3.65 (m, 1H), 3.66-3.74 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.85 (d, $J = 6.6$ Hz, 1H), 3.92 (d, $J = 6.1$ Hz, 1H), 3.94 (dd, $J = 2.3$, 10.4 Hz, 1H), 4.08 (dd, $J = 10.1$, 10.4 Hz, 1H), 4.39 (d, $J = 11.4$ Hz, 1H), 4.42 (d, $J = 12.1$ Hz, 1H), 4.49 (ddd, $J = 2.3$, 6.6, 10.1 Hz, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.77 (d, $J = 11.4$ Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.20-7.25 (m, 2H), 7.27-7.32 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = −2.8$ (CH$_3$), −2.1 (CH$_3$), 16.4 (CH$_3$), 18.1 (C), 25.3 (CH$_3$), 25.8 (CH$_3$), 27.5 (CH$_3$), 30.6 (CH$_3$), 35.5 (CH), 36.2 (CH$_2$), 55.4 (CH$_3$, 2x), 60.9 (CH$_2$), 68.8 (CH$_2$), 70.1 (C), 70.7 (CH$_2$), 73.1 (CH$_2$), 73.3 (CH), 77.7 (CH), 83.3 (CH), 84.4 (C), 88.6 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.8 (CH), 129.9 (C), 130.0 (C), 130.7 (C), 159.3 (C), 159.4 (C) ppm.

IR (ATR) $\nu$ 3437, 2929, 2856, 1514, 1302, 1249, 1090, 1037, 836, 779 cm$^{-1}$.

HRMS (ESI) calcd for C$_{37}$H$_{56}$O$_8$Si [M+Na]$^+$, 679.3642; found 679.3644 +/- 5ppm.

Optical Rotation: $[\alpha]^{20}_D(c 1.0, \text{CHCl}_3) = −83.5^\circ$. 

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Aldehydes 76a and 76b:
To a solution of IBX (126 mg, 0.45 mmol, 1.5 eq) in DMSO (1.5 mL) was added alcohol S22a (less polar diastereomer, 197 mg, 0.30 mmol, 1.0 eq) in DMSO (1.5 mL) and the reaction mixture was stirred for 3 hours at room temperature. As TLC-control showed total consumption of the starting material the reaction was terminated by the addition of H2O (3 mL) at 0 °C. The resulting suspension was filtered through a plug of Celite and the filtrate was diluted with Et2O (10 mL). The layers were separated and the aqueous phase was extracted with Et2O (3 x 10 mL). The combined organic fractions were washed with H2O (10 mL) and brine (10 mL) and dried over MgSO4. After filtration the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexane/EtOAc 5:1 to 3:1) delivering aldehyde 76a (163 mg) in 83% yield.

Aldehyde 76a:
1H NMR (400 MHz, CDCl3): δ = 0.12 (s, 3H), 0.18 (s, 3H), 0.80 (s, 9H), 1.05 (d, J = 6.8 Hz, 1H), 1.38 (s, 3H), 1.52 (s, 3H), 1.57 (s, 3H), 2.30 (ddd, J = 2.3, 7.9, 16.7 Hz, 1H), 2.37-2.48 (m, 1H), 2.74 (ddd, J = 1.5, 5.1 16.7 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.86 (d, J = 6.8 Hz, 1H), 3.97 (dd, J = 2.3, 10.5 Hz, 1H), 4.01 (d, J = 4.5 Hz, 1H), 4.06 (dd, J = 9.7, 10.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.48-4.53 (m, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.22-7.27 (m, 4H), 9.72 (dd, J = 1.5, 2.3 Hz, 1H) ppm.
13C NMR (100 MHz, CDCl3): δ = −2.7 (CH3), −2.1 (CH3), 16.4 (CH3), 18.1 (C), 25.3 (CH3), 25.8 (CH3), 27.5 (CH3), 30.7 (CH3), 33.5 (CH), 46.9 (CH2), 55.4 (CH2, 2x), 68.9 (CH2), 70.1 (C), 70.6 (CH2), 72.1 (CH), 73.2 (CH2), 77.8 (CH), 83.3 (CH), 87.1 (C), 89.5 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.7 (CH), 130.0 (C), 130.7 (C), 159.3 (C), 159.4 (C), 202.0 (CH) ppm.
IR (ATR) ν 2956, 2931, 2856, 1727, 1612, 1513, 1462, 1302, 1248, 1092, 836 cm⁻¹.
HRMS (ESI) calcd for C37H54O8Si [M+Na]+, 677.3486; found 677.3485 +/− 5ppm.
Optical Rotation: [α]20D(c 1.0, CHCl3) = +18.9°.
Starting from polar diastereomer S22b (150 mg, 0.23 mmol, 1.0 eq), diastereomeric aldehyde 76b, was isolated in 82% yield (122 mg).

