"Towards antifungal compounds : total synthesis of jerangolid D"

Pospisil, Jiri

Abstract
The main thrust of this Thesis is focused on the total synthesis of (+)-ambruticin. It was envisioned that our strategy, leading towards this molecule, will be short, efficient and highly versatile. Therefore, novel methodologies which would enable us to construct complex molecules starting from three or more fragments (multicomponent reactions) or novel C-C bond forming reactions, leading to the stereoselective formation of polysubstituted olefinic structures, were searched. To answer these challenges, two novel methodologies were developed. First among them, a multicomponent Sakurai reaction, based upon the chemistry of silicon, gave us a short and efficient access to dihydropyran subunits. The second methodology, which involves the chemistry of sulfur, is a modification of the classical Julia olefination method. However, it enables us to achieve the synthesis of tri- and tetrasubstituted olefins with high stereocontrol. The scope and limitations of these methods were studied in...

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TOWARDS ANTIFUNGAL COMPOUNDS: TOTAL SYNTHESIS OF JERANGOLID D

A Thesis Submitted for the Degree of Doctor of Sciences

JIŘÍ POSPÍŠIL

2006
Destiny is like a sword. It will cut you if you grip it by the blade.

Ann Marston in Kingmaker’s sword
Members of Jury:

Prof. P. De Clercq (Ghent University)

Prof. J.-F. Gohy (UCL)

Prof. J. Marchand (UCL, president)

Prof. I. E. Markó (UCL, promoter)

Prof. O. Riant (UCL)

Prof. E. J. Thomas (University of Manchester)
It would never be possible to finish this Thesis without the help of a huge number of persons.

On the first place, I would like to thanks to Prof. I. E. Markó. Without his leadership, enthusiasm (to present a novel approaches to targeted molecules, when all hope was almost lost) and patience (when another approach to desired molecule crashed in fume and flames) would be impossible.

My thanks belong to Prof. A. Schanck and Dr. D. Chapon for their help and advices during my fights with NMR machines and specters. I would like to thank also to Prof. M. Potáček, my former supervisor, because without the backgrounds he gave me, I would never be able to do my PhD.

My work in the laboratory would not certainly be possible without three very important persons: Juliette, René and Fabio. Juliette, an administrative wizard, which is able to turn “coal into the gold”, was not only to proceed repetitively my papers with an incredible speed through the university administration, but also was able to help to me, as well as to others, with a million each day life problems. To René, for the dry ice, solvents, liquid nitrogen… and to Fabio, for his help with the big scale synthesis of several starting materials, help with GC and HPLC apparatus… Even though he is Italian (Italy eliminated the Czech republic in the WC 2006), he is an excellent friend.

To my “exiled” co-workers from the zero floor, Corinne, Alain, Benoit, Bernard, Fanny, Gregory, Isabelle, Michael, Pierre and Thomas, for creating an excellent ambience.

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Mým rodičům, za jejich lásku a podporu a za jejich výchovu. Za to, že se nebáli mě poslat do světa ať se otrkám. Za to, že mě nechali vykoupat se v potížích, které jsem si připravil, ale že při mně vždy stáli když jsem to nejvíc potřeboval. Za to, že jsem byl vychován tak, abych se ve světě neztratil. Za to, že se nikdy nenechali obměkčit, když jsem si stěžoval, že jiní rodiče dělají pro svoje děti to a ono. Teď vidím, že to pro mě bylo to nejlepší.

Svému bratru Tomáši, za společnost a český jazyk.

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Summary
In our laboratory, we are interested in the convergent and efficient synthesis of various natural products. During this Thesis, the main thrust was focused on the synthesis of (+)-ambruticin 1 (Scheme 1). After several unsuccessful approaches, the antithetic analysis which divided the molecule 1 into four fragments, 100, 122, 182 and 183, was proposed.

Scheme 1
Since the synthesis of the left-hand portion 122 has already been established by T. Kumamoto and A.-E. Gies, our synthetic efforts were directed to the middle-right, middle-left and right-hand fragments.
To develop a short and efficient approach to the right-hand subunit 100, a novel variant of a multicomponent Sakurai reaction was disclosed. Gratifyingly, under the optimized conditions, TMSOTf-mediated condensation between aldehyde (S)-132b, silyl ether (R)-133 and allylsilane 131 yielded the desired adduct, syn-130b, in excellent yield and diastereoselectivity (Scheme 2). Ring closing metathesis of 130b, followed
Summary

by TBS-group removal and alcohol oxidation completed the synthesis of the right-hand fragment of 1.

\[
\begin{align*}
&(S)-132b + (R)-133 \
\rightarrow &\quad 131 \quad \text{TMSOTf (0.1 eq)} \quad \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \
&TBDPSO \quad \text{GC-1} \quad 2 \text{ mol %} \quad \text{CH}_2\text{Cl}_2, \Delta t \quad 94\%
\end{align*}
\]

Scheme 2

This highly diastereoselective multicomponent Sakurai reaction was then studied in details and the preliminary scope and limitations of the reaction were established (Scheme 3).

\[
\begin{align*}
&(S)-132 \quad \text{PG = TBS or TBDPS} \
\rightarrow &\quad 131 \quad \text{cat. TMSOTf} \quad \text{80\%, d.r. = >95:1} \
&\quad \text{13 other examples} \quad (67-89\%, \text{d.r. = >95:1})
\end{align*}
\]

Scheme 3

The synthesis of the middle-right fragment 183c started from the β-hydroxy ester 89 and furnished the desired compound 183c in a straightforward manner and 97% overall yield (Scheme 4).

\[
\begin{align*}
\text{MeO} &\quad \text{OH} \quad 89 \quad \rightarrow \quad \text{TBSO} \quad \text{SO}_2\text{Ph} \
\rightarrow &\quad 183c
\end{align*}
\]

Scheme 4
In the next stage, a standard Julia-Lythgoe coupling between 100 and 183c was attempted (Scheme 5).

Scheme 5

To our great surprise, this olefination gave rather low yields and thus, we had to propose a novel modification of the standard Julia olefination method based upon the use of sulfoxides. Gratifyingly, this variant proved to be highly efficient and enabled the stereoselective synthesis of di-, tri- and tetrasubstituted olefins in good to excellent yields and selectivity (Scheme 6).

Scheme 6

Finally, the synthesis of the middle-left fragment 182 was attempted. Thus, aldehyde 207 was reacted with subunit 191, yielding the diene 210 (Scheme
Summary

7). Stereoselective cyclopropanation of 210 (3 stereogenic centers formed) then afforded the desired eastern part 211 of ambruticin.

Scheme 7

Finally, our newly developed methodologies, the multicomponent Sakurai reaction and the sulfoxide-modified Julia olefination, were used as key steps in the synthesis of (R)-goniothalamin, (R)-goniothalamin oxide, (R)-kavain (Scheme 8), and jerangolid D (Scheme 9).
Summary

Scheme 8

Scheme 9
Summary
**Résumé**

Notre laboratoire s’intéresse au développement de synthèses convergentes et efficaces de divers produits naturels. Durant cette thèse, la synthèse de la (+)-ambruticine 1 a fait l’objet d’une étude approfondie (Figure 1). Après plusieurs approches inefficaces, une analyse rétrosynthétique divisant cette molécule en différents fragments 100, 122, 182 et 183, a été proposée.

La synthèse de la sous-unité droit 122 a été réalisée par T. Kumamoto et A.-E. Gies. Nous nous sommes donc concentré sur les fragments 182, 183 et 100.

Afin de développer une synthèse courte et efficace de 100, nous avons élaboré une nouvelle variante multicomposante de la réaction de Sakurai. Après optimisation des conditions expérimentales, nous avons observé la condensation, catalysée par du TMSOTf, de l’aldéhyde (S)-132b, avec l’éther silylé (R)-133 et l’allylsilane 131, fournissant le composé désiré syn-130b avec un excellent rendement et une haute diastéréosélectivité (Figure 1).
Résumé

2). La fermeture de cycle par métathèse, suivie par la déprotection et l’oxydation de l’alcool, termine la synthèse du fragment droit de l’ambruticine.

Cette réaction multicomposante de Sakurai est hautement diastéréosélective. Elle a donc été étudiée plus en détails (Figure 3).

Le fragment 183c a été synthétisé à partir du β-hydroxy ester 89 et le composé désiré 183c a été obtenu de manière directe avec un rendement de 97% (Figure 4).
Lors de l’étape suivante, le couplage de 100 et de 183c a été effectué par une oléfination de Julia-Lythgoe (Figure 5).

Figure 5

De manière surprenante, ce couplage a donné des rendements plutôt faibles. Nous nous sommes donc proposé de développer une nouvelle modification de l’oléfination de Julia, basée sur l’utilisation de sulfoxides. Ces nouvelles conditions nous ont permis de former des oléfines di-, tri- et tétrasubstituées avec de très bons rendements et d’excellentes sélectivités (Figure 6).

Figure 6

Enfin, la sous-unité centrale gauche 182 a été synthétisée. L’aldéhyde 207 et le fragment 191 ont fourni le diène 210 (Figure 7). La cyclopropanation...
Résumé

stéréosélective de 210 (formation de trois centers chiraux) a ensuite fourni la partie est de l’ambruticine 211.

\[
\begin{align*}
\text{MeO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{MeO} \\
\end{align*}
\]

\[207 + \text{PTO}_2\text{S} \quad \text{THF, -78°C to r.t.} \quad 65\% \quad E/Z = >95:1\]

\[
\begin{align*}
\text{MeO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{MeO} \\
\end{align*}
\]

\[210 \quad \text{N}_2\text{Et} (24 \text{ eq}) \quad \text{Pd(OAc)}_2 (20 \text{ mol%}) \quad \text{Et}_2\text{O, 0°C} \quad 74\%, \text{ d.r.} = >95:1\]

\[
\begin{align*}
\text{MeO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{MeO} \\
\end{align*}
\]

\[211\]

**Figure 7**

Finalement, nous avons appliqué nos deux nouvelles methodologies, la reaction de sakurai multicomposante et l’oléfination de Julia basée sur l’utilisation de sulfoxides, à la synthèse de la (R)-goniothalamine, l’oxyde de (R)-goniothalamine, la (R)-kavaine (Figure 8) et le jerangolide D (Figure 9).
Résumé

Figure 8

Figure 9
Abbreviations

Ac = acetyl
Acac = acetylacetoacetate
Ad, 1-adamantyl =
    tricycle[3.3.1,1^3,7]dec-1-yl
AMCR = asymmetric
    multicomponent reaction
Ar = aryl
Bn = benzyl
BT = benzo[d]thiazol
_n-butyl, nBu = normal-butyl
tert-butyl, tBu = tertiary-butyl
_i-Bu = 2-butyl
Bz = benzoyl
°C = degree Celsius
CALB = Candida antarctica lipase
    B
    cat. = catalytic
_mCPBA = meta-chloroperbenzoic acid
Cy = cyclohexyl
Δ = heating
δ = chemical shift (NMR)
d = doublet
DBB = di-tert-butyldicarboxylate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC = cyclohexylcarbodiimid
DCM = CH₂Cl₂
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H = diisobutyl aluminium hydride
DMAP = 4-dimethylaminopyridine
DMB = 2,4-dimethoxybenzyl
DMP = Dess-Martin reagent
DMPU = tetrahydro-1,3-dimethylpyrimidin-2-(1H)-one
de = diastereomeric excess
dMF = dimethylformamide
dMSO = dimethylsulfoxide
d.r. = diastereomeric ratio
E⁺ = electrophile
EDG = electron-donating group
ee = enantiomeric excess
eq. = equivalent
EtAc = ethyl acetate
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<td>electron-withdrawing group</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<td>GC</td>
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</tr>
<tr>
<td>hex</td>
<td>hexyl</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramidide</td>
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<td>I.R.</td>
<td>infrared</td>
</tr>
<tr>
<td>ISMS</td>
<td>intramolecular silyl-modified Sakurai reaction</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>L.A.</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
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<td>Lutidine</td>
<td>dimethylpyridine</td>
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<tr>
<td>min</td>
<td>minute</td>
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<td>m</td>
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<td>MCR</td>
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<td>Me</td>
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<td>MOM</td>
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<td>mass spectroscopy</td>
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<tr>
<td>n.a.</td>
<td>not available</td>
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<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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<tr>
<td>NMO</td>
<td>N-methylmorpholine oxide</td>
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<tr>
<td>NMR</td>
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</tr>
<tr>
<td>n.O.e.</td>
<td>nuclear Overhauser effect</td>
</tr>
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<td>n.r.</td>
<td>no reaction</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>P.E.</td>
<td>petroleum ether</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>1,2,2,6,6-pentamethylpiperidine</td>
</tr>
<tr>
<td>Iso-propyl, iPr</td>
<td>2-propyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>PPTS</td>
<td>pyridinium p-toluene sulfonate</td>
</tr>
<tr>
<td>PT</td>
<td>phenyl-1H-tetrazole</td>
</tr>
<tr>
<td>PTSA</td>
<td>4-methylbenzenesulfonic acid</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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<td>quant.</td>
<td>quantitative</td>
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<td>singlet</td>
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<td>starting material</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpyperidine N-oxide</td>
</tr>
<tr>
<td>TBAC</td>
<td>tetrabutylammonium chloride</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylphenylsilyl</td>
</tr>
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<td>TBHP</td>
<td>tert-butylhydroperoxyde</td>
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<tr>
<td>TBT</td>
<td>tert-butyl-1H-tetrazole</td>
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<tr>
<td>TBS</td>
<td>tert-butyltrimethylsilyl</td>
</tr>
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<td>tert-butyltrimethylsilyl triflate</td>
</tr>
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<td>triethylsilyl</td>
</tr>
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<td>TESCl</td>
<td>triethylsilyl chloride</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TfO</td>
<td>triflate</td>
</tr>
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<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylenediamine</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSNTf₂</td>
<td>trimethylsilyl bistriflamide</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>trimethylsilyl triflate</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
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<td>TS</td>
<td>transition state</td>
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Abbreviations
1. Introduction

The main thrust of this Thesis is focused on the total synthesis of (+)-ambruticin. It was envisioned that our strategy, leading towards to this molecule, will be short, efficient and highly versatile. Therefore, novel methodologies which would enable us to construct complex molecules starting from three or more fragments (multicomponent reactions) or novel C-C bond forming reactions, leading to the stereoselective formation of polysubstituted olefinic structures, were searched.

To answer these challenges, two novel methodologies were developed. First among them, a multicomponent Sakurai reaction, based upon the chemistry of silicon, gave us a short and efficient access to dihydropyran subunits. The second methodology, which involves the chemistry of sulfur, is a modification of the classical Julia olefination method. However, it enables us to achieve the synthesis of tri- and tetrasubstituted olefins with high stereocontrol.

The scope and limitations of these methods were studied in details. Additionally, the applicability of these methods was tested in the context of other natural products synthesis, leading to a short and efficient preparation of (+)-goniothalamin, (+)-goniothalamin oxide, (+)-kavain and jerangolid D. Finally, we have decided to apply our silicon and sulfur-based methodologies to a connective total synthesis of (-)-dactyloolide, which is itself a potent cytotoxic molecule. More interestingly, it is also a direct precursor (one step) to another natural product, (-)-zampanolide. This molecule is known for its high cytotoxic activity (~2ng/mL). Unfortunately, it is not available in sufficient amount for in depth biological studies.
Chapter 2. (+)-Ambruticin

2. (+)-Ambruticin

2.1 Introduction

(+)-Ambruticin S (1) was isolated from fermentation extracts of the Myxobacteria species Polyangium cellulosum var. fulvum by Warner-Lambert scientists in 1977 (Figure 2.1). It is an orally active antifungal agent showing in vitro and in vivo activity against a variety of pathogenic fungi, including Histoplasma capsulatum, Coccidioides immitis and Blastomyces dermatitides as well as dermatophytic filamentous fungi. Amino-analogs of 1 are also known.

![Chemical Structure of (+)-Ambruticin S (1)](image)

Figure 2.1

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Chapter 2. (+)-Ambruticin

*In vivo* as well as *in vitro* tests showed that ambruticin S (1) is, compared to its main opponent amphotericin B, less active and has to be used in approximately 10 times higher doses.\(^3\) It was also observed that all tested derivatives of 1 displayed worse or no biological activity against pathogenic fungi.\(^4\) It is important to point out that only some modifications of the left fragment of 1 were examined.\(^{4a,b}\) It has been also shown that the divinylcyclopropane moiety of 1 undergoes a sigmatropic rearrangement upon heating at 240°C, affording a cycloheptadiene derivative that possesses no biological activity, suggesting that the divinylcyclopropane is required for biological activity.\(^4c\)

In contrast to amphotericin B, (+)-ambruticin 1 displays potent inhibitory activity against the yeast strain *Hansenula anomala* with an MIC of 0.03 μg/mL.\(^5\)

Recently, biologists became again interested in ambruticin S (1) when it was discovered that its mechanisms of action is very different from other drugs used in the treatment of pathogenic fungi. The mode of action of ambruticin 1 resembles that of pyrrolnitrin. It means that its lethality to cells is achieved through interference with osmoregulation.\(^1c,6\)

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Chapter 2. (+)-Ambruticin

The relative and absolute stereochemistry of 1 has been established through a combination of spectroscopic studies,\textsuperscript{7} chemical degradation and single-crystal X-ray analysis of the fragments.\textsuperscript{8}

Ambruticin (1) has been attractive not only for pharmacologists, with its unique biological activities, but also with organic chemists, with its challenging architectural framework. This structurally intriguing molecule incorporates 10 stereocenters and three \(E\)-olefins within a relatively small framework bearing a dihydropyran, a tetrahydropyran bearing a diol function, and a trisubstituted divinylcyclopropane unit unique to this family of natural products. The diverse structural features of ambruticin, in conjunction with its potentially valuable biological activities, have stimulated considerable interest in the synthetic community\textsuperscript{8,9} and to date, four total syntheses, by Kende,\textsuperscript{10} Jacobsen,\textsuperscript{11} Martin\textsuperscript{12} and Lee\textsuperscript{13} have been documented. A comparison of all four syntheses can be found in Table 2.1
2.1.1 First Total Synthesis – Kende 1990

The first total synthesis of 1 was reported by Kende et al. in 1990.\textsuperscript{10} Ambruticin was retrosynthetically cleaved at C7-C8 and C13-C14 bonds into three fragments: 2, 3 and 4 (Scheme 2.1).

![Scheme 2.1](image)

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The left hand fragment 2 was then traced back to commercially available methyl α-D-glucopyranoside derivative 5, which was transformed in 3 steps into methyl 2,3-di-O-benzylglucopyranoside 11. After protecting the primary alcohol, compound 11 was submitted to Barton deoxygenation of the C4 hydroxyl. Photochemical Arndt-Eistert homologation of the appropriate acid 13 gave ester 14. Ester 14 was then transformed into the corresponding glycosyl fluoride 2 using Et2NSF3. In summary, the left hand fragment 2 was prepared in 15 steps and 17.6% overall yield (Scheme 2.2).

The synthesis of the middle fragment was based upon the diastereoselective double alkylation of dimethyl succinate 6 with CH3CHClBr, according to the protocol of Yamamoto (Scheme 2.3). It was found out that condensation of CH3CHClBr with diester 6 furnished the desired cyclopropane subunit in diastereomerically pure form. Selective hydrolysis of the menthyl ester, followed by functionalisation, gave acetylene 16 which, upon hydroalumination, generated in situ the middle fragment 17. Compound 17 was then condensed with glycosyl fluoride 2 to afford the desired β-C-glycoside 19. The “western” fragment 19 was thus prepared in 18 steps (longest linear sequence) and 7.1% overall yield.

---

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The synthesis of the remaining “eastern” fragment was based upon two key steps (Scheme 2.4): a hetero Diels-Alder reaction to establish the last ring of the molecule and Ireland-Claisen rearrangement to set up the correct double bond geometry of the final trisubstituted double bond (C16-C17). In the first step, the thermal hetero Diels-Alder reaction of 9 with 10 produced two diastereoisomers 8, and epi-8, in a 4:1 ratio. Resolution with (+)-PhCH(CH₃)NH₂ gave the required (+)-8 in >98% ee. The acid chloride derived from (+)-8 gave the (E)-enone, which underwent chelated Cram addition of MeMgBr to give, after acylation, the diene 7. Ireland-Claisen rearrangement of 7 produced the corresponding acid in a 12:1 ratio, which
was then converted to the desired sulfone 4 in 3 additional steps.\textsuperscript{20} The overall sequence, leading to the right hand fragment was accomplished in 11 steps and 1.3% yield.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme2.3}
\caption{Scheme 2.3}
\end{figure}

Finally, Julia-Lythgoe condensation between 4 and 19 afforded the desired, fully protected version of 1, in 32% yield along with 8% of its Z double bond isomer (E/Z = 4:1) at the C13-C14 double bond. Removal of the protecting groups then furnished (+)-ambruticin 1. To conclude, ambruticin 1 was

prepared in 41 steps (15 steps in the longest linear sequence) and 0.005% overall yield (0.25% for the longest linear sequence) (Table 2.1).

![Scheme 2.4](image)

2.1.2 One Decade Later – Jacobsen (2001)

At the beginning of the new millennium, three new total syntheses were published. The first of them was proposed by Jacobsen et al. The retrosynthetic approach was based upon enantioselective catalytic reactions.
Chapter 2. (+)-Ambruticin

to generate each of the stereochemical elements independently. This approach is nicely suited for the preparation of various stereoisomeric and structural analogs (Scheme 2.5).

Accordingly, ambruticin 1 was retrosynthetically cleaved at the C8-C9 bond, leading to two main fragments, 20 and 21. The left hand fragment 20 can then be easily disconnected to the hetero Diels-Alder precursors 22 and 23. On the other hand, the C9-C24 fragment 21 was prepared in a linear fashion, using two key steps: an asymmetric Simmons-Smith cyclopropanation and an asymmetric hydroformylation. Such disconnection leads to subunit 25.
which can be again seen as a hetero Diels-Alder adduct between the precursors 26 and 27.

The key step in the synthesis of fragment 20 is the chromium-catalyzed hetero Diels-Alder reaction\textsuperscript{21} between aldehyde 22\textsuperscript{22} and diene 23.\textsuperscript{23} The desired dihydropyran 31 was formed as a single diastereoisomer in 97% \textit{ee} (Scheme 2.6). A highly regio- and diastereoselective hydroboration/oxidation\textsuperscript{24} sequence installed the missing C6 hydroxy group. Protection of the resulting hydroxyl group, followed by debenzylation/oxidation of the primary alcohol, afforded the C1-C8 fragment 20 in 9 steps (longest linear sequence) and 20.9% yield. The global yield of 20 was 19.3% over 11 steps.

The carbon framework of subunit 35 was accessed through the asymmetric hetero Diels-Alder reaction between diene 27 and aldehyde 13. In the presence of (1\textit{R}, 2\textit{S})-33, dihydropyran 34 was generated in 87% yield and >99% \textit{ee}. The TBS protecting group was removed by hydroboration and acid-catalyzed elimination, a two step sequence which effected, at the same time, the reductive cleavage of the vinyl ether.\textsuperscript{25} The desired aldehyde 35 was obtained after Swern oxidation of the \textit{in situ} generated alcohol. All in all, right fragment 35 was prepared in 5 steps and 51.2% overall yield.

Scheme 2.6

The subsequent elongation of the right hand fragment 35 started with its conversion into an alkyne, using TMSC(Li)N₂, which upon addition of Bu₃SnCu(Bu)CN(Li)₂, followed by trapping with MeI and a stannane-iodine exchange, gave a vinyl iodide. This vinylic intermediate was then converted to the diene 25 by Kumada coupling in the presence of vinyl magnesium bromide. Regioselective hydroformylation of the 1,3-diene 25 gave, under the Nozaki hydroformylation conditions, the corresponding aldehyde with an excellent diastereomeric ratio (d.r. = 96:4).

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Scheme 2.7
This aldehyde was finally submitted to Takai olefination\textsuperscript{30} to furnish the vinyl iodide \textsuperscript{37}. A Heck reaction, followed by a reduction with DIBAL-H, gave the allylic alcohol \textsuperscript{24}. Ultimately, the fully functionalised portion \textsuperscript{21} was formed by an asymmetric Simmons-Smith cyclopropanation using the conditions developed by Charette\textsuperscript{31} and a one pot Mitsunobu/oxidation process.\textsuperscript{32} The synthesis of \textsuperscript{21} was accomplished in 15 steps and 11.9\% overall yield from \textsuperscript{32}.

\begin{center}
\textbf{Scheme 2.8}
\end{center}

The final coupling between the left hand fragment \textsuperscript{20} and the sulfone \textsuperscript{21}, under the Kociensky-Julia conditions,\textsuperscript{33} furnished the desired coupled product \textsuperscript{39}. The deprotection and oxidation of \textsuperscript{39} afforded ambruticin \textsuperscript{1}.

\textsuperscript{33} Blakemore, P. R.; Cole, W. J.; Kocienski, P. \textit{J. Synlett} \textbf{1998}, \textit{26-28}. 
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In summary, Liu and Jacobsen prepared ambruticin 1 in 29 steps (18 steps in longest linear sequence) and 1.75% overall yield (9.1% in longest linear sequence).

2.1.3 One decade later – Martin (2001)

Steve Martin’s total synthesis of ambruticin 1 was published nearly at the same time as that of Jacobsen. From the retrosynthetic point of view, ambruticin 1 was cleaved into three main fragments, which were supposed to be later on connected by Silvestre-Julia (C8-C9) and Julia-Lythgoe (C13-C14) olefination (Scheme 2.9).

The western subunit 40 was envisioned as the product of an intramolecular Michael addition of an alcohol derived from 43. Compound 43 can be easily traced back to the commercially available sugar derivative 48 (see later). The middle fragment 41 was envisioned to result from the asymmetric intramolecular addition of the diazo compound 44. The eastern portion 42 could be assembled by a [2,3]-Wittig rearrangement of compound 45. The dihydropyran ring system of 45 was then disconnected at the C20-C21 positions, since this double bond can be easily established by ring-closing metathesis. The RCM precursor 46 could then be reached via opening of epoxide 47.

The synthesis of the left hand fragment 40 started with some functional group transformations of the sugar derivative 48 (Scheme 2.10). After protection of the hydroxyl groups and removes of the OH group at the C2, the required α,β-unsaturated ethyl ester group was installed by a Horner-Emmons olefination to accomplish the synthesis of the desired intermediate.
43. In Intramolecular Michael addition, followed by epimerization of the C3 centre, protection, deprotection and oxidation completed the synthesis of the western subunit 40.

Scheme 2.9

The assembly of the middle fragment 41 began with the condensation of allylalcohol 49 and acyl chloride 50 to provide diazo compound 44 (Scheme

\[2,3\]-Wittig rearrangement
Chapter 2. (+)-Ambruticin

2.11. Asymmetric intramolecular cyclopropanation, mediated by chiral rhodium complexes, gave the desired bicycle 51 in 80% yield and 92% ee. Further elaboration of 51 involved the opening of the lactone, the protection of the resulting primary alcohol and finally the epimerization of the C10 stereogenic centre, affording the cyclopropane 52 in 83% yield. Amide 52 was then converted into the middle portion 41 in three steps, using an LDA/BH$_3$·NH$_3$ reduction protocol/a Mitsunobu reaction/and an oxidation sequence. The synthesis of 41 was thus accomplished in 8 steps and 25% overall yield.

\[
\begin{array}{c}
\text{HO} \quad \text{O} \\
\text{3} \quad \text{4} \\
\text{O} \quad \text{4} \\
\text{OH} \quad \text{OH} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} \\
\text{OTBS} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \quad \text{8} \\
\text{3} \quad \text{8} \\
\text{O} \\
\end{array}
\]

1) cat. PTSA, Me$_2$C(OMe)$_2$
2) Im, PPh$_3$, CCl$_4$
3) HCO$_2$H
4) DIBAL-H
5) Ph$_3$P=CHCO$_2$Et

47%

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} \\
\text{OTBS} \\
\end{array}
\]

1) H$_2$SO$_4$, then NaOMe, then H$_2$SO$_4$
2) TESCl, 2,6-lutidine, then TBSOTf
3) CF$_3$CO$_2$H
4) Dess-Martin

54%

Scheme 2.10

The left hand fragment 40 and the middle subunit 41 were then initiated using Silvestre-Julia’s olefination protocol \( (E/Z = 2.6:1) \) and the coupled product was converted in two operations (deprotection/oxidation) into the aldehyde 53, a substrate suitably functionalized for the final Julia-Lythgoe olefination step.

The synthesis of sulfone 42 (Scheme 2.12) began with the addition of alcohol 56 to the tosyl epoxide 47,\(^{44} \) according to the Hoffmann protocol,\(^{45} \) using a catalytic amount of BF\(_3\).Et\(_2\)O, to provide compound 46 after reduction of the tosylxy group. Subsequent RCM, in the presence of the 1\(^{st} \) generation Grubb’s catalyst (GC-1), followed by TPAP oxidation and (Z)-CH\(_2\)CH=CHMgBr addition (d.r. = >10:1), provided the desired [2,3]-Wittig rearrangement precursor 45. Allyl alcohol 45 was alkylated with Me\(_3\)SnCH\(_2\)I\(^{46} \) and the resulting ether underwent, upon treatment with n-BuLi, a rapid and stereoselective [2,3]-Wittig rearrangement (d.r. = >20:1).\(^{47} \) The resulting alcohol was converted into the desired sulfone 42. The synthesis of subunit 42 was thus accomplished in 13 steps (12 steps in the longest linear sequence) and 5.2% overall yield (9.8% in longest linear sequence).

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The sulfone 42 and the aldehyde 53 were then submitted to Julia-Lythgoe olefination conditions. The desired coupled product was formed in 56% yield and a 10:1 E/Z ratio. Finally, the protecting groups were removed and ambruticin 1 was obtained in 37 steps (16 steps in longest linear sequence) and 0.007% overall yield (5.72% in longest linear sequence).
2.1.4 The last but not least – Lee (2002)

So far, the last total synthesis of (+)-ambruticin (1) was achieved by Lee et al. in early 2002. As expected, 1 was retrosynthetically divided into three parts (Scheme 2.13). The core of the left hand fragment 59 is envisioned to be assembled by the intramolecular radical cyclization of intermediate 62. Compound 62 can be easily prepared from L-arabinose 63 via standard synthetic manipulations. The middle fragment 60 was prepared according to
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Kende’s protocol.\textsuperscript{10} The eastern subunit 61 was thought to originate as a product of methylcupration of ketone 64, itself prepared via an allylation/RCM/Grignard addition sequence from compound 65. The resulting three fragments should be assembled using two Kociensky-Julia olefination reactions.

Scheme 2.13
The synthesis of fragment 59 started with some modifications of L-arabinose 63 (Scheme 2.14). The hemiacetal function was transformed into the corresponding dithioacetal and the terminal diol function was protected in the form of an acetonide. The resulting free alcohol functions were benzylated to give the intermediate 66.\textsuperscript{48} The incorporation of the $\beta$-alkoxyacrylate substituent of 67 was performed by: (1) acetonide deprotection; (2) chemoselective TBS protection of the primary alcohol and (3) Michael addition of the secondary on methyl propiolate. The aldehyde, generated from dithioacetal 67, was reduced with NaBH$_4$ and the resulting alcohol was converted into the primary bromide 62. Radical cyclization\textsuperscript{49} of

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bromide 62 furnished the desired tetrahydropyran ring ($2.6\text{-cis:trans} = 10:1$). Finally, deprotection of the primary silyl ether, followed by oxidation of the alcohol to the aldehyde concluded the preparation of 59. This fragment was thus prepared in 11 steps and 24.8% overall yield.

The cyclopropane-containing subunit 60 was obtained according to Kende’s protocol (Scheme 2.15).\(^\text{10}\) Hence, dimethyl succinate 6 was stereoselectively dialkylated, then monoreduced to give alcohol 68. Protection of the alcohol in the form of a TBS ether, followed by reduction of the ester function furnished the monoprotected diol which was transformed into the corresponding TBDPS ether. Selective unravelling of the TBS-group and conversion of the deprotection resulting free alcohol into the sulfone 60 via a Mitsunobu substitution/mCPBA oxidation sequence, furnished the desired adduct 60 in 9 steps and 26.1% overall yield.

\[
\text{MentO}_2\text{C} - \text{CO}_2\text{Ment } \xrightarrow{1\text{) TBSCI, Im, CH}_2\text{Cl}_2} \xrightarrow{2\text{) LiAH}, \text{Et}_2\text{O}} \xrightarrow{3\text{) TBDPSCI, Im, CH}_2\text{Cl}_2} \xrightarrow{4\text{) cat. CSA, MeOH}} \xrightarrow{5\text{) PT-SH, DIAD, PPh}_3} \xrightarrow{6\text{) mCPBA, CH}_2\text{Cl}_2} \text{Me}\xrightarrow{1\text{) LTMP then Br(Cl)CHCH}_3, \text{THF}} \xrightarrow{2\text{) 10\% KOH, EtOH/H}_2\text{O}} \xrightarrow{3\text{) B}_2\text{H}_6/\text{THF}} \text{HO} \xrightarrow{38\%} \text{Me} \xrightarrow{68\%} \text{PTO}_2\text{S} \xrightarrow{\text{OTBDPS}} \text{H} \xrightarrow{68}\text{Me} \xrightarrow{68}\text{H} \xrightarrow{68}\text{H} \xrightarrow{68}\text{Me} \xrightarrow{68}\text{P}
\]

Scheme 2.15

The synthesis of the right hand fragment of 1 began with methacrolein 57, which was converted into (R)-3-hydroxy-2-methyl-1-pentene\(^\text{50}\) 56 by addition of EtMgBr followed by Sharpless kinetic resolution (Scheme 2.16).

The reaction of optically pure 56 with sodium bromoacetate, followed by

\(^{50}\) Paterson, I.; Perkins, M. V. *Tetrahedron* 1996, 52, 1811-1834.
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N-acyl oxazolidinone formation, gave the desired intermediate 65. Diastereoselective allylation of 65 proceeded smoothly, affording a 1,7-diene which underwent an intramolecular RCM reaction in the presence of 1st generation Grubbs catalyst. The resulting dihydropyran 69 was transformed into Weinreb amide and reacted with the Grignard reagent 70, yielding the ketone 64. Compound 70 was prepared from the commercially available methyl 2-(R)-β-hydroxy-2-methylpropionate 71, according to Garrett’s protocol.\(^\text{51}\)

Ketone 64 was transformed into sulfone 61 in 5 more steps. Thus, regioselective formation of the enol triflate and subsequent reaction with lithium dimethylcuprate\(^\text{52}\) installed the desired trisubstituted olefin. Debenzylation, followed by Mitsunobu reaction and sulphide oxidation completed the synthesis of the right hand fragment 61. To conclude, synthon 61 was prepared in 16 steps (13 steps in longest linear sequence) and 2.23% overall yield (5.0% in the longest linear sequence).

The assembly of the three subunits proceeded as follows: (Scheme 2.17). Initially, the left hand fragment 59 was reacted with sulfone 60, according to the standard Kociensky-Julia olefination protocol.\(^\text{53}\) The choice of the base and the solvent system proved to be essential for the reaction’s yield and double bond stereoselectivity. Eventually, NaHMDS and THF/HMPA (4:1) proved to be the conditions of choice, affording the desired coupled product in 78% yield (\(E:Z = 4:1\)). Deprotection of the TBPDS group, followed by Swern oxidation of the resulting alcohol led to the required aldehyde 72.


Treatment of aldehyde 72 with the anon derived from the right hand fragment 61, under essentially the same conditions as described above, generated, after deprotection, (+)-ambruticin 1. The olefination step gave the desired adduct in 66% yield and as a 2.2:1 ratio of $E$:Z isomers.

Scheme 2.16

In summary, (+)-ambruticin 1 was prepared in 42 steps (17 steps in the longest linear sequence) and 0.07% overall yield (4.81% in the longest linear sequence).
Chapter 2. (+)-Ambruticin

Scheme 2.17
Table 2.1: Comparison of all total syntheses of (+)-ambruticin

<table>
<thead>
<tr>
<th></th>
<th>Left fragment (2)</th>
<th>Middle fragment (17)</th>
<th>Right fragment (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kende (1990)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest linear sequence (yield)</td>
<td>15 (7.6%)</td>
<td>8 (26.2%)</td>
<td>11 (1.3%)</td>
</tr>
<tr>
<td>Overall number of steps (yield)</td>
<td>15 (7.6%)</td>
<td>8 (26.2%)</td>
<td>11 (1.3%)</td>
</tr>
<tr>
<td>Key step(s)</td>
<td>Barton deoxygenation; phospochemical Arndt-Einstert homologation</td>
<td>Damion addition to chiral 1,4-diesters</td>
<td>Hetero Diels-Alder reaction; resolution; Ireland-Claisen rearrangement</td>
</tr>
<tr>
<td>Coupling step</td>
<td>Glycosidation (F-sugar + vinyl aluminium species)</td>
<td>Julia-Lythgoe olefination</td>
<td></td>
</tr>
</tbody>
</table>

**Total synthesis**
- 15 (0.25%)
- 41 (0.005%)
<table>
<thead>
<tr>
<th><strong>Jacobsen (2001)</strong></th>
<th>Left fragment (20) (linear elongation of right fragment 35)</th>
<th>Eastern fragment (21)</th>
<th>Right fragment (35)</th>
<th>Total synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest linear sequence (yield)</td>
<td>9 (20.9%)</td>
<td>15 (11.9%)</td>
<td>5 (51.2%)</td>
<td>18 (9.1%)</td>
</tr>
<tr>
<td>Overall number of steps (yield)</td>
<td>11 (19.3%)</td>
<td>15 (11.9%)</td>
<td>5 (51.2%)</td>
<td>29 (1.75%)</td>
</tr>
<tr>
<td>Key step(s)</td>
<td>Asymmetric hetero Diels-Alder reaction</td>
<td>Asymmetric Simmons-Smith cyclopropanation; asymmetric hydroformylation</td>
<td>Asymmetric hetero Diels-Alder reaction</td>
<td>—</td>
</tr>
<tr>
<td>Coupling step</td>
<td>Kociensky-Julia olefination</td>
<td>(Higher-order) stannylcuprate addition</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Martin (2001)</strong></td>
<td><strong>Left fragment (40)</strong></td>
<td><strong>Middle-right fragment (41)</strong></td>
<td><strong>Right fragment (42)</strong></td>
<td><strong>Total synthesis</strong></td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Longest linear sequence (yield)</td>
<td>9 (25.6%)</td>
<td>8 (25.0%)</td>
<td>12 (9.78%)</td>
<td>16 (5.72%)</td>
</tr>
<tr>
<td>Overall number of steps (yield)</td>
<td>9 (25.6%)</td>
<td>8 (25.0%)</td>
<td>13 (5.18%)</td>
<td>37 (0.007%)</td>
</tr>
<tr>
<td>Key step(s)</td>
<td>Intramolecular Michael addition</td>
<td>Asymmetric intramolecular cyclopropanation</td>
<td>RCM; [2,3]-Wittig rearrangement</td>
<td>—</td>
</tr>
<tr>
<td>Coupling step</td>
<td>Silvestre-Julia olefination</td>
<td>Julia-Lythgoe olefination</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Left fragment ((59))</td>
<td>Middle-right fragment ((60))</td>
<td>Right fragment ((61))</td>
<td>Total synthesis</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------</td>
<td>---------------------------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Longest linear sequence (yield)</td>
<td>11 (24.8%)</td>
<td>9 (26.1%)</td>
<td>13 (5.0%)</td>
<td>17 (4.81%)</td>
</tr>
<tr>
<td>Overall number of steps (yield)</td>
<td>11 (24.8%)</td>
<td>9 (26.1%)</td>
<td>16 (2.28%)</td>
<td>42 (0.07%)</td>
</tr>
<tr>
<td>Key step(s)</td>
<td>Radical cyclization</td>
<td>Dianion addition to chiral 1,4-diester</td>
<td>Diastereoselective allylation; RCM; Grignard addition</td>
<td>—</td>
</tr>
<tr>
<td>Coupling step</td>
<td>Kociensky-Julia olefination</td>
<td>Kociensky-Julia olefination</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
2.2  (+)-Ambruticin: Previous results

2.2.1  First approach

Our interest in the synthesis of (+)-ambruticin 1 began about 10 years ago. This molecule was originally disconnected into three fragments (Scheme 2.18).

![Scheme 2.18](image-url)
The left hand fragment 73 and the right hand portion 82 were connected with the middle synthon 78 by a Suzuki-Miyaura coupling and a Julia-Lythgoe olefination, respectively.

Daniel J. Bayston, who, during his doctoral work, established the basis of the IMSC\textsuperscript{54} cyclization,\textsuperscript{55} synthesized the racemic version of sulfone 82\textsuperscript{56} (Scheme 2.19).

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.8]
\node (a) at (0,0) {\textbf{Scheme 2.19}};
\node (b) at (0,-1) {The readily available aldehyde 85\textsuperscript{57} was reacted with the lithium anion of alkyne 86, in the presence of CuI,\textsuperscript{58} affording the homopropargylic alcohol 87 in good yield. Protection of the free hydroxyl function, followed by}
\end{scope}
\end{tikzpicture}
\end{center}

\textsuperscript{54} For more details about IMSC see chapter 3: Silicon-based methodologies.
hydroalumination, iodination and methylation generated, after acidic treatment and silylation of the free hydroxyl group, the trisubstituted olefin \( 83 \) in good overall yield and high stereochemical purity.

TMSOTf catalyzed IMSC cyclization of vinylsilane \( 83 \) with aldehyde \( 84 \) resulted in the formation of the desired 5,6-dihydro-2\( H \)-pyran derivative \( 88 \) as 1:1 mixture of diastereoisomers at C17. Finally, both diastereoisomers \( 17 \) were oxidized into the sulfones \( 82 \) using \((\text{PhSe})_2/\text{H}_2\text{O}_2\) in excellent yield.\(^{59}\)

The synthesis of the middle fragment \( 78 \) was established by Thierry Giard during his post-doctoral stay in our laboratory (Scheme 2.20).\(^{60}\)

Thus, commercially available methyl ester \( 89 \) was protected and the ester \( 90 \) transformed into aldehyde \( 91 \) in two steps. The phosphonium ylide generated from \( 80 \) was reacted with \( 91 \) to provide the desired enyne \( 92 \) in 95% yield and a 9:1 ratio of \( E:Z \) isomers. Deprotection of the TMS group led to the monosubstituted alkyne which was hydroborated using catecholborane. Transesterification with chiral alcohol \( 93 \)\(^{61}\) gave diene \( 94 \). Cyclopropanation of \( 94 \), using \( \text{EtN}_2 \) in the presence of catalytic amount of \( \text{Pd(OAc)}_2 \), resulted in the selective monocyclopropanation of the diene, affording adduct \( 95 \) as a single diastereoisomer.\(^{61,62}\)

The coupling between sulfone \( 82 \) and 4-methylpentanal, which was used as a model compound for \( 78 \), was then attempted (Scheme 2.21).\(^{63}\)

Disappointingly, only product \( 97 \), resulting from the base-induced ring


opening of 82, followed by double bond migration, was observed in the crude reaction mixture.\footnote{60}

Faced with this unfortunate result, the retrosynthesis of (+)-ambruticin had to be redesigned.

\begin{equation*}
\text{TBDPSCI, Im, cat. DMAP} \quad \text{THF, -78°C to r.t.} \quad \text{MeO}_2\text{C} \quad \text{90}
\end{equation*}

\begin{equation*}
\text{DIBAL-H (2.1eq)} \quad \text{Et}_3\text{O, -78°C to r.t.} \quad \text{95%}
\end{equation*}

\begin{equation*}
\text{Swern ox.} \quad \text{95%}
\end{equation*}

\begin{equation*}
\text{1) TBAF, THF, 0°C} \quad \text{2) catechol borane, 70°C, neat} \quad \text{3) 93, THF, Δt} \quad \text{62%}
\end{equation*}

\begin{equation*}
\text{Et}_2\text{N, Pd(OAc)}_2, 0°C \quad \text{95%}
\end{equation*}

\begin{equation*}
\text{Scheme 2.20}
\end{equation*}
2.2.2 Second approach: modified fragments

The second approach to (+)-ambruticin was based upon similar strategic disconnections as the first one. Thus, 1 was divided into three main parts, the left hand subunit 73, the middle portion 98 and the right hand fragment 100, which should be connected together by Suzuki-Miyaura coupling (fragments 73 and 98) and Julia-Lythgoe olefination (fragments 98 and 100). Since there was no change in the vinyl iodide 73, as compared with the originally proposed retrosynthesis, the strategy leading to 73 did not change. On the other hand, fragments 98 and 100 exchanged their roles as nucleophilic and electrophilic species in the newly envisaged coupling. Their synthesis had thus to be redesigned (Scheme 2.22).