Aldehyde 76b:
1H NMR (400 MHz, CDCl3): δ = 0.11 (s, 3H), 0.19 (s, 3H), 0.79 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.39 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 2.32 (ddd, J = 1.8, 7.5, 16.3 Hz, 1H), 2.36-2.44 (m, 1H), 2.61 (ddd, J = 2.0, 5.3, 16.3 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.84 (d, J = 6.5 Hz, 1H), 3.85 (d, J
= 6.8 Hz, 1H), 3.95 (dd, J = 2.3, 10.5 Hz, 1H), 4.03 (dd, J = 9.8, 10.5 Hz, 1H), 4.36 (d, J = 11.3 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.49 (ddd, J = 2.3, 6.5, 9.5 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 11.3 Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.20-7.25 (m, 2H), 7.25-7.29 (m, 2H), 9.70 (dd, J = 1.8, 2.0 Hz, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = -2.8 (CH$_3$), -2.1 (CH$_3$), 16.8 (CH$_3$), 18.1 (C), 25.3 (CH$_3$), 25.8 (CH$_3$), 27.6 (CH$_3$), 30.5 (CH$_3$), 34.0 (CH), 47.6 (CH$_2$), 55.4 (CH$_3$, 2x), 68.8 (CH$_2$), 70.1 (C), 70.7 (CH$_2$), 72.7 (CH), 73.1 (CH$_2$), 77.8 (CH), 83.3 (CH), 83.9 (C), 89.0 (C), 108.9 (C), 113.9 (CH, 2x), 129.3 (CH), 129.8 (C), 129.9 (CH), 130.7 (C), 159.3 (C), 159.5 (C), 201.9 (CH) ppm.

IR (ATR) $\nu$ 2956, 2931, 2856, 1727, 1612, 1513, 1462, 1302, 1248, 1092, 836 cm$^{-1}$.

HRMS (ESI) calcd for C$_{37}$H$_{54}$O$_8$Si [M+Na]$^+$, 677.3486; found 677.3479 +/- 5ppm.

Optical Rotation: $[\alpha]_{20}^D$(c 1.0, CHCl$_3$) = -67.8°.
References

NMR-spectra

Solvent: CDCl$_3$

Instrument frequency: $^1$H: 400 MHz
$^{13}$C: 100 MHz
Appendix III  NMR-spectra
Appendix III  NMR-spectra

[Image: NMR-spectra of chemical structures]
Appendix III  NMR-spectra

[Chemical structures and NMR spectra images with ppm values]
Compound 50
Compound 50

[Diagram of NMR spectra with labeled peaks and connectivities]
Appendix III  NMR-spectra

NMR spectroscopy data and structures are shown here. The spectra display peaks at various ppm values, indicating the chemical shifts of different protons or other nuclei in the compound. The images include molecular structures labeled with chemical groups and atomic numbers.

For a detailed analysis, the specific ppm values and assignments for each peak would be necessary. The structures show the presence of PMBO, MOMO, and OTBS groups, which are typical in organic chemistry for protecting functionalities or providing stability.

Further interpretation would require a more detailed examination of the experimental conditions and the compounds' identities.
Appendix III  NMR-spectra

[Diagram of NMR spectra with chemical structures and ppm values]

[^226^]
Appendix III  NMR-spectra

[Diagram of NMR spectra with peaks labeled at specific ppm values.]

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Appendix III  NMR-spectra

![Chemical structure](image1)

[1H-NMR spectrum]

ppm: 7.5, 7.0, 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0

![13C-NMR spectrum]

ppm: 218, 264, 270, 76.5, 76.8, 77.1, 77.2, 77.4, 115.0, 173.3

S16
Appendix III

NMR-spectra
Appendix III

NMR-spectra

[Diagram of NMR spectra with peaks and ppm values listed]
Compound 62
Appendix III

Compound 62

NMR-spectra
Appendix III  NMR-spectra

![NMR-spectrum](image)

**62a**

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240
Appendix III  NMR-spectra

[Chemical structures and NMR spectra images]

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Appendix III

NMR-spectra
Appendix III  NMR-spectra

76b (minor diast.)