The approach to the middle fragment 98 underwent only minor changes; the chiral centre at the C15 being still borrowed from the commercial methyl ester 89.

On the other hand, the route to the ketone 100 had to be completely reexamined. Thus, ketone 100 was expected to be formed from ester 101,
which could be obtained as a product of the hetero Diels-Alder reaction between aldehyde 102 and diene 103. During the retrosynthetic analysis, it was also decided that the Julia-Lythgoe olefination step would be done prior to the establishing of the cyclopropane ring. Indeed, it was feared that 104 under the coupling conditions could provide compound 105 by the mechanism depicted in Scheme 2.23.

![Scheme 2.22](image-url)
The synthesis of the left-hand fragment 73 was accomplished by Anne-Elisabeth Gies\textsuperscript{64} and Takuya Kumamoto.\textsuperscript{65} In the first step, an ene reaction between aldehyde 77 and allylsilane 76 resulted in the racemic ene-adduct 74 (Scheme 2.24).\textsuperscript{66} Condensation of 74 with cinnamaldehyde 106, which was used as a model aldehyde, gave the desired dihydropyran 107 as a 1:1 mixture of axial/equatorial isomers at the C3 position.

Since in general, the IMSC reactions led to the formation of only one diastereoisomer,\textsuperscript{67} possessing the \textit{cis}-2,6-stereochemical relationship, this was a surprising result. A possible explanation could involve a stabilization of the transition state containing the alkynyl substituent in that axial position by $\pi$-interactions of the alkyne system with the proton adjacent to the oxonium cation (Figure 2.2).

\textsuperscript{65} Kumamoto, T. In \textit{Post-doc report}, 2002.
Chapter 2. (+)-Ambruticin

Based on these results, a slightly modified retrosynthesis of the left hand fragment was introduced (Scheme 2.25). Now, 108 contains, as compared to the previously desired fragment 73, a fully saturated side chain. As a consequence, the key asymmetric ene-reaction, that was foreseen to generate the new chiral centre at the C3 position, had to be abandoned.\textsuperscript{68} Thus, it was decided that this chiral centre will be established via the use of enzymatic resolution of the acetate derived from the ene-adduct 109.

Figure 2.2

The synthesis of 108 is shown in Scheme 2.26. Diol 111 was monobenzylated and the resulting alcohol was oxidized to give the first ene

\textsuperscript{68} In the literature there exists only one example of an asymmetric ene reaction using an activate aldehyde: Ooi, T.; Ohmatsu, K.; Uraguchi, D.; Maruoka, K. \textit{Tetrahedron Lett.} \textbf{2004}, \textit{45}, 4481-4484.
reaction precursor: aldehyde 110. Allylsilane 76 was prepared according to the standard protocol. The ene condensation between 76 and 110, mediated by Et₂AlCl, proceeded smoothly and furnished the desired adduct 113 in 77% yield. Alcohol 113 was acylated and acetate 114 was submitted to the enzymatic resolution. Various enzymes were screened (101 enzymes) but only the Amano PS proved to be selective. After a tedious reaction optimization, the desired, optically enriched, alcohol 109 was obtained in >98% ee and in 49% yield.
Chapter 2. (+)-Ambruticin

Scheme 2.26
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Optically enriched alcohol 109 was silylated and reacted with diethyl acetal 75, under the TMSOTf-catalyzed IMSC reaction conditions, furnishing the desired dihydropyran 116 in 70% yield.

Ozonolyzis of the exo-methylene double bond of 116 was next attempted. Surprisingly, neither O$_3$/SMe$_2$ nor the OsO$_4$/NaIO$_4$ system afforded the desired ketone. It was suggested that the TBS protecting group might be too bulky, thereby hindering the approach of the reagents on the olefin. Thus, an acyl group was introduced instead of the TBS substituent.

Gratifyingly, pyran 118 underwent smooth oxidative cleavage to give ketone 119. The last stereogenic centre at the C5 position was then established with the use NaBH$_4$/CeCl$_3$-mediated ketone reduction. Acyl protection of the resulting equatorial hydroxyl group, followed by the removal of benzyl protecting group gave compound 121. Finally, the desired left-hand fragment 122 was obtained by a two step transformation of the primary alcohol into the corresponding methyl ester.

\[ \text{Scheme 2.27} \]
To conclude, the left-hand fragment 122 was prepared in 19 steps (16 in the longest linear sequence) and 1.86% overall yield (3.6% in the longest linear sequence).

The synthesis of the middle fragment 98\textsuperscript{65} started again from the $\beta$-hydroxy ester 89 (Scheme 2.27). Initially, the hydroxyl group was replaced by a thiophenyl substituent via Mitsunobu-type reaction and the ester function was reduced with an excess of DIBAL-H to give alcohol 124. Swern oxidation furnished aldehyde 99, which was then reacted with the phosphonium ylide generated from the phosphonium salt 80 to yield the sulfide 125 in 64% yield as a 6:1 ratio of E:Z isomers. Molybdenum-catalyzed oxidation of sulfide 125 to sulfone 126 gave the desired coupling partner for the Julia-Lythgoe olefination. Based upon the previous results obtained in the laboratory,\textsuperscript{60,62,65} it was expected that further transformation of the alkyne to the desired cyclopropane ring should be simple and straightforward.

Finally, the synthesis of the modified right-hand fragment, ketone 100, was investigated.\textsuperscript{60} Thus, the chiral auxiliary based hetero-Diels-Alder reaction of diene 103 and (+)-menthylglyoxylate 111\textsuperscript{70} was investigated (Table 2.2). Disappointingly, despite a wide variety of conditions, the desired compound 101 was always obtained as a 1:1 mixture with its epimer 127.

Since the introduction of the chiral auxiliary proved to be inefficient, an asymmetric hetero-Diels-Alder reaction was attempted. Amongst a plethora of chiral catalysts developed for the hetero-Diels-Alder reaction, the bisoxazoline-Cu complex 128 attracted our attention.\textsuperscript{71} Unfortunately, the hetero-Diels-Alder reaction between ethylglyoxalate 129 and diene 103,

Chapter 2. (+)-Ambruticin
catalyzed by 128, proceeded in only 17% yield (Scheme 2.28). Moreover, the undesired anti-dihydropyran 127 was formed as the major product.

![Chemical structure](image)

**Table 2.2**

This last, unsuccessful attempt to apply the hetero-Diels-Alder reaction to the synthesis of the right-hand fragment of (+)-ambruticin tolled the bells of this route and a novel approach was considered.

![Chemical structure](image)

**Scheme 2.28**

2.2.3 Objectives

The main objective of this work is to finish the total synthesis of (+)-ambruticin 1 (Scheme 2.29). To reach this goal, several milestones have to be reached:

1) The synthesis of the middle fragment 126 has to be optimized and scaled-up.

2) The synthesis of the right-hand fragment 100 has to be revisited and performed in optically active form.

3) The synthesis of the left-hand fragment 122 has already been implemented and sufficient amounts of it are available. It will not be discussed in the rest of this Thesis.

4) The sequential coupling of the various fragments 100, 126 and 122 has to be performed.

Scheme 2.29
2.3 **Results and discussion**

2.3.1 **Right-hand fragment synthesis**

Our new retrosynthetic analysis of the right-hand fragment 100 of ambruticin 1 focused on the C20-C21 olefinic bond present in the dihydropyran ring (Scheme 2.30). We expected that this bond could be easily established by a metathesis reaction. Compound 130 was envisaged to originate from a silyl-modified Sakurai reaction (SMS) involving three simple starting materials, the allylsilane 131, the aldehyde 132 and the silylated alcohol 133.

It was expected that the stereogenic centre present in aldehyde 132 (C17 position) would direct the creation of the C18 chiral centre. To the best of our knowledge, there is no literature precedent describing the Sakurai multicomponent reaction or SMS reaction, in which the configuration of the newly created stereogenic centre (C18 in our case) would be based on the chirallity of the aldehydic component. Naturally, such an observation increased even more our interest in this reaction. As a consequence, it was decided to study this transformation a reaction in details and to explore its scope and limitations.

For these reasons, the optimization of this reaction as well as its application and proposed mechanism will be discussed in chapter 3. Herein, only the part important for the synthesis of the right-hand fragment 100 will be disclosed.
Allylsilane 131 being commercially available, our main interest focused on the silylated alcohol 133 and the aldehyde 132.

The synthesis of compound 133 was accomplished in two different ways. First, addition of EtMgBr 134 to methacrolein 135, followed by Sharpless kinetic resolution of the resulting alcohol (±)-136, gave enantiomerically enriched alcohol (R)-136 with >98% ee (Scheme 2.31). Silylation of (R)-136 furnished the desired compound 133 in 3 steps and 13% overall yield.

As an alternative approach, the catalytic asymmetric addition of Et₂Zn to methacrolein 135 was explored. For this purpose, the in situ generated chiral catalyst 137, developed by Zhang et al., was used (Table 2.3). Disappointingly, it was found out that this reaction is only effective for small scale synthesis (Table 2.3, Entry 1-3). When the addition reaction was...
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performed on 10 mmol scale, the ee of the chiral alcohol \((R)-136\) dropped dramatically (Table 2.3, Entry 4). The second disadvantage of this method is that 20 mol % of the chiral ligand 138 has to be used, can thought it is readily available, in one step, from the commercial arylsulfone 139 and cyclohexyldiamine 140 (Scheme 2.32).\(^{73c}\) The proposed transition states for the ZnCl\(_2\) addition to methacrolein are depicted in Figure 2.3.\(^{73a}\)

\[
\begin{align*}
\text{chiral ligand} & \text{138 (0.2 eq)} \\
\text{Ti(Oi-Pr)\_4 (1.4 eq)} & \text{hexane, } \Delta t \\
\text{aldehyde} & \text{135} \\
\text{chiral catalyst} & \text{137} \\
\text{ZnEt\_2 (1.8 eq), hexane, -23°C} & \text{(R)-136}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde [mmol]</th>
<th>Yield(^a) [%]</th>
<th>ee(^b) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>89</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>72</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>84</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>89</td>
<td>52</td>
</tr>
</tbody>
</table>

\(^a\) All yields refer to pure, isolated products
\(^b\) Determined by chiral GC

Table 2.3

The asymmetric catalytic ZnEt\(_2\) addition route furnished the desired silylated alcohol \((R)-133\) in only 2 steps and 81% yield. However, this method can not
be employed in higher than 1 mmol scale and thus, this method is not suitable for the multigram synthesis of compound \((R)-133\).

Next, the synthesis of aldehyde 132 drew our attention. Thus, the hydroxyl group of natural ethyl lactate \((S)-141\) was protected with a TBS or TBDPS group and the ester function was reduced to aldehyde using DIBAL-H (Scheme 2.33). Two different aldehydes \((S)-132a, b\) were obtained in 92 and 95% yield, respectively.

Having obtained all the required starting materials, the crucial SMS reaction was next attempted. Under optimized conditions, a mixture of allylsilane 131, aldehyde 132 and silylated alcohol 133 in \(\text{CH}_2\text{Cl}_2\) was cooled to -78°C and a catalytic amount (10 mol %) of TMSOTf was added (Scheme 2.34).
Chapter 2. (+)-Ambruticin

After work-up and purification, we were delighted to obtain our key intermediate, \textit{syn}-130, as a single diastereoisomer in 80\% yield.\cite{footnote1}

\[
\begin{array}{c}
\text{PGO} + \text{TMSO} \\
(\text{S})-132a, \text{PG}=\text{TBS} \\
(\text{S})-132b, \text{PG}=\text{TBDPS}
\end{array}
\] \quad \xrightarrow{131 \text{TMSOTT} (0.1 \text{ eq})} \quad \xrightarrow{\text{CH}_2\text{Cl}_2, -78^\circ\text{C}} \quad \begin{array}{c}
\text{OPG} \\
\text{syn}-130a, \text{PG}=\text{TBS}, 80\% \\
\text{syn}-130b, \text{PG}=\text{TBDPS}, 78\%
\end{array}

\textbf{Scheme 2.34}

With the key intermediate \textit{syn}-130 in our hands, three more steps remained to obtain the right-hand fragment 100 (Scheme 2.35). First, the metathetical cyclization forming the desired dihydropyran ring 143 was explored. For this purpose, the Grubbs 1\textsuperscript{st} generation ruthenium-based catalyst was used. Interestingly, a loading of only 2 mol \% of catalyst proved to be sufficient to reach full conversion in less than 15 hours.

Removal of the silicon protecting groups furnished the alcohol 144 in excellent yield. Finally, oxidation of the hydroxyl group to the ketone using, the Dess-Martin reagent,\cite{footnote2} completed the synthesis of the right-hand fragment 100 of ambruticin.

Two observations, effected during the deprotection/oxidation sequence, require a small commentary. First, the reaction time for the TBS or TBDPS-group deprotection was rather long and highly dependent upon the reaction scale (Table 2.4). In the case of the TBS-group (Table 2.4, Entry 1-4), deprotection was 6 hours if 0.5 mmol of the substrate 143a was used. However, when the amount of the substrate was increased (Table 2.4, Entry 2 and 3), so did the reaction time. On the other hands, the yield of the

\cite{footnote1} For detailed discussion about the SMS reaction and its mechanism see chapter 3.

66
alcohol 144 decreased. The direct addition of a 1.0 M TBAF solution to neat 143a was found to be a solution to our problem (Table 2.4, Entry 4). A similar behavior was observed during the deprotection of the TBDPS group (Table 2.4, Entry 5-8). An alternative desilylating agent, HF.py, proved to be less efficient (Table 2.4, Entry 9 and 10).

Scheme 2.35
Since ketone 100 is rather volatile, the oxidation of the alcohol 144 proved to be quite tricky and evaporation of the solvents under reduced pressure had to be avoided. Thus, an oxidation method that would give compound 100 sufficiently pure without additional purification using column chromatography was desired.

Chapter 2. (+)-Ambruticin

[Chemical structure images]

Table 2.4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reagent</th>
<th>Compound 143a [mmol]</th>
<th>Time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBS</td>
<td>TBAF&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>TBAF</td>
<td>1.0</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>TBAF</td>
<td>10.0</td>
<td>15</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>TBAF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10.0</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>TBDPS</td>
<td>TBAF</td>
<td>0.5</td>
<td>15</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>TBDPS</td>
<td>TBAF</td>
<td>1.0</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>TBDPS</td>
<td>TBAF</td>
<td>10.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>TBDPS</td>
<td>TBAF</td>
<td>10.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>TBS</td>
<td>HF.Pyr</td>
<td>1.0</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>TBDPS</td>
<td>HF.Pyr</td>
<td>1.0</td>
<td>18</td>
<td>72</td>
</tr>
</tbody>
</table>

<sup>a</sup> Concentration of the solution was 0.25M
<sup>b</sup> Commercially available 1.0 M sol. in THF was used
<sup>c</sup> TBAF solution in THF was added to neat 143

Among various oxidizing reagents, the Dess-Martin periodinate was found to be the best one (Table 2.5, Entry 4). As a great advantage, the desired product 100, prepared by Dess-Martin oxidation, was generally sufficiently pure after work-up not to require an additional purification by column chromatography.

To conclude, the right-hand fragment 100 was prepared in 8 steps (5 steps in the longest linear sequence) and 59% overall yield.
2.3.1.1 Towards the modified fragment 100

The synthesis of the right-hand fragment 100 presented above has one crucial drawback: the stereoselective formation of the C18 stereocentre is not possible if the SMS coupling agent is a primary silyl ether.\(^76\) Since it is expected that various derivatives of (+)-ambruticin will be required for biological-activity studies, another synthesis of the C22-des-ethyl right-hand fragment 145 was desired.

The retrosynthesis of compound 145 is shown in Scheme 2.36. Two crucial disconnections, akin to the previous retrosynthesis of the right-hand fragment 100 are proposed. The C20-C21 double bond should be formed by olefin metathesis and the bis-olefinic precursor 146 would be obtained by allylation of an optically active \(\alpha\)-hydroxy ketone 147, which could be prepared by Sharpless asymmetric dihydroxylation of the thermodynamic derived from ketone 149.

\(^{76}\) The discussion of this phenomenon is described in chapter 3.
Initially, the regio- and stereoselective formation of silyl enol ether 150 was evaluated (Table 2.6). It was found that the combination of TMSI/HMDS/THF gave the best compromise in term of internal vs. external enol ether formation and E/Z isomer ratio (Table 2.6, Entry 2). Moreover, the reaction could be performed on multigram scale without any problem yielding sufficiently pure silyl enol ether 150 directly after the simple work-up.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>150:151&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E/Z&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl/Nal/Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN, r.t.</td>
<td>80:20</td>
<td>79:21</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>TMSI/HMDS</td>
<td>THF, -20°C to r.t.</td>
<td>86:14</td>
<td>77:23</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>TMSI/HMDS</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -20°C to r.t.</td>
<td>88:12</td>
<td>71:29</td>
<td>95</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on 1H-NMR of the crude reaction mixture

Table 2.6

With silyl enol ether \(150\) in hands, the asymmetric dihydroxylation could be attempted (Table 2.7). Since it was not possible to separate compound \(150\) from its isomer \(151\), the dihydroxylation reaction was performed directly on the mixture.

The preparation of racemic \((\pm)-147\) (Table 2.7, Entry 1) was performed under the standard conditions, though it proceeded with poor yields. Product \((\pm)-147\) was employed for the ee determination. To obtain enantio enriched \(147\), commercially available AD-mix-\(\alpha\) and \(\beta\) were used. Several reaction conditions were evaluated and ultimately, it was found that addition of 4 mol % of OsO\(_4\) to the AD-mix-\(\beta\) mixture (Table 2.7, Entry 5) gave the best and reproducible results furnishing \((R)-147\) in 91% ee.

![Reaction scheme](image)  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>147:152(^a)</th>
<th>ee(^b) [%]</th>
<th>Yield of 147 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{K}_2\text{OsO}_6/\text{NMO})</td>
<td>acetone/H(_2)O = 2:1, (0^\circ)C to r.t.</td>
<td>3:1</td>
<td>1.0</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix-(\alpha)</td>
<td>(t)-BuOH/H(_2)O = 1:1, (0^\circ)C</td>
<td>3:1</td>
<td>91(^c)</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix-(\beta)</td>
<td>(t)-BuOH/H(_2)O = 1:1, (0^\circ)C</td>
<td>4.4:1</td>
<td>90</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>AD-mix-(\beta) + 4 mol% of OsO(_4) in H(_2)O</td>
<td>(t)-BuOH/H(_2)O = 1:1, (0^\circ)C</td>
<td>3.6:1</td>
<td>87</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>AD-mix-(\beta) + 4 mol% of OsO(_4)</td>
<td>(t)-BuOH/H(_2)O = 1:1, (0^\circ)C</td>
<td>7.1:1</td>
<td>91</td>
<td>51</td>
</tr>
</tbody>
</table>

\(^a\) Based on \(1\)H-NMR of the crude reaction mixture  
\(^b\) Based on the d.r. of 153  
\(^c\) Opposite \((S)-147\) enantiomer was obtained

Table 2.7

---

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The determination of the ee value of (R)-147 proved to be a problem, since chiral GC as well as chiral NMR shift reagent failed to separate the signals of both enantiomers. Thus, naproxen derivative of 147 was used to determine the enantiomeric excess (Scheme 2.37).

\[
\begin{align*}
\text{O} & \quad 147 \\
\text{OH} & \quad \text{DCC, DMAP, CH}_2\text{Cl}_2 \\
\text{r.t., 12h} & \quad \text{quant.}
\end{align*}
\]

The \(\alpha\)-hydroxy ketone 147 was next allylated with allyl bromide and transformed into dihydropyran 155 using the 1st generation Grubbs catalyst (Scheme 2.38).

\[
\begin{align*}
\text{O} & \quad 147 \\
\text{OH} & \quad \text{Br} \\
\text{NaH, THF, } \Delta t & \quad 94\% \\
3 \text{ mol\% GC-1} & \quad \text{CH}_2\text{Cl}_2, \Delta t \\
& \quad 91\%
\end{align*}
\]

Similarly, the construction of even more simple right-fragment 100 derivative, des-22-ethyl-des-17-methyl pyran 161, was not possible to accomplish by multicomponent Sakurai reaction. The synthesis of 156 was thus accomplished using the epoxide opening/allylation/metathesis sequence (Scheme 2.39). FeCl\(_3\)-mediated benzyl group removal then yielded the desired alcohol in 87\% yield. The final step, oxidation of the alcohol 160 to
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Aldehyde 161 was not attempted due to the expected low stability of the aldehyde 161.

\[
\text{Scheme 2.39}
\]

These simple protocols proved to be highly efficient and the desired compounds 155 and 160 were produced in 4 steps and in 41% overall yield (for 155) or 79% overall yield (for 160). Moreover, both enantiomers of 155 or 160 could be readily prepared.

2.3.2 Middle fragment's synthesis – reaction optimization

The assembly of the middle fragment 126 was performed by Dr. Takuya Kumamoto during his post-doctoral stay in our laboratory (Scheme 2.27).\(^{79}\)

The synthesis started with the commercially available β-hydroxy ester 89 which was transformed into sulfide 123. Reduction of the ester group using DIBAL-H followed by Swern oxidation of the resulting alcohol, furnished aldehyde 99. Wittig reaction of 99 using the ylide derived from the salt 80,

gave sulfide 125, which was then oxidized to the sulfone 126 using TBHP in the presence of a catalytic amount of MoO$_2$(acac)$_2$. Compound 126 was prepared in 6 steps and 26% overall yield.

Scheme 2.27

The synthesis was successfully reproduced and two steps of this sequence were closely examined. Since the Wittig reaction has already been studied in detail by Dr. Kumamoto, our attention focused on the synthesis of aldehyde. The Swern oxidation, which is convenient in many cases, often becomes a problem when the reaction is performed on the multigram scale. Moreover, the presence of a sulphur atom in substrate 124 limits the nature of the oxidizing agents.

Therefore our attention was focused on the aerobic copper(I)-catalyzed oxidation, developed in our laboratory over the past decade.\textsuperscript{80} It was shown that this method was highly efficient in the case of primary and secondary alcohols and that the reaction conditions tolerated acid and base-sensitive

substrates as well as heteroatoms, such as sulphur, nitrogen and phosphorous.

Only disadvantage of the method, however, is the instability of the Cu(I)-salt, generally CuCl, employed in this reaction. Indeed, CuCl, a grey crystalline solid, oxidizes rapidly to the green crystalline solid, CuCl₂. To avoid purification of CuCl,⁸¹ a more stable Cu(I) source was searched and the Cu(I)Cl(COD) complex attracted our attention. In view of its excellent stability, it was tested in the reaction.⁸² The oxidation mediated by CuCl(COD) as the precatalyst gave the same results as those catalyzed by Cu(I)Cl (Table 2.8), except that they proceeded 1.5 times slower when Cu(I)Cl(COD) was employed. Finally, it was observed that the reaction yields are constant regardless to the scale of the reaction (1–50 mmol)

The second transformation on which we focused was the oxidation of the sulfide 125 to the sulfone 126 (Table 2.9). Originally, a 5.5 M solution of TBHP in toluene and a catalytic amount of MoO₂(acac)₂ were used (Table 2.9, Entry 1). Initially, we tried to replace the TBHP solution in toluene (which had to be prepared) by a TBHP solution in dodecane (commercially available) (Table 2.9, Entry 2). The reaction yield was not affected by this switch, but the purification of the desired sulfone 126 proved to be rather tricky due to the presence of significant amounts of dodecane.

Thus, another system employing (NH₄)₆Mo₇O₂₄·7 H₂O as the catalyst and 35% aq. H₂O₂ as the oxidant was tested (Table 2.9, Entry 3). This process proved to be optimal and the desired sulfone was isolated in 97% yield.

---

⁸¹ In reality, I was too lazy to recrystalized it, thus I was looking for other possibility.
⁸² Cu(I)(COD) complex was chosen due to its air and moisture stability. It has to be protected from sun light. The idea to use it came from a discussion with Jerôme Hoet.
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\[
\begin{align*}
R-\text{CH}_2-\text{OH} & \quad 5 \text{ mol}\% \text{ Cu(I)}, 5 \text{ mol}\% \text{ phen}, 5 \text{ mol}\% \text{ DBAD}, C_6\text{H}_5\text{F} \\
& 7 \text{ mol}\% \text{ NMI}, 5 \text{ mol}\% \text{ t-BuOK}, O_2, 81^\circ\text{C} \\
\rightarrow & \quad R-\text{O} 
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(^{a,b}) [%]</th>
<th>Time(^a) [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-\text{SPh}</td>
<td>O-SPh</td>
<td>84 / 85</td>
<td>6 / 9</td>
</tr>
<tr>
<td>2</td>
<td>HO-\text{OTBS}</td>
<td>O-\text{OTBS}</td>
<td>90 / 88</td>
<td>5 / 7</td>
</tr>
<tr>
<td>3</td>
<td>\text{OMe}</td>
<td>\text{OMe}</td>
<td>87 / 88</td>
<td>9 / 13</td>
</tr>
</tbody>
</table>

\(^a\) CuCl / CuCl(COD) used as precatalysts  
\(^b\) Isolated yields

Table 2.8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MoO\textsubscript{2}(acac)\textsubscript{2} (5 mol %), TBHP in tol. (2.1 eq), CH\textsubscript{2}Cl\textsubscript{2}, 0°C to r.t.</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>MoO\textsubscript{2}(acac)\textsubscript{2} (5 mol %), TBHP in dodecane. (2.1 eq), CH\textsubscript{2}Cl\textsubscript{2}, 0°C to r.t.</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>(NH\textsubscript{4})\textsubscript{6}Mo\textsubscript{7}O\textsubscript{24}.7H\textsubscript{2}O (10 mol %), 35% aq. H\textsubscript{2}O\textsubscript{2} (10 eq), EtOH, 0°C to r.t.</td>
<td>97</td>
</tr>
</tbody>
</table>

To conclude, the middle fragment 126 was prepared in 6 steps (5 steps in the longest linear sequence) and 38% overall yield.
2.3.3 Middle and right-hand fragment coupling: Julia-Lythgoe olefination

Having accomplished the synthesis of the middle and right-hand fragment 126 and 100, respectively, it was time to couple them. A Julia-Lythgoe olefination was selected in order to unite sulfone 126 and ketone 100 and transform them into the required trisubstituted olefin.

Generally, the Julia-Lythgoe olefination is a two-step process in which the alkyl sulfone 166 is reacted with a carbonyl compound 167 to give the β-hydroxysulfone 162. Adduct 168 is then transformed, under reductive elimination conditions, to olefin 169 (Scheme 2.40).

It is important to note that this simple transformation, which works perfectly well for aldehydes (R³ = H), is generally rather difficult in the case of ketones. Indeed, an equilibrium exists between the starting anion α to the sulfone 89a and the ketone 90, on one side, and the adduct 93 on the other side (Scheme 2.41). In the case of the addition on an aldehyde, a secondary alkoxide 93 (R³ = H) is formed. However, if the ketone is reacted with the anion, a tertiary alcoholate is generated. In this case, the equilibrium between reactants and adduct is shifted on the side of the reactants. To favor the formation of the adduct 94, a trapping agent such as AcCl, BzCl or TMSCl is often added to the reaction mixture to quench the alcoholate 93.

84 The general aspects of Julia-Lythgoe olefination and the reaction mechanisms are discussed in great details in chapter 4.
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Since in our case, the sulfone anion was reacting with a ketone, it was decided to use BzCl as a trapping agent. The advantage of employing BzCl comes in the following reductive-elimination step. Some time ago, it was disclosed in our laboratory that β-benzoyloxysulfones underwent smooth, SmI$_2$-mediated, reductive-elimination under very mild conditions.\textsuperscript{85} Taking into account these two points, BzCl became the trapping agent of the choice. Before the real coupling step between sulfone 126 and ketone 100 was attempted, both coupling partners were examined in test reactions with a model aldehyde and a sulfone, respectively.

Thus, sulfone 126 was reacted with aldehyde 172 under the standard coupling conditions to give the coupled product 173 in 97% yield (Scheme 2.42). Much to our surprise, when the sulfone 174\textsuperscript{86} was added to the ketone 100, the coupled product 175 was obtained only in 47% yield (Scheme 2.43). SmI$_2$-mediated reductive-elimination of 175 furnished the desired olefin 176 in 80% yield as a 10:1 ratio of $E$:$Z$ isomers.

---


\textsuperscript{86} The synthesis of sulfone 174 as well as the other sulfones described in this chapter will be discussed in more details in the chapter 4.
Having verified that both coupling partners did not undergo undesired side reactions under the coupling conditions, our attention fully focused on the coupling step. Surprisingly, it was more difficult than expected. Although, various bases, trapping electrophiles and reaction conditions were tested, the desired coupled product 177 could only be obtained in 33% yield maximum (Table 2.10, Entry 1, X = Bz). Representative conditions are displayed in Table 2.10.

At this stage, it was decided to use H⁺ as the electrophile. Indeed, it was thought that the low yield of β-benzoyloxysulfone 177 could be due to the steric hindrance around the alkoxide in the adduct and that a small electrophile could be a more suitable quencher of this reaction. A couple of conformers of the β-hydroxysulfone 178, displayed in their local energy
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minima\textsuperscript{87} are shown in Figure 2.4 to illustrate the steric hindrance around the tertiary alcohol function.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Electrophile</th>
<th>Additive</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>BzCl</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>BzBr</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi</td>
<td>p-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}COCl</td>
<td>-</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi</td>
<td>Bz\textsubscript{2}O</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi</td>
<td>Ac\textsubscript{2}O</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi</td>
<td>BzCl</td>
<td>Et\textsubscript{2}O\cdotMgBr\textsubscript{2}</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi</td>
<td>BzCl</td>
<td>ZnCl\textsubscript{2}</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi</td>
<td>BzCl</td>
<td>LiCl</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>LDA</td>
<td>BzCl</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>EtMgBr</td>
<td>BzCl</td>
<td>-</td>
<td>\textsuperscript{a}</td>
</tr>
<tr>
<td>11</td>
<td>BrMgN(Pr\textsubscript{i})\textsubscript{2}</td>
<td>BzCl</td>
<td>-</td>
<td>\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} EtMgBr did not deprotonate sulfone 126
\textsuperscript{b} Deprotonation did occur, but no adduct 177 was formed

Table 2.10

Gratifyingly, when saturated aqueous solution of NH\textsubscript{4}Cl was used to quench the reaction, the β-hydroxysulfone 178 was obtained in 75% yield as a mixture of all four possible diastereoisomers (Scheme 2.44).

The SmI\textsubscript{2}-mediated reductive elimination of β-hydroxysulfones has been described previously.\textsuperscript{88} Compound 178 was submitted to the reductive-elimination conditions, but the desired olefin 179 was obtained in only 24% yield.

\textsuperscript{87} Optimization of the energy minimum implemented in MM2 of the ChemDraw software was used.

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yield (Table 2.11, Entry 4). The classic reductive-elimination protocol developed by Julia,\(^89\) using Na(Hg)/MeOH system, was not attempted, since it was expected that retro-addition would occur under these basic conditions.

![Diastereoisomers of 178](image)

**Figure 2.4:** A syn and anti diastereoisomers of 178

![Scheme 2.44](image)

**Scheme 2.44**

---

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In view of these poor yields, the benzylation of the hydroxysulfone 178, with various sources of benzoyl group, was attempted. However, the desired benzoyl derivative 177 could never be observed (Table 2.12), the alcohol obstinately refusing to react.

Finally, sulfoxide 180 was prepared from sulfide 125 and its anion was added to ketone 100 in the hope a performing a sulfoxide variant of the Julia olefination (Scheme 2.45). Unfortunately, in this case, the desired adduct 181 was not obtained.

---

Table 2.11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature [°C]</th>
<th>Yield [%]</th>
<th>E : Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>24</td>
<td>&gt;98:1</td>
</tr>
<tr>
<td>5</td>
<td>25 deg.</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

a Degradation of the S.M. was observed

---

90 Sulfoxide-Julia olefination, as a new modification of the classical Julia olefination developed during this PhD. work, will be discussed in chapter 4.
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### Table 2.12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzoyl source</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bz$_2$O</td>
<td>Sc(OTf)$_3$ (5-10 mol%), CH$_3$CN</td>
<td>n.r.</td>
</tr>
<tr>
<td>2</td>
<td>Bz$_2$O</td>
<td>Yb(OTf)$_3$ (5-10 mol%), CH$_3$CN</td>
<td>n.r.</td>
</tr>
<tr>
<td>3</td>
<td>BzBr</td>
<td>DMAP (0.1 eq), pyr (2 eq), CH$_2$Cl$_2$</td>
<td>n.r.</td>
</tr>
<tr>
<td>4</td>
<td>BzBr</td>
<td>DMAP (0.1 eq), Et$_3$N (2 eq), CH$_2$Cl$_2$</td>
<td>n.r.</td>
</tr>
<tr>
<td>5</td>
<td>BzBr</td>
<td>DMAP (0.1 eq), pyr (2 eq), Et$_2$O</td>
<td>n.r.</td>
</tr>
<tr>
<td>6</td>
<td>BzBr</td>
<td>DMAP (0.1 eq), Et$_2$N (2 eq), Et$_2$O</td>
<td>n.r.</td>
</tr>
<tr>
<td>7</td>
<td>BzOTf</td>
<td>pyr (2 eq), CH$_2$Cl$_2$</td>
<td>deg.</td>
</tr>
<tr>
<td>8</td>
<td>BzOTf</td>
<td>pyr (2 eq), Et$_2$O</td>
<td>deg.</td>
</tr>
<tr>
<td>9</td>
<td>BzOTf</td>
<td>Et$_2$N (2 eq), CH$_2$Cl$_2$</td>
<td>deg.</td>
</tr>
<tr>
<td>10</td>
<td>BzOTf</td>
<td>Et$_2$N (2 eq), Et$_2$O</td>
<td>deg.</td>
</tr>
</tbody>
</table>

### Scheme 2.45

**2.3.4 Third generation retrosynthesis**

Since the coupling between the middle 126 and the right-hand 100 fragments failed, our retrosynthetic approach had to be reconsidered. It was suggested
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that one of the factors which was responsible for the poor yields of the coupling step, was the enyne system present in the middle fragment 126.

![Scheme 2.46]

The goal of this new retrosynthesis was to introduce a sulfone-based fragment, which would be as simple as possible and, in the same time, would allow a wide range of modifications for future structure modifications. As a result, this antithetic analysis divided ambruticin 1 into four fragments (Scheme 2.46). The left-hand fragment 122 and the right-hand fragment 100 are the same as in the previous approach. However the middle subunit was now divided into two parts, a middle-left and a middle-right fragments 182 and 183, respectively. It was envisaged that Kociensky-Julia olefination could be used to connect these synthons together.
2.3.4.1 Middle-right fragment and the coupling step

To test the viability of this new route, a variety of middle-right fragments were prepared (Figure 2.5).  

![Figure 2.5](image)

Initially, compounds 183a-d were tested in the coupling reaction with ketone 100 (Table 2.13). In the case of sulfones 183a and 183b (Table 2.13, Entry 1 and 2), a competitive base-induced silyl-group migration was observed (Figure 2.6).

![Figure 2.6](image)

If a TBS-protecting group is used (sulfone 183c), no silyl migration occurs and the reaction affords the desired coupling product 186c in 67% yield.
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(Table 2.13, Entry 3). Surprisingly, if the more bulky TBDPS-containing sulfone 183d is employed, the yield of adduct 186d drops to 11% (Table 2.13, Entry 4).

<p>|</p>
<table>
<thead>
<tr>
<th>Entry</th>
<th>Middle-right fragment</th>
<th>PG</th>
<th>Coupling product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>183a</td>
<td>TMS</td>
<td>186a&lt;sup&gt;c&lt;/sup&gt;</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>183b</td>
<td>PhMe&lt;sub&gt;2&lt;/sub&gt;Si</td>
<td>186b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>183c</td>
<td>TBS</td>
<td>186c</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>183d</td>
<td>TBDPS</td>
<td>186d</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mixture of four diastereoisomers  
<sup>b</sup> Isolated yield  
<sup>c</sup> Rearranged compound 187a was isolated (12%)  
<sup>d</sup> Rearranged compound 187b was isolated (7%)

Table 2.13

The synthesis of all middle-right fragments will be described in Chapter 4.
Figure 2.7: Two out of the four possible diastereoisomers of 186c and 186d.
Mukaiyama rationalized this low selectivity by invoking the facile formation of benzylic oxonium cations which prefer to react via $S_N1$ type transition states with reduced chiral induction. His catalyst was prepared in situ by the addition of silver triflate to chlorodiphenylborane in a 1:1 ratio.

In 1991, Markó and Mekhalfia\textsuperscript{118} employed the readily available trimethylsilyl triflate (TMSOTf) as the catalyst and decided to call this reaction SMS, for Silyl Modified Sakurai condensation. Carbon tetrachloride appeared to be the best solvent and the presence of two chlorine atoms at the ortho, ortho’ positions of the aromatic ring provided good selectivity (Scheme 3.9). The ketones were also tolerated as a substrate in the reaction conditions.

Since 1995, Tietze et al.\textsuperscript{119} studied the use of the norpseudoephedrin derivative 258 as a chiral auxiliary in order to perform diastereocontrolled

\begin{table}
\centering
\begin{tabular}{cccc}
\hline
Entry & R & Yield (%)\textsuperscript{a} & $de$ (%) \\
\hline
1 & PhCH$_2$CH$_2$ & 71 & 93 (R) \\
2 & cyc-C$_6$H$_{11}$ & 74 & 85 (S) \\
3 & i-Pr & 66 & 99 (S) \\
4 & PhCH$_2$O(CH$_2$)$_2$ & 81 & 90 (S) \\
5 & Ph & 77 & 48 (S) \\
\hline
\end{tabular}
\caption{Table 3.6}
\end{table}

\textsuperscript{a} All yields refer to pure, isolated products

Chapter 2. (+)-Ambruticin

The lower yield in the coupling step observed in the case of the TBDPS protected sulfone 183d can be again explained by steric reasons (Figure 2.7). The TBDPS-group has a bigger steric requirement than the TBS, PhMe₂Si or TMS group. Thus, the newly formed coupling product 186d is far more crowded than in the other cases. As a consequence, the addition of sulfone 183d to the ketone 100 is probably more difficult and lower yields ensue.

With the coupled products 186a-d in hands, the reductive-elimination step was next examined. Adduct 186c was used as the substrate in order to optimize the conditions for the reductive elimination step (Table 2.14).

Initially, the SmI₂/DMPU system was tested. It is known that SmI₂/DMPU-mediated reductive-elimination step proceeds with better E/Z selectivity than in the case of the SmI₂/HMPA-promoted system. As expected, the reductive-elimination mediated by SmI₂/DMPU system gave the desired olefin 189c in >95:1 E/Z ratio, but the yield of the reaction varied from poor (Table 2.14, Entry 1-4) to moderate (Table 2.14, Entry 5 and 6). Gratifyingly, the use of the SmI₂/HMPA system afforded the desired coupled product 189c in 95% yield. Amazingly, the E/Z stereoselectivity was >95:1.

The optimized reductive-elimination conditions were then applied to the other three coupled products 186a,b and d, furnishing the corresponding olefins 189a,b and d in excellent yields and stereoselectivity (Scheme 2.47).

Finally, the deprotection of the TBS group, followed by a one-pot Mitsunobu/oxidation sequence, completed the synthesis of sulfone 191 (Scheme 2.48).

---

Chapter 2. (+)-Ambruticin

Table 2.14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Equivalent</th>
<th>Temp. [°C]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMPU</td>
<td>1.0</td>
<td>-78</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DMPU</td>
<td>5.0</td>
<td>-78</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>DMPU</td>
<td>10.0</td>
<td>-78</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>DMPU</td>
<td>15.0</td>
<td>-78</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>DMPU</td>
<td>10.0</td>
<td>-40</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>DMPU</td>
<td>15.0</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>HMPA</td>
<td>5.0</td>
<td>-78</td>
<td>95</td>
</tr>
</tbody>
</table>

*E/Z ratio was in all cases >95:1

Scheme 2.47

To summarize, sulfone 191 was prepared from the sulfone 183c in 5 steps and 47% overall yield.

At this stage, a shorter and more efficient access to the sulfone 191 was searched. For this purpose, we investigated the use of middle-right fragments that would possess a substituent at both termini that could be employed in double, sequential Julia olefinations. As a consequence, sulfone 107 was prepared.

---

94 Detailed discussion about all these variants of the Julia methods is provided in chapter 4.
In the literature, there are only few examples employing ketones as partners in Kociensky-Julia olefination reactions. Indeed, these reactions proceed generally in low yields and with poorer E/Z ratios than in the case of aldehydes.

Nevertheless, we decided to examine the Kociensky-Julia coupling between the sulfone 184 and the ketone 100 (Scheme 2.48). Different, non-nucleophilic bases and various solvents were tested. In the best cases, the sulfide 192 was formed in up to 80% yield (Table 2.15, Entry 6 and 9). Disappointingly, the E/Z selectivity was very poor and, generally, a 1:1 ratio of E/Z isomers was obtained.
Since the Kocienski-Julia olefination proved to be rather inconvenient for the coupling of a ketone with a sulfone, a hybrid derivative between 183 and 184, synthon 185a was prepared. In this reagent, the phenyl sulfone on one side (part taken from the 183) was to be initially coupled with the ketone 100. On the opposite side of the molecule, the PTS group serves as a precursor for the phenyltetrazolyl sulfone. After the first coupling, the derived sulfone should connect with the middle-left fragment 182 (Scheme 2.49).

The desired adducts 193a and b were obtained in 54% and 49% yield, respectively. The reductive-elimination using the SmI2/HMPA system proceeded smoothly and the corresponding olefins 192a and 192b were obtained in 96% and 95% yield, respectively. However, the E/Z selectivity ranged between 3:1 and 5:1.
2.3.4.2 Middle-left fragment and east fragment construction

The key step in the middle-left fragment synthesis is the diastereoselective Pd(0)-catalyzed cyclopropanation of vinyl boronates by diazo compounds (Figure 2.8). The facial selectivity was to be established by the chiral auxiliary, which will be present on the olefinic substrate in the form of a boron ester. This chiral auxiliary effectively shields one of the faces of the olefin. The shielding ability of can be seen in Figure 2.8. This working hypothesis is in agreement with single crystal X-Ray analysis of and with the absolute configuration of the chiral centers formed.


Contrary to the known role of the chiral auxiliary in the facial discrimination of the reaction, the mechanism of the Pd(0)-catalyzed cyclopropanation of olefins with diazo compounds is unknown. Additionally, very high regioselectivity was observed during the cyclopropanation of dienyl boronates (Figure 2.9) and the olefin linkage bearing the boron atom is always cyclopropanated, even if the diazo compound is added in large excess.

At this stage, it is necessary to point out that most palladium-catalyzed cyclopropanations of the vinylboranes were attempted with diazomethane ($\text{N}_2\text{CH}_2$). Other diazoalkanes were overlooked (Scheme 2.50).
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Scheme 2.50
Recently, in our laboratory, Dr. T. Kumamoto developed suitable conditions for cyclopropanation of vinylboronates using N₂CHCH₃ and N₂CH(CH₂)₂CH₃. Various vinyl boronates were tested under these cyclopropanation conditions and it was observed that the stereoselectivity at the C3-position was highly dependent upon the steric requirements of the silicon protecting group (Scheme 2.51). Increasing the size of the protecting group led to an increase in the stereoselectivity of the reaction.

Based on these results, we decided to prepare various vinylboronates bearing silicon protecting groups of different sizes to evaluate their impact on the selectivity of the reaction (Scheme 2.52).

Scheme 2.51
The synthesis of started with the protection of the propargyl alcohol with the appropriate silicon groups. Hydroboration of the corresponding silyl ethers’ with catecholborane gave unstable vinylboronates in quantitative yields. Transesterification of the catechol with the chiral auxiliary furnished the stable vinyl boronates 196.

Compounds 196a-c were then submitted to the cyclopropanation conditions (Table 2.16). The influence of the size of the silicon protecting group on the selectivity of the reaction proved to be again important. However, in these cases, vinyl boronate 196a bearing the most bulky TBDPS protecting group gave the worst selectivity (Table 2.16, Entry 1). When the steric demands of the silicon substituent decreased, the ratio between the desired diastereoisomer 205 and undesired 206 changed in favor of 205 (Table 2.16, Entry 2 and 3). To decrease the steric hindrance even further, the cyclopropanation was performed on the hydroxyl containing vinyl boronate 196d. Remarkably, the cyclopropanes 205d and 206d were obtained in an improved ratio of 95:5 (Table 2.16, Entry 4). Substrate 196d was prepared by the selective deprotection of 196b (Scheme 2.53).
Chapter 2. (+)-Ambruticin

Based upon these results, it can be anticipated that, to reach even higher stereocontrol in the cyclopropanation, the steric hindrance around the olefin to be reacted has to be reduced even further.

Table 2.16

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl borane</th>
<th>R</th>
<th>Products&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>196a</td>
<td>TBDS</td>
<td>205a + 206a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>196b</td>
<td>TBS</td>
<td>205b + 206b</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>196c</td>
<td>TMS</td>
<td>205c + 206c</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>196d</td>
<td>H</td>
<td>205d + 206d</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields

<sup>b</sup> Determined from the <sup>1</sup>H-NMR of the crude

Scheme 2.53

Scheme 2.54
Chapter 2. (+)-Ambruticin

To verify this hypothesis, we have prepared the aldehyde 207 and the diene 208 (Scheme 2.54). Thus, alcohol 196d was oxidized using TEMPO to give the aldehyde 207 in 99% yield. This aldehyde proved to be highly unstable and had to be used immediately after its preparation. The diene 208 was synthesized from the aldehyde, using a Kociensky-Julia reaction, in 86% yield.

The cyclopropanation of the aldehyde 207 and the diene 208 furnished the desired cyclopropanes in essentially diastereoisomerically pure form (Table 2.17). As a disadvantage, the yield of the cyclopropyl aldehyde 209a was only 25%. Since aldehyde 207 is a rather unstable compound, this low yield is not really surprising. In contrast, the cyclopropanation of diene 208 proceeded smoothly and regioselectively, affording the desired and stable adduct in excellent yield.

Encouraged by these results, we focused our attention on the synthesis of the eastern fragment of (+)-ambruticin 1 (Scheme 2.55). The synthesis began with aldehyde 207, which was reacted with sulfone 181 under standard Kociensky-Julia conditions, furnishing diene 210 in 65% yield and >95:1 E/Z selectivity. Regioselective cyclopropanation of 210 under optimized
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conditions, gave the desired eastern fragment 211 in 74% yield and >95:1 d.r.

In summary, the eastern fragment 211 of (+)-ambruticin 1 was prepared from propargyl alcohol 125 in 7 steps and 23% overall yield.

![Scheme 2.55](image)

2.4 Conclusions and perspectives

To conclude, the synthesis of the eastern fragment 211 was accomplished in 25 steps (17 steps in the longest linear sequence) and 5.9% overall yield (14.2% in the longest linear sequence).

Since our original retrosynthesis failed, a new and highly versatile approach was introduced. This new strategy led us to disconnect (+)-ambruticin 1 into four main fragments (Figure 2.10). Following this route, a convergent and highly flexible synthesis of the eastern fragment 211 could be accomplished.
Interestingly, this approach enables us to modify at will, any of the four subunits which could then be simply connected together. Various novel analogs of 1 could thus be readily prepared.

Additionally, during our synthetic studies towards the different fragments of ambruticin 1, several original methodologies were developed. Along with the novel three component coupling and sulfoxide-Julia olefination, which will be described in details in chapters 3 and 4, respectively, we have introduced a stable form of CuCl in the aerobic Cu(I)-promoted oxidation of alcohols and have also optimized the conditions for the diastereoselective cyclopropanation of olefins using other diazoalkanes than diazomethane. This work led to the preparation of a variety of optically active, functionalized, cyclopropanes.

As a perspective, the conditions for the Suzuki coupling of the eastern fragment 211 with left-hand fragment 127 have to be developed and optimized. With this final step, the total synthesis of (+)-ambruticin 1 should be accomplished.
Figure 2.10
3. Silicon-based methodologies

Silicon belongs to one of the most common elements on the earth. Because of its easy accessibility and simple purification, silicon has found a large variety of applications, starting with glass and finishing with computer components.

In organic synthesis, silicon has also found a unique and non exchangeable position due to its specific properties. Silicon is $\sigma$-donor (its electronegativity is 1.8) as compared to carbon (2.5) and its energetically low-lying empty d-orbitals make it a good $\pi$-acceptor (Figure 3.1).

![Figure 3.1](image)

Additionally, silicon stabilizes an anion at the $\alpha$ position and a cation at the $\beta$ position. The $\alpha$ effect is explained by the dilution of the negative charge into the $\sigma^*$ (Si-C) bond and the $\beta$ effect is due to the interaction between the carbon-silicon $\sigma$-bond and the empty p orbital (Figure 3.2).

Moreover, most of the organosilicon compounds are stable enough to be easily prepared, handled and stored with a minimum of precautions.

Chapter 3. Silicon-based methodologies

This chapter is focused on multicomponent condensations involving allylsilanes, aldehydes and alcohols.\(^{100}\)

![Figure 3.2](image)

Figure 3.2

### 3.1 Sakurai multicomponent reaction

#### 3.1.1 Introduction: The beauty of multicomponent reactions

The length of a synthesis is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve the formation of several bonds (multi-bonds) in one operation is becoming one of the major challenges in searching for straightforward and convergent synthesis. An ideal multi-bonds process should satisfy the following requirements:

(a) to be regio-, stereo- and chemoselective

(b) to start from readily available and, if possible, simple starting materials

(c) the reaction should be operationally simple and atom efficient\(^{101}\)

---


Chapter 3. Silicon-based methodologies

Multicomponent reactions (MCRs),\(^{102}\) in which three or more reactants are combined in a single step to afford products that incorporate substantial portions of all the starting components, naturally comply with many of these stringent requirements for ideal organic synthesis.\(^{103}\) The asymmetric multicomponent reactions (AMCRs) are those reactions that belong to the finest art of this chemistry.\(^{104}\) The definition of AMCR is rather similar to the definition of MCR. Thus, the AMCR is a reaction in which three or more chiral and/or achiral reactants are combined in a single step to generate products that incorporate substantial portions of all the starting components. Additionally, a novel stereogenic centre has to be created during this process.

The Ugi reaction (4 components MCR) can serve as an example of a highly efficient and, in some cases, also stereoselective MCR transformation. The classical Ugi reaction involves the interaction of a carbonyl compound, an isonitrile, an amine and a carboxylic acid to obtain an \(\alpha\)-acylaminoamide. Since the esters of \(\alpha\)-amino acids can be conveniently used as the amine component in the Ugi reaction, in principle, they can be used as chiral auxiliaries. An example of such an asymmetric condensation is shown in Scheme 3.1.\(^{105}\)


3.1.2 The Sakurai reaction and its extension

The transformation known now-a-days as the Sakurai or the Sakurai-Hosomi reaction was first described in 1974 by Calas et al.\textsuperscript{106} For the first time, they reported that an allylsilane 131 added to an activated aldehyde 218, in the presence of a Lewis acid such as AlCl\textsubscript{3}, GaCl\textsubscript{3} or InCl\textsubscript{3}, furnishing the homoallylic alcohol 219 (Scheme 3.2).

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & $R^1$ & $R^2$ & Yield$^a$ [$\%$] & (S):(R) \\
\hline
1 & Bn & Et & 61 & <5:95 \\
2 & i-Pr-CH\textsubscript{2} & Me & 49 & <5:95 \\
3 & 4-(OH)C\textsubscript{6}H\textsubscript{4}CH\textsubscript{2} & Me & 71 & 9:91 \\
4 & MeSCH\textsubscript{2}CH\textsubscript{2} & Me & 64 & <5:95 \\
\hline
\end{tabular}

$^a$ Calculated to aldehyde 215
\end{center}

\textbf{Scheme 3.1}

\textbf{Scheme 3.2}

Two years later, in 1976, Sakurai and Hosomi\textsuperscript{107} extended this reaction to a wide range of non-activated carbonyl compounds 220, using TiCl$_4$ as the Lewis acid (Table 3.1). In this case, the allylation occurred rapidly at r.t. and was applicable to both aldehydes and ketones.

![Scheme 3.3](image)

**Table 3.1**

| Entry | $R^1$ | $R^2$ | Time (min) | Yield (%)$^a$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pr</td>
<td>H</td>
<td>0.5</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>H</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>-CH$_2$-(CH$_2$)$_3$-CH$_2$-</td>
<td>3</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ All yields refer to pure, isolated products

Later on, the condensation of allylsilane 131 with acetals 222 was reported (Table 3.2).\textsuperscript{108} The reaction furnished homoallylic ethers 223 in excellent yields, even though the condensation is slower than with aldehydes or ketones.

The extension of the reaction conditions to acetals led, consequently, to the development of the catalytic version of the reaction.\textsuperscript{109} In this case, 10 mol\% of TMSI was used as a Lewis acid (Table 3.3). The postulated mechanism is depicted in Scheme 3.3.

The acetal 222, activated by the iodotrimethylsilane 224, produces the oxonium cation 226 which can be intercepted by allylsilane 131 yielding

\textsuperscript{107} Hosomi, A; Sakurai, H. *Tetrahedron Lett.* 1976, 17, 1295-1298.

\textsuperscript{108} Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* 1978, 941.

homoallylic ether 226, one equivalent of methoxytrimethylsilane 225 and the catalyst 224.

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}_1 & \text{R}_2 & \text{Time [h]} & \text{Yield [%]} \\
1 & i\text{-Bu} & H & 3 & 90 \\
2 & Ph & H & 1 & 74 \\
3 & Me & Me & 3 & 98 \\
4 & PhCH_2CH_2 & Me & 3 & 71 \\
\end{array}
\]

**Table 3.2**

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}_1 & \text{R}_2 & \text{Time [h]} & \text{Yield [%]} \\
1 & i\text{-Bu} & H & 2.5 & 70 \\
2 & Ph & H & 8 & 81 \\
3 & Me & Me & 3.5 & 83 \\
4 & PhCH_2CH_2 & Me & 6 & 95 \\
\end{array}
\]

**Table 3.3**
Chapter 3. Silicon-based methodologies

These results led to the development of numerous methods for allylation of carbonyl functions and acetals. Since the 1980s, chemists have attempted to develop novel Lewis acids and Lewis bases able to catalyze the Sakurai-Hosomi reaction with full diastereo- and enantiocontrol. A review by Denmark and Fu summarizes the most recent advances in this area.\textsuperscript{110} The history of the Sakurai multicomponent reaction started in 1982 when Sakurai published a review dealing with the acetalyzation of carbonyl compounds.\textsuperscript{111} There, in one of the footnotes, he presented a previously unpublished observation that in the presence of catalytic amounts of TMSI and one equivalent of tetramethoxysilane 227, allyltrimethylsilane 131 underwent smooth condensation with benzaldehyde 228 furnishing adduct 229 in good yield (Scheme 3.4). The Sakurai multicomponent condensation was born.

Employing a silylether instead of 227 provided a connective assembly of homoallylic ethers. This three-component reaction leads to the formation of homoallylic ethers 233 via activation of the carbonyl 220 by the Lewis acid 224. The in situ generated oxonium cation 230 can then be trapped by the nucleophilic silylether 231 affording 232. The new species can then react with allyltrimethylsilane 131, to form the desired ether 233 with subsequent regeneration of the catalyst and lost of TMSOTMS 234 (Scheme 3.5).

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Scheme 3.5

A wide variety of silyl ethers can be employed, leading to functionalized homoallylic alcohols or ethers. This three components coupling reaction, which generates in a single operation a range of homoallylic ethers, does not require the initial and independent synthesis of the acetal (or ketal) derived from 220. Interestingly, the three-component coupling is, when compared to its two component modification, rather overlooked by synthetic community.¹¹² In the case of the two-components Sakurai MCR, the allylsilane moiety and the silyl ether function are present in the same molecule 235. This substrate is then reacted with a carbonyl compound 220, in the presence of a Lewis acid, and yields the cyclic derivative 237 containing an oxygen atom (Scheme 3.6).¹¹³ Such a reaction is called intramolecular silyl-modified Sakurai reaction (ISMS), since only a catalytic amount of the TMS⁺ donating Lewis acid is required (Scheme 3.7).

If the component 235 contains the allylsilane and one hydroxyl group (R³ = H), the Lewis acid (generally BF₃.OEt₂) has to be used in equimolar amount. This type of condensation is known as intramolecular Sakurai condensation (IMSC).¹¹⁴

Scheme 3.6

In the next two sections, both inter- and intramolecular versions of the Sakurai multicomponent reaction will be presented.

Scheme 3.7

3.1.3 Three component reaction – intermolecular version

In 1984, two years after the Sakurai multicomponent reaction was disclosed for the first time, Sakurai et al. described a variant of the process in which the catalyst was generated in situ. Thus, mixing a catalytic amount of iodine with a free alcohol 245, a carbonyl derivative 228 and two equivalents of allylsilane 131 provided, in 89% yield, homoallylic adduct 229 (Scheme 3.8).\(^{115}\)

The use of alcohol 245 is attractive as it avoids the preliminary silylation step. The second equivalent of allylsilane 131 is consumed whilst generating the catalyst (iodotrimethylsilane).

Disappointingly, this method did not find any response in the organic community and, generally, the already silylated alcohol was used.

\[\text{MeOH} + \text{Ph} + \text{TMS} \xrightarrow{2.0 \text{ eq}} \xrightarrow{131} \text{I}_2 \xrightarrow{\text{cat}} \xrightarrow{\text{CH}_2\text{Cl}_2, \Delta t} \text{OMe} + \text{TMSOTMS} \]

Scheme 3.8

A year later, Seebach and Imwinkelried\(^ {116}\) employed the dialkoxydichlorotitanium complex 247 instead of the free alcohol in the same condensation. Using this procedure, the homoallylic ethers 249 were obtained in good yields (Table 3.4).

Interestingly, the use of the optically active alcohol 250 in this protocol leads, after cleavage of the benzylic ether in the initial adduct 251, to the enantiomerically enriched homoallylic alcohol 252. This approach appears to

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\(^{116}\) Imwinkelried, R.; Seebach, D. Angewandte Chemie 1985, 97, 781-782.
be the first asymmetric preparation of homoallylic alcohols via open-chain acetal derivatives (Table 3.5).

![Chemical structure diagrams]

**Table 3.4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>i-Pr</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Et</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Allyl</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂CH₂</td>
<td>i-Pr</td>
<td>95</td>
</tr>
</tbody>
</table>

*a All yields refer to pure, isolated products

**Table 3.5**

Inspired by this work, Mukaiyama\(^{117}\) used the silylated chiral alcohol 253 and performed the same reaction using diphenylborotriflate as the catalyst. In all cases, the yields were good and the diastereoisomeric excesses excellent, except for benzaldehyde (Table 3.6, Entry 5).

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SMS reaction. Further cleavage of the benzylic ether bond of 259 by Na/NH₃ led to the optically active homoallylic alcohols 249 with good yields and selectivity (Table 3.7).

![Scheme 3.9](image)

**Scheme 3.9**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>d.r.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>82</td>
<td>89:11</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂CH₂</td>
<td>63</td>
<td>91:9</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>53</td>
<td>&gt;95:5</td>
<td>85</td>
</tr>
</tbody>
</table>

* All yields refer to pure, isolated products
* Yields refers to the allylating step
* Yields refers to the cleavage step

**Table 3.7**

This method is remarkable in that ketones can also be allylated with high levels of enantiocontrol, a transformation that is rarely encountered in the literature. Tietze postulated that the cyclic oxazolidinium cation 260 acted as the key intermediate in the asymmetry-inducing allylation step (Figure 3.3).


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Next, Rychnovsky and Cossrow\textsuperscript{120} preferred to use the optically pure $\alpha$-trimethylsilylbenzylether 261 as the chiral auxiliary. In this case, the oxocarbenium intermediate 262 adopts a well-defined conformation, proposed initially by Linderman,\textsuperscript{121} which provides the maximum $\beta$-silyl-effect. The nucleophile then approaches from the opposite side to the TMS group (Table 3.8).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3_3}
\caption{Figure 3.3}
\end{figure}

Optically pure crotylsilane 264 was used by Panek et al.\textsuperscript{122} in the synthesis of functionalized homoallylic ethers 266 (Scheme 3.10). The $\text{syn}$ relationship between the methyl and the ether function is usually favored (up to 30:1) in

\begin{table}
\centering
\begin{tabular}{ccccc}
\hline
Entry & R       & Yield (\%\textsuperscript{a}) & d.r.  \\
\hline
1   & cyc-C$_6$H$_{11}$ & 87    & 97:3  \\
2   & $n$-C$_6$H$_{11}$ & 86    & 97:3  \\
3   & Ph          & 96    & 91:9  \\
4   & TBDPSOCH$_2$CH$_2$ & 69    & 95:5  \\
\hline
\end{tabular}
\caption{Table 3.8}
\textsuperscript{a}All yields refer to pure, isolated products
\end{table}

agreement with an open transition state. This reaction allows the creation of a new chiral centre and the transfer of another one.

\[
\text{SiMe}_2\text{Ph} \quad \text{O} \quad \text{R} \\
\text{TMSOMe} \quad \text{TMSOTf} \quad \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \\
\text{OMe} \quad \text{CO}_2\text{Me} \quad \text{OMe} \quad \text{CO}_2\text{Me}
\]

\[
\text{R} = \text{Me} (97\%, d.r. = 2:1) \\
\text{R} = \text{i-Pr} (60\%, d.r. = 19:1)
\]

Scheme 3.10

In summary, The SMS or Sakurai Multicomponent reaction is truly an efficient process, possessing a broad scope, and applicable to a number of carbonyls, allylsilanes, alcohols (silyl ethers) or amines.\(^{123}\) Its usefulness was validated in several total syntheses\(^{124}\) and demonstrated by the preparation of chiral homoallylic alcohols. On the other hand, it is true to say that the SMS reaction stays in the shadow of its intramolecular version, the topic of the next part of this chapter.


3.1.4 Intramolecular Sakurai condensation

The IntraMolecular Sakurai Condensation (IMSC) can be considered as one of the most powerful synthetic tools for the stereocontrolled construction of polysubstituted tetrahydropyran rings. The synthesis of five to seven membered rings, their nitro analogs and a variety of spiro compounds can be accomplished using this methodology. Since the IMSC reaction is not the main topic of this thesis, only the synthesis of the tetrahydropyran rings will be discussed in the following paragraph.

Tetrahydropyran rings are presented in numerous natural products and therefore, versatile and rapid syntheses of such ring systems are valuable tools for synthetic chemists.

Nowadays, the intramolecular Sakurai cyclization stands as one of the most suitable methodologies for the assembly of such subunits. However, when Markó et al. in 1991 initially published the TMSOTf-catalyzed condensation (ISMS) of aldehyde with TMS-ether, the results of this reaction were far from perfect (Scheme 3.11). Indeed, this condensation

resulted in the formation of three products. Surprisingly, not only the expected adduct 269 was formed, but also the isomerized derivatives 270 and 271 were present in the reaction mixture.

The condensation utilizing aldehyde 267 and alcohol 268b gave even less satisfactory results.

\[
\begin{align*}
\text{Hex} & \quad \text{H} \\
\text{267} & \quad \text{TMS} \quad \text{268} \quad \text{TMSOTf (0.1 eq)} \\
\quad & \quad \xrightarrow{-15^\circ\text{C}, \text{CCl}_4} \\
\text{Hex} & \quad \text{O} \\
\text{269} & \quad \text{270} \quad \text{271}
\end{align*}
\]

\[
\frac{269}{270} : \frac{271} = 16 : 3 : 2, \text{ overall yield } = 88\% \\
\frac{269}{270} : \frac{271} = 7 : 10 : 4, \text{ overall yield } = 91\%
\]

Scheme 3.11

Those early problems, mostly related to the adventitious presence of triflic acid, were readily solved and the scope and limitations of the methodology rapidly uncovered. The advantage of the IMSC reaction lays in the highly stereoselective formation of dihydropyran rings 272 and tetrahydropyran rings 273 and 274 (Figure 3.4). In most cases, only one of all the possible diastereoisomers is formed with a high degree of diastereoselectivity.

\[
\begin{align*}
\text{R} = \text{H, alkyl, aryl, alkoxy,...}
\end{align*}
\]

Figure 3.4

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3.1.4.1 Dihydropyran

Dihydropyran of the general structure 272 can be prepared by two complementary strategies starting from aldehyde 275a or 275b. Condensation with vinylsilane 276 or allylsilane 277 affords in each case the adduct 272 (Scheme 3.12).

Markó et al. used the vinylsilane annulating agent 278 and aldehyde 279a as key fragments for the synthesis of the right-hand subunit of ambruticin 280a (Scheme 3.13). The ISMS cyclization afforded the desired product 280a in 83% yield. Interestingly, the reaction is highly stereoselective and only the cis-2,6-disubstituted dihydropyran 280 are produced (for another examples see). The cis-stereochemical relationship between the substituents at carbon centers C2 and C6 is explained by invoking a mechanism proceeding through the cyclic transition state 70. In this six-membered transition state, both substituents at carbon centers C2 and C6, occupy equatorial positions. The

trimethylsilyl moiety is locked in the pseudo axial position due to the olefin geometry (Figure 3.5).\textsuperscript{134}

\begin{center}
\begin{tabular}{c}
\begin{tikzpicture}
\node (a) at (0,0) [draw, thick, circle] {278};
\node (b) at (2,0) [draw, thick, circle] {279};
\node (c) at (4,0) [draw, thick, circle] {280};
\node (d) at (2,-2) [draw, thick, circle] {279a};
\node (e) at (2,-4) [draw, thick, circle] {279b};
\node (f) at (4,-2) [draw, thick, circle] {280a};
\node (g) at (4,-4) [draw, thick, circle] {280b};
\draw (a) -- (b);
\draw (b) -- (c);
\draw (c) -- (d);
\draw (c) -- (e);
\draw (c) -- (f);
\draw (c) -- (g);
\end{tikzpicture}
\end{tabular}
\end{center}

\textbf{Scheme 3.13}

Another approach towards dihydropyrans 283 and 284 was developed by Panek et al.\textsuperscript{136} In this methodology, the two enantiomerically enriched diastereoisomers, \textit{syn} or \textit{anti}-allylsilanes 282, were allowed to react with a range of aldehydes in the presence of catalytic amounts of TMSOTf (0.1 eq) (Table 3.9).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) [draw, thick, circle] {281};
\node (b) at (0,2) [draw, thick, circle] {281$^\dagger$};
\end{tikzpicture}
\end{center}

\textbf{Figure 3.5}

It was observed that the cyclization of \textit{syn}-282 produced mainly the dihydropyran 283a, accompanied by dihydropyran 283b as a minor diastereoisomer. In contrast, the cyclization of \textit{anti}-282 provided dihydropyran 284b as the major isomer and the all \textit{cis}-substituted dihydropyran 284a as the minor product. In all cases, the diastereoselectivity ranges from good to excellent.

A similar reaction was studied by Roush et al.\textsuperscript{137} However, in this case, the cyclization of \textit{anti}-allylsilane \textsuperscript{285} resulted in the production of only \textit{cis}-2,6-disubstituted dihydropyrans \textsuperscript{286}. No \textit{trans}-2,6-disubstituted dihydropyrans \textsuperscript{287} were formed. Moreover, significant amounts of adducts \textsuperscript{288} and \textsuperscript{289} were observed (Table 3.10). These products probably originate from a side chain exchange process (vide infra).

\textsuperscript{137} Roush, W. R.; Dilley, G. J. \textit{Synlett} 2001, 955-959.
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This side-reaction, which complicates the condensation of allylsilanes \textit{anti-285}, was suppressed by using \textit{\textalpha}-acetoxy acetals such as \textit{anti-290} as the oxonium cation precursor. Under these conditions, the desired \textit{cis}-2,6-disubstituted dihydropyrans \textit{291} was isolated in moderate yields but high diastereoselectivity ($d.r. = 94:6$; Table 3.11).

Roush and Dilley suggested\textsuperscript{137} that the preferential formation of \textit{cis}-2,6-disubstituted dihydropyrans \textit{286} and \textit{291} instead of the expected \textit{trans}-2,6-disubstituted dihydropyrans \textit{287}, as well as the unanticipated exchange of allylsilane side chains (leading to products \textit{288} and \textit{292}, respectively), can be explained by invoking competitive and extremely facile oxonia-Cope rearrangements during the intramolecular allylation process (Scheme 3.14).\textsuperscript{138}

\begin{table}[h]
\centering
\begin{tabular}{cccccc}
\hline
Entry & R & R' & Yield (%)\textsuperscript{a} & \textit{dr}; \textit{C}_2:\textit{C}_6-syn:anti  \\
\hline
1 & PhCH\textsubscript{2}CH\textsubscript{2} & PhCH\textsubscript{2}CH\textsubscript{2} & 82 & 94:6  \\
2 & i-Pr & PhCH\textsubscript{2}CH\textsubscript{2} & 17\textsuperscript{b} & 94:6  \\
\hline
\end{tabular}
\caption{Table 3.10}
\end{table}

\textsuperscript{a} All yields are for pure, fully characterized, products
\textsuperscript{b} Products \textit{288} (50\%) and \textit{289} (3\%) are also formed

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Based upon the retention of stereochemistry observed during the course of the reaction (Table 3.11, Entry 2), they proposed that the reaction proceeded via a boat-like transition state 293 (Scheme 3.14). Such a transition state rationalizes the formation of the cis-2,6-disubstituted dihydropyran 286, with retention of stereochemistry, whilst the oxonia-Cope rearrangement explains the formation of product 292. This compound originates from the exchange process 296 \(\rightarrow\) 297.

Based upon this postulated mechanism, the formation of cis-2,6-disubstituted dihydropyran 283a and trans-2,6-disubstituted dihydropyran 284b (Table 3.9) can also be rationalized. It appears that the formation of 283a and 284b proceeds preferentially through the chair-like transition states 299 (leading to 283a) and 301 (leading to 284b) (Scheme 3.15). Indeed, the boat-like transition states 298 and 300, in which the oxonium ions adopt the more stable (\(E\))-geometry, suffer from eclipsing interactions involving the aldehyde R group and the methyl substituent present in the crotylsilanes 282.

Table 3.11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)(^a)</th>
<th>d.r.; (C_2;C_6)-cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf (1.5 eq) CH(_2)Cl(_2) -78°C</td>
<td>50(^b)</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>SnCl(_4) (1.5 eq) toluene, -78°C (\rightarrow) -15°C</td>
<td>60(^d)</td>
<td>94:6</td>
</tr>
</tbody>
</table>

\(^a\) All yields are for pure, fully characterized, products  
\(^b\) Product 292 was formed in 3%  
\(^c\) Product 292 was formed in 4%  
\(^d\) Product 291 was formed with 94% ee purity
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The transition state 298 also suffers from repulsive interaction between the pseudo axial CO$_2$Me group and the pseudo axial –SiMe$_2$Ph (Scheme 3.15).

Scheme 3.14

The absence of products derived from the oxonia-Cope rearrangement in the Panek study$^{136}$ can be explained by the presence of the CO$_2$Me group, which would destabilize the oxonia-Cope product 296 (R = CO$_2$Me) because the electron withdrawing group is directly attached to the oxonium ion carbon. Rychnovsky et al. have postulated the same mechanism during their study of the α-acetoxy acetal 302 cyclization and of the condensation of alcohol 304 with cinnamyl aldehyde (Scheme 3.16).$^{139}$ In both cases, the desired adducts 303a,b were obtained in good yields and excellent diastereoselectivity.

---

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Scheme 3.15

Already in 1997, Hiemstra and Speckamp postulated the participation of an oxonia-Cope rearrangement as a crucial step during the cyclization of vinylsilane 305 (Scheme 3.17).\textsuperscript{140} Both (\textit{E})- and (\textit{Z})-vinylsilanes were used in this study. The cyclization proceeded in both cases in good to excellent yields, furnishing the 2,6-disubstituted dihydropyrans 306. Surprisingly, the cyclization of (\textit{E})-vinylsilanes (\textit{E})-305 gave \textit{anti}-2,6-dihydropyran as the major stereoisomer, whilst in the case of (\textit{Z})-vinylsilane, the \textit{syn}-dihydropyran was formed as the major product.

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<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>68</td>
</tr>
</tbody>
</table>

* All yields are for pure, fully characterized, products

Scheme 3.16

The preferred formation of the *anti*-product from the *(E*)-vinylsilane can be explained by the mechanism shown in Scheme 3.18. The initially generated carbocation **310** (drawn in its most stable chair like conformation) is in equilibrium with **311** via a cationic oxonia-Cope equilibrium. Intermediate **311** is probably more stable than **310** due to the destabilizing effect of the electron-withdrawing group on the oxonium. However, the cyclization of **311**, which would lead to the *syn* product, appears to be slow because the silyl group is not well orientated to assist the ring closure. Chair-chair interconversion of **311** generates the oxocarbenium ion intermediate **312** that features an allylsilane with an axial silyl function. Cyclization of **312** now becomes a fast process and leads to the product *anti*-**306**.
In the case of the (Z)-vinylsilane (Z)-305, the observed syn selectivity results from the cyclization of intermediate 308 in which the TMS group is already axially orientated due to the (Z)-double bond geometry of the precursor.
3.1.4.2 Vinyl tetrahydropyrans

Tetrahydropyrans of the general formula 273 can be prepared from aldehydes or ketones 220 (or acetals and ketals) and allylsilanes 313 (Scheme 3.19).
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Scheme 3.19

When Mohr,\textsuperscript{141} in 1995, initially published the synthesis of vinyltetrahydropyrans \textbf{316}, the reaction conditions required 4 to 5 equivalents of starting acetal \textbf{315} per equivalent of allylsilane \textbf{314}. The condensation was catalyzed by the Brönsted acid: \textit{p}-TSA (Scheme 3.20). It proceeded with an excellent stereoselectivity and generally, the \textit{syn-anti}-trisubstituted tetrahydropyran \textbf{316} was formed with overwhelming preference. However, \textbf{316} proved to be rather difficult to purify and was always contaminated by 5\% or less of the other three stereoisomers. The yields of the reaction varied from moderate to good.

Three years later, in 1998, Ito et al. published\textsuperscript{142} a similar reaction using the enantio enriched allylsilane \textbf{317} (Scheme 3.21). This condensation furnished the \textit{trans}-2,3-disubstituted tetrahydropyrans \textbf{318} with 92.1 to 93.4\% \textit{ee} (indicating that the reaction proceeded with nearly complete chirality transfer), high diastereoselectivity and very good yields. In this case, the reaction was mediated by TMSOTf (1.1 eq) and the first steps presumably involved the silylation of the free alcohol function. It is noteworthy that the double bond in \textbf{318} possesses exclusively the (\textit{E})-geometry.

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**Scheme 3.20**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Ph</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> All yields refer to compounds contaminated with 5% or less of the other three isomers.

**Scheme 3.21**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>trans/cis&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Hex</td>
<td>92</td>
<td>&gt;10:1</td>
<td>92.1</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>98</td>
<td>99:1</td>
<td>92.8</td>
</tr>
<tr>
<td>3</td>
<td>tert-Bu</td>
<td>88</td>
<td>9:1</td>
<td>93.6</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>MeC=C=CH</td>
<td>72</td>
<td>9:1</td>
<td>92.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> All yields refer to pure, isolated products.
<sup>b</sup> Refers to stereochemistry of six-member ring.
<sup>c</sup> The values (+/-0.2) were determined by HPLC.
<sup>d</sup> Reaction in MeCN at -30°C in the presence of TMSOTf (0.1 eq).

Finally, Szabó et al. examined the reactions of disubstituted allylsilanes 319 with aldehydes. In the presence of TMSOTf, the 2,3,5,6-tetrasubstituted tetrahydropyrans 320 were formed in good yields (Scheme 3.22). In complete analogy with the results of Ito<sup>142</sup> and Mohr<sup>141</sup>, a remarkably high stereoselectivity was also observed.

---

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Based upon the previously described cyclization reactions, a possible transition state for the ISMS condensations leading to product 273 can be postulated (Scheme 3.23). It appears that the reaction is proceeding through the chair-like transition state 321, in which all the bulky substituents adopt the thermodynamically preferred equatorial positions.

\[
\begin{array}{cccc}
\text{Entry} & R^1 & R^2 & R^3 & \text{Yield (%)}^a \\
1 & \text{Me} & H & \text{i-Pr} & 70 \\
2 & \text{Ph} & H & \text{i-Pr} & 70 \\
3 & H & \text{HOCH}_2 & \text{i-Pr} & 64^c \\
4 & H & \text{HOCH}_2 & \text{Ph} & 62^c \\
\end{array}
\]

^a All yields refer to pure, isolated products
^b 2.4 eq. of TMSOTf was used

**Scheme 3.22**

4.1.4.3 Exo-methylene tetrahydropyrans

Finally, the IMSC methodology can be employed successfully for the preparation of 4-exo-methylene tetrahydropyrans of the general structure

\[
\text{Si = SiMe}_3, \text{SiMe}_2\text{Ph, SiMe}_2\text{OMe,}...
\]

**Scheme 3.23**

These can be obtained in two steps starting from allylsilane 322 or allylstannanes 323 (Figure 3.6).

Markó et al. initially employed allylsilane 322 during their study on the scope and limitations of the IMSC methodology in 1993 and expected to obtain the *exo*-methylene tetrahydrofurans 326 (Scheme 3.24). However, none of the desired furan derivatives 326 were formed when a mixture of 322 and aldehydes 325 was treated with a range of Lewis acids. Rather, the diastereomerically pure *exo*-methylene tetrahydropyrans 324 were isolated, albeit in modest yields (Scheme 3.24). In 1995, Oriyama et al. published the IMSC reaction of acetals with allylsilane 322, yielding the desired tetrahydrofurans 326 in the presence of the SnCl2/AcCl system. Interestingly, product 324 was not formed when the corresponding acetals were used instead of the aldehydes in this coupling reaction and vice-versa.

---

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Closer examination of tetrahydropyrans 324 clearly reveals that two molecules of aldehyde 325 have been appended onto allylsilane 322 via a novel three components coupling reaction. Markó et al. proposed the mechanism depicted in Scheme 3.25.\textsuperscript{147b} Formation of heterocycles 324 is described as a sequence of two processes: an initial ene-type reaction,\textsuperscript{148} which leads to alcohol 328 via the chair-like transition state 327, in which both the aldehydic R-group and the OTMS substituent assume an equatorial position. The high regio- and stereoselectivity observed in this ene-reaction can be nicely explained by considering the stabilizing β-silicon effect and the repulsive 1,3-diaxial interactions. Transition state 327 contains no 1,3-diaxial interactions and benefits fully from the stabilizing β-silicon effect\textsuperscript{149} (for more detailed transition state discussion see\textsuperscript{150}).

Further condensation of the free hydroxyl group of 328 with another molecule of aldehyde 325 generates the oxonium cation 329, which undergoes an IMSC reaction, producing the \textit{exo}-methylene tetrahydropyran 330 in which all the substituents occupy an equatorial position. Desilylation during the work-up finally gives the observed product 324.

An interesting observation that lends some credit to the above-proposed mechanism comes from the reaction of allylsilane 322 with various aldehydes 325 in the presence of Et₂AlCl. This reaction afforded for the first time, the silylenol ether 328 as a single double bond isomer. When 328 was further treated with Et₂O.BF₃ in the presence of a second equivalent of aldehyde 325, smooth formation of 324 ensued indicating that 328 is a plausible intermediate in the transformation of 322 to 324 (Scheme 3.26).\(^{150}\)

The problem of the rather moderate yields of ene-adducts 328 was solved when the more robust TBDMS protecting group was employed. Using reagent 331 instead of 322, a smooth ene-reaction occurred, affording the silyl enol ethers 332 in improved yields (Scheme 3.27).
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The substituted homoallylic alcohols 332 were then transformed into the desired exo-methylene derivatives 333 by the addition of an aldehyde 325 in the presence of Et₂OBF₃ (Scheme 3.28). In general, good to excellent yields of heterocycles 333, in which the robust TBDMS group has been retained, were obtained. In all cases, the substituents around the ring occupy equatorial positions, according to the suggested chair-like transition state 329. It is noteworthy that the reaction conditions tolerate a wide range of functionalities, both in the aldehyde 325 and the silyl enol ether 332.

Similarly, tetrahydropyrans 336, containing an all cis substitution pattern could be easily synthesized by using the (Z)-enol carbamate 335, the
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geometric isomer of 332. Such a compound was readily prepared by applying the modified allyl-metallation protocol reported by Hoppe for the carbamate derivative 334 (Scheme 3.29).\(^{151}\)

![Scheme 3.29 Image]

IMSC reactions of 335 proceeded smoothly and afforded the expected tetrahydropyran 336 with exquisite diastereoselectivity. In every case, the carbamate substituent adopts an axial position, in agreement with the geometry of the starting olefin 335 and the proposed chair-like transition state 337 (Figure 3.7).

The same allyl-metallation protocol can be used for the preparation of allylstannane 338. Taking advantage of the greater nucleophilic propensity of the allylstannane function over the allylsilane, 338 was treated with various aldehydes in the presence of Et\(_2\)O BF\(_3\), affording the homoallylic

alcohols 339 in excellent yields (Scheme 3.30). It is noteworthy that complete syn-stereocontrol is observed in all these transformations.

The homoallylic alcohol 339 can be easily transformed into the corresponding exo-methylene tetrahydropyrans 336 by a Bi(III)-promoted IMSC condensation (Scheme 3.31). Tetrahydropyran 336 is obtained in excellent yields and with complete stereocontrol.

Recently, Yu et al. and Keck et al. reported the synthesis of enantio enriched homoallyl alcohols 341. Alcohols 341 are prepared from the allylstannane 340, by using chiral Ti(IV)-based catalysts, with ee’s ranging from 90 to 96% (Scheme 3.32).

The optically active homoallylic alcohols 341 were then used in subsequent TMSOTf or TMSNt2 promoted IMSC condensations providing enantio enriched tetrahydropyrans 342 in excellent yields and diastereoselectivity (Scheme 3.33).
Rychnovsky et al. used another approach for the generation of exo-methylene tetrahydropyrans of the general structure 274. In this case, enol ethers 342 and 343 were reacted with various aldehydes in the presence of a Lewis acid, to furnish tetrahydropyrans 344 and 345 respectively (Scheme 3.34).\(^\text{154}\)

The yields ranged from good to excellent and the syn-2,6-disubstituted adducts 344 were formed stereoselectively. The facial selectivity in the addition to the aldehyde, however, was minimal, as might be expected considering the distance between the reactive end of the enol function and the stereogenic center in enols 342 and 343.

A plausible mechanism for the reaction is depicted in Scheme 3.35. Enol ether 342 reacts with the activated aldehyde to give the oxonium cation 346. This species is trapped intramolecularly by the allylsilane nucleophile and a new tetrahydropyran ring 344 is formed.

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![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Epimer ratio</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>1.2:1</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>1:1</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>TBSOCH₂CH₂</td>
<td>1.8:1</td>
<td>87</td>
</tr>
</tbody>
</table>

^a All yields refer to pure, isolated products

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Epimer ratio</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>1.3:1</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>1.1:1</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>TBSOCH₂CH₂</td>
<td>1.2:1</td>
<td>70</td>
</tr>
</tbody>
</table>

^a All yields refer to pure, isolated products

Scheme 3.34

Another elegant way leading to tetrahydropyrans 347 was described by Overman et al.\(^{155}\) Thus, the homoallylic alcohol 348 was reacted with

various aldehydes in the presence of TfOH to furnish the carbonyl-
substituted tetrahydropyrans 347 along with its C-4 stereoisomer 349
(Scheme 3.36). The reaction is highly stereoselective and the syn-2,4,6-
trisubstituted tetrahydropyrans 347 were obtained as the major products in

good yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>135 : 138</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>8:1</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂CH₂</td>
<td>18:1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>14:1</td>
<td>65</td>
</tr>
</tbody>
</table>

*All yields refer to pure, isolated products

The proposed mechanism for the reaction is shown in Scheme 3.37. In the
initial step, the oxonium cation 350, formed by TfOH catalyzed

Scheme 3.36

Scheme 3.37

The proposed mechanism for the reaction is shown in Scheme 3.37. In the
initial step, the oxonium cation 350, formed by TfOH catalyzed
condensation of an aldehyde with alcohol 348, undergoes an intramolecular cyclization to form the tertiary carbocation 351. In a subsequent step, cation 351 undergoes a pinacol rearrangement, leading to the observed tetrahydropyran 347.

4.1.4.4 Conclusions
The IMSC methodology is a highly efficient and versatile process, possessing a broad scope and encompassing a wide range of carbonyls, allylsilanes, alcohols or amines. A large number of oxygen and nitrogen-containing heterocycles can be rapidly prepared by this connective method. Additionally, various spiro-compounds can be constructed using this multi-component methodology.