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0.97  1.07  1.03  1.03

1.02  1.11  1.03  1.00

2.97  3.04  2.08  1.03

1.01  1.01  1.08  1.02

3.07  3.05  3.12  3.10

10 ppm

3.05  3.12  3.10  3.03

1.07  1.01  1.01  1.07

2.97  3.04  2.08  1.03

1.02  1.11  1.03  1.00

2.06  2.10  2.24  1.07

0.97  1.07  1.03  1.03

1.02  1.11  1.03  1.00

2.97  3.04  2.08  1.03

1.01  1.01  1.08  1.02

3.07  3.05  3.12  3.10

10 ppm

3.05  3.12  3.10  3.03

1.07  1.01  1.01  1.07

2.97  3.04  2.08  1.03

1.02  1.11  1.03  1.00

2.06  2.10  2.24  1.07

0.97  1.07  1.03  1.03

1.02  1.11  1.03  1.00

2.97  3.04  2.08  1.03

1.01  1.01  1.08  1.02

3.07  3.05  3.12  3.10

10 ppm

3.05  3.12  3.10  3.03

1.07  1.01  1.01  1.07

2.97  3.04  2.08  1.03

1.02  1.11  1.03  1.00

2.06  2.10  2.24  1.07

0.97  1.07  1.03  1.03

1.02  1.11  1.03  1.00

2.97  3.04  2.08  1.03

1.01  1.01  1.08  1.02

3.07  3.05  3.12  3.10

10 ppm

3.05  3.12  3.10  3.03

1.07  1.01  1.01  1.07

2.97  3.04  2.08  1.03
8. CURRICULUM VITAE

RITA FÜRST, MAG.

Department of Organic Chemistry
University of Vienna
Währinger Straße 38
1090 Vienna, Austria

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Personal Data

Date of birth: May 12, 1984 in Oberpullendorf, Austria
Citizenship: Austria

Education and Qualifications

05/2009 – present Ph.D. Thesis, University of Vienna
“Synthetic Studies Toward the Total Syntheses of the Jatrophane Diterpenes Pl-3 and Pl-4”
Supervisor: Univ.-Prof. Dr. Johann Mulzer

03/2009 Graduation with honors, University of Vienna

03/2008 – 03/2009 Diploma Thesis, University of Vienna
“Synthesis and Biological Evaluation of Novel Combretastatin A-4 Analogs”
Supervisor: Univ.-Prof. Dr. Johann Mulzer

10/2003 – 03/2009 Studies of Chemistry, University of Vienna
Focus: Organic Chemistry, Biochemistry and Analytical Chemistry

06/2003 Matura (Graduation) with honors

09/1998 – 06/2003 Gymnasium für Studierende der Musik Oberschützen, Austria
(Secondary school with emphasis on music, upper grade)

Research Experience

Natural product synthesis (jatrophane diterpenes, combretastatin analogs) and supporting analytical methods (NMR, mass spectrometry, HPLC, IR).

Scholarships and Awards

01/2010 – 06/2012 DOC-fFORTE [Women in Research and Technology]; Ph.D. grant, financed by the Austrian Academy of Sciences.

2009 Leistungsstipendium (excellence scholarship), University of Vienna.
### Employment History

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<td>10/2007 – present</td>
<td>Teaching assistant, University of Vienna Tutor and lecturer in different chemistry laboratory courses of graduate and undergraduate students.</td>
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<tr>
<td>08/2006</td>
<td>Montanuniversität Leoben (University of Leoben), Austria, University internship at the Department of Polymer Engineering and Science.</td>
</tr>
<tr>
<td>08/2004 + 2005</td>
<td>Ökolab (Subsidiary company of Austria Tabak, Vienna), Internship at the Department of Tobacco Analysis.</td>
</tr>
</tbody>
</table>

### Language, Special Skills

**Languages**
- German: Native language
- English: spoken – excellent; comprehension – excellent; written – excellent
- Latin: high school level

**Technical**
- Profound experience with a variety of chemistry software, such as Topspin, Beilstein, Scifinder, ChemOffice and most common office tools (Excel, Word, Power Point). Experience with advanced NMR techniques, IR, and other analysis methods (HPLC, mass-spectrometry).