The power of the IMSC methodology has been demonstrated in numerous total syntheses in which a highly stereoselective heterocycle-ring formation is generally one of the key-steps.

3.2 Objectives
In this chapter, the development of a three component condensation between aldehyde 132, allylsilane 131 and silyl ether (R)-133 leading to the diene 130, direct precursor to the right-hand fragment of (+)-ambruticin 1, will be discussed (Scheme 3.38).

Our initial objective was to optimize the above-mentioned coupling in order to furnish the desired adduct 130 in a highly diastereoselective manner. Additionally, the scope and limitations of this reaction as well as mechanism were studied.
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3.3 Three component coupling: Key step in right-hand fragment synthesis

3.3.1 Development of the reaction’s conditions

The development of the three-component coupling reaction started with the preparation of the chiral aldehydes 132. Both the natural (S) and unnatural (R) lactates 141 were transformed into the corresponding aldehydes 132 via a two step protection/reduction sequence (Table 3.12).

Since the synthesis of the second component required for the coupling, the chiral secondary silyl ether (R)-133, was already described in Chapter 2.3 and since allylsilane 131 is commercially available, the three-component coupling reaction could be attempted.

As our first choice, the condensation reaction between aldehyde (S)-132c, allylsilane 131 and silyl ether 133 was attempted (Table 3.13, Entry 1). Disappointingly, the reaction furnished the desired product 130c in only 18% yield and as a 1:1 diastereomeric ratio of C3 epimers. The undesired hemiacetal 352c, was, in this case, isolated as the main product of the reaction.
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Since the hemiacetal 352c probably originates from the hydrolysis of one of the possible reaction intermediates,\textsuperscript{156} it appears that either oxonium cation formation or addition of the allylsilane onto that oxonium species is impeded. It was suggested that the free lone pairs of the benzyl ether oxygen might be responsible for the observed lack of reactivity of 132, by sequestering the Lewis acid.

Based upon this expectation, it was decided to use bulky protecting groups, such as TBS and TBDPS, to avoid these undesired interactions (Table 3.13, Entries 2 and 3). Gratifyingly, in these cases, the reaction proceeded in 50-60% yield. Much to our surprise, an excellent diastereoselectivity was observed. Alas, the undesired side product 352a,b was still formed in

\textsuperscript{156} For the mechanistic discussion see paragraph 3.3.3.
significant amount. Therefore, various quenching methods and additives were examined (Table 3.13, Entries 2-7).

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Work-up</th>
<th>Additive</th>
<th>Yield [%][a]</th>
<th>d.r.[b]</th>
<th>352 [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>sat. NaHCO₃</td>
<td>-</td>
<td>18</td>
<td>1:1</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>sat. NaHCO₃</td>
<td>-</td>
<td>56</td>
<td>&gt;95:1</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>TBDPS</td>
<td>sat. NaHCO₃</td>
<td>-</td>
<td>62</td>
<td>&gt;95:1</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>pyridine</td>
<td>-</td>
<td>80</td>
<td>&gt;95:1</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>TBDPS</td>
<td>pyridine</td>
<td>-</td>
<td>81</td>
<td>&gt;95:1</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>TBS</td>
<td>pyridine</td>
<td>2,6-di-tert-butyl-4-methyl pyridine</td>
<td>65</td>
<td>&gt;95:1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>TBS</td>
<td>iPr₂EtNH</td>
<td>-</td>
<td>85</td>
<td>&gt;95:1</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

[a] Yields refer to pure, isolated compounds.
[b] Determined by ¹H-NMR.

As can be seen in Table 3.13, the addition of pyridine, as a TMSOTf and TfOH trapping agent, gave superior results than NaHCO₃ (Entries 4 and 5). Addition of 2,6-di-tert-butyl-4-methyl pyridine (DTBMP) to the reaction mixture successfully suppressed the formation of 352 but led to incomplete conversion and therefore lower yields of the desired product 130 (Entry 6). Finally, the use of iPr₂EtNH gave superior results than pyridine (Entry 7).⑮

⑮ This observation was done approximately 2 years after the use of pyridine become common practice. Thus, all the results presented in chapters 2 and 3 are obtained using
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The determination of the absolute configuration of \(130a\) was done by converting the products \((2S,3R,5R)-130a\) and \(b\) into the right-hand fragment of (+)-ambruticin \(1\).\(^{158}\)

Having obtained these results, we focused our attention on the optimization of the additional reaction parameters. Thus, the influence of the reaction’s concentration (Table 3.14) and of the amount of allylsilane \(131\) (Table 3.15) on the reaction yield was evaluated.

\[
\begin{align*}
\text{Entry} & \quad \text{Concentration} & \quad \text{Yield [%]} \\
1 & 0.1 & 56 & 38 \\
2 & 0.2 & 62 & 31 \\
3 & 0.3 & 69 & 27 \\
4 & 0.4 & 75 & 19 \\
5 & 0.5 & 80 & 12 \\
6 & 0.6 & 67 & 26 \\
\end{align*}
\]

Table 3.14

pyridine as a quenching agent. The use of Hünig’s base will always be indicated in the reaction conditions.

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It was observed that the reaction proceeded best when the concentration of the reaction mixture was 0.5M (in aldehyde \((S)-132a\)) and when 1.1 equivalent of allylsilane \(131\) was used. With higher loading of \(131\), the competitive Sakurai allylation reaction of aldehyde \((S)-132a\) starts to be significant and leads to decreased yields of the desired coupled product \((2S,3R,5R)-130a\).

Finally, it was noticed that when aldehyde \((S)-132a\) was used, the reaction time strongly depended upon the reaction scale (Table 3.16, Entries 1 to 3). Surprisingly, such was not the case for the TBDPS protected aldehyde \((S)-132b\) (Entry 4 and 5).

Table 3.15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylsilane ((\text{eq}))</th>
<th>Yield [%]</th>
<th>(352a)</th>
<th>(353)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>77</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>80</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>50</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
<td>25</td>
<td>31</td>
<td>42</td>
</tr>
</tbody>
</table>

\(353, \text{dr} = 1.1:1\)
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3.3.2 Preliminary scope and limitations

In order to broaden the scope of this multicomponent condensation, (S)-132b was reacted with a variety of silyl ethers and allylsilanes, under the standard reaction conditions (Table 3.17).

Disappointingly, the condensations employing the primary silyl ethers 353a and 353b were not diastereoselective and the desired products were obtained in a 1.2:1 to 1.5:1 ratios of the 2,3-syn:2,3-anti isomers respectively (Table 3.17, Entries 1 and 2). In contrast, when the cyclic secondary silyl ether 353c was employed, the adduct 354c was formed in an increased 8:1 syn:anti ratio (Table 3.17, Entry 3). Other secondary and tertiary silylated alcohols gave exclusively the 2,3-syn-diastereomer (Table 3.17, Entries 4-7). It is noteworthy that the stereogenic centre present in the silyl ether has no influence on the diastereoselectivity of the reaction (Table 3.17, Entries 4 and 5).

Table 3.16

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Amount of (S)-132 [mmol]</th>
<th>Time [h]</th>
<th>Yield [%] (2S,3R,5R)-130</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBS</td>
<td>0.1</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>1.0</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>10.0</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>TBDPS</td>
<td>0.1</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>TBDPS</td>
<td>10.0</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

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![Chemical Reaction Diagram](image)

Table 3.17

<table>
<thead>
<tr>
<th>Entry</th>
<th>TMS-OR(^1)</th>
<th>Product(s)</th>
<th>Yield [%][(a)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSO-Ph</td>
<td>OTBDPS(2S,3S)-354a</td>
<td>87% (d.r. = 1.2:1)</td>
</tr>
<tr>
<td>2</td>
<td>OTMS</td>
<td>OTBDPS(2S,3R)-354b</td>
<td>79% (d.r. = 1.5:1)</td>
</tr>
<tr>
<td>3</td>
<td>TMSO-CH₂CH₂</td>
<td>OTBDPS(2S,3R)-354c</td>
<td>89% (d.r. = 8:1)</td>
</tr>
<tr>
<td>4</td>
<td>OTMS</td>
<td>OTBDPS(2S,3R,5S)-354d</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>OTMS</td>
<td>OTBDPS(2S,3R,5R)-354d</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>OTMS</td>
<td>OTBDPS(2S,3R)-354e</td>
<td>72%</td>
</tr>
<tr>
<td>7</td>
<td>OTMS</td>
<td>OTBDPS(2S,3R)-354f</td>
<td>67%</td>
</tr>
</tbody>
</table>

[a] Overall yields refer to pure, isolated products.
The lack of a match-mismatch effect in the condensation reaction proved to be an unexpected bonus. Indeed, by the judicious choice of the enantiomerically pure aldehyde 132 and silyl ether 133, all four possible 2,3-syn-configured adducts 130b could be prepared in high yield and with complete control of both the relative and absolute stereochemistry of the newly formed stereogenic centre (Table 3.18).

Next, β and γ substituted allylsilanes 355a-c were tested. The reaction of β or γ methyl substituted allylsilanes 355a and 355b proceeded with high diastereoselectivity furnishing the desired coupling products 356a and 356b in good to very good yields (Table 3.19, Entries 1 and 2). However, if the γ methyl ester-containing allylsilane 355c was used; no product was obtained presumably due to the diminished allylsilane reactivity (Table 3.19, Entry 3). The correct configuration at the C8 centre of 356a was determined by converting adduct 356a into dihydropyran 357 (Scheme 3.39). $^1$H-NMR analysis by n.O.e. and comparison with already known compounds$^{159}$ established that the C8 methyl substituent and CH(OTBDPS)Me chain are in cis relationship (Figure 3.8).

![Scheme 3.39](image)

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![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Silyl ether</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBDPS</td>
<td>CHO (S)-132</td>
<td>OTBDPS (R)-133</td>
<td>(2S,3R,5R)-130b</td>
</tr>
<tr>
<td>2</td>
<td>OTBDPS</td>
<td>CHO (S)-132</td>
<td>OTBDPS (R)-133</td>
<td>(2S,3R,5S)-130b</td>
</tr>
<tr>
<td>3</td>
<td>OTBDPS</td>
<td>CHO (R)-132</td>
<td>OTBDPS (R)-133</td>
<td>(2R,3S,5R)-130b</td>
</tr>
<tr>
<td>4</td>
<td>OTBDPS</td>
<td>CHO (R)-132</td>
<td>OTBDPS (R)-133</td>
<td>(2R,3S,5S)-130b</td>
</tr>
</tbody>
</table>

[a] Overall yields refer to pure, isolated products.

Table 3.18
Chapter 3. Silicon-based methodologies

![Chemical reaction diagram](image)

**Table 3.19**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylsilane</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-132b (1.0 eq)</td>
<td>OTBDPSCHO + TMSO + TMSOTf (0.1 eq)</td>
<td>-78°C, 5h</td>
</tr>
<tr>
<td>2</td>
<td>(R)-133 (1.05 eq)</td>
<td>OTBDPS + TMSOTf (0.1 eq)</td>
<td>-78°C, 5h</td>
</tr>
<tr>
<td>3</td>
<td>MeO₂C-TBDPS</td>
<td>TMSO + TMSOTf (0.1 eq)</td>
<td>-78°C, 5h</td>
</tr>
</tbody>
</table>

**Figure 3.8**

R¹ = CH₂CH₃
R² = CH(OTBDPS)CH₃

n.O.e

10%
3.3.3 Mechanistic study and the origin of the diastereoselectivity

Our interest in the mechanism of the Sakurai MCR reaction grew up as two main questions appeared during the study of the scope and limitations of this process.

The first question was why did the reaction proceed with none or very low diastereoselectivity in the case of primary and strained secondary alkyl trimethylsilyl ethers, in contrast to other secondary and tertiary alkyl silanes, for which one diastereoisomer is formed (Table 3.17).

Trying to shed some light on this question, we have decided to study the reaction mechanism of the Sakurai MCR process. Our working hypothesis, concerning the reaction mechanism, is based upon the expectation that the first role of the Lewis acid, TMSOTf, is the activation of the aldehyde ([S]-132b) (Scheme 3.40). Intermediate 358 then undergoes the addition of the silyl ether ([R]-133), furnishing intermediate 359. Migration of the silyl group proceeds via 360 and leads to the intermediate 361. It is important to point out that all these intermediates are believed to be in equilibrium. The desired compound (2S,3R,5R)-130b can arise from the intermediate 361 via two borderline mechanisms, SN1-like or SN2-like.

In the SN1-like mechanism, it is believed that the TMS2O group is displaced from the substrate prior to the addition of the allylsilane 131 onto oxocarbenium ion 362. On the other hand, in the SN2-type mechanism, the direct displacement of the good leaving group, TMS2O, by the allylsilane 131 is invoked. It was proposed that the reaction of allylsilane 131 with either intermediate 361 or oxocarbenium ion 362 might be the rate determining step of the reaction.
Before describing the study that focused on the question if an S_N1 or an S_N2-type mechanism operating in the Sakurai MCR reaction, we were curious to know if the stereoselectivity of the addition of the silyl ether (R)-133 on aldehyde (S)-132b had some influence on the establishment of the new stereogenic centre.
Indeed, the addition of a nucleophile to aldehyde (S)-132b is known to proceed via a Felkin-Anh transition state. Accordingly, the silyl ether (R)-133 should follow the pathway and generate predominantly the intermediate (2S,3R,5R)-358 (Scheme 3.41). This means that, in principle, kinetic resolution of a racemic mixture of 133 should be possible using (S)-132b.

To investigate this possibility, aldehyde (S)-132b was reacted with (±)-133 under the standard Sakurai MCR conditions (Scheme 3.42). If no selectivity is observed, all 4 diastereoisomers of 359 should be obtained and may react at the same rate. However, if one of these four diastereoisomers reacts much faster than the other three in the subsequent allylation step, a kinetic resolution favoring either (R) or (S)-133 might occur.
Thus, when aldehyde (S)-132b was treated with racemic silyl ether 133 and allylsilane 131, in the presence of catalytic amount of TMSOTf, desired adducts 130b were obtained in a 1.2:1 ratio (Table 3.20, Entry 1). Interestingly, if 2.1 equivalents of 133 were used, adduct (2S,3R,5R)-130b was formed as the major product in a 2.2:1 ratio (Table 3.20, Entry 2). When 5.1 equivalents of 133 were employed, the ratio increased even further to 4.0:1 in favor of (2S,3R,5R)-130b (Table 3.20, Entry 5).

At this stage it was decided to verify the postulated equilibrium between adducts 359. It was envisioned that if aldehyde (S)-132b and silyl ether 133 would be stirred in the presence of TMSOTf, a thermodynamic equilibrium should be established between the four intermediates 359. The delayed addition of allylsilane 131 should then reflect this situation by altering of the ratios between the adducts (2S,3R,5R)-130b and (2S,3R,5S)-130b.

Therefore, aldehyde (S)-132b was stirred with 2.1 equivalents of racemic silyl ether 133, in the presence of catalytic amounts of TMSOTf. To this
mixture, allylsilane 131 was added after 30 and 120 minutes, respectively (Table 3.20, Entries 3 and 4). As can be seen, a decrease in the reaction selectivity was observed. The same situation held true when 5.1 equivalents of 133 were used (Table 3.20, Entry 6).

Table 3.20

<table>
<thead>
<tr>
<th>Entry</th>
<th>133 [eq]</th>
<th>Time of allylsilane addition [min]</th>
<th>Yield [%]</th>
<th>(2S,3R,5R)-130b</th>
<th>(2S,3R,5S)-130b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.05</td>
<td>0</td>
<td>65</td>
<td>1.2:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.1</td>
<td>0</td>
<td>75</td>
<td>2.2:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>30</td>
<td>63</td>
<td>1.5:1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>120</td>
<td>52</td>
<td>1.4:1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.1</td>
<td>0</td>
<td>76</td>
<td>4.0:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5.1</td>
<td>30</td>
<td>65</td>
<td>3.5:1</td>
<td></td>
</tr>
</tbody>
</table>

In summary, the experiments presented in Table 3.20 suggest that there is a dynamic equilibrium between all the species generated prior to the allylsilane addition. The second information gleaned from these experiments is that the addition of 133 to 132b shows some match/mismatch effect, which decreases rapidly as the equilibrium is established between the various reactive intermediates.

As all the reactions prior to the addition of the allylsilane appear to be in equilibrium, it seems plausible to postulate that the addition of the allylsilane is the rate-determining step. Obviously, this means that all equilibria occur faster than the nucleophilic attack of the allylsilane.
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From the literature, it is known that the addition of allylsilanes to acetal-type intermediates never proceed by a concerted $S_N2$-type mechanism. However, on certain substrates, an $S_N2$-type mechanism accruing via close ion pair intermediates was observed. This particular mechanism was described and studied in detail by Scott Denmark et al. It was observed that in these specific cases, the stereogenic centre of the acetal was inverted during the allylsilane addition, furnishing the final adduct with opposite absolute configuration (Scheme 3.43). It was also noted that this mechanism was highly substrate, Lewis acid and solvent dependent, switching easily to the $S_N1$-type addition of the allylsilane to an oxocarbenium ion.

In our particular case, the $S_N2$ mechanism is highly improbable since $S_N2$-type reactions generally proceed on substrates which are not sterically encumbered. The same holds true if a close ion pair mechanism would be operating. From the stereochemical point of view, if an $S_N2$-type mechanism is operating, the configuration of the intermediate 361 has to be reflected in the final adduct(s). In other words, the configuration at C3 of 361, which is established during the addition of silyl ether 133 to aldehyde 132b, has to be inverted during the attack of allylsilane 131 (Scheme 3.44). According to the Felkin-Anh transition state, one can expect that the silyl ether 133 will

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preferentially add on aldehyde 132b to form (2S,3R,5R)-361. Intermediate (2S,3R,5R)-361 will then undergo allylsilane addition, affording the adduct (2S,3S,5R)-130b which should possess the opposite absolute configuration at the C3 stereogenic centre to the one which was experimentally observed. Moreover, if an S_N2-type mechanism is operational, the reaction of the primary alkyl silyl ether should proceed with the same or higher diastereoselectivity than in the case of secondary or tertiary ones. The opposite is true (Table 3.17).

All these observations strongly suggest that an S_N2-type mechanism is not operating in our case.

The second borderline mechanism is S_N1-type addition of the allylsilane to oxocarbenium ion 362. If the reaction mechanism follows this pathway, the configuration of the centre C3 in 361 created by the addition of silyl ether 133 to aldehyde 132b, is not important, since it will be destroyed during the formation of intermediate 362. The stereochemistry of the addition of 131 to
362 could then be based upon the Felkin-Anh transition state TS-2 due to the similarity between the activated aldehyde (TS-1) and the oxocarbenium ion 362 (Scheme 3.45).

The stereoselective formation of adduct 356a can be also explained via Felkin-Anh approach (Scheme 3.46). Indeed, the addition of allylsilane to oxocarbenium ion 362 according to the TS-2 will create the C3 centre of 356a with correct configuration. The stereoselective formation of the remaining C8 centre might be than rationalized on the bases of the addition of allylsilane to oxocarbenium ion 362 according to the open transition state TS-3.
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TS-2 can also explain the poor match/mismatch effect induced by the stereogenic centre present in the silyl ether part of the molecule, since this centre is rather remote from the approaching allylsilane trajectory (Bürgi-Dünitz trajectory). In contrast, TS-2 cannot explain the drop in the stereocontrol at the C3 position of 130, when primary silyl ethers are used (Table 3.17). If thus transpires that the steric hindrance created around the oxocarbenium ion 362 has to have some influence on the observed diastereoselectivity.

To evaluate the effect of the environment of the oxocarbenium ion 362 on the reaction’s selectivity, it was decided to investigate the effect of various solvents and Lewis acids.

Initially the solvent effect was studied. The reaction between aldehyde (S)-132b, silyl ether 133 and allylsilane 131 was chosen as a model system and CH$_2$Cl$_2$, CH$_3$CN, Et$_2$O and toluene as solvents. It was expected that polar solvents such as CH$_3$CN and Et$_2$O, could help in stabilizing the oxocarbenium ion. In contrast, non polar solvents, such as toluene should
favor the formation of the close ion pairs over the oxocarbenium ion. The results of these experiments are presented in Table 3.21.

Interestingly, whilst in polar solvents aldehyde 132b was completely consumed within 2h (Table 3.21, Entries 1-3), in toluene, full conversion of 132b was never reached, even when higher temperatures or prolonged reaction times were employed (Table 3.21, Entries 4 and 5). Surprisingly, better diastereocontrol at the C3 centre was observed when nonpolar solvents were used. In polar solvents, the ratio remained constant in throughout (Table 3.21, Entries 1-3).

![Chemical structure](chart)

Table 3.21

The influence of toluene on the diastereoselectivity of the reaction is rather obscure. Indeed, toluene as a non-polar solvent, should favor S_N2-type reaction. However, in this case, generally higher reaction rates are observed.\(^\text{161}\) The very slow and incomplete reactions observed in our case,

\(^\text{161}\) D. Bayston *PhD. Thesis.*
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suggest that, even in toluene, the reaction proceeds via an oxocarbenium ion, but one in which the TMS$_2$O or TfO’ are very closely associated. This increase in steric hindrance may result in enhanced facial discrimination. Since the nature of the counter ion might have a significant importance, it was decided to test other Lewis acids under otherwise similar reaction conditions (Table 3.22). The condensation of aldehyde 132b, silyl ether 353a or his hydroxy derivative 366 and allylsilane 131 was used as a model system.

Initially, it was verified that the free alcohol 366 could be used instead of the silyl ether 353a (Table 3.22, Entries 1 and 2). In this case, the adduct 354a was formed in approximately 20% lower yield. This observation is not surprising since it is expected that silylation of the hydroxyl group proceeds in situ prior to the coupling step.

Next, four stronger and four weaker Lewis acids were tested (Table 3.22, Entries 3-15). Surprisingly, none of the Lewis acids tested yielded the adduct 354a, regardless if the silyl ether 353a or the alcohol 366 was used. In the reactions mediated by the strong Lewis acids, such as Et$_2$O.BF$_3$, Et$_2$AlCl, SnCl$_4$ or TiCl$_4$, only the hemiacetal 365 was formed (Table 3.22, Entries 3-10). When weaker Lewis acids were employed, no reaction was observed (Table 3.22, Entries 11-15).

This observation strongly suggests that the formation of TMS$_2$O is a prerequisite for a successful coupling. Another explanation could be that TMS$_2$O group is a much better leaving group than any other L.A.-OTMS complex which is formed when Lewis acids other than TMSOTf are employed.
Finally, NMR studies of the condensation between aldehyde 132b, silyl ether 133 and allylsilane 131 were conducted. Initially, the addition of aldehyde 132b to silyl ether 133, in the presence of TMSOTf (0.1 eq), was studied (Figure 3.9). Figure 3.9 shows that an equilibrium between aldehyde 132b, silyl ether 133 and some intermediates was established within 20 min. The amount of unreacted aldehyde 132b remains constant after this time. The olefinic region between 4.5 ppm and 5 ppm also displays a large number of Lewis acid entries. The table below shows the conversion of (S)-132b and the formation of 354a:365.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid [eq]</th>
<th>R</th>
<th>Conv. of (S)-132b [%]</th>
<th>354a:365</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf (0.1)</td>
<td>TMS</td>
<td>&gt;98</td>
<td>7:1</td>
</tr>
<tr>
<td>2</td>
<td>TMSOTf (1.1)</td>
<td>H</td>
<td>&gt;98</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O.BF₃ (1.1)</td>
<td>H</td>
<td>&gt;98</td>
<td>0:100</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O.BF₃ (1.1)</td>
<td>TMS</td>
<td>&gt;98</td>
<td>0:100d</td>
</tr>
<tr>
<td>5</td>
<td>Et₂AlCl (1.1)</td>
<td>H</td>
<td>&gt;98</td>
<td>0:100</td>
</tr>
<tr>
<td>6</td>
<td>Et₂AlCl (1.1)</td>
<td>TMS</td>
<td>&gt;98</td>
<td>0:100d</td>
</tr>
<tr>
<td>7</td>
<td>SnCl₄ (1.1)</td>
<td>H</td>
<td>&gt;98</td>
<td>0:100</td>
</tr>
<tr>
<td>8</td>
<td>SnCl₄ (1.1)</td>
<td>TMS</td>
<td>&gt;98</td>
<td>0:100d</td>
</tr>
<tr>
<td>9</td>
<td>TiCl₄ (1.1)</td>
<td>H</td>
<td>&gt;98</td>
<td>0:100</td>
</tr>
<tr>
<td>10</td>
<td>TiCl₄ (1.1)</td>
<td>TMS</td>
<td>&gt;98</td>
<td>0:100d</td>
</tr>
<tr>
<td>11c</td>
<td>Bi(O Tf)₃ (1.1)</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12c</td>
<td>Bi(O Tf)₃ (1.1)</td>
<td>TMS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13c</td>
<td>Sc(O Tf)₃ (1.1)</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14c</td>
<td>Sc(O Tf)₃ (1.1)</td>
<td>TMS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15c</td>
<td>Yb(O Tf)₃ (1.1)</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.22

---

[a] All reactions were performed in CH₂Cl₂ (0.05M)
[b] Determined by GC.
[c] Reaction was stirred at r.t. for additional 24h.
[d] 5 to 15% of Sakurai product was formed.
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of signals, suggesting the formation of several intermediates (Figure 3.10). The $^1$H-NMR spectrum of the silyl ether (R)-133 is shown in Figure 3.11.

However, a totally different situation occurred when TMSOTf was added to the mixture of aldehyde 132b, silyl ether 133 and allylsilane 131. In this case the rapid disappearance of the aldehyde signal at ~9.8 ppm was observed. This observation suggests that the equilibrium, established between aldehyde 132b, silyl ether 133 and theirs adducts, leads to a reactive species which is quickly transformed into the desired adduct. Since it was observed that the reaction of TBDPS-bearing aldehyde 132b proceeds faster than the TBS-containing aldehyde 132a, an additional study of the aldehyde 132a was performed (Figure 3.13).

To our great surprise, when the TBS-bearing aldehyde 132a was used, full conversion was not observed even after 1h (Figure 3.14). The difference in the reaction rate between aldehyde 132a and 132b is magnified in this NMR study as compared to Table 3.16, because the concentration employed during the NMR study was 0.05M instead of 0.5M, used in the case of experiments presented in Table 3.16.

Disappointingly, in none of our experiments, were we able to detect the postulated oxocarbenium ion 159.
Figure 3.9
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Figure 3.10

Figure 3.11
Figure 3.12
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Figure 3.13
3.4 Conclusions

In summary, we have described the first chiral aldehyde-based Sakurai MCR, furnishing the coupled products in good to excellent yields (67-87%) and with complete diastereoccontrol in the case of secondary and tertiary silyl ethers. It was demonstrated that various allylsilanes and silyl ethers are tolerate in this reaction.

It was postulated that the observed diastereoselectivity originates from the addition of the allylsilane on an oxocarbenium ion, according to the Felkin-Anh transition state (Figure 3.15). This model can be generalized for secondary and tertiary silyl ether, but it fails in the case of the primary silyl ethers.
Our mechanistic studies suggest that, in the case of the secondary and tertiary silyl ethers, the reaction is proceeding via an oxocarbenium ion, whereas in the case of the primary silyl ethers the situation is more complicated and probably more that one reaction pathway is followed. Interestingly, we have observed that the steric environment created around the aldehyde-silyl ether adduct is important for the selectivity of the reaction. From the $^1$H-NMR studies, it is obvious that the reaction of the less sterically crowded TBS-aldehyde $132a$ proceeds more slowly than with TBDPS-bearing aldehyde $132b$.

To our great surprise, it was observed that TMSOTf is the only Lewis acid that was able to promote the three component coupling. These observations suggest that the reaction requires a good leaving group that does not complex with other substrates and/or is rather bulky. Nevertheless, the role of TMS$_2$O in the reaction mechanism is still unclear at this stage.

### 3.5 Perspectives

From the scope and limitations point of view, the role of the allylsilane and silyl ether parts has been established but the role of aldehyde part remains undefined. Thus, it is important to test the steric and electronic influence of the aldehydic R chain on the yield and selectivity of the reaction (Figure 3.16). Additionally, it would be interesting to see if another heteroatom, such
as S or N, might be tolerated instead of the TBS or TBDPS-protected oxygen, under the reaction conditions. Finally, it would be useful to know if ketone \ref{369} can be used instead of an aldehyde \ref{367}. In this case a quaternary stereogenic centre would be generated. It is noteworthy that general and stereoselective routes to quaternary stereogenic centers are rather rare.

![Figure 3.16](image)

Even the products obtained so far via the Sakurai MCR reaction might be further developed. We have already shown that the products of the condensation might be transformed into dihydropyrans of the general structure \ref{371} (Scheme 3.47).

Additionally, OTBDPS group can be, after the protecting group deprotection, transformed into phenylsulfid, halogen or the stereochemistry of the centre might be just inverted via Mitsunobu reaction. However more possibilities offers the transformation of the adduct \ref{370} to ketone \ref{373}. Ketone function in \ref{373} can be used in various olefination reactions (Julia olefination, Ti-based olefinations,…), can be transformed into epoxide \ref{376} via Corey-Tchaykovsky reaction or can be transformed into the kinetic enolate \ref{374}. Depending on the nature of [M] in \ref{374}, enolate can be further used in the aldol reaction (Mukaiyama aldol reaction (M = TMS),…), ozonolysis of electron rich enol ether should furnish acid \ref{378} and finally, if [M] = Tf, Pd or Fe-mediated coupling can be attempted.
The same operations might be attempted on the dihydropyran 371 furnishing a highly functionalized dihydropyrans. Some examples of these structure modifications are shown in Figure 3.17.
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Figure 3.17
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4. Sulphur-based methodologies

Sulphur has been known in its uncombined form since prehistoric times. The first record referring to sulphur can be found in the legendary destruction of Sodom and Gomorrah by brimstone. One of the most recent discoveries is the detection of sulphur (together with H₂SO₄) as a major component in the atmosphere of the planet Venus.

Sulphur is the 16th most abundant element on the Earth (twice more than carbon). Most of the sulphur is converted, via SO₂/SO₃, into sulphuric acid. Additionally, sulphur and its derivatives are used in the rubber vulcanization, petrol refining, paints, pigments, steel picking, detergents, explosives, synthesis of various drugs, insecticides and fungicides, paper manufacturing and cellulose modification.

From the reactivity point of view, sulphur unites directly with all elements except the noble gases, nitrogen, tellurium, iodine, iridium, platinum, and gold. The enhanced affinity of sulphur for most of the transition metals makes the sulphur-containing chiral molecules excellent ligands for asymmetric catalysis.

In organic synthetic chemistry, alkyl and aryl sulfides, sulfoxides and sulfones, as well as heteroaromatic molecules containing-sulphur, occupy a paramount position. A wide variety of very specific transformations such

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162 Genesis 19, 24.
163 (a) http://www.nasa.gov/worldbook/venus_worldbook.html.
   (b) http://www.solarviews.com/eng/venus.htm.
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as the Pummerer rearrangement,\textsuperscript{166} the Corey-Tchaykovski reaction,\textsuperscript{167} the Ramberg-Bäcklund contraction\textsuperscript{168} or the Julia olefination method\textsuperscript{169} would not be possible without it (Scheme 4.1).

![Scheme 4.1](image)

What makes the sulfur atom so special? By varying the oxidation state of the sulfur atom (sulfide-sulfoxide-sulfone), the acidity of the hydrogen atom $\alpha$ to sulfur is increasing simultaneously with the anion stability (Table 4.1).\textsuperscript{170} Additionally, sulfides can be alkylated by common electrophiles, furnishing

\textsuperscript{166} Magnus, P.D. \textit{Tetrahedron} 1977, 33, 2019.
\textsuperscript{167} Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. \textit{Tetrahedron} 1987, 43, 2609.
sulfonium salts.\textsuperscript{171} These salts can be used as extremely soft alkylating agents, but more importantly, the deprotonation $\alpha$ to sulfur leads to the formation of the very useful sulfur ylides.\textsuperscript{167}

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>pKa (DMSO)</th>
<th>Remarque</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_3\text{C}-\text{S}-\text{CH}_3$</td>
<td>Sulfide</td>
<td>(45)</td>
<td>$\text{CH}_4$ (pKa ~56)</td>
</tr>
<tr>
<td>$\text{H}_3\text{C}-\text{S}=\text{CH}_3$</td>
<td>Sulfoxide</td>
<td>~35</td>
<td>$\text{NH}_3$ (pKa ~41)</td>
</tr>
<tr>
<td>$\text{H}_3\text{C}=\text{S}=\text{CH}_3$</td>
<td>Sulfone</td>
<td>~31</td>
<td>$\text{H}_2\text{O}$ (pKa 31)</td>
</tr>
<tr>
<td>$\text{Me}\uparrow\downarrow\text{S}\uparrow\downarrow\text{Me}$</td>
<td>Sulfonium salt</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>$\text{H}_3\text{C}=\text{S}^\ominus\text{CH}_3$</td>
<td>Oxo-sulfonium salt</td>
<td>18.2</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1

In this chapter, our main interest will be focused on sulfones and sulfoxides and their use in the Julia olefination reaction.

### 4.1 Julia olefination – An introduction

The formation of C-C double bonds is one of the most important transformations in organic synthesis since alkenes are present in a wide range of biologically active natural products and they are useful substrates for numerous subsequent functionalisations. Thus, the reactions leading to

the formation of novel olefin linkages between two molecules are highly
important and the Julia reaction\textsuperscript{172} owns a prominent place in this field.
The Julia olefination is a two step process embodying a condensation and a
reductive elimination. Thus, the coupling between an anion $\alpha$ to a sulfone
residue 395 and a carbonyl compound 396, generated the $\beta$-hydroxysulfone
397, which undergoes a reductive elimination to afford the alkene 398
(Scheme 4.2).

\begin{center}
\begin{tikzpicture}
\t\node [draw, rectangle, inner sep=0.5cm] (a) {$R^3\text{SO}_2\text{Ar}$};
\t\node [draw, rectangle, inner sep=0.5cm, right of=a] (b) {$R^4\text{R}^1\text{R}^2\text{OH}$};
\t\node [draw, rectangle, inner sep=0.5cm, right of=b] (c) {$R^2\text{R}^1\text{R}^3\text{R}^4$};
\t\node [draw, rectangle, inner sep=0.5cm, right of=c] (d) {$R^3\text{R}^1\text{R}^2\text{398}$};
\t\node [draw, rectangle, inner sep=0.5cm, right of=d] (e) {Reductive
\t\text{Elimination}};
\t\node [draw, rectangle, inner sep=0.5cm, right of=e] (f) {$R^3\text{R}^1\text{R}^2\text{397}$};
\t\draw [-] (b) -- (c);
\t\draw [-] (c) -- (d);
\t\draw [-] (d) -- (e);
\t\draw [-] (e) -- (f);
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{Scheme 4.2}
\end{center}

After the initial condensation, derivatisation of the $\beta$-hydroxysulfone 397
can lead to useful products. For instance, functionalisation or activation of
the hydroxyl group of 397 often facilitates the reductive elimination to 398.
Moreover, when the sulfone is either primary ($R^3\text{=}R^1\text{=H}$) or secondary ($R^4$
or $R^3\text{= H}$), elimination, to provide the useful vinyl sulfones 400, can easily be
induced from 397 or 399 (Scheme 4.3).

\begin{flushright}
\end{flushright}
4.1.1 Coupling step – Towards β-hydroxysulfone derivatives

The disconnection of a C=C double bond into two fragments via a retro-Julia reaction offers two complementary possibilities. Each subunit can alternatively be chosen as either the carbonyl compound or the sulfone derivative (Figure 4.1). The choice is often made after considering several aspects of the connective step in order to avoid potential problems.

Figure 4.1

Typical factors that should be taken into account are the nature and number of substituents of the sulfone-bearing fragment, the nature of the counter-ion and the nature and reactivity of the carbonyl compound – aldehyde or ketone – generated by this disconnection. The careful choice of the disconnection
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can considerably influence the reaction yield of the sequence and the $E/Z$-selectivity of the olefin.

4.1.1.1 Terminal olefins

Since both possible C-1 fragments coming out of the two different disconnections are generally commercially available (e.g. MeSO$_2$Ph and HCHO), the choice of the path $a$ or $b$ depends upon the synthetic accessibility of the opposite coupling partner. Regardless to the chosen C-1 fragment, the olefination reaction leading to terminal olefins is generally easy and proceeds with very high yields. An example of such a reaction is presented in Scheme 4.4.$^{173}$

4.1.1.2 1,2-disubstituted olefins

Similarly to the terminal olefins, 1,2-disubstituted alkenes are easily prepared by the Julia method. However, in this case, the $E/Z$-selectivity has to be controled. Depending upon the conditions of the reductive elimination, the $E/Z$-selectivity can be modulated. However, in general, $E$-olefins are

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usually easier to obtain. This stereocontrol will be discussed in greater details in chapter 4.1.2 which deals with the reductive elimination.

Excluding special cases, 1,2-disubstituted olefins are easily generated using a Julia sequence, since the sulfone derivative is unhindered and the carbonyl compound, an aldehyde, is often reactive enough to minimize retrograde fragmentation to the starting materials. This retro-aldol-type reaction is commonly encountered under the basic conditions required for the initial addition of the sulfone anion to the carbonyl moiety (Scheme 4.5).

```
BnSO₂OH -> base -> BnSO₂Me + MeCHO
```

Scheme 4.5

However, care must be taken when particularly well stabilized α-sulfonyl carbanions are used. Indeed, the conjugation or chelation of the anion with a proximal heteroatom can favor the reverse addition. There are several solutions to this problem. For instance, varying the nature of the counter anion can efficiently shift this unfavorable equilibrium. Thus, replacing lithium by magnesium or using a lithiated sulfone/boron trifluoride combination has proved to be effective. Two examples, illustrating these approaches are shown in Scheme 4.6.

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Another possibility is to shift the equilibrium in favor of the desired adduct by trapping the in situ generated β-alkoxy sulfone by Ac₂O, BzCl, MsCl or TMSCl. Interestingly, the derivatized β-hydroxy sulfone generally reacts better in the following reductive elimination step (see later).

Another serious problem accompanying the addition reaction is the competitive enolization of the carbonyl derivative. As a consequence, a large amount of recovered starting material can be obtained after the reaction. Generally, changing of the solvent to more polar one suppresses the undesired enolization of the starting carbonyl compound.  

Scheme 4.6


4.1.1.3 Trisubstituted olefins

To achieve the smooth formation of trisubstituted olefins by the Julia olefination, a correct choice of the coupling partners has to be made. Disappointingly, both possible disconnections suffer from some shortcomings.

For example, addition of an aldehyde $\text{416}$ to a secondary $\alpha$-sulfonyl carbanion $\text{402}$ (path $\text{a}$) may lead to undesirable enolisation, whilst condensation between a more reactive primary sulfone $\text{419}$ and a ketone $\text{396}$ (path $\text{b}$) is usually plagued by retroaldolisation (Scheme 4.7).

![Scheme 4.7](image)

To avoid the addition to ketones, path $\text{a}$ is often preferred. If the ketone is used as the carbonyl partner, the equilibrium of the reaction between $\text{396}/\text{419}$ and $\text{420}$ strongly disfavours the desired adduct $\text{420}$. To overcome this problem, the trapping protocols mentioned above have to be used.

An
example of this strategy, developed in our laboratory, is shown in Table 4.2.\textsuperscript{179}

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
Entry & R\textsuperscript{1} & R\textsuperscript{2} & R\textsuperscript{3} & Yield (%)\textsuperscript{a} \\
\hline
1 & nC\textsubscript{6}H\textsubscript{13} & PhCH\textsubscript{2}CH\textsubscript{2} & CH\textsubscript{3} & 81 \\
2 & CH\textsubscript{3} & PhCH\textsubscript{2}CH\textsubscript{2} & CH\textsubscript{3} & 82 \\
3 & CH\textsubscript{3} & nC\textsubscript{6}H\textsubscript{13} & CH\textsubscript{3} & 93 \\
\hline
\end{tabular}
\caption{Table 4.2}
\end{table}

An alternative generation of β-hydroxy sulfones was discovered by Falck and Mioskowski.\textsuperscript{180} In this case, the bissulfone \textbf{423} was treated by a solution of SmI\textsubscript{2}. The reducing power of SmI\textsubscript{2} caused the cleavage of one of the C-S bonds, furnishing the corresponding anions, which then added on aldehydes or ketones. It is expected that the Sm\textsuperscript{III} salts, generated during the reaction, act as a strong Lewis acid (activation of the ketone) and form a tightly bound cationic complex with the initially generated alkoxide, thus preventing the retroaldol reaction (Scheme 4.8).

\begin{scheme}[h]
\centering
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{423}};
\node (b) at (2,0) {1. 3 eq. SmI\textsubscript{2}, THF, r.t., 15 min};
\node (c) at (4,0) {\textbf{424}, 77\%, ax: eq = 4:1};
\node (d) at (0,-1) {\textbf{424}};
\node (e) at (2,-1) {2. O\textsubscript{t}Bu, nPr, SO\textsubscript{2}Ph, SO\textsubscript{2}Ph};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\end{tikzpicture}
\caption{Scheme 4.8}
\end{scheme}


4.1.1.4 *Tetrasubstituted olefins*

As might be obvious from the results discussed above, the coupling reactions between secondary \(\alpha\)-branched sulfonyl carbanions and ketones are rather difficult and, therefore, rarely encountered in the literature.\(^{181}\) The yields of the desired coupling products, the \(\beta\)-hydroxy sulfones, are generally below 5%.

The only exception in this field is the method reported by Falk and Mioskowsky.\(^{180}\) In this case, the expected tetrasubstituted \(\beta\)-hydroxy sulfones are prepared in excellent yield (Scheme 4.9).

![Scheme 4.9](image)

4.1.2 *Reductive-elimination step*

Since 1973, most of the improvements concerning the Julia olefination sequence have been directed towards the reductive elimination steps. Before 1990, this reaction was mostly effected using Na(Hg) amalgam. However, examples involving other reducing agents had already been reported, such as RMgX/Pd, Fe or Ni catalyst;\(^{182}\) \(\text{Bu}_3\text{SnH}\);\(^{183}\) \(\text{Li naphtanelide}\);\(^{184}\) \(\text{Li or Na in}

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liquid ammonia or in ethylamine;\textsuperscript{185} Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4};\textsuperscript{186} Raney Nickel;\textsuperscript{187} Potassium graphite;\textsuperscript{188} electroreductive reactions;\textsuperscript{189} Te/NaBH\textsubscript{4};\textsuperscript{190} Al(Hg) amalgam and LiAlH\textsubscript{4}, with or without CuCl\textsubscript{2}.\textsuperscript{191} In 1990, Kende successfully applied samarium diiodide to the reductive elimination of β-hydroxy imidazolyl sulfones.\textsuperscript{192} Subsequently, Inanaga\textsuperscript{193} and Künzer\textsuperscript{194} highlighted the crucial role of HMPA in reductive desulfonylation. Since then, the combination of SmI\textsubscript{2}/HMPA or SmI\textsubscript{2} with various additives\textsuperscript{195} has continued to prove its usefulness.\textsuperscript{196} In addition, other reductive methods are regularly reported, such as the use of Mg/HgCl\textsubscript{2},\textsuperscript{197} NaTeH\textsubscript{4} and sulfoxide – alkyl lithium combinations.\textsuperscript{198}

\textsuperscript{194} Huang, X.; Pi, J.; Huang, Z. Heteroatom Chem. 1992, 535.
4.1.2.1 β-Hydroxy sulfones

Already in the first paper describing the reaction that bears its name, Julia et al. explored the reductive-elimination of a wide range of functionalities. Reduction of vinyl sulfones and reductive-elimination of vicinal hydroxyl-, acetyl-, mesyl- and tosyl sulfones, to afford the corresponding alkene, were carried out using Na(Hg) in MeOH. It was observed that the yields of the desired olefins were always higher when any other group than a free β-hydroxyl was employed (Scheme 4.10).

![Scheme 4.10](image)

The expected reaction mechanism is shown in Scheme 4.11. First, due to the basicity of the Na(Hg)/MeOH system (MeONa is always presented), the alkoxide 432 is formed and the retrograde fragmentation to 429 and 430 takes place. In fact, this fragmentation is generally believed to be responsible for the low yields of the reductive-elimination step using this system.

Then, the sodium, which serves as one electron donor, transfers an electron to the sulfone residue and generates a radical anion which collapses (liberates PhSO$_2^-$), leading to the radical species 433. Over-reduction of 433

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by another equivalent of sodium results in the formation of the anion 434. Vicinal antiperiplanar elimination of Na₂O and/or NaOH (since Na₂O is a rather poor leaving group, it is expected that the alkoxy anion might be trapped by the proton source, liberating NaOH) affords the olefin 435. The required anti arrangement of the intermediate 434 was proven by several carefully controlled experiments.²⁰²

From the stereochemistry of the elimination step, it is obvious that the generated anionic species are neither configurationally nor conformationally stable and that a dynamic equilibrium is rapidly established between intermediates 438 and 441. The initially formed radical intermediate 437

also equilibrates rapidly, adopting an overall planar – or at least little pyramidalised – structure and the elimination proceeds according to the Hammond’s postulate. In general, 1,2-disubstituted olefins produced under these conditions possess predominantly the $E$ configuration (Scheme 4.12). More substituted olefins are usually obtained as a mixture of $E$/Z isomers.

Scheme 4.12

In 1990, Kende et al. introduced SmI$_2$ as a non-basic equivalent of Na(Hg) in MeOH. In this case, higher yields are generally observed (Scheme 4.12).
4.13). It is believed that the greater efficiency of the SmI$_2$-based protocol is due to the change in the nature of the leaving group (presumably HOSmI$_2$) and the absence of the retro-addition reaction; no $\beta$-alkoxide intermediate being generated under these conditions.

![Scheme 4.13](image)

**Scheme 4.13**

4.1.2.2 Leaving group $\beta$ to sulfones

The derivatization of the $\beta$-hydroxy sulfones to $\beta$-substituted oxy sulfones is always beneficial in the Julia olefination reaction. The first benefit is obtained during the coupling step, since the desired alkoxy adduct is trapped in situ and the equilibrium of the reaction is shifted towards the formation of the product (see chapter 4.1.1).

Secondly, the absence of the free hydroxyl group suppresses the retrograde aldol reaction, which might occur in the presence of a base during the reductive-elimination step.

From a mechanistic viewpoint, only the reductive-elimination of $\beta$-acetoxy sulfones with Na(Hg) or SmI$_2$ has been investigated so far. The deuterium labelling experiments designed by Keck et. al., surprisingly revealed that the mechanism of the $\beta$-acetoxy sulfones reductive-elimination differs depending upon the reductant employed.$^{204}$

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In the case of SmI\textsubscript{2}-mediated reductive-elimination, the reaction proceeds according to the mechanism postulated for the \(\beta\)-hydroxy sulfones (Scheme 4.11).

However, if the Na(Hg)/MeOH system is used, it was observed that the base-mediated elimination of the acetate group took place rapidly, leading to the vinyl sulfone 447 (Scheme 4.14).

![Scheme 4.14](image)

The resulting vinyl sulfone 447 is then reduced to the vinyl radical 449. Rapid equilibration between the \(E\) and \(Z\)-forms 449 and 450 then ensues. Further reduction of the most favoured \(E\)-isomer to the configurationally stable vinyl anion 451, followed by subsequent protonation, yields the olefin 452 as a major isomer. This mechanism nicely rationalizes the high stereoselectivity generally observed if the Na(Hg)/MeOH-system is used (Scheme 4.15). It also accommodates the presence of one deuterium atom in the final olefin when the reductive-elimination is performed in deuterated methanol.
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\[ \text{Scheme 4.15} \]

4.1.2.3 Reverse reduction order

So far, all the reductive-eliminations of β-alkoxy sulfones always implied the initial fragmentation of the C-S bond. Thus, in all cases, the initial single electron transfers to the sulfone moiety. It was reasoned that, by a suitable modification of the β-hydroxy substituent, an inverse process could be introduced. In other words, a functional group with a lower reduction potential than a sulfone was searched.

The generation of a radical α to a sulfonyl group, followed by elimination of \(\text{ArSO}_2\cdot\), was initially reported by Lythgoe et al. using the Barton-McCombie deoxygenation of the corresponding aryl sylfonyl radical.\(^{205}\) Later on, Williams et al. reported high yields for olefination employing the methyl xanthate derivatives of β-hydroxy sulfones.\(^{206}\)

In 1996, Markó et al. described a reverse Julia olefination of β-sulfoxybenzoates using the SmI\(_2\)/HMPA system.\(^{207}\) Based upon the enormous differences in rate for the formation of the same alkene, starting


either from the β-hydroxy sulfone 459 or from the corresponding β-sulfoxybenzoate 455, they proposed the following mechanism (Scheme 4.16).

After a single electron transfer from SmI₂ to 455, it is believed that the radical anion is located on the benzoate moiety of 456. The intermediate 456 decompose to PhCO₂⁻ and the radical species 457, which is then over-reduced by another equivalent of SmI₂, leading to the olefin 435, after elimination of PhSO₂SmI₂.

In the case of the β-hydroxy sulfone 459, the reduction proceeds by the conventional way. Thus, the radical anion is located onto the sulfone moiety and its decomposition generates radical 461 and PhSO₂⁻. Olefin 435 is again generated, but the elimination proceeds by the opposite sense.

Scheme 4.16
4.1.3 Second generation Julia olefination

When in 1991 Sylvestre Julia reported\(^{208}\) the direct synthesis of olefins from carbonyl compounds and lithiated heterocyclic sulfones, a new generation of Julia olefination was born (Scheme 4.17).\(^{209}\) The advantage of this novel method is that the formation of the olefin proceeds immediately after the addition of the \(\alpha\)-sulfonyl carbanion 463 to aldehyde 464. Indeed, the intermediate \(\beta\)-alkoxy sulfone 465 undergoes a cascade of reactions involving the addition of the alkoxide anion to the sulfone residue to generate the spiro derivative 466, which breaks down to afford the sulenate anion 467. Final elimination of SO\(_2\) and of the alkoxide moiety 469 furnishes the desired olefin 435.

\[ \text{Scheme 4.17} \]


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Sylvestre Julia et al. also found that the elimination reaction proceeded in a stereospecific manner.\textsuperscript{208c} Indeed, the syn-\(\beta\)-hydroxy-BT-sulfone, \textit{syn-470}, yields the corresponding Z-alkene \textit{471}, the \textit{anti-}\(\beta\)-hydroxy-BT-sulfone, \textit{anti-470}, affords the \textit{E}-olefin \textit{471} exclusively (Scheme 4.18). More interestingly, it was observed that the elimination of the \textit{syn}-isomer is much faster than that of the \textit{anti}-isomer.

\[
\text{SO}_2\text{BT} \text{C}_6\text{H}_{13} \quad \text{OTBS} \quad \text{H}_2 \text{C}_6 \text{H}_{13} \quad \text{OTBS}
\]

\begin{align*}
\text{syn-470} & \quad \text{TBAF 10 eq., THF} \\
& \quad 0^\circ\text{C to } 18^\circ\text{C, 18 h.} \\
& \xrightarrow{} \text{Z-471, 92\%, E/Z } >99:1
\end{align*}

\[
\text{SO}_2\text{BT} \text{C}_6\text{H}_{13} \quad \text{OTBS} \quad \text{H}_2 \text{C}_6 \text{H}_{13} \quad \text{OTBS}
\]

\begin{align*}
\text{anti-471} & \quad \text{TBAF 10 eq., THF} \\
& \quad 0^\circ\text{C to } 18^\circ\text{C, 18 h.} \\
& \xrightarrow{} \text{E-471, 56\%, E/Z } >99:1
\end{align*}

\textbf{Scheme 4.18}

A plausible explanation for the stereospecificity and the difference in the reaction’s rate is shown in Scheme 4.19.\textsuperscript{208c} In the case of \textit{syn-465}, \(R^1\) and \(R^2\) are in an \textit{anti} relationship during the transfer of the BT moiety (intermediate \textit{472b}). However, in the case of \textit{anti-465}, \(R^1\) and \(R^2\) are in a \textit{syn} relationship. As a consequence, the resulting destabilizing gauche interaction increases the relative energy of \textit{472a} over \textit{472b} and results in the slower reaction rate. The main drawback of the BT sulfones lies in the dual nucleophilic-electrophilic character of the \(\alpha\)-sulfonylcarbanion \textit{463}. Thus, this anion could react not only with carbonyl compound but also with itself, generating undesired homocoupling by-products. As a consequence, only the “Barbier-type” conditions could be generally used for the Silvestre-Julia coupling (using BT-SO\(_2\)-R reagent).
To overcome this problem, Kociensky et al. introduced in 1998 two new heterocyclic sulfones: the 1-phenyltetrazoyl (PT) and the 1-tert-butyltetrazoyl (TBT) substituents (Figure 4.2).\textsuperscript{210} These groups proved to be superior to the BT moiety in terms of the reaction’s yield (mainly PT group) and stereoselectivity. It appears that the PT and the TBT-bearing sulfones are far less prone to self condensation than the BT-bearing sulfones. The 2-sulfonylpyridine moiety (PYR) is another group commonly used in 2\textsuperscript{nd} generation Julia olefinations (for its use see later).

\textsuperscript{210} Blakemore, P.R.; Cole, W.J.; Kocienski, P.J.; Morley, A. Synlett 1998, 26.
In the meantime, an important influence of the nature of the counter-ion and of the solvent on the control of the olefin \( E/Z \)-ratio was observed. An example is presented in Table 4.3. Based upon the various examples known in the literature, these effects could be generalized (Figure 4.3). Since it is known that the elimination reaction is stereospecific, the olefin \( E/Z \) ratio is determined during the addition of the \( \alpha \)-sulfenyl carbanion to the carbonyl compound. Thus, the polarity of the solvent and the size of the counter-ion can influence the TS of the addition. A non-polar solvent and a small counter-ions (Li) will favor the closed transition state, by reinforcing the intramolecular coordination in the TS. In contrast, polar solvents and a large counter-ion should favor an open, non-chelating TS such as.

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At this stage, it is necessary to point out that this generalization is valid only for the BT and PT groups. In the case of the PYR and TBT group, the Z-selectivity is generally favored over the E-selectivity. The counter-ion and the solvent effects are the same as before, but their magnitude is less important. This is due to the steric (TBT) and electronic (PYR) properties of the TBT and PYR sulfones that strongly favor closed (chelated) TS during the coupling step.

### Table 4.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>E/Z&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHMDS</td>
<td>DMF</td>
<td>3.5:1</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>THF</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>toluene</td>
<td>1:10</td>
</tr>
<tr>
<td>4</td>
<td>KHDMDS</td>
<td>THF</td>
<td>1.2:1</td>
</tr>
<tr>
<td>5</td>
<td>KHDMDS</td>
<td>toluene</td>
<td>1:3.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratio determined by <sup>1</sup>H-NMR
4.1.4 Sulfoxides and Julia olefination

At the end of this short overview concerning the Julia olefination, the role of the sulfoxides, as sulfone alternatives, will be discussed. Sulfoxides were used initially by Durst et al. in 1973 (Scheme 4.24). Both the coupling step and the NCS-mediated reductive elimination proceeded in excellent yields, affording the desired olefin in 91% overall yield.

Surprisingly, this reaction was forgotten and the next example using sulfoxides in the Julia olefination reaction was reported approximately a

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quarter of century later. In 1998, Satoh et al.\textsuperscript{213} decided to use the sulfoxides in place of the sulfones because they believed that the greater reactivity of the anion $\alpha$ to the sulfoxide, as compared to a sulfone,\textsuperscript{214} would lead to improved yields in the condensation with aldehydes and especially ketones (Table 4.4). Furthermore, the higher energy of these anions should strongly disfavor retroaldolization reaction. The coupling step proceeded as expected and the desired $\beta$-hydroxyl sulfoxides 481 and 482 were produced in good to excellent yields.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {478};
  \node (b) at (2,0) {Ph\;\text{Ph}};
  \node (c) at (1.5,0) {Li\;tBuS};
  \node (d) at (3,0) {479, 95\%};
  \node (e) at (4.5,0) {480, 96\%};

  \draw[->] (a) -- node[above] {1) $t$BuLi} (b);
  \draw[->] (b) -- node[above] {2) H$_2$O} (d);
  \draw[->] (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.20}

The problem in Satoh’s approach lies in the elimination step. After mesylation of 482 and 483, the corresponding $\beta$-mesyloxy sulfoxides 484 were submitted to an alkyl metal-mediated ($t$BuLi, $n$-BuLi or EtMgBr) elimination. Thus, despite the fact that the elimination of the $\beta$-mesyloxy sulfoxides 484 yielded the desired olefins 485 in high yields and with a good double bond selectivity (Scheme 4.21), the use of an excess of very strong bases made it incompatible with most of the common functional groups presented in organic substrates.


\textsuperscript{214} For the pKa of the hydrogen $\alpha$ to sulfone and $\alpha$ to sulfoxide, see Table 4.1
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**Table 4.4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>&lt;chem&gt;Ph&lt;/chem&gt;</td>
<td>&lt;chem&gt;Ph&lt;/chem&gt;</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after silica gel column chromatography

**Scheme 4.21**

The reductive-elimination of the β-mesyloxy sulfoxides 484 deserves some comments. First, the reductive elimination can be a priori described by two pathways (Scheme 4.22). The first one involves the direct β-elimination of the sulfinyl and mesyloxy groups via a sulfoxide-metal exchange (path a) whilst the second one would involve a two-step mechanism transiting through the initial formation of a vinyl sulfoxide 486, generated by the base-
catalysed elimination of the mesylate leaving group. Subsequent sulfoxide-metal exchange would then lead to the vinyl anion 487 which is protonated, affording the desired alkene 485 (path b). Based on the deuterium-labelled studies, Satoh et al. postulated that the reaction proceeded via path a.

It is also interesting to note that this elimination is highly stereoselective and that the geometry of the newly formed olefin depends upon the relative configuration of the β-hydroxysulfoxide. Thus, if anti-488 was subjected to n-BuLi-mediated reductive elimination, E-489 was preferentially formed. In contrast, if syn-488 was used, then Z-489 was generated as the major product. The influence of additional stereogenic centers present on the sulfur atom on the stereoselectivity of the reaction was not studied (Scheme 4.23).
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4.2 Previous work in the lab

Our interest in the Julia olefination method started in the mid-nineties. During her work on the total synthesis of mylbemycin β3, Fiona Murphy had to prepare stereoselectively a trisubstituted double bond (Figure 4.4). The Julia olefination was chosen as the most suitable method for this purpose. Disappointingly, at this time, the synthesis of trisubstituted olefins via the coupling of α-sulfonyl carbanion with ketones has been little studied and it was decided to investigate this area in detail.

As a consequence, two efficient methods for the obtention of β-substituted oxy sulfones by coupling sulfone 421 with ketones were developed. Both routes were based on the in situ trapping of the alkoxy anion adduct (for more details see chapter 4.1.1.3). In the first case, TMSCl was used as a quenching agent. Since there is no method describing the reductive-elimination of β-trimethylsilyloxy sulfones, the TMS group was removed

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upon acidic work-up, furnishing the desired \( \beta \)-hydroxy sulfones 491 in good yields (Table 4.5).

![Figure 4.4](image)

**Figure 4.4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( C_6H_{13} )</td>
<td>( \text{PhCH}_2\text{CH}_2 )</td>
<td>( \text{CH}_3 )</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>( \text{CH}_3 )</td>
<td>( \text{C}_4\text{H}_9 )</td>
<td>( \text{CH}_3 )</td>
<td>86</td>
</tr>
</tbody>
</table>

\( ^a \) All yields are for pure, fully characterized, products

| Table 4.5 |

The second method used benzoyl chloride as a trapping agent and furnished the \( \beta \)-benzoyloxy sulfones 422 (Table 4.2, for more details see chapter 4.1.1.3). Both compounds 422 and 491, when were submitted to the SmI\(_2\)/HMPA mediated reductive elimination, yielded the desired trisubstituted olefins 485 with excellent yields but poor stereoselectivity (Table 4.6).

More interestingly, it was found that the reductive-elimination of the β-benzoyloxy sulfones 422 and the β-hydroxy sulfones 491 proceeded via different mechanisms (see chapter 4.1.2). Later on, Raphaël Dumeunier took advantage of this observation during the synthesis of the northern fragment of polycavernoside A 493, accomplishing the selective reductive-elimination of the ω-benzoyloxy sulfone in the presence of the β-hydroxy sulfone (Scheme 4.24).

Table 4.6

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>E/Z</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{C}<em>6\text{H}</em>{13} )</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>H</td>
<td>2:1</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)</td>
<td>C(_4)H(_9)</td>
<td>CH(_3)</td>
<td>H</td>
<td>2:1</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>( \text{oC}<em>9\text{H}</em>{13} )</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)</td>
<td>nC(_4)H(_9)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^a\) All yields are for pure, fully characterized, products

More interestingly, it was found that the reductive-elimination of the β-benzoyloxy sulfones 422 and the β-hydroxy sulfones 491 proceeded via different mechanisms (see chapter 4.1.2). Later on, Raphaël Dumeunier took advantage of this observation during the synthesis of the northern fragment of polycavernoside A 493, accomplishing the selective reductive-elimination of the ω-benzoyloxy sulfone in the presence of the β-hydroxy sulfone (Scheme 4.24).

Table 4.6

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>E/Z</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{C}<em>6\text{H}</em>{13} )</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>H</td>
<td>2:1</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)</td>
<td>C(_4)H(_9)</td>
<td>CH(_3)</td>
<td>H</td>
<td>2:1</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>( \text{oC}<em>9\text{H}</em>{13} )</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)</td>
<td>PhCH(_2)CH(_2)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)</td>
<td>nC(_4)H(_9)</td>
<td>CH(_3)</td>
<td>Bz</td>
<td>2:1</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^a\) All yields are for pure, fully characterized, products

More interestingly, it was found that the reductive-elimination of the β-benzoyloxy sulfones 422 and the β-hydroxy sulfones 491 proceeded via different mechanisms (see chapter 4.1.2). Later on, Raphaël Dumeunier took advantage of this observation during the synthesis of the northern fragment of polycavernoside A 493, accomplishing the selective reductive-elimination of the ω-benzoyloxy sulfone in the presence of the β-hydroxy sulfone (Scheme 4.24).
4.3. Objectives

The work discussed in this chapter concentrates on two different subjects. First, the use of \( \beta \)-benzoyloxy sulfoxides 497 in the context of the Julia olefination will be discussed (Scheme 4.25). Since the coupling step is rather well established (see above), the main emphasis of our research will be focused on the reductive-elimination step and its mechanism. Finally, the scope and limitations of this reaction will be disclosed.

In the second part, the synthesis of various bifunctional molecules containing two sulfone groups, suitable for a 1\textsuperscript{st} and/or 2\textsuperscript{nd} generation Julia olefination coupling, will be discussed (Figure 4.5). It is expected that these molecules will serve as highly versatile building blocks in diversity orientated synthesis. Their assembly and subsequent applications will be disclosed.
4.4 Sulfoxides and Julia olefination

The synthesis of 1,2-disubstituted olefins is an area of high interest in organic synthesis. So far, a variety of methods based upon phosphoruous (Wittig, Horner-Wittig and Horner-Warswordth-Emmons reactions),\textsuperscript{217} silicon (Peterson olefination)\textsuperscript{218} or sulfone (Julia olefination)\textsuperscript{208,209,219} were extensively studied in this context. Disappointingly, the synthesis of tri- and tetrasubstituted olefins via these, most widely used, methods is rather limited.

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During our work on the synthesis of (+)-ambruticin, the stereoselective construction of the C16-C17 trisubstituted olefin was expected to be one of the key connective steps, allowing a highly convergent synthesis of 1. Initially, our modification of the Julia reaction, based upon the trapping of the alkoxide-intermediate by benzoyl chloride, was envisaged as the method of choice (see chapter 4.2).

However, our preliminary results showed that the coupling step might be even trickier than we thought (see chapter 2.5). Thus, inspired by Satoh, it was decided to use the sulfoxides instead of the sulfones. It was reasoned that the higher pKa of the hydrogen α to sulfoxides compared to sulfones (4 orders higher, Table 4.1) should destabilize the corresponding sulfoxide-containing carbanion 509. Thus, the equilibrium of the addition reaction should be shifted to the right and, as a consequence, more of the trapped product should be obtained (Scheme 4.26).

![Scheme 4.26](image)

Since the reductive-elimination step used by Satoh does not tolerate a wide range of functional groups, SmI₂-mediated reductive-elimination of the corresponding β-benzoyloxy sulfoxides was proposed as an alternative (Scheme 4.27).

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4.4.1 Towards an efficient olefination method

To test the feasibility of the reductive-elimination, $\beta$-benzoyloxy sulfoxide $514$ was prepared from sulfoxide $511a$ and aldehyde $512$. Sulfoxide $511a$ was chosen because it is known that the anion of the corresponding sulfone does not react with carbonyl compounds under similar reaction conditions. The generated $\alpha$-sulfonyl carbanion which, in this case is highly stabilized by the sulfonyl substituent and by the phenyl group is essentially unreactive. Typically, the addition of benzylphenylsulfones to aldehydes results in $<10\%$ yield of adduct.\textsuperscript{213}

Thus, the sulfoxide $511a$ was reacted after deprotonation, with aldehyde $512$ and the in situ generated $\beta$-hydroxysulfoxide $513$ was trapped with benzyol chloride to give the $\beta$-(benzoyloxy)sulfoxide $514$. Since two new stereogenic centres are formed during the addition of the sulfoxide anion to aldehyde $512$, the intermediate $514$ is obtained as a mixture of all four possible diastereoisomers. To avoid their tedious separation, it was decided to use the mixture of adducts $514$ in the subsequent reductive-elimination step (Table 4.7).
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$$\text{Ph} \quad \text{S} \quad \text{Ph}$$

$$\text{O} \quad + \quad \text{O} \quad \text{H}$$

511a 512 513

LDA (1.1 equiv)
THF, -78 °C

1. BzCl (1.5 equiv)
-78 °C to r.t.

2. Me₂NCH₂CH₂CH₂OH (1.55 equiv)

$$\text{Ph} \quad \text{S} \quad \text{O} \quad \text{OBz} \quad \text{Ph} \quad \text{Ph}$$

514

SmI₂ (3.5 equiv)
THF, -78 °C additive

$$\text{Ph} \quad \equiv \quad \text{Ph}$$

515a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Equiv. to SmI₂</th>
<th>Temp. (°C)</th>
<th>Yielda (%)</th>
<th>E / Zb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-78</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>HMPA</td>
<td>0.25</td>
<td>-78</td>
<td>25</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>4</td>
<td>HMPA</td>
<td>0.5</td>
<td>-78</td>
<td>34</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>5</td>
<td>HMPA</td>
<td>0.75</td>
<td>-78</td>
<td>43</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>6</td>
<td>HMPA</td>
<td>1.0</td>
<td>-78</td>
<td>67</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>7</td>
<td>HMPA</td>
<td>2.0</td>
<td>-78</td>
<td>64</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>8</td>
<td>DMPU</td>
<td>15.0</td>
<td>-78</td>
<td>2</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>DMPU</td>
<td>15.0</td>
<td>-50</td>
<td>12</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>DMPU</td>
<td>15.0</td>
<td>-25</td>
<td>32</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>11</td>
<td>DMPU</td>
<td>15.0</td>
<td>0</td>
<td>48</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>12</td>
<td>DMPU</td>
<td>15.0</td>
<td>25</td>
<td>10</td>
<td>n/a</td>
</tr>
<tr>
<td>13</td>
<td>DMPU</td>
<td>5.0</td>
<td>0</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>14</td>
<td>DMPU</td>
<td>10.0</td>
<td>0</td>
<td>11</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>15</td>
<td>DMPU</td>
<td>20.0</td>
<td>0</td>
<td>41</td>
<td>&gt;95:1</td>
</tr>
</tbody>
</table>

a Overall yields refer to pure, isolated products
b Determined by capillary GC

Table 4.7
Chapter 4. Sulphur-based methodologies

It was observed that SmI$_2$ itself does not promote the reductive elimination, not even at room temperature (Table 4.7, Entry 1 and 2). Therefore, HMPA and DMPU were added as additives$^{220}$ to increase the reduction potential of SmI$_2$ (-1.33 V, THF (0.5M), without additives).$^{221}$ It was found that the presence of only small quantities of HMPA (0.25 eq) promoted the reductive elimination and afforded the desired olefin $^{515a}$ in 25% yield (Table 4.7, Entry 3). Further optimization of the reaction conditions showed that addition of one equivalent of HMPA was optimal (Table 4.7, Entry 6) and that a greater amount of HMPA loading did not give better results (Table I, Entry 7). This observation suggests that a reduction potential of -1.43 V (HMPA/SmI$_2$ = 1/1, THF (0.5M)) is the optimum potential required for the reductive-elimination. If the potential is increased (Table 4.7, Entry 7) to -1.46 V (HMPA/SmI$_2$ = 2/1), the reaction does not proceed faster or with better yields.

DMPU was next employed as an alternative, non-toxic HMPA equivalent. However, under all the reaction conditions tested, the yields remained lower than with HMPA (Table 4.7, Entry 8-15). Moreover, a large excess of DMPU and higher temperatures (0°C to room temperature) had to be employed (Table 4.7, Entry 11-15). Using this additive, as for HMPA, the best results were obtained when a reduction potential of -1.42 V was reached.$^{222}$

Next, the amount of SmI$_2$ required for the reaction was evaluated. It was expected that 2 equivalents of SmI$_2$ (one electron donor species) are required

\[ \text{SmI}_2 \text{ (2 eq)} + \text{olefin} \rightarrow \text{desired olefin} \]


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for the reaction (for more details about the mechanism, see chapter 4.4.3). Since, the crude mixture was used in the reductive-elimination step, it was thought that some impurities might be present that would require a higher loading of SmI₂ (Table 4.8).

![Chemical structure](image)

Table 4.8

<table>
<thead>
<tr>
<th>Entry</th>
<th>SmI₂/HMPA [equiv.]</th>
<th>Yielda [%]</th>
<th>E/Z b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>67</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>66</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>60</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>4c</td>
<td>2.1</td>
<td>51</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>5</td>
<td>4.0</td>
<td>68</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>66</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>7d</td>
<td>2.1 + 0.5</td>
<td>64</td>
<td>&gt;95:1</td>
</tr>
</tbody>
</table>

a Overall yields refer to pure, isolated products
b Determined by capillary GC
c Reaction uncompleted
d Additional SmI₂/HMPA was added

In the event, it was observed that 3.0 eq of SmI₂ or more are essential for obtaining yields in this reaction (Table 4.8, Entry 1, 2, 5 and 6). A lower SmI₂ loading results in diminished yields and, if 2.1 eq. of SmI₂ are used, the typical blue color of SmI₂ disappears upon the addition of 514 (Table 4.8, Entry 4) indicating rapid consumption of all the available reducing agent in the reaction mixture. This experiment was reproduced once more (Table 4.8, Entry 7) and, when all the SmI₂ had been consumed, an additional 0.5 eq. of
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SmI₂/HMPA-complex was added. In this case, a still acceptable yield of 64% was obtained, indicating that additional SmI₂ can be added directly to the reaction mixture without influencing its yield and/or selectivity.

Finally, the influence of some common bases on the yield of this reaction was tested (Table 4.9).

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equiv. to 126a</th>
<th>Yield (a) (%)</th>
<th>E/Z (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1.1</td>
<td>67</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>1.2</td>
<td>68</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>1.5</td>
<td>67</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>4</td>
<td>nBuLi</td>
<td>1.1</td>
<td>59</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>5</td>
<td>nBuLi</td>
<td>1.2</td>
<td>63</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>6</td>
<td>nBuLi</td>
<td>1.5</td>
<td>64</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>7</td>
<td>secBuLi</td>
<td>1.1</td>
<td>66</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>8</td>
<td>secBuLi</td>
<td>1.2</td>
<td>68</td>
<td>&gt;95:1</td>
</tr>
<tr>
<td>9</td>
<td>secBuLi</td>
<td>1.5</td>
<td>67</td>
<td>&gt;95:1</td>
</tr>
</tbody>
</table>

(a) Overall yields refer to pure, isolated products
(b) Determined by capillary GC
(c) 2.0 M sol. in THF
(d) 1.6 M sol. in hexane
(e) 1.6 M sol. in hexane

Table 4.9
Chapter 4. Sulphur-based methodologies

If LDA or sec-BuLi were used as a base, the reaction sequence proceeded with essentially the same yields (Table 4.9, Entry 1-3 and 7-9). Surprisingly, when n-BuLi was employed, the reaction yields were somewhat lower (Table 4.9, Entry 4-6). Based upon these results, 1.1 equivalent of LDA was selected as a standard base for the reaction.

4.4.2 Scope and limitations

Having designed suitable reaction conditions for the sulfoxide modified Julia olefination, the scope and limitations of this protocol were investigated. First, our attention focused on the formation of 1,2-disubstituted olefins. Thus, sulfoxide 511a was reacted with aliphatic and aromatic aldehydes, affording the corresponding 1,2-disubstituted olefins 515a-515e in good yields and with excellent stereoselectivities (Table 4.10, Entry 1-5). We were delighted to observe that some of the most commonly used OH-protecting groups are perfectly tolerated in this transformation (Table 4.10, Entry 3-5).

Next, the coupling of the more hindered sulfoxide 511b was examined under these reaction conditions. It was found that if 511b was reacted with aliphatic aldehydes (Table 4.10, Entry 7), the desired olefin 511g was formed in good yield and with very high selectivity ($E/Z = 94:6$). Surprisingly, when 511b was reacted with benzaldehyde, the desired alkene 515f was formed with only moderate selectivity $E/Z = 76:24$, though in a similar yield (Table 4.10, Entry 6).

The formation of trisubstituted olefins also proceeded smoothly (Table 4.11). Sulfoxides 511a and 511b were reacted with various ketones furnishing the desired adducts 516a-i in yields ranging from 51 to 71%. The stereoselectivity of the C-C bond linkage was lower with trisubstituted olefins than in the case of 1,2-disubstituted ones.
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Generally, aryl-substituted alkenes, formed by the reaction of 511a with ketones, gave slightly lower E/Z ratios than those bearing an isopropyl side-chain. Additionally, it was observed that the E/Z selectivity depended upon the steric discrimination between the groups present in the ketone molecule.

Table 4.10

<table>
<thead>
<tr>
<th>Entry</th>
<th>511</th>
<th>R^2CHO</th>
<th>Product</th>
<th>Yield^a</th>
<th>E / Z^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>511a</td>
<td>OHC&lt;Ph</td>
<td>515a</td>
<td>67%, &gt;95:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>511a</td>
<td>O&lt;Ph</td>
<td>515b</td>
<td>75% &gt;95:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>511a</td>
<td>OHC&lt;OBz</td>
<td>515c</td>
<td>71%, &gt;95:1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>511a</td>
<td>OHC&lt;OAc</td>
<td>515d</td>
<td>68%, &gt;95:1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>511a</td>
<td>OHC&lt;OTBS</td>
<td>515e</td>
<td>70%, &gt;95:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>511b</td>
<td>O&lt;Ph</td>
<td>515f</td>
<td>70% 76:24</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>511b</td>
<td>OHC&lt;Ph</td>
<td>515g</td>
<td>69%, 94:6</td>
<td></td>
</tr>
</tbody>
</table>

^a Overall yields refer to pure, isolated products

^b Determined by ^1H NMR spectroscopy
Table 4.11

<table>
<thead>
<tr>
<th>Entry</th>
<th>511</th>
<th>R²R³C=O</th>
<th>Product</th>
<th>Yieldᵃ E / Zᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>511a</td>
<td></td>
<td></td>
<td>51% 76:24</td>
</tr>
<tr>
<td>2</td>
<td>511b</td>
<td></td>
<td></td>
<td>57% 91:9</td>
</tr>
<tr>
<td>3</td>
<td>511a</td>
<td></td>
<td></td>
<td>68% 65:35</td>
</tr>
<tr>
<td>4</td>
<td>511a</td>
<td></td>
<td></td>
<td>71%, 52:48</td>
</tr>
<tr>
<td>5</td>
<td>511b</td>
<td></td>
<td></td>
<td>64% 74:26</td>
</tr>
<tr>
<td>6</td>
<td>511b</td>
<td></td>
<td></td>
<td>64% 88:12</td>
</tr>
<tr>
<td>7</td>
<td>511b</td>
<td></td>
<td></td>
<td>63%, 68:32</td>
</tr>
<tr>
<td>8</td>
<td>511b</td>
<td></td>
<td></td>
<td>63% 75:25</td>
</tr>
<tr>
<td>9</td>
<td>511b</td>
<td></td>
<td></td>
<td>51%, 79:21</td>
</tr>
</tbody>
</table>

ᵃ Overall yields refer to pure, isolated products
ᵇ Determined by ¹H NMR spectroscopy

When the carbonyl function was bound to a methyl group on one side and a linear alkyl on the other side, the newly formed double bond was generated with low selectivity (Table 4.11, Entries 4 and 7). In the case of bulkier
alkyl, the $E$ isomer was formed preferentially (Table 4.11, Entries 2, 6 and 9). Remarkably, this modified Julia olefination proceeds smoothly when enones are employed as substrates though the highly conjugated, thermodynamically more favored olefin was formed only in a moderate $E/Z$ ratio (Table 4.11, Entries 3 and 8).

Based on these results, it can be concluded that, during the reductive elimination step, the steric requirements of the substrate are overruling the conjugative effect present in the final adduct.

Finally, the formation of tetrasubstituted olefins was examined under our standard conditions. Accordingly, sulfoxide 517 was reacted with various ketones to give tetrasubstituted olefins 518 in low yield but excellent $E/Z$ selectivity (Table 4.12).

In this context, two points require further comments. First, it was observed that the formation of conjugated olefins (Table 4.10, Entry 6 and Table 4.11, Entry 1, 3-6 and 8) proceeded generally with lower selectivity than non-conjugated olefins. It thus transpires that in the reductive elimination of $\beta$-sulfoxybenzoates, steric hindrance in the substrate is much more important than electronics.

Moreover, the formation of tetrasubstituted olefins proceeded with lower yields, around 30%. Such situation is probably caused by the competitive enolization of the ketone. Thus, avoiding the enolization should increase the yield of the coupling step and, consequently, the yield of the final tetrasubstituted olefins.\textsuperscript{223}

\textsuperscript{223} For more detailed discussion see chapter 4.4.4: Conclusions and perspectives.
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**Table 4.12**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^2 R^3 C=O )</th>
<th>Product</th>
<th>Yield(^a)</th>
<th>( E / Z )(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O=C</td>
<td>518a</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>O-( \text{-Pr} )</td>
<td>518b</td>
<td>29%</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>O-( \text{-Ph} )</td>
<td>518c</td>
<td>32%</td>
<td>91:9</td>
</tr>
</tbody>
</table>

\(^a\) Overall yields refer to pure, isolated products  
\(^b\) Determined by \(^1\)H NMR spectroscopy

**4.4.3 Mechanistic studies**

Having established the basic scope and limitations of the sulfoxide-Julia reaction, our attention focused on the mechanisms of this olefination. We wondered if the reductive elimination, mediated by the SmI\(_2\)/HMPA system, was a stereoselective or a stereospecific process. Therefore, the syn-and \textit{anti-}\(\beta\)-(benzoyloxy)sulfoxides 522 were prepared (Scheme 4.28)\(^{224}\) and independently subjected to the reductive elimination conditions.

Synthesis of anti-515

\[
\text{trans-515b} \xrightarrow{\text{mCPBA (1.0 eq), NaHCO}_3, \text{CH}_2\text{Cl}_2, \text{r.t.}} \text{anti-519} \xrightarrow{\text{PhSH, cat. TBAF, neat, 50°C}} \text{anti-520}
\]

or

\[
\text{mCPBA, NaHCO}_3, \text{CH}_2\text{Cl}_2, \text{r.t.} \xrightarrow{\text{PhSH, cat. TBAF, neat, 50°C}} \text{anti-520}
\]

Synthesis of syn-137

\[
\text{cis-515b} \xrightarrow{\text{mCPBA (1.0 eq), NaHCO}_3, \text{CH}_2\text{Cl}_2, \text{r.t.}} \text{syn-519} \xrightarrow{\text{PhSH, cat. TBAF, neat, 50°C}} \text{syn-520}
\]

Scheme 4.28

In both cases, olefin 515b was obtained in an excellent E/Z ratio of > 95:1, indicating that the reductive-elimination step proceeds via a stereoselective process (Scheme 4.29).

To generalize our observation, the syn- and anti-sulfoxides 523 were prepared and their reductive elimination was examined (Scheme 4.30). Since direct access to each individual diastereoisomers of 523 would have been prohibitive, 523 was synthesized according to the standard Julia olefination procedure, as a mixture of isomers. The desired four diastereoisomers (a pair...
Chapter 4. Sulphur-based methodologies

of syn-523 and a pair of anti-523) were then separated via tedious column chromatography (7 columns required).225

![Scheme 4.29](image)

Interestingly, the reductive elimination of the pure syn and anti-sulfoxides 523 gave essentially the same E/Z ratio, ranging from 86:14 to 91:9. When the reaction was repeated with a mixture of all four diastereoisomers, an 88:12 E/Z ratio was obtained, which is a good average of the individually measured stereoselectivities. This observation clearly suggests that the double bond geometry of the final alkene 516f is independent of the relative stereochemistry of the sulfoxide adduct 523.

Based upon these results, we can safely claim that the reductive-elimination process is not stereospecific and is thus independent from the relative configuration of the starting β-benzoyloxy sulfoxides.

225 The relative stereochemistry determination of 523 will be discussed at the end of the chapter.
This observation also suggest that the reductive-elimination of β-(benzoyloxy)sulfoxides proceeds in the same way as that of the β-(benzoyloxy)sulfones (Scheme 4.31). Thus, transfer of a single electron to the benzoate moiety, which appears to be the lowest energy pathway, leads to the radical anion 525. Subsequent collapse of this intermediate

226 See chapter 4.1.2.3 Reverse reduction order.
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liberates the benzoate anion and produces radical $\text{526}$. Further transformation of $\text{526}$ to the organosamarium intermediate $\text{527}$, followed by elimination of the phenylsulfinyl group, eventually affords the olefin $\text{528}$.

\[ R_1 R_2 R_3 \overset{\text{Sml}_2}{\rightarrow} R_1 R_2 R_3 \overset{\text{Sml}_2}{\rightarrow} \overset{\text{Sml}_2}{\rightarrow} \overset{\text{Sml}_2}{\rightarrow} \overset{\text{Sml}_2}{\rightarrow} \]

Scheme 4.31

It is plausible that the formation of the organosamarium species $\text{527}$ is a slower process than epimerization of the radical-bearing centre. Moreover, the samarium derivative $\text{527}$ might not be configurationally stable and inversion might occur faster than elimination to $\text{528}$. The elimination of the phenylsulfinyl group is believed to proceed through an $\text{E}_2$ type process, leading to the general model for the stereoselectivity of the double bond formation depicted in Figure 4.6. Based on this model, steric hindrance, provided by the substituents present on the sulfoxide and on the carbonyl substrate, play a crucial role in the final $E/Z$ stereoselectivity.

However, the syn-elimination of the samarium derivative $\text{527}$ can not be ruled out at this stage and it still remains a viable possibility. Nevertheless, even if the syn-elimination mechanism is operating, the steric hindrance of

$^{227}$ In this context, it is interesting to note that the reductive cleavage of a benzoate group could be easily effected using Sml$_2$ or electrochemical conditions, suggesting a great acceptor ability of the benzoyl function. Kuenzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* 1991, 32, 1949.
the substituents will provide the same effect, as depicted in the Mnemonic below.

![Mnemonic](image)

**Figure 4.6**

4.4.3.1 Determination of the relative configuration of the $\beta$-benzoyloxy sulfoxide

The determination of the relative configuration of sulfoxides *anti*-522 and *syn*-522 was not a problem, since this relative stereochemistry was established during the synthesis (Scheme 4.28).\(^{228}\)

On the other, in the case of sulfoxides 523, the attribution of their relative stereochemistry proved to be more demanding. Initially, the separated, four diastereoisomers of 523 were oxidized to the corresponding sulfones (Scheme 4.32). It was observed that the two less polar sulfoxides 523 furnished an identical sulfone, *syn*-529. Similarly, both more polar sulfoxides 523 yielded sulfone *anti*-529.

The conversion of the sulfoxides 523 to sulfones 529 indicated that each pair of sulfoxides possesses the same relative configuration at C4 and C5 but differs only in the configuration at the sulfur atom.

---

Additionally, from the polarity of the sulfones 529, we can assume that due to their greater dipole moment, the more polar sulfone possesses the anti configuration between C3 and C4. From the literature, it is also known that the shift of the H3 hydrogen is slightly shielded in the case of the syn sulfones (Table 4.13). The same is true for the sulfoxides (Table 4.14). Disappointingly, the direct attribution of the relative configuration based on
the Bravo’s report\textsuperscript{229} could not be done, since this rule is valid only for 1,2-disubstituted \( \beta \)-hydroxysulfoxides.

\[ \text{PhO}_2\text{S} \quad \text{OBz} \quad \text{H} \quad \text{PhO}_2\text{S} \quad \text{OBz} \quad \text{H} \]

\[ \text{syn-529} \quad \text{anti-529} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>( \delta (\text{H}3) )\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\text{syn - 529}</td>
<td>3.83</td>
</tr>
<tr>
<td>2</td>
<td>\text{anti - 529}</td>
<td>3.89</td>
</tr>
</tbody>
</table>

\textsuperscript{a} \( ^{1}\text{H-NMR (300 MHz, CDCl}_3\)\)

Table 4.13

Additional NMR experiments (NOESY, NOEdiff) did not shed more light into the structure determination.

\[ \text{PhS} \quad \text{OBz} \quad \text{H} \quad \text{PhS} \quad \text{OBz} \quad \text{H} \]

\[ \text{less polar syn-523} \quad \text{more polar syn-523} \quad \text{less polar anti-523} \quad \text{more polar anti-523} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>( \delta (\text{H}3) )\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>less polar syn - 523</td>
<td>3.89</td>
</tr>
<tr>
<td>2</td>
<td>more polar syn - 523</td>
<td>4.02</td>
</tr>
<tr>
<td>3</td>
<td>less polar anti - 523</td>
<td>4.26</td>
</tr>
<tr>
<td>4</td>
<td>more polar anti - 523</td>
<td>4.36</td>
</tr>
</tbody>
</table>

\textsuperscript{a} \( ^{1}\text{H-NMR (300 MHz, CDCl}_3\)\)

Table 4.14

\textsuperscript{229} The half high width of the \( ^1\text{H-NMR} \) signal of the hydrogen on the carbon bearing the hydroxyl group of acyclic \( \beta \)-hydroxysulfoxides was reported to be about 18 Hz (\textit{anti}) and 24
4.4.4 Conclusions and perspectives

In summary we have developed a novel modification of the classical Julia olefination method. By replacing the sulfone moiety with a sulfoxide, the equilibrium of the reaction between 494 and 495 was shifted more towards the adduct 510. Furthermore, we have developed and optimized the conditions for the reductive-elimination of β-benzoyloxy sulfoxide 510 yielding the desired olefins 398. The overall sequence, consisting of the three steps (addition, trapping with benzoyl chloride, reductive-elimination), furnishes the olefins 398 in good to acceptable yields and moderate to excellent E/Z selectivity (Scheme 4.33).

Scheme 4.33

Compare to the classical Julia olefination method, the sulfoxide modification enabled, for the first time, the preparation of tetrasubstituted olefins. Moreover, this method also allows the formation of styrene derivatives by reacting benzylphenylsulfoxide with aldehydes or ketones. In stark contrast, if benzylphenylsulfone is reacted with carbonyl compounds, the desired coupled product is generally isolated with <10%. Indeed, the anion

generated $\alpha$ to the sulfone is stabilized by the neighboring sulfonyl and phenyl groups and is thus unreactive.

We have shown that this method is suitable for benzyl and branched alkyl phenyl sulfoxides as well as for various aldehydes and ketones. It was also discovered that, in the case of highly hindered $\alpha$-branched sulfoxides and ketones (Table 4.12), the reaction yield decreases rapidly and the tetrasubstituted olefins are obtained in $\sim$30%. This situation is probably caused by the enolization of the ketone competitively with the addition reaction. To overcome this problem highly oxophylic Lewis acids such as SmI$_3$ or TiX$_4$ ($X = \text{Cl or OPr}^i$) should be tested (Figure 4.7). In this case, one can imagine that the Lewis acid will activate the carbonyl moiety for the addition and more importantly, at the same time, could coordinate with the oxygen of the sulfoxide, forming a tight transition state such as the one displayed in Figure 4.7.

![Figure 4.7](image)

The SmI$_2$/HMPA-promoted reductive-elimination reaction was found to produce 1,2-di-, tri- and tetrasubstituted olefins as the predominantly $E$ isomer in good to excellent overall yields. Surprisingly, it was observed that the electronic effects of the substituents did not greatly influence the double bond geometry of the newly formed olefins. On the other hand, the role of steric effects on the reaction’s selectivity was found to be important. This
observation led us to propose an empirical selectivity model for the sulfoxide-modified Julia olefination method (Figure 4.8).

Concerning the scope and limitations in term of substrates, it was observed that the conditions of the reaction are compatible with most commonly used protecting groups in organic chemistry (TBS, Bn, Ac).

Finally, we became interested in the reaction’s mechanism. We believe that the reductive-elimination proceeds according to the same order of events as originally proposed for β-benzoyloxysulfonyls (see chapter 4.1.2.3). Thus, the benzoyloxy group is initially reduced. The elimination of the sulfoxide group then proceeds via an anti or syn elimination from organosamariun species \( \text{527} \). This mechanism is still speculative and direct proofs for or against it are not available for the moment.

We have also demonstrated that the reaction was stereoselective and not stereospecific, the same stereochemical outcome being obtained, regardless of the configuration of the starting β-benzoyloxysulfoxide.

From a practical viewpoint, it might be interesting to evaluate sulfoxide groups other than phenyl. Indeed, one can expect that the presence of an heteroatom, such as sulfur or nitrogen in the aryl sulfoxide unit, would affect the selectivity of the reductive-elimination step. It is possible that in this case, \( \text{Sm}^{3+} \) present in organo sammarium intermediates \( \text{527} \) might interact (presumably coordinate) with the heterocyclic ring and form a chelate such
as the one shown in Figure 4.9. In this intermediate, the steric effects of the substituents should be even more pronounced and the olefins should be formed with higher E/Z selectivity (Figure 4.9).

Moreover, these heteroatoms might also be useful during the coupling step since they would stabilize the addition product by forming a strong chelated structure (Figure 4.7).

\[ \text{L} = \text{large} \quad \text{S} = \text{small} \]

4.5 Convergence in total synthesis: bifunctional substrates

4.5.1 Total synthesis and 21st century

The total synthesis of natural products is an extremely important topic in modern organic chemistry.\textsuperscript{230} Besides its role in the training of the researchers (organic synthesis is still the most complete training in chemistry), synthesis provides unambiguous structural proofs and help in generating variable quantities – often small ones – of particularly interesting natural products.

\textsuperscript{230} Markó, I.E. Science 2001, 294, 1842-1843.
Moreover, it is a rich source of analogues that could be tested and would help establishing a structure-activity relationship study. Furthermore, to reach these goals, the total synthesis of natural products had and still has an important impact on the development of novel synthetic methodologies, since the complexity of the target molecules very often require novel and original approaches.

Efficiency is a new dimension that has recently been added to organic synthesis. Indeed, some 20 years ago, the main emphasis was on the synthesis itself (to prepare the compound regardless of the overall yields and/or number of steps). Nowadays, a major goal of synthesis is to prepare the desired compound in reasonable amounts for additional biological screening. Additionally, the synthesis should be convergent and sufficiently flexible to allow the preparation of various analogs of the target molecule, without big changes in the established synthetic sequence.

As a consequence, a convergent total synthesis, in which the molecule is divided into several fragments that are prepared independently then combined, is preferred over a linear approach (Figure 4.10). Moreover, a convergent synthesis leads to numerous structural variations in the final product by simply modifying each fragment at a time or together.
4.5.2 Convergence and efficiency

Over the past decade, we have been interested in the total syntheses of various natural products.\textsuperscript{231} As important criteria in our synthesis, efficiency, convergency and flexibility for structural modifications have always been required. Based upon these criteria, various elegant syntheses of several natural products’ fragments were accomplished (Figure 4.11).\textsuperscript{232}


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Examination of a range of published total synthesis revealed that in most cases, a rather simple molecule (e.g. \(533\), Figure 4.12)\(^{233}\) serves the important role of a linker designed to connect the remaining, rather complicated, parts together.

This observation triggered our interest and it was decided to prepare several “simple” thought properly functionalized reagents with which we could, by simple modification in one of the intermediates, change the size of a macrocycle, incorporate a new chiral centre or modify the conformation of the targeted molecule.

Therefore, our goal became the synthesis of reagents containing two ArSO_2 groups connected together via an alkyl, alkenyl or alkynyl linker (Figure 4.13). The ArSO_2 groups should be used to connect these linkers with aldehydes or ketones via a double Julia reaction.  

---

4.5.3 Synthesis of the bifunctional linkers

4.5.3.1 Alkyl-chain containing linkers

Initially, we have focused on the synthesis of the linkers containing an alkyl chain (Scheme 4.34). As the starting material, diols 534 were chosen. Their transformation into the corresponding sulfides 535, using standard Mitsunobu conditions, followed by oxidation to the corresponding sulfones, furnished the hydroxysulfones 536. A second Mitsunobu reaction yielded the desired alkyl-containing linkers 499 in 21-40% overall yields.
The modest overall yields of this sequence were due mostly to the last step, involving the second Mitsunobu substitution. As a matter of fact, this reaction proceeded with complete conversion of the starting alcohol 536, but the desired sulfide 499 was rather difficult to separate from the side product, compound 537.

Having in mind the development of an efficient and easy to scale up synthesis of 499, another synthetic route was investigated (Scheme 4.35). Thus, the diols 534 were monoprotected with a TBS group and the resulting ethers 538 were transformed into the sulfides 539 by a mesylation/substitution sequence. Sulfides 539 were then oxidized to the sulfones and the TBS group was deprotected, furnishing the desired hydroxyl sulfones 536 in 5 steps and 75-77% overall yield. Finally, the remaining hydroxyl group was transformed into the sulfide by a second mesylation/substitution sequence. The required compounds 499 were obtained in 89-90% yield.

236 The PT-SH was always used in excess to avoid undesired side reactions, which could be caused by the presence of the strong base in the media.
To summarize, the second synthesis of 499 was achieved in 7 steps, starting from commercially available diols 534, and proceeded in 67-69% overall yield. Interestingly, this sequence required only two purifications by column chromatography (after the monoprotection of the diol 538 and at the end of the sequence) and was easy to perform on a 10g scale.

At this stage, our attention was drawn towards possible problems related to the PTSO<sub>2</sub>-containing linkers. It is known from the literature that Kociensky-Julia olefination generally proceeds with very high stereoselectivity only if 1,2-disubstituted olefins are formed. However, if a ketone is used as a coupling partner, the E/Z selectivity of the trisubstituted olefin is rather low.\(^{237}\)

Therefore, the synthesis of linkers containing a phenyl sulfone or phenyl sulfoxide group, suitable for the Julia-Lythgoe and the sulfoxide-modified Julia olefination, instead of the PTSO<sub>2</sub> substituent, was envisaged. The

\(^{237}\) See chapter 4.1.3.
synthesis of these linkers, containing either a sulfone group, compound 544, or a sulfoxide group, compound 542, is shown in Scheme 4.36.

4.5.3.2 Unsaturated-chain containing linkers

Having established a general route to fragments 499, we then focused our efforts on the preparation of linkers 501 and 503 containing an unsaturated system.

The synthesis of 501 (Scheme 4.37) began with fumaric acid monoethyl ester 545 which underwent selective monoreduction\textsuperscript{238} to alcohol 546. This alcohol 546 was converted into a PTS group via a mesylation/substitution...
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sequence, yielding sulfide 547 in 3 steps and 67% overall yield. Ester group reduction, followed by sulfide oxidation, transformed 547 into hydroxy sulfone 548. Finally, conversion of the hydroxyl group to PTS sulfide completed the synthesis of the trans-olefin containing linker 501, in 7 steps and 41% overall yield.

Scheme 4.37

The alkyne-containing linker 503 was prepared from 1,4-butyndiol 166 according to the procedure developed for the alkyl-chain containing linker 499 (Scheme 4.38). Product 503 was obtained in 7 steps and 61% overall yield.

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4.5.3.3 Chiral alkyl-chain containing linkers

To broaden the synthetic potential of our linkers, we have decided to prepare some of them bearing a stereogenic centre. Thus, compound 184, a possible precursor to 3-methyl-1,5-disubstituted penta-1,4-dienes 553, was chosen (Figure 4.14). This structural motif is commonly found in nature and can be recognized in various natural products, e.g. (+)-ambruticin, 239 myriaphorone 1, 240 tenadoline 241 and (+)-clathrin A. 242 Potentially, such a compound might also serve as a chiral bidentate ligand in transition metal catalysis.

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The synthesis of 184 began with the commercially available ester 554, which was transformed into sulfide 555 (Scheme 4.39). The ester function of 555 was reduced to the alcohol and the synthesis of the hydroxy sulfone 556 was completed by a sulfide oxidation. Finally, the hydroxyl function of 556 was transformed into a PTS group, using the usual mesylation/substitution sequence. The desired, chiral linker 184 was thus prepared in 6 steps and 70% overall yield.

Interestingly, both enantiomers of β-hydroxy ester 554 are commercially available. 243

243
In this case too, the mixed linkers 185b and 185a, bearing functionalities suitable for the classical Julia olefination as well as for the 2nd generation Julia olefination method, were prepared (Scheme 4.40).
4.5.4 Linkers in action

To evaluate the potential of our linkers in diversity orientated synthesis, sulfone 184 was tested in coupling reactions with various aldehydes. Some pertinent results are collected in Table 4.15.

\[
\text{PTS-SO}_2\text{PT} \quad \text{R} \quad \text{PTS} \quad \text{R} \\
\text{184} \quad \text{O} \\
\]

Table 4.15

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Comp.</th>
<th>Yield[a] [%]</th>
<th>E/Z[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>559a</td>
<td>95</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>PhCH=CH</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>559b</td>
<td>81</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂CH₂</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>559c</td>
<td>93</td>
<td>83:17</td>
</tr>
<tr>
<td>4</td>
<td>n-Pr</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78</td>
<td>559d</td>
<td>78</td>
<td>82:18</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>LiHMDS</td>
<td>toluene</td>
<td>-70</td>
<td>559a</td>
<td>35</td>
<td>54:46</td>
</tr>
<tr>
<td>6</td>
<td>PhCH=CH</td>
<td>LiHMDS</td>
<td>toluene</td>
<td>-70</td>
<td>559b</td>
<td>57</td>
<td>57:43</td>
</tr>
<tr>
<td>7</td>
<td>PhCH₂CH₂</td>
<td>LiHMDS</td>
<td>toluene</td>
<td>-70</td>
<td>559c</td>
<td>22</td>
<td>69:31</td>
</tr>
<tr>
<td>8</td>
<td>n-Pr</td>
<td>LiHMDS</td>
<td>toluene</td>
<td>-70</td>
<td>559d</td>
<td>21</td>
<td>73:28</td>
</tr>
</tbody>
</table>

[a] Refers to pure, isolated compounds.
[b] Based on \(^1\)H-NMR of the crude reaction mixture.

Initially, the aldehydes were reacted with sulfone 184 under the standard Kociensky-Julia conditions, using KHMDS as a base and THF as a solvent (Table 4.15, Entries 1-4). The desired olefins 559a-d were obtained in good to excellent yields (78-95%) and selectivity (E/Z = 82:18-99:1).

Attempted inversion of the double bond geometry by replacing KHMDS by LiHMDS and THF by toluene, proceeded poorly (Table 4.15, Entries 5-8). The reaction yields (21-53%) and the E/Z (54:46-73:28) ratios were

244 For the discussion about reaction mechanism, reaction TS and influence of the counter ion and the solvent on the stereoselectivity of the olefination reaction: see chapter 4.1.3.
particularly modest. It could be possible to favour the Z-isomer by using a tert-butyl tetrazolyl group instead of the phenyl tetrazolyl substituent.\textsuperscript{245}

Having successfully accomplished the first olefination, we focused our attention on the synthesis of 1,4-pentadienes (Scheme 4.41).

Thus, the monofunctionalized intermediates \textbf{559a} and \textbf{559b} were oxidized to the corresponding sulfones which were reacted with cinnamaldehyde and benzaldehyde, respectively. The resulting 1,4-dienes (\textit{R})- and (\textit{S})-\textbf{560} were obtained in excellent yields and good selectivity. Interestingly, the condensation of the bifunctional sulfone-sulfide \textbf{184} with two different aldehydes can furnish each enantiomer of the desired 1,4-pentadienes by simply inverting the order of addition of the aldehydes.

Additional reactions of bifunctional sulfone-sulfides \textbf{184}, \textbf{185b} and \textbf{185a} can be found in chapter 2.5, where they were used in the context of the ambruticin synthesis.

Finally, it was decided to submit compounds \textbf{561} to the olefination conditions (Figure 4.15). Silyl ethers \textbf{561} are easily accessible since they are prepared as one of the first intermediates during the synthesis of \textbf{499} (Scheme 4.35).

\textbf{Figure 4.15}

\textsuperscript{245} Kocienski, P. J.; Bell, A.; Blakemore, P. R. \textit{Synlett} 2000, 365-366.
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Scheme 4.41

It was thought that these compounds would lead to a simple and highly versatile synthesis of $O$-TBS protected allylic, homoallylic and other $\omega$-hydroxy olefins. Whilst this should hardly be a problem for 561b and 561c ($n = 2$ and 4), such is not the case for 561a ($n = 1$) in which rapid $\beta$-elimination might occur during the generation of the anion (Figure 4.16).\(^{246}\)

\(^{246}\) Examples of the $\beta$-elimination of $\beta$-oxy substituted sulfones have been reported in the literature: (a) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* 1999, 1, 188. (b) Keck, G. E.;
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It was hoped that, in this particular case (TBS-protecting group and 1-phenyltetrazol group), the undesired β-elimination would be suppressed because the bulky TBS group should disfavor the correct (antipleriplanar) orientation of the anion and the leaving group. Moreover, it was expected that the heteroatoms present on the PT-group might interact with the cation and make the anion α to the sulfone less basic.

In the event, compounds 561a-c, when reacted with aldehyde 165 under the standard Kociensky-Julia conditions, yielded the desired olefins in 81-91% yield and with E/Z ratios of up to 96:4 (Table 4.16).

![Figure 4.16](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone</th>
<th>n</th>
<th>Olefin</th>
<th>Yielda [%]</th>
<th>E/Zb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>561a</td>
<td>1</td>
<td>562a</td>
<td>89</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>561b</td>
<td>2</td>
<td>562b</td>
<td>91</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>561c</td>
<td>4</td>
<td>562c</td>
<td>81</td>
<td>90:10</td>
</tr>
</tbody>
</table>

^a Refers to pure, isolated compounds.

^b Based on 1H-NMR of the crude reaction mixture.

Table 4.16


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In all cases, the olefination reaction proceeded smoothly, even for sulfone 561a which afforded the desired O-TBS protected allyl alcohol in 89% yield and an 24:1 E/Z ratio.

4.5.5 Conclusions and perspectives

In summary, we have developed an efficient and easy to scale up route to bifunctional molecules bearing aryl and heteroaryl sulfones and sulfides. In general, only two purifications by column chromatography were required in these sequences.

The synthetic power of these molecules was then demonstrated using compound 184. Reacting sulfone 184 with benzaldehyde and cinnamaldehyde, under the standard Kociensky-Julia conditions, afforded both enantiomers of 560 by simply inverting the order of addition of the aldehydes.

We also studied the reactivity of silyl ethers 561, which are early intermediates in the synthesis of linkers 499 and are thus easily accessible on large scale. When 561 was reacted with aldehyde 165, the O-TBS protected allylic, homoallylic or trishomoallylic ethers were obtained. This reaction is quite useful, especially in the case of 561a, since it represents a simple and highly stereoselective way to TBS-protected allylic alcohols 564 (Scheme 4.42). Now-a-days, protected allylic alcohols are generally prepared via a three step sequence involving a stabilized Wittig or Horner-Emmons olefination, followed by the reduction of the ester to the alcohol and a final
alcohol protection. The desired olefin 564 can be obtained in 75-80% yield and 95:5 E/Z ratio.\textsuperscript{247}

It is also expected that the free allylic alcohol could be prepared directly, if the TBS group is deprotected upon the work-up of the reaction.

**Classical protocol**

\[
\begin{align*}
\text{O} & \quad \text{R} \\
\text{563} & \quad \text{1) PhH} = \text{CO}_2\text{Me} \\
& \quad \text{2) Reduction} \\
& \quad \text{3) TBS protection} \\
\text{TBS} & \quad \text{O} \quad \text{R} \\
\text{564} & \quad \text{O} \quad \text{R}
\end{align*}
\]

Using compound 561a

\[
\begin{align*}
\text{O} & \quad \text{R} \\
\text{565} & \quad \text{TBS} \\
& \quad \text{SO}_2\text{PT} \\
\text{561a} & \quad \text{TBS} \\
& \quad \text{O} \quad \text{R} \\
\text{564} & \quad \text{O} \quad \text{R}
\end{align*}
\]

**Scheme 4.42**

We think that these synthons can find some use in diversity orientated synthesis, ligand synthesis \textit{etc.}, since a wide variety of analogues of the final product analogues could be prepared. Moreover, \textit{pseudo}-symmetric bifunctional molecules as 184 can be easily assembled, allowing rather simple and versatile access to both enantiomers of the final adduct as shown in Scheme 4.41.

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Chapter 4. Sulphur-based methodologies
5. General route to styryl lactones

5.1 Introduction

Chiral lactones are commonly present in a number of natural products that possess pheromone or medicinal properties. Surprisingly, these small exogenous molecules exert powerful effects on the cell functions, making them useful for understanding life processes and treating life-threatening diseases.

Styryl lactones are a group of secondary metabolites commonly isolated from the genus Goniothalamus. Recent studies have demonstrated that these compounds display cytotoxic and antitumor properties. (R)-Goniothalamin 566 is a typical representative of this class of the compounds (Figure 5.1).

(R)-Goniothalamin 566 was isolated in 1967 from the dried bark of Cryptocarya caloneura and given (S)-configuration. A decade later, the configuration of the stereocentre has been revised and established as being (R). Later on, 566 was isolated from Cryptocarya moschata, Bryonopsis laciniosa and various species of Goniothalamus. 115

References:


species\textsuperscript{254} distributed throughout the tropics and subtropics). Some of the isolated goniothalamin-based derivatives are shown in Figure 5.1.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure5_1.png}
\caption{Figure 5.1}
\end{figure}

\textit{(R)-Goniothalamin} \textsuperscript{566} has shown \textit{in vitro} cytotoxic effects, especially by inducing apoptosis\textsuperscript{255} on different cell lines including MCF-7, T47D and


\textsuperscript{255} Apoptotic cell death involves complex biochemical processes leading to well-characterized features such as condensation of chromatin and internucleosomal DNA cleavage. Current paradigms of apoptosis suggest that the loss of mitochondrial transmembrane potential occurs earlier in the commitment phase of apoptosis which results in the release of mitochondrial apoptogenic inducing factor. Cytochrome-c in the presence of dAPT or APT interacts with Apaf-1 resulting in the activation of caspase-9. Active caspase-9 subsequently processes the executioner caspase-3 and -7 into their catalytically active subunits. These executioner caspases are responsible for the degradation of many cellular substrates including the DNA
Chapter 5. General way to styryl lactones

MDA-MB-23566 (breast carcinoma), HeLa cells (human cervical carcinoma), gastric carcinoma (HGC-27), leukemia carcinoma (HL-60) and ovarian carcinoma (Caov-3). This cytotoxic activity was observed on cancer cell lines but surprisingly, it was shown to be minimal on non-malignant cells. In vivo studies revealed that (R)-566 displays tumoricidal and tumoristatic effects on Sprague-Dawley rats with 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors.

membrane potential and activation of initiator caspase-9.\textsuperscript{9a} Chien\textsuperscript{9c} and Azimahtol\textsuperscript{9d} showed that \((R)-566\) was able to modulate the \textit{Bax} expression increasing pro-apoptotic protein (\textit{Bax}) levels without affecting the anti-apoptotic \textit{Bcl-2} expression. It was also demonstrated \textit{in vivo} that p53 tumor suppressor protein accumulation was more pronounced in rat tumor treated with \((R)-566\).\textsuperscript{257}

Recently, Pilli \textit{et al.} studied the biological activity of unnatural \((S)\)-goniothalamin 566 enantiomer.\textsuperscript{258} It was observed that the cytotoxic activity of \((S)-566\) was similar to \((R)-566\), but generally higher doses were required.\textsuperscript{259}

The structure-biological activity relationship studied by Pilli \textit{et al.} showed that both olefins are essential for biological activity (Figure 5.2). Moreover, it was observed that the \textit{E}-olefin geometry was essential. It was also shown that the presence of an EDG on the aromatic ring increased the cytotoxic activity of the molecule against some cancer cell lines up to 100 times in comparison with the original structure of 566.\textsuperscript{260}

Additionally to all these studies, Mosaddik \textit{et al.} revealed that \((R)-566\) was a very potent mosquito larvicide, at least in the laboratory conditions.\textsuperscript{261}

\textsuperscript{259} In the case of some cancer cell lines much higher cytotoxic activity was observed.
\textsuperscript{260} The cytotoxic activity might be even higher since the optical purity of the EDG-containing derivatives was only between 90-95%.
Chapter 5. General way to styryl lactones

Figure 5.2

(R)-Kavain 570 and (R)-methysticin 571 are styryl lactone-derivatives structurally similar to (R)-goniothalamin 566 (Figure 5.3). They can be found in the Kava plant (Piper methysticum).

Figure 5.3

The Kava plant has a long and colorful history, spanning several thousand years. Kava has been used by Pacific Island societies to prepare an intoxicating ceremonial beverage recognized for its relaxing effects and

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253
ability to promote sociability. Modern use of Kava root, commonly available in dietary supplements labeled “Kava Kava”, has extended to its purported anxiolytic\textsuperscript{263} and soporific qualities. Analgesic,\textsuperscript{264} anesthetic, antifungal, antithrombotic,\textsuperscript{265} anticonvulsive,\textsuperscript{266} and muscle-relaxing\textsuperscript{267} properties have also been reported.\textsuperscript{262}

The psychoactive principals comprise a family of 15 $\alpha$-pyrone derivatives, known as the kavalactones, that constitute roughly 15\% of the dried rootstock. The most prevalent of these include kavain\textsuperscript{570} dihydrokavain\textsuperscript{571} and methysticin\textsuperscript{572}. Structurally, the kavalactones differ chiefly with respect to their arene substitution patterns and the presence or absence of double bonds along their carbon backbones. Although a few of the kavalactones, such as yangonin\textsuperscript{573}, are achiral, the majorities has a single stereogenic center at C6 and are optically pure.

Several clinical studies indicate that the kavalactones have a demonstrable anxiety-reducing effect.\textsuperscript{263} The pharmacological mechanism of this anxiolysis, however, is still unclear.\textsuperscript{268} Understanding the mode of action of these compounds is complicated since although the mixtures of the

\begin{thebibliography}{99}
\end{thebibliography}
kavalactones are readily available from the crude extract of cultivated Kava, large quantities of isolated, enantiopure kavalactones are not.\textsuperscript{269}

## 5.2 Previous total synthesis

### 5.2.1 Goniotalamin

Due to the interesting biological activities of (\(R\))-\textsuperscript{566}, several successful syntheses of this natural product have been described.\textsuperscript{270} Even though, the most commonly used antithetic approach to \textsuperscript{566} is based on the C2-C3 and/or C6-C7 olefin bonds disconnection (Figure 5.4), other methods such as asymmetric hetero-Deals-Alder or intramolecular nucleophilic addition to ketenes have been employed. Herein, the two most commonly used approaches will be discussed.

\[ \text{(R)-goniothalamin 566} \]

\textsuperscript{269} Häberlein, H.; Boonen, G.; Beck, M. A. \textit{Planta Med.} \textbf{1997}, 63, 63.

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So far the shortest approach to \((R)-566\) is based on cinnamaldehyde 576 asymmetric allylation/acylation/metathesis sequence (Scheme 5.1).

\[(R)-goniothalamin 566 \quad \xrightarrow{\text{Scheme 5.1}} \quad 574 \quad \xrightarrow{\text{Scheme 5.1}} \quad 575\]

\(+\)-\(-\)-allyldiisopinocamphenylborane 577 was used by Ramachandran et al. to produce the desired homoallyl alcohol 575 in 72\% yield and 92\% ee. Acylation of 575, followed by metathesis, resulted in the formation of \((R)-566\) in 76\% yield and 92\% ee (Scheme 5.2).271 Similarly, Pilli et al. used Maruoka’s bidentate Ti-based catalyst 578 to achieve asymmetric allylation of 576.273 The desired homoallylic alcohol 575 was obtained in 78\% yield and 96\% ee. Compound 575 was then submitted to the acylation/metathesis sequence described by Ramachandran, furnishing \((R)-566\) in 78\% yield over two steps (Scheme 5.3).

In both cases, the desired \((R)-566\) was prepared in 4 steps from commercially available compounds. Excellent overall yields (55-62%) and high optical purity (92-96% \(ee\)) are the landmarks of these approaches.

\[
\begin{align*}
\text{Scheme 5.2} \\
\text{The synthesis of } (R)-566 \text{ by Hansen et al. was based on the same approach as that of Pilli and Ramachandran. However, the chirallity was introduced by an enzymatic resolution process (Scheme 5.4).}^{274} \text{ Thus, racemic homoallylic alcohol } rac-575 \text{ was reacted with vinyl acrylate in the presence of } Candida antartica \text{ lipase B (CALB) yielding } (R)-9 \text{ in 93% } ee \text{ and } (S)-575 \text{ in 74% } ee. \text{ (R)-9 was then treated with the 1st gen. Grubbs catalyst (8 mol%), delivering the desired } (R)-566 \text{ in 92% yield and } \geq 98\% \text{ } ee. \text{ The origin of the surprising enantiomeric enrichment occurring during the metathesis process, which was}
\end{align*}
\]

\cite{Sundby:2004}

reproducible and observed also in the case of the (S)-566 synthesis (74% to 85% ee), remained unexplained.

\[
\text{(R)-BINOL} (10 \text{ mol\%}) \quad \text{Ti(OPr\text{Pr})}_4 (15 \text{ mol\%}) \quad \text{TiCl}_4 (5 \text{ mol\%}) \quad \text{Ag}_2\text{O} (10 \text{ mol\%}) \quad \text{allyltributyltin} (1.1 \text{ eq.})
\]

\[
\text{CH}_2\text{Cl}_2, -20^\circ\text{C} \quad \text{78\%, 96\% ee}
\]

\[
\text{(R)-goniothalamin 566}
\]

\[
\text{Scheme 5.3}
\]

\[
\text{Scheme 5.4}
\]
The key step in the second, most commonly used approach to \((R)-566\) is based on the formation of the C6-C7 double bond (Scheme 5.5). The crucial intermediate, alcohol 579, was accessed by various methods.

\[
\begin{align*}
\text{(R)-566} & \xrightarrow{\text{Ph}} \text{579} + \text{580}, \ Z = \text{PPh}_3^+X^-, \text{SO}_2\text{Ar}
\end{align*}
\]

Scheme 5.5

Pilli et al. based their synthesis of alcohol 579 on the asymmetric allylation of the aldehyde 581 according to the Keck’s\(^{275}\) protocol (Scheme 5.6).\(^{276}\) Homoallylic alcohol 582 was then converted to the desired lactone-containing alcohol 579 via an acylation/metathesis/deprotection sequence. Swern oxidation of 582 furnished an unstable aldehyde, which was immediately reacted with \textit{in situ} generated benzylidetriphenylphosphorane, yielding \((R)-566\) in 53% yield and as a 1:3 mixture of \textit{E}:\textit{Z} isomers. Since the reaction furnished predominantly the unwanted double bond isomer \((Z)-566\), Pilli et al. decided to employ the Kociensky-Julia olefination protocol instead of the Wittig procedure. In this case, the reaction furnished only \((E)-566\) but in very low yield (18%).

Just et al. prepared alcohol 579 starting from the aldehyde 583 which was converted to the alkyne 584 via the Corey-Fucks protocol (Scheme 5.7).\(^{277}\) Selective hydrogenation of 584 using Lindlar’s catalyst followed by acid


mediated intramolecular cyclization, led to the desired alcohol 579. Swern oxidation of 579 to the corresponding aldehyde, followed by Wittig olefination using in situ generated benzylidenetriphenylphosphorane, furnished (R)-566 in 57% and as a 1:9 E/Z ratio of geometric isomers.

Scheme 5.6

The synthesis of (S)-566 published by Enders et al. used acetal 585 instead of alcohol 579 as a key intermediate (Scheme 5.8).278

The synthesis of 585 started with diketoester 586, which was reduced enantio- and chemoselectively to hydroxyketoester 587 by the NADP-dependent alcohol dehydrogenase of Lactobacillus brevis (recLBADH). Hydroxyketoester 587 was then submitted to a non-selective reduction of the remaining ketone, followed by a cyclization/elimination sequence, yielding the desired lactone 588 in 78% yield. Protection of the α,β-unsaturated

lactone in the form of an acetal enabled the chloride-AcO exchange. Base-catalyzed ester hydrolysis led to the formation of the key intermediate 585. Alcohol 585 was oxidized to the corresponding aldehyde, which was reacted with the benzylic phosphorus-based ylide generated in situ according to the Crimmins protocol.\textsuperscript{279} The desired styryl lactone (S)-566 was finally obtained by the PCC-mediated acetal oxidation in 41% yield.

\begin{align*}
\text{O} & \quad \text{MeO}_2\text{C} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}

1) Swern oxidation
2) BnPPh$_3$Br$^-$, nBuLi
Et$_2$O, -78°C to r.t.

62%

\begin{align*}
\text{E} : \text{Z} & = 1:9 \\
\text{O} & \quad \text{OH}
\end{align*}

\begin{align*}
\text{1) H}_2, \text{Lindlar} \\
\text{2) 1\% HCl, MeOH}
\end{align*}

Scheme 5.7

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Scheme 5.8

5.2.2 Kavain

It is surprising that since mixtures of the kavalactones are readily available from the crude extracts of cultivated Kava, large quantities of isolated enantiopure kavalactones are not.\(^{280}\) Similarly, the racemic syntheses of the kavalactones are numerous in the literature,\(^{281}\) but no generally applicable


asymmetric synthesis has been developed. To the best of our knowledge, up till now, there are only two published \(^{282}\) total syntheses of (+)-kavain \(^{570}\), accomplished by Smith \(^{283}\) and Yue. \(^{284}\)

### 5.2.2.1 Year 2004 – Smith is rising the flag

The first total synthesis of (R)-kavain was reported by Smith et al. in 2004, \(^{283a}\) according to two different approaches. The first route was based on the diastereoselective aldol condensation using the thiazolidinethione-based chiral auxiliary (Scheme 5.9, path a). The second route rested upon an asymmetric Mukaiyama aldol reaction developed by Carreira \(^{285}\) and Sato \(^{286}\) (Scheme 5.9, path b).

**Path a** started with the tin triflate-mediated \(^{287}\) aldol reaction between aldehyde \(^{593}\) and chiral acetylated auxiliary \(^{594}\) (Scheme 5.10). The desired aldol product \(^{591}\) was formed in 83\% yield, with an excellent diastereoselectivity (>99:1). Displacement of the thiazolidinethione auxiliary with potassium monoethyl malonate \(^{288}\) in the presence of MgCl\(_2\), furnished

---

\(^{282}\) A hetero Diels-Alder approach was used to produce kavain in 13\% ee: Togni, A. *Organometallics* **1990**, 9, 3106.


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β-ketoester 595 in 82% yield. Interestingly, the free hydroxy group at the C5 position is tolerated under these conditions.

\[
\text{path } a \quad \xrightarrow{\text{EtO\textsubscript{2}C-C\textsubscript{2}O}} 590 \quad + \quad \text{path } b \quad \xrightarrow{\text{SnBu\textsubscript{3}}} 592
\]

**Scheme 5.9**

The resulting β-ketoester 595 was cyclized under basic conditions, yielding the corresponding lactone, which was immediately O-methylated, providing the (R)-kavain precursor 596. Stille coupling with appropriate aryl iodides then led to (R)-kavain 570 or (R)-methisticin 571, respectively. Both natural products were prepared in 5 steps and 40% or 24% overall yield, respectively, starting from aldehyde 593 and amide 594.

The asymmetric synthesis of intermediate 596 via path b began with the Carreira complex 597\textsuperscript{289} catalyzed addition of silyl enol ether 592 to aldehyde 593 (Scheme 5.1). Adduct 598 was formed in 79% yield and 92\% ee. Base-induced hydrolysis of 598 yielded the desired β-ketoester that spontaneously cyclized to lactone 599. Crude lactone 599 was then transformed into intermediate 596 using Me\textsubscript{2}SO\text{₄}.

Scheme 5.10

In summary, Smith et al. developed two independent and general routes to kavalactones and prepared (R)-kavain \(570\) in 5 (path a, 40% overall yield) and 4 steps (path b, 39% overall yield), respectively, starting from aldehyde \(593\).\(^{290}\)

\(^{290}\) Available in two steps from commercial 3,3-diethoxy-1-Propyne, see Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, 7, 2289-2291.
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Scheme 5.11

5.2.2.2 Yue and Wang – Blaise reaction in action

One year after Smith et al. published their second total synthesis of (R)-kavain 570, Yue and Wang reported\(^\text{291}\) their own results on the preparation of (R)-570. In their case, the assembly of the key intermediate β-ketoester 600 was envisioned as occurring form an intermolecular Blaise reaction between hydroxynitrile 601 and methyl bromoacetate 602 (Scheme 5.12). In the first step of the synthesis, aldehyde 603\(^\text{292}\) was transformed into olefin 604 (E/Z = 3:1) via a Wittig reaction (Scheme 5.13). The acetal group was deprotected and the primary alcohol was transformed into the corresponding cyanide via a tosylation/KCN-substitution sequence, yielding intermediate


\(^{292}\) Aldehyde 603 could be prepared in 3 steps, starting from the commercially available dimethyl ester of D-malic acid. See e.g.: Dias, L. C.; Meira, P. R. R. J. Org. Chem. 2005, 70, 4762-4773.
in 48% overall yield. The double bond was then isomerized, in the presence of Pd(II) catalyst giving, stereochemically pure nitrile 601 in 91% yield.

\[
\begin{align*}
\text{MeO}\_\text{Ph} & \quad \text{MeO}\_\text{Ph} \\
(\text{R})\text{-kavain } 570 & \quad 600 \\
\end{align*}
\]

An ultrasound-assisted Blaise reaction\(^{293}\) was then used to transform nitrile 601 into \(\beta\)-hydroxyketone 600. It is interesting to note that the free hydroxyl group is again tolerated under the reaction conditions.

The synthesis was completed by a base-mediated cyclization and an O-methylation, yielding (R)-kavain 570 in 7 steps and 25% overall yield starting from aldehyde 603.

5.3 Objectives

We became interested in total syntheses of (R)-goniothalamin 566 and (R)-kavain 570 because of their styryl motive (Figure 5.5). As was shown in chapter 5.2.1, all the previous total syntheses of 566, using the formation of the C6-C7 double bond as a key step, failed due to the low yield\textsuperscript{294} or selectivity\textsuperscript{295} during the installment of this olefinic linkage.

\textsuperscript{294} de Fátima, Â.; Pilli, R. A. \textit{ARKIVOC} \textbf{2003}, \textit{10}, 118-126.

It was suggested that our sulfoxide-modified Julia olefination, described in chapter 4.4, might overcome this limitation and furnish the desired styryl derivatives with complete $E$ selectivity.\textsuperscript{296}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure5.5.png}
\caption{Figure 5.5}
\end{figure}

To verify our hypothesis, it was decided to prepare the corresponding aldehydes 606 and 607a (Figure 5.6) and submit them to the sulfoxide-modified Julia olefination reaction.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure5.6.png}
\caption{Figure 5.6}
\end{figure}

### 5.4 Total synthesis of gonoiothalamin and kavain

#### 5.4.1 Retrosynthesis

Our retrosynthesis of (R)-gonoiothalamin 566 and (R)-kavain 570 was designed to use the sulfoxide-modified Julia olefination as the key step to

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establish the styryl motive of 566 and 570 at the end of the sequence (Scheme 5.14). As a consequence, both natural compounds 566 and 570 were disconnected at the C6-C7 position, leading to aldehydes 606 and 607a, respectively and sulfoxide 608.

![Scheme 5.14](image)

Since the aldehyde 607a, required for the synthesis of (R)-kavain 570, belongs to the same family as the lactones 607b and 607c (Figure 5.7) that were needed for the synthesis of jerangolid A and D, full discussion of all the strategies that were investigated for their assembly will be given in chapter 6.

![Figure 5.7](image)

Suffice it to say at this stage that the retrosynthetic analysis of the aldehyde 606 is based upon two key steps – a ring closing metathesis and selective epoxide ring opening (Scheme 5.15).

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2005, 70, 1953.
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5.4.2 Synthesis of goniothalamin and its derivatives

Our approach to (R)-goniothalamin 566 was based on three key steps: opening of the epoxide, ring-closing metathesis and sulfoxide-modified Julia olefination. In the context of the synthesis of lactone 606, the ring-opening/metathesis approach was previously used during a synthesis of (R)-argentilactone 610 (Figure 5.8).

To test the general synthetic utility of this approach, it was decided to evaluate the influence of four most commonly used protecting groups (Bn, Pospíšil, J.; Markó, I. E. *Tetrahedron Lett.* 2006, 47, 5933-5937. Hansen, T. V. *Tetrahedron: Asymmetry* 2002, 13, 547.)
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PMB, TBS and TBDPS) on the reaction sequence in terms of yields and selectivity.

The synthesis began with commercially available (R)-glycidol (R)-611, which was protected with PMB, TBS and TBDPS-group, yielding the corresponding epoxy ethers (R)-156b-d (Scheme 5.16). Benzyl glycidol (R)-156a is commercially available. CuI-mediated epoxide (R)-156 opening with vinyl magnesium bromide furnished the optically enriched homoallylic alcohols 612a-d in excellent yield and purity. As an advantage, additional purification after the reaction work-up was not required and in some cases even proved to be undesirable.

![Scheme 5.16](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>PG</th>
<th>Conditions</th>
<th>Yielda [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-156a</td>
<td>Bn</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>(R)-156b</td>
<td>PMB</td>
<td>NaH, PMBCl</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>(R)-156c</td>
<td>TBS</td>
<td>TBSCI, Im, CH2Cl2</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>(R)-156d</td>
<td>TBDPS</td>
<td>TBDPSCI, Im, CH2Cl2</td>
<td>99</td>
</tr>
</tbody>
</table>

a Refers to pure isolated compounds
b Commercially available

Acylation of alcohols 612a-d with an acryloyl unit then finished the metathesis precursors 609a-d (Table 5.1). It was observed that in the case of the Bn protected alcohol 612a, the acylated product 609a did slowly

299 Homoallylic alcohol 612c was unstable on silica gel.
300 See e.g. (a) Hansen, T. V. Tetrahedron: Asymmetry 2002, 13, 547. (b) de Fátima, Â.; Pilli, R. A. ARKIVOC 2003, 10, 118-126.
decompose under the reaction conditions (Table 5.1, Entry 2). This trend remained even if less nucleophilic bases were used (Table 5.1, Entries 3-6). As a consequence, two alternative protocols were assessed with the DCC-mediated coupling affording the best yields (Table 5.1, Entries 7-9).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>X</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Cl</td>
<td>TEA, CH₂Cl₂, 0°C, 30'</td>
<td>609a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>Cl</td>
<td>TEA, CH₂Cl₂, 0°C, 1h</td>
<td>609a</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Cl</td>
<td>py, CH₂Cl₂, 0°C, 30'</td>
<td>609a</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Cl</td>
<td>py, CH₂Cl₂, 0°C, 1h</td>
<td>609a</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Cl</td>
<td>2,6-lutidin, CH₂Cl₂, 0°C, 30'</td>
<td>609a</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>Cl</td>
<td>2,6-lutidin, CH₂Cl₂, 0°C, 1h</td>
<td>609a</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>OMe</td>
<td>MeLi, THF, r.t., 24h</td>
<td>609a</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>OMe</td>
<td>MeLi, Et₂O, r.t., 24h</td>
<td>609a</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>OH</td>
<td>DCC, CH₂Cl₂, r.t., 12h</td>
<td>609a</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>PMB</td>
<td>OH</td>
<td>DCC, CH₂Cl₂, r.t., 12h</td>
<td>609b</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>PMB</td>
<td>Cl</td>
<td>TEA, CH₂Cl₂, 0°C, 30'</td>
<td>609b</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>TBS</td>
<td>Cl</td>
<td>TEA, CH₂Cl₂, 0°C, 30'</td>
<td>609c</td>
<td>89</td>
</tr>
<tr>
<td>13</td>
<td>TBDPS</td>
<td>Cl</td>
<td>TEA, CH₂Cl₂, 0°C, 30'</td>
<td>609d</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 5.1

Finally, the metathesis step was evaluated. It was observed that the nature of the protecting group in substrate 609 has a great influence on the rate of the metathesis (Table 5.2). When the ring closing reaction, promoted by the 1st generation Grubbs catalyst (GC-1), was attempted on the benzyl protected substrate 613a, only very low conversions were observed (Table 5.2, Entry 1). It was reasoned that the free lone pairs of the benzyl ether function might
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compete with the olefins for vacant coordination sites present on GC-1.\textsuperscript{301}
Even though this process is reversible, it slows down the reaction rate and, more importantly, the prolonged reaction time leads to thermal decomposition of the catalyst. Higher loading of the catalyst are then mandatory.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\includegraphics[width=0.5\textwidth]{reaction_diagram.png}};
\end{tikzpicture}
\end{center}

Even though this process is reversible, it slows down the reaction rate and, more importantly, the prolonged reaction time leads to thermal decomposition of the catalyst. Higher loading of the catalyst are then mandatory.

To overcome this problem, Ti(OPr\textsuperscript{i})\textsubscript{4} was added as an additive.\textsuperscript{301a,302} Ti(OPr\textsuperscript{i})\textsubscript{4} preferentially interacts with oxygen lone pairs and diminish their ability to interact with GC-1. As a consequence, when substrate 609\textsuperscript{a} was submitted to GC-1/Ti(OPr\textsuperscript{i})\textsubscript{4}-metathesis conditions, the desired lactone 613\textsuperscript{a} was yielded in 92% yield (Table 5.2, Entry 2).

A similar situation was observed in the case of the PMB-protected compound 609\textsuperscript{b} (Table 5.2, Entries 3-5). In this case, even the use of

\begin{table}
\centering
\begin{tabular}{cccccc}
Entry & PG & Grubbs cat. & Additive & Product & Yield\textsuperscript{a} \\
\hline
1 & Bn & GC-1, 0.1 eq & - & 613\textsuperscript{a} & 45 \\
2 & Bn & GC-1, 0.1 eq & Ti(OPr\textsuperscript{i})\textsubscript{4} & 613\textsuperscript{a} & 92 \\
3 & PMB & GC-1, 0.1 eq & - & 613\textsuperscript{b} & <10 \\
4 & PMB & GC-1, 0.1 eq & Ti(OPr\textsuperscript{i})\textsubscript{4} & 613\textsuperscript{b} & 78 \\
5 & PMB & GC-2, 0.05 eq & Ti(OPr\textsuperscript{i})\textsubscript{4} & 613\textsuperscript{b} & 99 \\
6 & TBS & GC-1, 0.1 eq & - & 613\textsuperscript{c} & 96 \\
7 & TBDPS & GC-1, 0.1 eq & - & 613\textsuperscript{d} & 89 \\
\end{tabular}
\caption{Table 5.2}
\end{table}

\textsuperscript{a} Refers to pure, isolated compounds

\footnotesize{

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GC-1/Ti(OPr i) 4 did not lead to complete conversion of 609b to 613b. Thus the more reactive 2nd generation Grubbs catalyst (GC-2)/Ti(OPr i) had to be employed (Table 5.2, Entries 5).

In the case of the TBS and TBPDS protected substrates 609c and 609d, the addition of Ti(OPr i) 4 was not necessary because the steric requirements of these protecting groups effectively inhibit undesired interactions of the oxygen lone pairs with Grubbs catalysts (Table 5.2, Entries 6 and 7).

Having lactones 613a-d in our hands, their deprotection was attempted (Table 5.3). Initially, removal of the benzyl group of 613a was investigated. From the literature, it is known that selective deprotection of a benzyl group can be accomplished in the presence of activated olefins if FeCl 3 is used (Table 5.3, Entry 1). However, we had some problems with reproducibility of the reaction and thus an alternative protocol using BCl 3 was employed and proved highly successful (Table 5.3, Entry 2).

As expected, DDQ-mediated deprotection of the PMB group proceeded smoothly, yielding alcohol 614 in 92% yield (Table 5.3, Entry 3).

The deprotection of both silicon-based protecting groups was achieved using TBAF. In these cases, it was observed that the polarity of the solvent appeared to influence the yields of the reaction (Table 5.3, Entries 4-6). If THF was used as a solvent, a large amount of side products was generated. The desired alcohol 614 could be isolated in 43% yield (Table 5.3, Entry 5).


It was observed that the quality of FeCl 3 is extremely important for the reaction’s reproducibility. For more details about the evaluation of FeCl 3-quality see experimental section.
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On the other hand, if DMF was employed as the solvent, TBAF-mediated deprotection of 613c and 613d smoothly furnished the desired alcohol 614 in 88% and 87% yields, respectively.

![Diagram of lactone and alcohol conversion](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>FeCl₃, CH₂Cl₂, r.t., 5'</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>BCl₃, CH₂Cl₂, -78°C, 2h</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>PMB</td>
<td>DDQ, CH₂Cl₂, r.t., 2.5 h</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>TBAF, THF, 0°C, 3h</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>TBS</td>
<td>TBAF, DMF, 0°C, 12h</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>TBDPS</td>
<td>TBAF, DMF, 0°C, 12h</td>
<td>88</td>
</tr>
</tbody>
</table>

*Refers to pure, isolated compounds

Table 5.3

Oxidation of the alcohol 614 to aldehyde 606 proved to be more difficult than expected. Among the tested reagents, only the Swern oxidation proved to be able to accomplish the oxidation of the alcohol in good yield (Table 5.4, Entry 5). This is presumably due to the unstability of aldehyde 606. Indeed, all our attempts to purify compound 606 failed and crude aldehyde 606 had to be used in the next step, immediately after the work-up procedure.

Aldehyde 606 was then reacted with benzyl phenyl sulfoxide, under the standard sulfoxide-modified Julia olefination conditions (see chapter 4.4).


306 Aldehyde 606 did decompose on silica gel, deactivated silica gel (15 % of TEA (V/V)), basic alumina and even in the freezer over 2 days time.
Chapter 5. General way to styryl lactones

Gratifyingly, the desired \((R)\)-goniothalamin \(566\) could be isolated in 78% yield (starting from alcohol \(614\)) and excellent \(E/Z\) selectivity (Table 5.4).

\[
\begin{align*}
\text{Entry} & \quad \text{Conditions} & \quad \text{Yield}^a \quad \text{[\%]} \\
1 & \quad \text{Dess-Martin} & \quad 32 \\
2 & \quad \text{PCC} / \text{AcONa} & \quad 30 \\
3 & \quad \text{PCC} / \text{Celite} & \quad <10 \\
4 & \quad \text{PDC} & \quad <10 \\
5 & \quad \text{Swern oxidation} & \quad \sim 95
\end{align*}
\]

\(^a \text{1H-NMR yield, aldehyde used in the next step without further purification.}\)

Table 5.4

At this stage, it is important to highlight that the sulfoxide-modified Julia olefination furnished the natural product \(566\) in both excellent yield and \(E/Z\) selectivity. In stark contrast, other olefination methods such as the Wittig, classical Julia or Kociensky-Julia olefination accomplished this transformation in either poor yields and/or selectivity (Table 5.5).
Since it is known that (R)-goniothalamin 566 is a precursor to other natural products, its stereoselective conversion into (R)-goniothalamin oxide 567 was attempted. From the literature, it was known that if 566 was reacted with 70% mCPBA, in refluxing CH2Cl2, (R)-goniothalamin oxide 567 was produced in 69% yield and as a 3:2 mixture of diastereoisomers (Table 5.6, Entry 1).

After a short optimization of reaction’s conditions, (R)-goniothalamin oxide 567 was obtained in 98% yield and an excellent 19:1 diastereoselectivity.
5.4.3 Synthesis of kavain

Since the synthesis of the alcohol 615a, a key intermediate in (R)-kavain 570 synthesis, will be discussed in details in the context of the total synthesis of jerangolid A, herein, only the sulfoxide-modified Julia olefination step will be described.

Thus, alcohol 615a was transformed to aldehyde 607a via Swern oxidation. Lactone 607a was immediately reacted with benzyl phenyl sulfoxide under the standard Sulfoxide-Julia olefination conditions (Scheme 5.17), affording (R)-kavain in 65% yield and an excellent E/Z selectivity.
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5.5 Conclusions and perspectives

In summary, we have demonstrated that the sulfoxide-modified Julia olefination is a very important and connective C-C bond formation method, allowing the selective generation of olefins previously not accessible via standard olefination techniques (Table 5.5). Moreover, it was shown that this reaction could be successfully used in the context of natural product synthesis.

Using the sulfoxide-modified Julia olefination, (R)-goniothalamin 566 was prepared in 6 (51-55% overall yield) and 5 steps (55% overall yield), respectively, starting from commercially available (R)-glycidol (R)-611 and (R)-benzyl glycidol (R)-156a (Scheme 5.18).
Chapter 5. General way to styryl lactones

Scheme 5.18

As an advantage over all previous total syntheses of 566, in our case the styryl subunit of 566 could be efficiently introduced at the last step. Since it is known that changes in electronic properties of the phenyl group strongly affect the biological activities, our approach provides an efficient access to various derivatives of goniothalamin 566.

Importantly, (R)-goniothalamin 566 serves as a precursor in the synthesis of other natural products isolated from various species of Goniothalamus. This was demonstrated by the stereoselective transformation of (R)-566 to (R)-goniothalamin oxide 567 (Scheme 5.19). Additionally, it is known from the literature that (R)-566 might be easily transformed into epi-(+)-4-dehydroxygoniotriol epi-568 and (+)-9-deoxygoniopyrone 569.308

The total synthesis of (R)-kavain 570 was also accomplished using a sulfoxide-modified Julia olefination as a key step, in 7 steps and 16% overall yield (Scheme 5.20).

Chapter 5. General way to styryl lactones

![Diagram of reaction scheme]


Scheme 5.19

![Diagram of reaction scheme]

Scheme 5.20
Chapter 6. Total synthesis of jerangolid D

6. Total synthesis of jerangolid D

6.1 Introduction

Jerangolids A, B, D, E and H (Figure 6.1) are secondary metabolites produced by the myxobacterium *Sorangium cellulosum* (strain So ce 307), a species isolated in 1987 in the soil of Jerusalem. In vitro tests suggested that jerangolid A and D might be potential antifungal agents (other jerangolid derivatives were not tested), since they exhibit interesting activity against the developing cells of *Hansenula anomala* and *Mucor hiemalis* (~70 ng/mL), *Pichia membranaefaciens*, *Debaryomyces hansenii* and *Trichosporon terrestr* (0.1-0.4 μg/mL) and *Trichoderma hamata*, *Botritis cinerea* and *Candida albicans* (4-7 μg/mL). The mechanism of their action is believed to be similar to that of ambruticin, another well-known myxobacterium isolate. However, even in the case of ambruticin, this mode of the action is still not clear.

To the best of our knowledge, the total synthesis of these products has not been reported so far. The only exception is a biosynthetic preparation of jerangolid A, recently patented by Kosan Biosciences, Inc. using modified enzymes.

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Chapter 6. Total synthesis of jerangolid D

![Chemical structures of jerangolid A, D, E, and H](image)

Figure 6.1

### 6.2 Objectives

Our interest in the synthesis of the jerangolid-family compounds arose from its close structural similarity and biological-activity pattern with (+)-ambruticin. Since both ambruticin and the jerangolids possess the same C6-C17 motive (jerangolid numbering) and similar biological activity, it appears that this part of the molecule might be responsible for the anti-fungal activity of these molecules.

Driven by these considerations and having already established an easy access to the C7-C17 fragment 191 of jerangolid A (616) and D (617), it was decided to focus our synthetic efforts towards the simplest member of the jerangolid family, jerangolid D (617) (Scheme 6.1). To do so, a short and efficient approach to the C1-C6 fragment, lactone 607b, had to be established.
Chapter 6. Total synthesis of jerangolid D

![Diagram of Jerangolid D (617) and 607b](image)

**Scheme 6.1**

### 6.3 Synthesis of the C1-C6 lactone part

#### 6.3.1 First approach – via Sharpless dihydroxylation

Our first approach towards lactone \(607b\) was based on the C1-O5 cyclization. It was envisioned that the C5 stereogenic centre present in the cyclization precursor \(621\), would be established via a Sharpless Asymmetric Dihydroxylation (AD) of the alkene derivative \(622\). Two different approaches towards olefin \(622\) were considered (Scheme 6.2).

The initial route to \(622\) was based upon the addition of the silyl enol ester \(623\) to the highly reactive ketene \(626\)\(^{311}\) formed *in situ* from crotyl chloride \(624\) (Scheme 6.3). This reaction should afford the silyl enol ether \(626\) which, upon selective hydrolysis, would yield the desired β-ketoester \(622\). As a consequence, the C4-C5 double bond in the starting acyl chloride \(624\) will be

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Chapter 6. Total synthesis of jerangolid D

translocated\textsuperscript{312} to the C5-C6 position. Our synthetic evaluation of this transformation is summarized in Table 6.1.

\[ \text{Scheme 6.2} \]

\[ \text{Scheme 6.3} \]

\textsuperscript{312} For other examples see: Murphy, J. P.; Hadden, M.; Stevenson, P. J. \textit{Tetrahedron} 1997, 53, 11827-11834.
Chapter 6. Total synthesis of jerangolid D

Initially, the quench of enolate 627 with 1.0 M aqueous solution of HCl was investigated (Table 6.1, Entry 1). It was observed that only traces of the desired product 622 were formed. The main product of the reaction proved to be ketone 629, the regioisomer of 622. To inverse the 622 to 629 ratio in favour of 629, the effect of the solvent and work-up method was investigated. In the best case, a 2.67:1 ratio of 622:629 was obtained (Table 6.1, Entry 7).

Unfortunately, compounds 622 and 629 are difficult to separate by methods other than column chromatography. Disappointingly, it was observed that on silica gel, 622 was rapidly inverted into the thermodynamically more stable isomer 629 (Table 6.1, Entry 7). Faced with unexpected drawback, it was...
Chapter 6. Total synthesis of jerangolid D

decided to abandon this approach to 622 and to focus on the second route, which was based on the allylation of nitrile 625.

Our second approach to β-ketoester 622 relied upon a BCl$_3$-mediated allylation$^{313}$ of cyanoester 625. The synthesis started with monomethylation of methyl 3-cyanoacetate 620 using NaH as a base and MeI as a methylating agent (Table 6.2). After some optimization of the reaction conditions, it was observed that traces of MeOH are essential to maintain the reproducibility of the yields (Table 6.2, Entry 4).

```
\[ \begin{align*}
\text{Entry} & \quad \text{Conditions} & \quad \text{Yield of 625}^a \quad \text{Yield of 631}^b \\
1 & \quad \text{Et}_2\text{O}, \text{r.t.} & \quad - & \quad - \\
2^b & \quad \text{THF}, \Delta t & \quad >5 & \quad 48 \\
3^c & \quad \text{THF}, \text{r.t.} & \quad 32-72 & \quad 5-31 \\
4^d & \quad \text{THF, MeOH (0.05 eq), r.t.} & \quad 54-75 & \quad >5-11
\end{align*}\]
```

$^a$ Refers to pure isolated products.
$^b$ 47% of 630 was re-isolated.
$^c$ Reaction was difficult to reproduce. Yields from 4 attempts: 72%, 32%, 41%, 65%.
$^d$ Traces of MeOH made the reaction more reproducible. Yields from 4 attempts: 75%, 69%, 72%, 54%.

Table 6.2

Having a sufficient amount of nitrile 625 in our hands, we could focus on the allylation step (Table 6.3). It was observed that the reaction of 625 with allyltrimethylsilane 131 proceeded smoothly, yielding the desired allyl ketoester 622 in good yields and purity (Table 6.3, Entry 3). However, it was also observed that the reaction was difficult to scale up.$^{314}$

Table 6.3

In any case, we had enough material to test our key step, the Sharpless AD (Scheme 6.4). Disappointingly, the reaction failed to produce even traces of diol 621, under all conditions tested. It appears that degradation of 622 occurs due to the competitive dihydroxylation of the enol form of compound 622. This route was definitely abandoned.

Scheme 6.4

6.3.2 Second route – metathesis approach

Since our first approach towards jerangolid D lactone subunit 607b failed, a new route had to be established. It was envisioned that a metathesis approach might be a good choice (Scheme 6.5). Therefore, lactone 607b was disconnected at the C2-C3 olefinic bond to give intermediate 632. Diene 632
might be obtained by acylation of enol 633. Two different routes towards the monoprotected diol 633 were proposed.

![Chemical structure diagram]

**Scheme 6.5**

Our first route is based on the opening\(^\text{315}\) of epoxide (R)-156c by vinyl lithium species\(^\text{316}\) (Table 6.4). Initial attempts were performed using the less volatile ethyl vinyl ether 636. Thus, ethyl vinyl ether 636 was transformed into its lithium derivative 637 and its formation was proved by trapping it with TMSCl\(^\text{317}\) (Table 6.4, Entries 1-3). Once being sure that the vinyl anion 637 was formed in sufficient amount, epoxide (R)-156c was added. Disappointingly, the desired adduct 639 was obtained in rather low yields (Table 6.4, Entries 4-6).

Two key factors appear to contribute to the poor yields of epoxide opening.\(^\text{315}\) First, from other experiments (see chapter 5) it was observed that the stability of our final products was not very high. Additionally, the

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\(^{317}\) This experiment was done, because we did find several rather different protocols describing the synthesis of α-lithium derivatives of 22. E.g. see: Braish, T. F.; Saddler, J. C.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3647-3658.
Chapter 6. Total synthesis of jerangolid D

generation of the vinyl lithium species \textit{637}, directly from \textit{636}, proved to be rather difficult (a large excess of both \textit{tBuLi} and ether \textit{636} had to be used). To generate only \textit{637}, recourse to its \(\alpha\)-tributyltin equivalent\textsuperscript{318} becomes mandatory.

Nevertheless, since the synthesis of \textit{633} via epoxide opening did cause already a number of problems, we decided to abandon this route in favour of the second approach.

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
Entry & Condition of \textit{638} formation & \textit{E}\textsuperscript{+} & Conditions & Product & Yield\textsuperscript{a} [%] \\
\hline
1 & \textit{tBuLi} (1.2 eq) \(-78^\circ\text{C}, 30\) & TMSCl (1.0 eq) & \textit{-78^\circ\text{C} (10') to r.t.} & \textit{638} & >5 \\
2 & \textit{tBuLi} (0.7), \(-78^\circ\text{C} (10') to 0^\circ\text{C (30')}, back to \(-78^\circ\text{C}\) & TMSCl (1.0 eq) & \textit{-78^\circ\text{C} (10') to r.t.} & \textit{638} & 53 \\
3 & \textit{tBuLi} (2.0 eq), \textit{636} (3.0 eq), \(-78^\circ\text{C} (10') to 0^\circ\text{C (30')}, back to \(-78^\circ\text{C}\) & TMSCl (1.0 eq) & \textit{-78^\circ\text{C} (10') to r.t.} & \textit{638} & >99 \\
4 & \textit{tBuLi} (2.0 eq), \textit{636} (3.0 eq), \(-78^\circ\text{C} (10') to 0^\circ\text{C (30')}, back to \(-78^\circ\text{C}, \text{BF}_3\text{.OEt (1.1eq) } \) & rac-156c (1.0 eq) & \textit{-78^\circ\text{C} (1h), NaHCO}_3 & \textit{639} & 34 \\
5 & \textit{tBuLi} (2.0 eq), \textit{636} (3.0 eq), \(-78^\circ\text{C} (10') to 0^\circ\text{C (30')}, back to \(-78^\circ\text{C}, \text{BF}_3\text{.OEt (1.1eq) (15') }\) & rac-156c (1.0 eq) & \textit{-78^\circ\text{C} (1h), NaHCO}_3 & \textit{639} & 36 \\
6 & \textit{tBuLi} (2.0 eq), \textit{636} (3.0 eq), \(-78^\circ\text{C} (10') to 0^\circ\text{C (30')}, back to \(-78^\circ\text{C}\) & rac-156c (1.0 eq) & \textit{-78^\circ\text{C} (15'), \text{BF}_3\text{.OEt (1.1eq) (1h at -78^\circ\text{C) NaHCO}_3} & \textit{639} & 12 \\
\hline
\end{tabular}
\caption{Table 6.4}
\end{table}

\textsuperscript{a} Refers to pure, isolated product.

Chapter 6. Total synthesis of jerangolid D

The second approach to monoprotected diol 633 was envisioned from D-malic acid 640 (Scheme 6.6).

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
633 & \quad \text{OTBS} \\
635 & \quad \text{MeO} \\
640 & \quad \text{OH} \\
\end{align*}
\]

**Scheme 6.6**

However, before embarking on the synthesis of the real substrate, it was decided to test our key-step on a model substrate, ethyl 3-hydroxypropionate 641 (Table 6.5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tebbe rgt, -78°C to r.t.</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Tebbe rgt, py (1.1 eq), -78°C to r.t.</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Tebbe rgt, 1 mmol scale, as above</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>Petasis (1.0 eq), 65°C, 6 h</td>
<td>53(^a)</td>
</tr>
<tr>
<td>5</td>
<td>Petasis (3.0 eq), 85°C, 12h</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Petasis (3.0 eq), 65°C, 12h</td>
<td>66(^b)</td>
</tr>
<tr>
<td>7</td>
<td>Petasis, 65°C, 12h (after 6h more of rgt added)</td>
<td>25(^c)</td>
</tr>
<tr>
<td>8</td>
<td>Takai-Utimoto, CH₂Br₂, r.t. 12 h</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>Takai-Utimoto, CH₂Br₂, r.t. 48 h</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>Takai-Utimoto, CH₂Br₂, r.t. 48 h, (10 mmol)</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^{a}\) 12% conversion, yield recalculated to 100% conversion.
\(^{b}\) 25% conversion, yield recalculated to 100% conversion.
\(^{c}\) 45% conversion, yield recalculated to 100% conversion.

**Table 6.5**

Thus, the hydroxy group of 641 was silylated with TMSCl and the conversion of the ester group of 642 into the enol ether 643 was investigated.
Chapter 6. Total synthesis of jerangolid D

All three most commonly used protocols, the Tebbe reagent,\textsuperscript{319} the Petasis reagent\textsuperscript{320} and the Takai-Utimoto alkylation,\textsuperscript{321} were tested (Table 6.5). The Takai-Utimoto alkylation gave the best yields of the desired enol ether 643. This transformation was reproducible, even in larger scale (Table 6.5, Entries 9 and 10).

In the next step, the TMS-protecting group was removed and the acylation of alcohol 644 was attempted (Table 6.6). Disappointingly, this step failed under all conditions tested.

![Chemical diagram]

### Table 6.6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)\textsubscript{3}, CH\textsubscript{3}CN, 0°C to r.t.</td>
<td>deg.</td>
</tr>
<tr>
<td>2</td>
<td>Et\textsubscript{3}N, DCM, 0°C to r.t.</td>
<td>deg.</td>
</tr>
<tr>
<td>3</td>
<td>py, THF, 0°C to r.t.</td>
<td>deg.</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{3}N, DCM, 0°C to r.t.</td>
<td>deg.</td>
</tr>
<tr>
<td>5</td>
<td>py, THF, 0°C to r.t.</td>
<td>deg.</td>
</tr>
</tbody>
</table>

Even though the acylation of 644 was not successful, it was decided to transpose our approach to the real substrate 633. Thus, D-malic acid 640 was


Chapter 6. Total synthesis of jerangolid D

transformed into the dimethyl ester 646\textsuperscript{322,323} which was selectively reduced to 1,2-diol 647\textsuperscript{324} (Scheme 6.7).

Scheme 6.7

The selective monoprotection of diol 647 was next attempted (Table 6.7). This transformation proved to be more difficult than expected.

Table 6.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>646:647</th>
<th>Yield\textsuperscript{a} [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSCI, Im, cat. DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>2:1</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>TBSCI, Im, cat. DMAP, THF</td>
<td>2.5:1</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>TBSCI, py, cat. DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>3:1</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>TBSCI, py, cat. DMAP, THF</td>
<td>2:1</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>TBSCI, 2,6-lutidin, cat. DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>6:1</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>TBSCI, Im, cat. DMAP, DMF</td>
<td>4:1</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>TBSCI, py, cat. DMAP, DMF</td>
<td>3:1</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>TBSCI, py, DMF</td>
<td>5:1</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>TBSCI, Et\textsubscript{3}N, cat. DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>12:1</td>
<td>86</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Refers to pure, isolated product.

\textsuperscript{322} This reaction was performed on large scale by F. Lucaccioni in 97% yield.
\textsuperscript{323} Starting on January 1\textsuperscript{st}, 2006 the dimethyl ester 646 became cheaper than acid 640 and thus, was used as the starting material.
Chapter 6. Total synthesis of jerangolid D

Much to our delight, the use of TBSCI/\(\text{Et}_3\text{N/DMAP}\) system enabled us to obtain the desired monoprotected diol 648 in 86% yield as a 12:1 mixture of 648:649 (Table 6.7, Entry 9).

The remaining C5 alcohol of 648 was silylated and the resulting bis-protected diol was submitted to Takai-Utimoto alkylation. The key intermediate 633 could be isolated in 73% yield over 2 steps (Scheme 6.8).

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{OH} \\
\text{36} & \quad \text{OTBS} \\
1) \text{TMSCl, Et}_3\text{N, CH}_2\text{Cl}_2, 98\% & \quad 2) \text{Takai-Utimoto, 74\%} \\
\text{MeO} & \quad \text{3} \\
\text{5} & \quad \text{5} \\
633 & \quad \text{21}
\end{align*}
\]

Scheme 6.8

Finally, chemoselective TMS-deprotection of 633 in the presence of the TBS group and the highly sensitive enol ether, was attempted (Table 6.8). Gratifyingly, the use of MeLi accomplished this transformation in excellent yield (Table 6.8, Entry 5).

\[
\begin{align*}
\text{MeO} & \quad \text{3} \\
\text{5} & \quad \text{5} \\
633 & \quad \text{650}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield[a] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(t)-BuOK, THF, -78°C</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>(t)-BuOK, THF, 0°C to r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>(n)-BuLi, THF, -78°C to r.t.</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>MeLi, THF, -78°C to r.t.</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>MeLi, THF, 0°C to r.t.</td>
<td>quant.</td>
</tr>
</tbody>
</table>

[a] Refers to pure, isolated product.

Table 6.8

At this stage, the crucial acylation of alcohol 650 was attempted. Taking into account our previously unsuccessful attempts, performed on the model substrate 645 (Table 6.6), and the conditions required for the selective TMS
deprotection, it appeared to us that the only successful combination would be a strong base and an excess of acylating agent in the form of ester (Table 6.9). After a short optimization, we were delighted to observe that our expectations were fulfilled and that ester 632 was formed in 82% yield (Table 6.9, Entry 2).

It is obvious that the success of this reaction is based upon the generation of the lithium alkoxide from 650 which, upon treatment with an excess of methyl acrylate, produces MeO\(\text{Li}^+\) as the side product. Therefore, the sensitive enol ether function of adduct 632 survives these conditions.

Encouraged by this success, a one-pot transformation of bis-protected alcohol 633 to ester 632 was carried out, affording the desired product 632 in an excellent 92% yield (Scheme 6.9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Conversion&lt;sup&gt;a&lt;/sup&gt; [%]</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>Nolan - carben, THF, 24 h</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>(n\text{BuLi}, 0^\circ\text{C to r.t.}, \text{THF})</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>(n\text{BuLi},\text{Et}_3\text{N}, 0^\circ\text{C to r.t.}, \text{THF})</td>
<td>100</td>
<td>deg.</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>(t\text{BuOK}, \text{THF, 0^\circC to r.t.})</td>
<td>100</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on \(^1\text{H-NMR spectra of the crude reaction mixture.}\)

<sup>b</sup> Refers to pure, isolated compounds.

Table 6.9
Having established an easy access to the desired intermediate 632, our last key step, the Grubbs’ metathesis, could be challenged. From the literature, it is known that the metathesis reaction of electron-rich olefins, \(^{325}\) and in particular enol ethers, is rather difficult and requires harsh conditions, e.g. prolonged reaction times and higher catalyst loading. For this reasons, the use of Schrock’s more reactive, thought more sensitive, catalyst \(^{326}\) is generally preferred over the Grubbs’ catalyst. The reason for the low reactivity of these complexes towards electron-rich olefins is presumably the high stability of the intermediate carbeine complex generated during the early phase of the reaction. \(^{327}\)

The sensitivity of the Schrock carbeine prompted us to perform our reactions using the 2\(^{nd}\) generation Grubbs’ catalyst (GC-2) in a non-polar solvent. \(^{325a}\) Thus, ester 632 was treated with GC-2 in deuterated benzene or toluene and the influence of the reaction conditions on the conversion was monitored (Table 6.10). It was observed that the metathesis reaction proceeded somewhat better in toluene at 50°C (Table 6.10, Entry 4), than in benzene, even at higher temperature. In all cases, the catalyst was fully decomposed.


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under the reaction conditions within 5-7h. Therefore, constant addition of the catalyst over a period of 66h (5 mol% of GC-2 each 6h) was performed. The starting material 632 gradually disappeared, yielding the desired lactone 651 in 88% yield (Table 6.10, Entry 8). Unfortunately, up to 55 mol% of GC-2 was consumed in this single experiment.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conversion[^a] [%]</th>
<th>Yield[^a] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^b]</td>
<td>5 mol%, benzene (0.01M), 12h, 70°C</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%, benzene (0.01M), 12h, 60°C</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>3[^b]</td>
<td>5 mol%, benzene (0.01M), 12h, 80°C</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>5 mol%, toluene (0.011M), 12h, 50°C</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>5[^b]</td>
<td>5 mol%, toluene (0.011M), 12h, 60°C</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>5 mol%, toluene (0.011M), 12h, 70°C</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>5 mol%, toluene (0.011M), 12h, 80°C</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>8[^c]</td>
<td>55 mol%, toluene (0.011M), 66h, 50°C</td>
<td>91</td>
<td>88[^d]</td>
</tr>
</tbody>
</table>

\[^a\] Based on \(^1\)H-NMR spectra.

\[^b\] Conversion stopped after 5-7h.

\[^c\] 5 mol% of GC-2 was added every 6h.

\[^d\] Isolated yield.

Table 6.10

These results, although rather encouraging, could not be reconciled with our idea of useful synthetic transformation. It was suggested that the low reactivity of 632 could be due to its difficulty in adopting an (S)-cis conformation and hence, allow the two alkene ends to reach a proper

distance for reaction to occur.\textsuperscript{328} To overcome this problem and to reduce catalyst’s loading, we have decided to use the modified metathesis precursor 652 (Figure 6.2).

![Figure 6.2](image_url)

**Figure 6.2**

The synthesis of 652 started with the monoprotected diol 648 which was transformed into acetals 653a and 653b via PPTS catalyzed transacetalization of acrolein dimethyl acetal and methacrolein dimethyl acetal,\textsuperscript{329} respectively (Scheme 6.10). Acetals 653a and 653b were then submitted to the Takai-Utimoto olefination yielding the desired precursors 652a and 652b in 80 and 85% yield.

![Scheme 6.10](image_url)

**Scheme 6.10**


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With the desired substrate in our hands, the crucial ring closing metathesis could be tested (Table 6.11). Much to our surprise, no important changes in the reactivity of 652a, as compared to substrate 632, was observed (Table 6.11, Entries 1-3). The reaction proceeded with a slightly higher conversion, but decomposition of the catalyst under the reaction conditions was still significant. To avoid this decomposition, the reaction was attempted at r.t. in the presence of 50 mol% of GC-2 (Table 6.11, Entry 4). After 24h, a 39% conversion of acetal 652a to cyclic lactol 654a was reached, and allowing the cyclization to proceed longer led to improved conversions.

![Chemical structure of 652a, 652b, 654a, and 654b]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>GC-2 loading</th>
<th>Conditions</th>
<th>Yielda [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>20 mol%b</td>
<td>benzene, 50°C, 4h</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>30 mol%b</td>
<td>benzene, 70°C, 6h</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>30 mol%b</td>
<td>toluene, 50°C, 6h</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>50 mol%</td>
<td>benzene, r.t., 24h</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>10 mol%</td>
<td>benzene, r.t., 72h</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>10 mol%</td>
<td>benzene, r.t., 84h</td>
<td>95</td>
</tr>
</tbody>
</table>

* Based on the $^1$H-NMR-spectra

b 10 mol% of GC-2 was added every 2h

Table 6.11

Under the optimized conditions, only 10 mol% of GC-2 were required to fully transform 652 to 654 (Table 6.11, Entries 5 and 6). 330 The oxidation of

330 Interestingly, the same reaction conditions were applied to the cyclization of 632, but only very low conversion (~20%) was observed.
lactols 654 with PCC then afforded the desired lactones 655a and 655b in 56% and 51% yield, respectively, over two steps. Removal of TBS group of 655b then furnished the left-hand fragment alcohol 615b, in 81% yield (Scheme 6.11). The C2 desmethyl lactone 615a was also deprotected (82% yield) and used in a synthesis of (R)-kavain (see chapter 5).

Scheme 6.11

In summary, the penultimate precursor of the left-hand fragment of jerangolid D, alcohol 615b, was prepared in 7 steps and 16% overall yield from commercially available dimethyl D-malate 646.

6.3.3 Third approach – via Reformatsky-type reaction

When we encountered the first problems with the metathesis approach to the left hand fragment 607b, an alternative route using an intramolecular Reformatsky reaction331 was proposed (Scheme 6.12). It was envisioned that the intramolecular Dieckman cyclization of an organozinc or organosamarium species derived from halide 657, should afford

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β-ketolactone \(656a\). Its subsequent methylation, followed by deprotection of alcohol C6 and oxidation would then lead to the desired left-hand fragment \(607b\). Surprisingly and to the best of our knowledge, there is only one reported example of an intramolecular Reformatsky reaction between an \(\alpha\)-bromoester and an ester function present in the same substrate.\(^\text{332}\)

![Scheme 6.12](image)

**Scheme 6.12**

In order to test the viability of this approach, the model substrate \(658\) was prepared and submitted to various cyclization conditions (Table 6.12).

Surprisingly and despite varying the conditions for the Reformatsky reaction no traces of the desired cyclized product \(659\) could be observed. Generally, only the product of reductive debromination \(660\) was obtained in nearly quantitative yields (Table 6.12, Entries 1-5). The same results were observed when magnesium\(^\text{333}\) was used instead of zinc (Table 6.12, Entries 6 and 7). Only in the case of SmI\(_2\) did the cyclization proceed, though in a modest 21% yield and accompanied the reduction of the newly created C3 ketone (Table 6.12, Entries 8-9). Some unreacted starting material was also isolated.


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![Chemical structure](image)

### Table 6.12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn (2.0 eq), cat. I₂, r.t. to Δt, THF</td>
<td>660</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Zn (2.0 eq), TMSCl (0.1 eq), r.t. to Δt, THF</td>
<td>660</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Zn (2.0 eq), TMSCl (0.1 eq), o), THF</td>
<td>660</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>Zn (5.0 eq), TMSCl/ Et₂O = 4:1 (v/v)</td>
<td>660</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>Zn (4.0 eq), PbBr (0.1 eq), TMSCl/THF = 1:4</td>
<td>660</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Mg, r.t. to Δt, o), Et₂O</td>
<td>660</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>Mg, r.t., Et₂O</td>
<td>660</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>Sml₂ (2 eq), -78°C to r.t.</td>
<td>661&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>Sml₂ (6 eq), 0°C to r.t.</td>
<td>661&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup> Refers to pure, isolated products.
<sup>b</sup> Nothing else recovered, probably lost during the work-up.
<sup>c</sup> 21% of 50 isolated, other side products not identified, probably the products of over reduction.

These unsuccessful cyclizations produced a large amount of debrominated ester 660 which was submitted to base-induced cyclization (Scheme 6.13). Not surprisingly, only degradation was observed.

### Scheme 6.13

Since the direct ring-closure of α-bromoester 658 failed, it was decided that a more reactive aldehyde could be used instead of an ester function (Scheme 6.14). In this case, a samarium-promoted Reformatsky cyclization on a
similar substrate was known in the literature.\textsuperscript{334} In fact, the only difference between the published system and ours is the presence of the methyl group at the C2 carbon position.

\begin{center}
\includegraphics[width=\textwidth]{scheme6.14.png}
\end{center}

**Scheme 6.14**

Thus, it was decided to reproduce the published procedure and then investigate the influence of the C2 methyl group on the reaction in terms of yields and selectivity (Scheme 6.15).

\begin{center}
\includegraphics[width=\textwidth]{scheme6.15.png}
\end{center}

**Scheme 6.15**

Therefore, epoxide \((R)\)-156 was opened with vinyl Grignard reagent, in the presence of Cu(I) salts, and the resulting homoallylic alcohol 612a was acylated with 2-bromoacetyl bromide and 2-bromopropionyl chloride. Ozonolysis of \(\alpha\)-bromooctoesters 662a and 662b yielded the unstable aldehydes 662a and 662b, which were immediately treated with SmI\(_2\). In the case of aldehyde 662a (\(R = H\)), only 661a was formed as single diastereoisomer.\(^{335}\) However, the cyclization of aldehyde 662b led to the formation of 661b as a mixture of isomers.\(^{336}\) The stereoselectivity of this reaction is not important in our case, since all the newly created stereocenters (C3 centre in the case of lactone 661a and C2 and C3 centres in the case of 661b) will be destroyed in the next step of the synthesis.

Finally, an oxidation/cyclization/debenzylation sequence then completed the assembly of the left-hand subunit 615b (Scheme 6.16). In this context, it is interesting to note that the oxidation of the C3 alcohol proved to be more difficult than expected and that only the Swern and Jones oxidations were able to accomplish it (Table 6.13).

Using this approach, 615b was prepared in 7 steps and 26% overall yield. The only disadvantage of this route is lack of originality, since the core of the synthetic sequence is based on already published material.\(^{334}\) Accordingly, another approach, which would be based on the Reformatsky-type reaction, was searched.

\(^{335}\) These results are in agreement with those published. See ref. 334.

\(^{336}\) The ratio was not optimized, since we did not care about the stereochemistry of the product. Thus, it is quite possible that the selectivity might be improved or varied.
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Scheme 6.16

Table 6.13

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reagent</th>
<th>Yield[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>PDC (6.0 eq), CH₂Cl₂, r.t., 24h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>PDC (6.0 eq), DMF, r.t., 24h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>PCC (6.0 eq), CH₂Cl₂, r.t., 24h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>PCC (6.0 eq), Celite, CH₂Cl₂, r.t., 24h</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Dess-Martin periodinate</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Swern oxidation</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Jones oxidation</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>Swern oxidation</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Jones oxidation</td>
<td>73</td>
</tr>
</tbody>
</table>

* ¹H-NMR-spectra based yield.
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After a brief literature search, the Blaise reaction\footnote{Blaise, E. E. C. R. Acad. Sci. 1901, 132, 478.} attracted our attention. Taking into account that this reaction is more than a century old,\footnote{Blaise, E. E. C. R. Acad. Sci. 1901, 132, 978.} it has earned so far only very little significance in synthetic organic chemistry. This is rather surprising, since this condensation represents a short and efficient route to β-ketoesters of general structure $669$, starting from α-bromoesters $667$ and nitriles $666$ (Scheme 6.17). By careful hydrolysis of $668$, 3-amino-α,β-unsaturated esters might be also obtained.

\[
\begin{align*}
R^1 \equiv N + \text{Br} & \quad \text{O}^2 \quad \text{OR}^3 \\
666 & \quad \text{Zn} \quad 667 \quad \text{Zn} \\
669 & \quad \text{H}^+ 
\end{align*}
\]

\textbf{Scheme 6.17}

Despite its versatility, the use of the Blaise reaction is rather limited, due to low yields, narrow scope and undesired side reactions.\footnote{Carson, J.; Rinehart, K. L. Jr., Thornton, S. D. Jr. J. Org. Chem. 1953, 18, 1594.} The first breakthrough in term of reaction yields and reproducibility was made by Kishi, who used activated zinc prepared by washing it with a 3.0 M aqueous solution of HCl and slowly added the α-bromoacetate to the reaction mixture to minimize self-condensation.\footnote{Kagan, H. B.; Suen, Y.-H. Bull. Chim. Soc. Fr. 1966, 1819.} Recently, ultrasonic assistance\footnote{Konrad, J.; Jezo, I. Chem. Izvesti. 1980, 34, 125; Chem. Abstr. 1980, 93, 150172.} and the

use of added zinc oxide\textsuperscript{341} were also shown to have a beneficial effect on the reaction. However, from a practical point of view, the most important modification was introduced in 2004 by Shin \textit{et al.}\textsuperscript{342} They demonstrated that traces (0.5 mol\%) of MeSO\textsubscript{3}H were sufficient to generate activated Zn dust (30 min reflux in THF) that is highly active under the reaction conditions. From these literature data, it was decided to base our next approach to the left-hand precursor \textit{615b} on an intramolecular Blaise reaction (Scheme 6.18).

\begin{equation}
\begin{array}{c}
\text{MeO} \\
\text{607b} \\
\text{O} \\
\text{O} \\
\text{1} \\
\text{3} \\
\text{2} \\
\text{5} \\
\end{array} 
\xrightarrow{\text{Et\textsubscript{2}AlCN-mediated epoxide (R)-156 opening}}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{1} \\
\text{5} \\
\text{2} \\
\text{3} \\
\end{array} 
\begin{array}{c}
\text{O} \\
\text{670} \\
\text{O} \\
\text{Bn} \\
\text{3-CN} \\
\text{671} \\
\end{array}
\end{equation}

\textbf{Scheme 6.18}

Surprisingly, only one example of an intramolecular Blaise reaction was published in the literature.\textsuperscript{343} Nevertheless, it was felt that this route to \textit{615b} would be interesting and the cyclization step was challenged (Scheme 6.19). The synthesis of the substrate \textit{671} started with the Et\textsubscript{2}AlCN-mediated epoxide (\textit{R})-156 opening,\textsuperscript{344} yielding the β-hydroxy nitrile \textit{672} in near quantitative manner. Acylation with 2-bromoacetyl bromide and 2-bromopropionyl chloride, respectively, then afforded the cyclization precursors \textit{671a} and \textit{671b} in 80% and 89% yield, respectively.

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Disappointingly, under all conditions tested, no cyclization product could be observed (Table 6.14).

Table 6.14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
<th>Yielda [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(Ag) (2.0 eq), Δt, THF</td>
<td>673</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Zn (2.0 eq), ZnO (0.1 eq), Δt, THF</td>
<td>673</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Zn (2.0 eq), cat. I2, Δt, THF</td>
<td>673</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>Zn (2.0 eq), MeSO3H (0.1 eq), Δt, THF</td>
<td>673</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Zn (4.0 eq), PbBr (0.1 eq), Δt, THF</td>
<td>673</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>Zn (4.0 eq), SmI2 (2 eq), 0°C</td>
<td>673</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>SmI2 (2 eq), 0°C</td>
<td>671a</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>SmI2 (2 eq), 0°C to r.t.</td>
<td>-</td>
<td>deg.</td>
</tr>
<tr>
<td>9</td>
<td>SmI2 (6 eq), 0°C</td>
<td>671a</td>
<td>93</td>
</tr>
</tbody>
</table>

*a Refers to pure, isolated products.

Faced with this failure, we had to redesign our approach and we have decided to base it on the intermolecular Blaise reaction (Scheme 6.20).
Chapter 6. Total synthesis of jerangolid D

The intermolecular Blaise condensation was easy to test since it is known that unprotected hydroxy groups are tolerated under the reaction conditions.\(^\text{345}\) Therefore, the previously prepared \(\beta\)-hydroxynitrile 672 was reacted with methyl bromoacetate in the presence of activated zinc dust (Scheme 6.21).

To our delight, the reaction proceeded smoothly and produced the desired \(\beta\)-ketoester 674a in 70\% yield. Similarly, when 672 was reacted with methyl 2-bromopropionate, the corresponding \(\beta\)-ketoester 674b was obtained in 78\% yield. Base-mediated cyclization\(^\text{346}\) of 674a and 674b, followed by \(O-\)

---


methylation, afforded the protected left-hand precursors 664a and 664b in 52% and 62% yield, respectively. Finally, benzyl group deprotection completed the synthesis of the \((R)\)-kavain left-hand precursor 615a and the jerangolid D western subunit 615b.

In an attempt to increase the overall yield of this sequence, the use of a silicon protecting group instead of a benzyl one was envisaged (Scheme 6.22). Much to our surprise, although a TBS protecting group was found to be tolerated under the Blaise conditions and during the epoxide opening, it proved to be totally incompatible with the final base-mediated cyclization.

In summary, using a Reformatsky-based approach, we were able to prepare 615b in 7 steps and 26% overall yield, using a SmI\(_2\)-promoted intramolecular cyclization, or in 5 steps and 34% overall yield, using an intermolecular Blaise reaction. In both cases, the sequence started from the commercially available epoxide \((R)\)-611.
6.3.4 Fourth approach – via aldol reaction

Our last attempted approach towards left-hand fragment 615b of jerangolid D, was based upon aldol condensation. With an easy access to large quantities of diol 647, we decided to use it as a starting point for our two slightly different approaches towards 607b (Scheme 6.23).

According to route 1, methyl ester 677a was envisaged as a cyclization precursor. As a consequence, base as well as acid mediated-closures might be attempted. Following route 2, the tert-butyl ester 678 was proposed as a key-intermediate. In this case, only acid-catalysed cyclization could occur.

Our synthesis of the β-ketoester 677a was based on the addition of an ester enolate to the Weinreb amide 680, which was readily prepared by protection of diol 647, followed by its conversion into 680 using iPrMgCl and NMe(OMe).HCl (Scheme 6.24). To our surprise, when amide 680 was reacted with the lithium enolate generated from methyl propanoate,347 only

traces of the desired β-ketoester 677a were obtained (Table 6.15, Entries 1-6). On the other hand, the reaction of the enolate generated from the corresponding tert-butyl ester afforded the β-ketoester 677b in 88% yield (Table 6.15, Entry 7).

![Scheme 6.24](image)

**Table 6.15**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>THF</td>
<td>-78 (2h)</td>
<td>n.r.</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (2h)</td>
<td>677a</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (2h), 0 (1h)</td>
<td>677a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (8h), -40 (2h)</td>
<td>677a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (24h)</td>
<td>677a</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (6h)</td>
<td>677b</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>t-Bu</td>
<td>Me</td>
<td>Et₂O</td>
<td>-78 (18h)</td>
<td>677b</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>H</td>
<td>Et₂O</td>
<td>-78 (18h)</td>
<td>677c</td>
<td>94</td>
</tr>
</tbody>
</table>

<sup>a</sup> 36% of the product 77 of homoaddition was obtained
Chapter 6. Total synthesis of jerangolid D

Since the tert-butyl ester-containing adducts 677b and 677c can be obtained by an easier route, this approach towards the left fragment 615b of jerangolid D was revisited.

The second aldol-based route started also with diol 647 (Scheme 6.25). Initially, a selective protection of the primary alcohol with a benzyl group was attempted. Unfortunately, the reaction led, not only to the selective monoprotection of the C6 alcohol, but also to transesterified benzyl ester.

At the beginning, we did not worry too much for this change, but soon it was discovered, that benzyl ester 682 did not undergo the addition of the enolate generated from tert-butyl propanoate. On the other hand, the anion derived from tert-butyl acetate reacted smoothly with 682 affording β-ketoester 678a in a good yield of 87%. CF$_3$CO$_2$H-promoted cyclization followed by O-methylation yielded the desired lactone 664a in a modest 39% yield.

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Scheme 6.25
The chemoselective selective benzoylation of the C6 alcohol was accomplished using classical Ag₂O-BnBr conditions, albeit in moderate yield (Scheme 6.26). In this case, the formation of the β-ketoesters 678a and 678b proceeded smoothly and both products were obtained in excellent yields. Subsequent acid-mediated cyclization then afforded the lactones 664a and 664b in 39% and 42% yield, respectively. FeCl₃-promoted deprotection of the benzyl group finally completed the synthesis of alcohols 615a and 615b.

Scheme 6.26

In summary, the aldol approach to the left-hand fragment of jerangolid D furnished the desired adduct 615b in 7 steps and 13% overall yield from commercial dimethyl D-malate 646.

6.4 Right hand fragment and final coupling steps

Having established an efficient access to the left-hand fragment of jerangolid D, the synthesis of the right-hand subunit and the final coupling step still had to be accomplished before reaching the natural product. We have already

349 For the deprotection see Scheme 6.16.
prepared ketone 100 previously\textsuperscript{350} and, for the purpose of the jerangolid D synthesis, this sequence was reproduced. Thus, the C10-C17 fragment 100 was prepared using the Multicomponent Sakurai reaction (Scheme 6.27).

\begin{align*}
\text{(S)-132a} & \quad \text{OTBS} \\
\text{(R)-133} & \quad \text{TMS} \\
\text{131} & \quad \text{TMS} \\
\text{143a} & \quad \text{TBSO} \\
\text{144} & \quad \text{HO} \\
\text{15} & \quad \text{H} \\
\text{100} & \quad \text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 48\text{h} \\
\end{align*}

\textbf{Scheme 6.27}

Originally, this subunit was connected to the sulfone 183c yielding the coupled product 189c in 64% yield using a Julia olefination method. In the context of the synthesis of jerangolid D, we have decided to use our newly developed sulfoxide-modified Julia olefination strategy. Thus, alcohol 124 was protected as the TBS ether and the resulting sulphide 684 was oxidized with mCPBA, affording sulfoxide 685 in 96% yield over 2 steps (Scheme 6.28). Sulfoxide 685 was then coupled with ketone 100 under the sulfoxide-modified Julia olefination conditions, leading to the desired adduct 189c in 77% yield. TBS protected C7 alcohol was then transformed into the desired sulfone 191 via TBS removal/Mitsunobu-substitution sequence.

\textsuperscript{350} See chapter 2.
Finally, the reunion of the sulfone 191 and aldehyde 607b under the standard Kociensky-Julia conditions accomplished the first total synthesis of jerangolid D.

Disappointingly, the olefination step proceeded with low yield of 28% and thus this reaction step has to be further optimized. On the other hand, the
desired natural product, jerangolid D 617, was obtained as a single E/Z isomer.

6.5 Conclusions and perspectives

During our campaign towards jerangolid D 617, both fragments 607b and 191 have been prepared and coupled. Several routes towards the left-hand fragment 607b were disclosed and, in the best case, the precursor 615b was prepared in 5 steps and 34% overall yield (Scheme 6.29). The C10-C17 fragment of 617, dihydropyran 100, was obtained using a Multicomponent Sakurai reaction, as described in chapter 2. Subunit 100 was then coupled with the sulfoxide 685 using our sulfoxide-modified Julia olefination conditions, a novel variant of the classical Julia process developed recently in our laboratory (chapter 4).

In summary, the first total synthesis of jerangolid D was accomplished in 23 steps (9 steps in longest linear sequence) and 0.3% overall yield (9.3% yield in longest linear sequence).

As a part of our programme aimed at the preparation of various antifungal compounds, we plan to prepare a range of jerangolid analogues. One of the possible approaches to the left-hand part of jerangolid A 616 is presented in Scheme 6.30.

The key step of this approach involves a Blaise reaction between 687 and 672. This route is based upon the observation we reported in chapter 4 that an anion generated α to a SiOCH₂ group does not undergoes rapid α elimination.
Chapter 6. Total synthesis of jerangolid D

**Scheme 6.29**

**Scheme 6.30**
Chapter 6. Total synthesis of jerangolid D

Additionally, it might be highly interesting to develop an organocatalytic-based approach to subunit 607b. Recently, a highly active and selective organocatalyst for aldol reaction was developed in our laboratory. Using this catalyst, Dr. de Paolis was able to perform the aldol reaction between α-chloro cinnamaldehyde 689 and tert-butyl acetoacetate 690, affording the aldol product 691 in 56% yield and 97% ee. This molecule could be then transformed into the left fragment 607b via a C2-methylation/cyclization/O-methylation/ozonolyzis sequence (Scheme 6.31).

Finally, a one-pot approach to jerangolid D, starting from the fragments 607b, 692 and 100 could be investigated (Scheme 6.32). The differential reactivity of the C7 tetrazole subunit and the C9 phenyl sulfone in 692, will play an important role in this projected synthesis.

![Scheme 6.31](image-url)
Indeed, it is expected that when bis-sulfone 692 is treated with KHMDS (1.0 eq), deprotonation of the C7 hydrogen should occur with a slightly higher probability. However, and more importantly, when the C7 anion will react with aldehyde 607b, spontaneous elimination yielding the C6-C7 double bond should take place. The addition of the C9 anion to aldehyde 607b is a reversible process under the reaction conditions and therefore no product of C9-C6 coupling should be obtained. When all the aldehyde is consumed, the reaction mixture will be again cooled to -78°C and sulfone 693 will be reacted with ketone 100 using standard benzoyl-based Julia olefination method. SmI₂-mediated reductive olefination of the resulting β-benzoyloxy sulfone should then afford jerangolid D 617 in an essentially two-pot process.
7. Total synthesis of (-)-dactylolide

7.1 Introduction

(+)-Dactylolide 694 (Figure 7.1) was isolated in 2001 by Riccio et al. from the Vanuatu sponge Dactylospongia sp. The cytotoxic activity of (+)-694 (63% inhibition of L1210 (lymphatic leukemia) and 40% inhibition of SK-OV-3 (ovarian cancer) tumor cell lines at 3.2 μg/mL), although modest in comparison to potent cytotoxic agents such as the spongistatins and phorboxazoles, is nevertheless remarkable in view of the rather simple structure of 694. Moreover, in 2003, Hoye and Hu showed that the unnatural enantiomer of (+)-694, (-)-694 is a straightforward precursor to (-)-zampanolide 695, a highly potent cytotoxic agent (Scheme 7.1).

![Figure 7.1](image-url)

Chapter 7. Total synthesis of (+)-dactylolide

(-)-695 was isolated in 1996 by Higa et al.\textsuperscript{355} and, regardless of the lack of material (only 3.9 mg of 695 were isolated from 0.480 kg of the marine sponge \textit{Fasciospongia rimosa}) biological tests performed on this novel macrolide exhibited significant activity against a variety of tumor cell lines. In particular, (-)-695 has proven to be active against the P388, A549, HT29 and MEL28 cell lines with IC\textsubscript{50} values ranging from 1 to 5 ng/mL.\textsuperscript{355}

Since (+)-694 possesses an unusual structure (unsaturated macrolactone and a \textit{cis}-2,6-disubstituted 4-\textit{exo}-methylene tetrahydropyran ring system) and is a potent cytotoxic agent (itself or as a direct precursor to 695), there has been some important synthetic efforts dedicated to the preparation of this target, over the past 5 years. So far, six total syntheses of (+) or (-)-694 have been published in the literature.\textsuperscript{356}

Chapter 7. Total synthesis of (+)-dactylolide

7.1.1 Smith, III. was first

Smith’s interest in the total synthesis of dactylolide 694 originated from the close structural similarity with zampanolide 695. Smith et al. had just finished the total synthesis of (+)-zampanolide 695 in 2001, when they observed that (+)-695 was converted into (+)-dactylolide 694 when refluxed in benzene (Scheme 7.2).

Scheme 7.2

The construction of macrocycle (+)-694 was based upon an intramolecular Horner-Emmons reaction of 696 (Scheme 7.3). The macrocycle precursor 696 was further disconnected into vinyl bromide 697, epoxide (S)-156e and phosphonate 698. Uniting these fragments was envisioned to take place via a higher-order cuprate opening of epoxide (S)-156e followed by the acylation of the resulting secondary alcohol. It was envisaged that vinyl bromide 697 could be obtained from sulfone 699 and aldehyde 700 via

Chapter 7. Total synthesis of (+)-dactyloide

Kociensky-Julia olefination. The assembly of the crucial 2,6-cis-tetrahydropyran 699 was based on a stereoselective Petasis-Ferrier rearrangement.

![Scheme 7.3](image)

The synthesis of (+)-694 began with the Brown asymmetric allylation of aldehyde 702, followed by the protection of the hydroxy group as the TES

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ether. Ozonolyis yielded aldehyde 703 in 68% yield (Scheme 7.4). Oxidation\textsuperscript{364} of aldehyde 703 to the corresponding acid and TES deprotection gave the requested β-hydroxy acid 704 in 84% yield. Bissilylation,\textsuperscript{365} followed by TMSOTf-promoted\textsuperscript{366} condensation with \textit{E}-3-bromobut-2-ene\textsuperscript{367} furnished the dioxanone 704 in 82% yield and as a 10:1 mixture of C15 epimers.

Methylation with Petasis’ reagent\textsuperscript{368} led to the formation of the corresponding enol ether (6:1 epimer at C15) which, upon treatment with Me\textsubscript{2}AlCl, underwent a Petasis-Ferrier rearrangement, affording the desired 2,6-cis-pyranone 706 (5:1 = cis:trans pyranone).

Wittig reaction followed by desilylation and transformation of the free hydroxy group into the corresponding sulfone completed the synthesis of the south fragment 699 of dactylolide.

The synthesis of the eastern subunit began with the Lewis acid-mediated epoxide (\textit{R})-156a\textsubscript{363} opening by the anion derived from methyl propionate (Scheme 7.5). A selective \textit{cis} addition of Me\textsubscript{2}CuLi to the triple bond followed by the reduction of the ester to the alcohol generated a diol. Protection of both alcohols in the form of TBS ethers and transformation of the primary benzyl ether into an aldehyde produced synthon 700, ready to be coupled with 699.

Chapter 7. Total synthesis of (+)-dactylolide

Scheme 7.4

Scheme 7.5

At this stage, fragments 699 and 700 were united via a Kociensky-Julia olefination affording polyene 709 with an excellent E/Z selectivity (Scheme 328).
7.6). The vinyl bromide 709 was then transformed into the corresponding high-order cuprate which was used to open the epoxide (S)-156e yielding alcohol 710 in 40% yield.

Scheme 7.6
Chapter 7. Total synthesis of (+)-dactylolide

Introduction of acyl phosphonate substituent was realized using the Steglich conditions. This was followed by desilylation and oxidation of the C3 alcohol, resulting in the formation of the key-enal 712. NaHMDS-mediated Horner-Emmons macrcyclization then led to diene 713 in 72% yield. The synthesis of (+)-694 was completed by the removal of the protecting groups followed by oxidation of the C6 and C20 hydroxy groups.

In summary, (+)-694 was prepared in 37 steps and 0.26% overall yield (30 steps and 0.57% in longest linear sequence).

7.1.2 2003 – Hoye and Ti(IV)-mediated macrolaconization

One year later, Hoye and Hu published the second total synthesis of dactylolide 694. This time, it was the (-)enantiomer, which then served as a direct precursor in the synthesis of zampanolide (-)-695 (Scheme 7.1). The retrosynthesis of (-)-694 was based on a Ti(IV)-mediated macrcyclization by opening of an epoxy-alcohol with an acid, as originally disclosed by Sharpless (Scheme 7.7). The synthesis of the precursor 714 was envisioned via the addition of an organolithium species, generated from vinyl iodide 716 to aldehyde 715. 2,6-Cis-dihydropyran 716 should then be obtained via a Lewis or Broensted acid-mediated IMSC condensation between aldehyde 717 and allylsilane 718.

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Scheme 7.7

The synthesis began with the IMSC of aldehyde 717 and allylsilane 719 (Scheme 7.8). Surprisingly, even though the condensation proceeded smoothly and in good yields, under various reaction conditions, the desired 2,6-dihydropyran 720 was generally obtained as a 2,6-cis/trans mixture. Only when a Brønsted acid, such as (±)-CSA, was employed, did the cis-isomer be formed exclusively. In this case, the desired dihydropyran cis-720 was obtained as a single diastereoisomer in 78% yield. Vinyl iodide 721 was then prepared from pyran 720 via pivalate removal/oxidation/Kishi olefination.

373 Since the full paper has not been published yet, details about the synthesis of compounds 717 and 719 are not available.
Chapter 7. Total synthesis of (+)-dactylolide

Scheme 7.8

The C21 alcohol required for the Sharpless epoxidation was freed via TBAF-mediated TBDPS-group deprotection. Interestingly, all the undesired
Chapter 7. Total synthesis of (+)-dactylolide

Z-iodovinyl isomer was transformed during the deprotection into the corresponding, easily separable, alkyne. Sharpless asymmetric epoxidation set the important C19 stereocentre with ~25:1 d.r. Re-protection of the C21 hydroxyl group as a TBS ether then yielded intermediate 722.

The final assembly of the macrocyclization precursor 723 was accomplished by addition of the vinyl lithium species, derived from vinyl iodide 722, to aldehyde 715 to form the C7-C8 bond, generating at the same time carbinol 723 as a ~1:1 mixture of epimers.

A series of protection and oxidation steps then ensued, leading to the macrocyclization precursor 725 (Scheme 7.9). Exposure of a solution of 725 to Ti(OiPr)_4 at 75°C resulted in closure to the macrocycle 726. To minimize some undesired side reactions, the macrocyclization was stopped after ~50% conversion and therefore proceeded only in 40% yield. The starting material, 725 was isolated in 30% yield. Importantly, 726 was produced as a ~1:1 mixture of C7 epimers, demonstrating that the two epimers of 725 are competent substrates for the key macrocyclization step.

The final stage of the synthesis involved deprotection of the C17 TBS ether, followed by selective oxidation of the resulting alcohol into the ketone.\(^{374}\)

Finally, cleavage of the C20-C21 diol with Pb(OAc)_4 provided (-)-694.

In summary, it was shown that Ti(IV)-mediated epoxide opening can be used as a valuable macrocyclization method. Since the full paper of this work has not yet been published, the comparison of this total synthesis with the others can not be made.

7.1.3 2005 – Floreancig – First in fruitful 2005 year

Based on the number of total syntheses, dactylolide 694 became a popular natural product in 2005. The first total synthesis was published that year by Floreancig et al.\textsuperscript{375}

His retrosynthesis was based on the following key steps: a Horner-Emmons macrocyclization to establish the C2-C3-bond of the macrocycle, a Prins cyclization to assemble the cis-2,6-dihydropyran ring preceded by the formation of an acetal to unite the two fragments 728 and 729 (Scheme 7.10).

The first fragment, aldehyde 729, was prepared according to a sequence reported by Evans et al.376 during the total synthesis of callipeltoside (Scheme 7.11). Thus, the stereogenic centre at C19 of 729 was established by using an asymmetric vinylogous Mukaiyama aldol reaction between aldehyde 731 and silyl ketene acetal 732. The condensation was catalyzed by Cu-pybox 733 and afforded the aldol product 734 in 82% yield and 95% ee. TBS-protection of the C19 hydroxy group, followed by a two-step transformation of the C15 ester into an aldehyde function, delivered the requisite fragment 729.

The synthesis of the second fragment, dihydroxy ester 728, started with the stereoselective assembly of the trisubstituted olefin 736 (Scheme 7.12). It was set through the hydroalumination reaction of 735 with Red-Al, followed by quenching of the resulting alane ate complex with Bu₃SnCl. Subsequent TBS-protection of the allylic alcohol yielded isomerically pure vinyl stannane 736 in 81% yield. Palladium-mediated coupling of 736 with bromide 737, followed by in situ acetal hydrolysis, provided enal 738 in 80% yield.

In the absence of a chelating group in 738, Denmark’s bisphosphoramidate catalytic system 740,\textsuperscript{381} in conjunction with SiCl\textsubscript{4}, was used to effect the coupling between 738 and ketene acetal 739. Alcohol 741 was obtained in 67% yield and 93\% ee. Thermolysis of 741 in BuOH, followed by syn-reduction of the resulting keto ester with Et\textsubscript{2}BOMe and NaBH\textsubscript{4},\textsuperscript{382} completed the synthesis of diol 728.

Scheme 7.12


Chapter 7. Total synthesis of (+)-dactylolide

After silylation of both hydroxy functions of 728 (Scheme 7.13), condensation with aldehyde 729 under Noyori’s conditions\textsuperscript{383} yielded ester 742 in 83% yield. Addition of an excess of TMSCH\textsubscript{2}MgCl, in the presence of CeCl\textsubscript{3},\textsuperscript{384} afforded, after basic work-up, a crude Peterson olefination precursor 743.

Alcohol 743 was subjected to TfOH\textsubscript{py}/MgSO\textsubscript{4}-mediated sequential Peterson olefination and Prins cyclization, generating the desired cis-2,6-dihydropyran 744 in 75% yield. At this stage, transposition of the C9 hydroxy group to the C7 position, via a selenium variant of the Mislow-Evans\textsuperscript{385} rearrangement, provided the desired allylic alcohol in 62% yield. Protection in the form of a p-methoxybenzyloxymethyl ether,\textsuperscript{386} followed by removal of the TBDPS-protecting group\textsuperscript{387} and oxidation of the allylic alcohol, yielded enal 745.

Acylation of the hydroxyl group at C19 with diethylphosphonoacetic acid and DCC provided the corresponding phosphonoacetate, which, upon treatment with NaHMDS, engaged in an intramolecular Horner-Emmons reaction to provide macro lactone 746 in 69% yield from 745.

The synthesis was competed by the oxidative cleavage of both protecting groups with DDQ, followed by a double oxidation with Dess-Martin periodinane to provide dactylolide (+)-694.

In summary, (+)-694 was prepared in 27 steps and 0.47% overall yield (19 steps and 2.40% overall yield in longest linear sequence).

Chapter 7. Total synthesis of (+)-dactylolide

Scheme 7.13

7.1.4 2005 – Jennings – In close touch

Soon after Floreancig, Jennings and Ding⁴⁸⁸ published their total synthesis of dactylolide (-)-694. In this case, metathesis was chosen to bring about the formation of the macrocycle (Scheme 7.14). It was expected that the esterification of alcohol 748 by acid 749 would lead to the macrocyclization precursor 747.

![Scheme 7.14](image)

Fragment 748 was assembled from (R)-glycidol (R)-611, which was initially transformed into propargylic alcohol 750⁴⁸⁹ (Scheme 7.15). Deprotonation, followed by electrophilic quench with ethyl chloroformate, yielded the corresponding acetylenic ester in 99% yield. Conjugate addition of the thiolate anion selectively provided the (Z)-configured α,β-unsaturated

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Chapter 7. Total synthesis of (+)-dactylolide

ester. The vinylic thiol ether was then replaced by a methyl group, via a copper-promoted MeMgBr addition, affording (E)-adduct 751 with complete retention of configuration. Subsequent reduction of the ester group into the corresponding alcohol, followed by oxidation and asymmetric allylation of the resulting aldehyde using Brown’s reagent, provided the homoallylic alcohol 752 with the correct C15 stereochemistry.

Further transformation of the alcohol 752 into the acryloyl ester and Grubbs-carbene mediated ring-closing metathesis yielded lactone 753 in 67% yield from 752. Epoxidation of lactone 753 with basic hydrogen peroxide, provided the epoxy-lactone which was then selectively reduced with in situ generated PhSeH. The resulting lactol 754 was immediately transformed into the oxocarbenium cation, in the presence of TFA, and reduced with Et3SiH to furnish the cis-2,6-disubstituted tetrahydropyran ring. Full desilylation, followed by selective 1,2-diol protection, afforded acetonide 755 in 81% and in two steps.

Transformation of the hydroxy group of 755 into the exo-olefin was performed via an oxidation/Wittig olefination sequence. Removal of the acetonide, followed by selective silylation of the primary alcohol completed the synthesis of the southern fragment 748.

The assembly of the second subunit started with the transformation of lactone 756 into aldehyde 757 (Scheme 7.16). Aldehyde 757 was reacted with triethylphosphonoacetate affording the expected E,Z-conjugated ester.

Subsequent HF.py-mediated desilylation of the TBS group resulted in the formation of the free alcohol 758 in 90% yield over two steps. Homoallylic oxidation followed by vinyl Grignard reagent addition, resulting alcohol protection with a TBS group and ester hydrolysis accomplished the synthesis of the northern fragment 759.

Scheme 7.15
Subunits 748 and 759 were coupled together utilizing Yamaguchi’s protocol, affording the unsaturated ester 740 in 99% yields (Scheme 7.17). Ring-closing metathesis on the bis-TBS protected intermediate 740 was initially attempted but failed to provide expected macrocycle. Therefore, the TBS-groups were removed using HCl in MeOH/CH₂Cl₂ mixture. Subsequent subjecting of the corresponding diol to 10 mol% of 2nd generation Grubbs’ catalyst yielded the thought-after macrocyclic product 741 in 93% yield. Final oxidation of both C19 and C7 hydroxyl groups resulted in the formation of (-)-dactylolide 694 in 90% yield.

In summary, Jennings and Ding accomplished the synthesis of (-)-694 in 29 steps and 0.47% overall yield (24 steps and 4.80% in longest linear sequence).

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7.1.5 2005 – Keck is closing the year

The last total synthesis of dactylolide 694 that appeared in 2005 was published by Keck and Sanchez. Keck’s interest in the total synthesis of 694 stemmed from its molecular structure, since they did develop earlier a short and efficient route to cis-2,6-dihydropyrans.

The route chosen by Keck is outlined in Scheme 7.18. Similarly to Smith and Floreancig, an Horner-Emmons macrocyclization was envisioned to close the 20-membered ring. Furthermore, the same reaction could also be used to join the C3-C8 fragment 743 to the dihydropyran subunit 742.

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cis-2,6-dydropyranyl fragment 742 was envisaged to arise from a condensation between aldehyde 744 and allylsilane 745.

Scheme 7.18

The synthesis of aldehyde 744 started with the catalytic asymmetric allylation of aldehyde 731,\textsuperscript{399} using the functionalized stannane 746,\textsuperscript{400} to give the desired (R)-homoallylic alcohol 747 in 75% yield and 93% ee (Scheme 7.19). Hydroxyl group protection and double bond isomerization yielded the (E)-\(\alpha,\beta\)-unsaturated ester 748 as a 32:1 mixture of E/Z isomers. Finally, reduction of the ester function followed by oxidation of the resulting alcohol afforded the desired aldehyde 744.

\textsuperscript{399} Prepared from allyl alcohol in two steps and 91% yield. See Scheme 7.11
\textsuperscript{400} Prepared from commercial 3-chloro-2-(chloromethyl)prop-1-ene in two steps and 56% yield. See: Keck, G. E.; Yu, T. Org. Lett. 1999, 1, 289.
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Scheme 7.19

The synthesis of the second annulation partner 745 was again effected via a catalytic asymmetric allylation using stannane 750 and (S)-BITIP as the catalyst to afford the allylsilane 77 in 91% yield and with 95% ee (Scheme 7.20). TMSOTf-mediated condensation between aldehyde 744 and hydroxy allylsilane 745 then produced the cis-2,6-dihydropyran subunit as a single diastereoisomer and in 85% yield. Selective removal of the TBPDS-group with TBAF/AcOH, followed by TPAP/NMO oxidation of the C9 hydroxy group afforded aldehyde 752 in 89% yield.

β-ketoester 743 was prepared from homopropargyl alcohol 753 in 9 steps (Scheme 7.21). Initially, alkyne 753 was transformed into the α,β unsaturated ester 754. Reduction of the ester group to the alcohol, followed by its protection as a TBDPS ether, generated the disilyl ether. Selective deprotection of the TBS ether was accomplished using CSA/MeOH. The resulting alcohol was oxidized to the aldehyde which was reacted with the lithium salt of methyl dimethyl phosphonate. A final

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oxidation, using the Dess-Martin periodinate, afforded the desired \( \beta \)-ketophosphonate 743.

\[
\begin{align*}
\text{Scheme 7.20} \\
\text{Scheme 7.21}
\end{align*}
\]

\[\text{Still, W. C.; Gennari, C.; Nogues, J. A.; Pearson, D. A.} \quad \textit{J. Am. Chem. Soc.} \quad 1984, \quad 106, \quad 260.\]
Chapter 7. Total synthesis of (+)-dactylolide

The aldehyde 752 and phosphonate 743 were then united using Paterson’s modification\textsuperscript{404} of the Horner-Emmons reaction (Scheme 7.22). Since it was expected that acidic hydrogens $\alpha$ to the C7 ketone might cause problems during the macrocyclization step, this function was reduced and the resulting alcohol was protected as a PMB ether.

\begin{equation}
\text{PMBO} \quad \text{OTBS} \quad \text{OTBDPS} \quad \text{PMBO} \quad \text{OTBS} \quad \text{OTBDPS} \\
\begin{array}{c}
\text{752} \\
\text{743} \\
\text{756}
\end{array}
\end{equation}

\begin{equation}
\text{PMBO} \quad \text{OTBS} \quad \text{OTBDPS} \\
\begin{array}{c}
\text{757} \\
\text{758}
\end{array}
\end{equation}

Chapter 7. Total synthesis of (+)-dactylolide

Scheme 7.22
At this stage, the desired phosphono-ester required for the macrocyclization step could be installed. Selective deprotection of the THS group afforded the corresponding alcohol which was transformed into the desired phosphonate 757 using polymer-bound DCC (PS-DCC). The C2 aldehyde was then generated in situ by a TBSPDS-deprotection/oxidation sequence. Finally, NaHMDS-mediated Horner-Emmons macrocyclization yielded the desired lactone 758 in 60% yield. Further deprotection of both PMB ethers followed by oxidation of the resulting alcohols completed the total synthesis of (+)-694.

In summary, Keck and Sanchez prepared dactylolide (+)-694 in 0.63% overall yield and 35 steps (19 steps and 3.84% overall yield in longest linear sequence).

7.1.6 2006 – McLeod – Last but certainly not least

So far, the last total synthesis of dactylolide (-)-694 was published by McLeod et al. early in 2006. From a retrosynthetic point of view, a Grubbs’ metathesis (macrocyclization), an Ireland-Claisen rearrangement (introduction of the C19 stereogenic centre) and an asymmetric hetero-Diels-Alder reaction (cis-2,6-dihydropyran) were all considered as logical key-steps, leading ultimately to simple fragments such as 763 and 764 (Scheme 7.23).

The synthesis of tetrahydropyran 762 began with the [4+2] cycloaddition of the triethylsilyl enol ether 763\textsuperscript{406} with aldehyde 764,\textsuperscript{407} catalyzed by the chiral tridentate chromium(III) complex 765 (Scheme 7.24).\textsuperscript{408}

\begin{center}
\includegraphics[width=\textwidth]{scheme7_23.png}
\end{center}

\textbf{Scheme 7.23}

The desired tetrahydropyran ring 766 was formed in 82% yield and in 99\% ee. DDQ-mediated removal of the PMB protecting group, oxidation of the resulting alcohol to the corresponding aldehyde,\textsuperscript{409} Wittig olefination and TBS ether deprotection afforded alcohol 767 in 42\% yield over 4 steps. The C16 hydroxyl was transformed into an aldehyde which was directly treated with the isoprenyl Grignard reagent. The addition took place via a Cram-

\textsuperscript{406} Available in 4 steps and 68\% overall yield from butyn-4-ol. See: Paterson, I.; Tudge, M. \textit{Tetrahedron} 2003, 59, 6833.

\textsuperscript{407} Available from allyl alcohol in 2 steps and 94\% yield.

\textsuperscript{408} Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. \textit{Angew. Chem., Int. Ed.} 1999, 38, 2398.

transition state\textsuperscript{410} and afforded the desired allylic alcohol as a 86:14 mixture of epimers, in favor of the desired (16\textit{S})-isomer. The resulting alcohol was esterified with PMB protected glycolic acid to give ester 761 in 91\% yield.

Scheme 7.24

The Ireland-Claisen [3,3] sigmatropic rearrangement\textsuperscript{411} of ester 761 afforded a carboxylic acid which was immediately reduced, giving the primary

alcohol 768 as a single diastereoisomer. The synthesis of the southern fragment 759 was then completed by TBS protection of with the primary alcohol 768 followed by removal of the PMB group.

The assembly of the northern subunit 760 began with the ester 769 which was transformed into the corresponding lactone via a Grubbs’ metathesis. Partial reduction of the lactone into the lactol, followed by treatment with methyltriphenylphosphorane, resulted in the formation of the diene 770 in 82% yield over 3 steps.

Oxidation of the C7 alcohol generated an aldehyde which was reacted with vinyl magnesium bromide. After TBS protection of resulting allylic alcohol, hydrolysis of the ester function finally led to the C1-C8 fragment 771.

Subunits 759 and 771 were then connected via a Mitsunobu esterification protocol413 (Scheme 7.26). As a consequence, the C19 stereogenic centre was inverted, generating the correct C19 absolute configuration. Removal of

\[ \text{Scheme 7.25} \]


the silyl ether protecting groups afforded the corresponding diol 772 which was then subjected to ring-closing metathesis mediated by Grubbs’ 2\textsuperscript{nd} generation ruthenium catalyst. The desired macrocycle 773 was formed in 48% yield. Further oxidation of two hydroxyl groups then completed the total synthesis of (-)-694.

![Image of chemical structures]

**Scheme 7.26**

In summary, McLeod et al. prepared dactylolide (-)-694 in 32 steps and 0.42% overall yield (20 steps and 1.69% overall yield in the longest linear sequence).
Table 7.1: Comparison of all total syntheses of dactylylode.

<table>
<thead>
<tr>
<th>Total synthesis</th>
<th>Macrocyclization</th>
<th>Tetrahydropyran subunit</th>
<th>Number of steps(^a)</th>
<th>Overall yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (2001)</td>
<td>Horner-Emmons</td>
<td>Petasis-Ferrier rearrangement</td>
<td>37 (30)</td>
<td>0.26% (0.57%)</td>
</tr>
<tr>
<td>Floreancig (2005)</td>
<td>Horner-Emmons</td>
<td>Prins cyclization</td>
<td>27 (19)</td>
<td>0.47% (2.40%)</td>
</tr>
<tr>
<td>Jennings (2005)</td>
<td>Metathesis</td>
<td>Metathesis/addition to oxonium ion</td>
<td>29 (24)</td>
<td>0.47% (4.80%)</td>
</tr>
<tr>
<td>Keck (2005)</td>
<td>Horner-Emmons</td>
<td>IMSC cyclization</td>
<td>35 (19)</td>
<td>0.63% (3.84%)</td>
</tr>
<tr>
<td>McLeod (2006)</td>
<td>Metathesis</td>
<td>Hetero-Diels-Alder</td>
<td>32 (20)</td>
<td>0.42% (1.69%)</td>
</tr>
</tbody>
</table>

\(^a\) Data in brackets refers to yields obtained in longest linear sequence of the synthesis.
7.2 Objectives

Our interest in the synthesis of (+)-dactylolide stemmed, similarly to Keck, from its molecular structure, since our previous work in the laboratory has provided an exceptionally facile and stereoselective access to 2,6-cis-4-methylene tetrahydropyrans. Additionally, we wanted to confront our recently introduced sulfur-based olefination methods in the context of polyolefin synthesis. Moreover, it was expected that our approach will offer a shorter and more versatile access to dactylolide-type structures. Our objective is to prepare multigram quantities of 694 and, later on, of 695. Keeping this stringent prerequisite in mind, a chiral-pool approach was preferred over a catalytic asymmetric one.

7.3 Retrosynthesis

Based upon the above-mentioned criteria, the original structure of 694 was divided into four fragments, which would be united via an esterification (C1-C19), a Kociensky-Julia olefination (C8-C9), a Julia olefination (C16-C17) and finally by a metathesis reaction (C4-C5) (Figure 7.2).

It was envisioned that this four-unit approach would give us added flexibility, since we should be able to freely modify the order of coupling of the various fragments. More importantly, these variations will enable us to select the macrocyclization method that proceeds with the best yields. Finally, by altering a subunit at a time, we should be able to obtain a large variety of analogues without modifying too deeply the overall synthesis.

414 See chapter 3. Silicon based methodologies.
At the onset, a macrocyclization approach based upon the formation of the C4-C5 double bond was chosen to be tested first (Scheme 7.27). Precursor 774 would then be assembled from the four components: 775-778. Since the acid 775 is commercially available, it is the easiest fragment to obtain. Our efforts toward the synthesis of the remaining three subunits will be discussed in the rest of the chapter.
7.4 Synthesis of the western fragment

The synthesis of the western fragment 776 was based on the ring opening of the PMB (S)-156b (Scheme 7.28). At this stage, it was suggested that our originally proposed Julia olefination might be replaced by a Kociensky-Julia reaction. However, we were rather concerned about the selectivity of the trisubstituted olefin formation and decided to prepare both reagents and test them in the olefination reaction. Thus, ethyl sulfide 781 and sulfones 782 were chosen as anion precursors for the epoxide opening.
Initially, the commercially available (S)-glycidol (S)-611 was transformed into its PMB ether (S)-156b.\textsuperscript{415} Ether (S)-156b was then reacted with sulfide 781 or sulfones 782a and 782b (Table 7.2).

Our first attempts to open the epoxide (S)-156b with the α anion of sulfide 781 or sulfone 782a failed (Table 7.2, Entries 1 and 2). Slightly better results were obtained when the activation of the epoxide via a Lewis acid\textsuperscript{416} was employed (Table 7.2, Entries 3-6).

It was suggested that the failure of this reaction was caused by the sensitivity of sulfone 782a and sulfide 781 towards nucleophilic attack, which may lead to the degradation of the anion species prior to epoxide opening (Figure 7.3).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure7.3.png}
\caption{Nucleophilic attack}
\end{figure}


Chapter 7. Total synthesis of (+)-dactylolide

\[
\text{O} \quad \text{NaH (1.2 eq)} \quad \text{OPMB} \quad \text{EtSO}_x\text{Ar} \\
\text{OH} \quad \text{PMBCl (2.2 eq)} \quad \text{TBAI (0.2 eq)} \quad \text{DMF, r.t., 24h} \quad 85\%
\]

Table 7.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>X</th>
<th>Conditions</th>
<th>Yield\textsuperscript{a} [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PT</td>
<td>2</td>
<td>n-BuLi, THF, -78°C to r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>PT</td>
<td>0</td>
<td>n-BuLi, THF, -78°C to r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>PT</td>
<td>0</td>
<td>n-BuLi, BF\textsubscript{3}OEt\textsubscript{2} (3.0 eq), EtO\textsubscript{2}, -78°C to r.t.</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>PT</td>
<td>0</td>
<td>n-BuLi, Et\textsubscript{2}AlCl (3.0 eq), THF, -78°C to r.t.</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>PT</td>
<td>2</td>
<td>LDA, BF\textsubscript{3}OEt\textsubscript{2} (2.0 eq), THF, -78°C to r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>6</td>
<td>PT</td>
<td>2</td>
<td>LDA, BF\textsubscript{3}OEt\textsubscript{2} (4.0 eq), THF, -78°C to r.t.</td>
<td>S.M</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>2</td>
<td>LDA, BF\textsubscript{3}OEt\textsubscript{2} (2.0 eq), THF, -78°C to r.t.</td>
<td>S.M.</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>2</td>
<td>n-BuLi, BF\textsubscript{3}OEt\textsubscript{2} (2.0 eq), THF, -78°C to r.t.</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>2</td>
<td>n-BuLi, BF\textsubscript{3}OEt\textsubscript{2} (3.0 eq), THF, -78°C to r.t.</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>2</td>
<td>n-BuLi, BF\textsubscript{3}OEt\textsubscript{2} (6.0 eq), THF, -78°C to r.t.</td>
<td>25</td>
</tr>
<tr>
<td>11\textsuperscript{b}</td>
<td>Ph</td>
<td>2</td>
<td>n-BuLi, THF/HMPA = 10:1 (v/v), -78°C to r.t.</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>PT</td>
<td>2</td>
<td>n-BuLi, THF/HMPA = 10:1 (v/v), -78°C to r.t.</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} S.M. means that the epoxide was recovered in 98% to quant. yield. The sulfone or sulfide was not observed in the crude reaction mixture. Thus, its degradation under the reaction conditions is expected.

\textsuperscript{b} 3 eq. of sulfone were used. If 2 eq are used the yield is slightly lower (91%).

As a consequence, the epoxide opening using the phenyl-bearing sulfone \textsuperscript{782b} was tested. In the case of Lewis acid-promoted epoxide opening, the desired product was only obtained in modest yields (Table 7.2, Entries 7-10). Therefore, we have changed our strategy and decided to increase the nucleophilic property of the sulfone by adding HMPA as a co-solvent.\textsuperscript{417} It was expected that the HMPA would coordinate Li\textsuperscript{+} in the solution and thus, make the anion \( \alpha \) to sulfone group more reactive. Using these conditions, we

were delighted to obtain the western fragment 776 in an excellent 98% yield (Table 7.2, Entry 11). Disappointingly, these conditions proved to be inefficient in the case of PT-based sulfone 782a epoxide opening (Table 7.2, Entry 12).

In conclusions, the western fragment of (-)-694 was prepared in 3 steps\textsuperscript{418} and 82.5% overall yield (2 steps and 83.3% in longest linear sequence).

### 7.5 Synthesis of the southern fragment

Based upon previous work done in our laboratory, it appeared to us quite obvious to assemble the 2,6-cis-4-methylenetetrahydropyran ring 777 by an IMSC cyclization. The retrosynthesis of 777 is shown in Scheme 7.29.

![Scheme 7.29](image)

The assembly of the southern fragment began with the preparation of the aldehyde 780. Thus, propane-1,3-diol was monoprotected with TBSCI and

\textsuperscript{418} Sulfone 782b was prepared by reacting EtI with PhSO\textsubscript{2}Na\textsuperscript{+} in DMSO in 99% yield. See experimental section.
the resulting alcohol $538b$\textsuperscript{419} was oxidized using buffered PCC to aldehyde $110$ (Scheme 7.30).

![Scheme 7.30](image)

Alcohol $779$ was then prepared starting from vinyl bromide $784$ which was initially transformed into trichloroallylsilane $785$ (Scheme 7.31). Exhaustive methylation with MeMgBr then produced the volatile allyltrimethylsilane $786$.\textsuperscript{420} Vinyl bromide $786$ was transformed into the corresponding organo magnesium species and reacted with epoxide (S)-156b, in the presence of CuBr.SMe$_2$, yielding the desired alcohol $779$ in 93% yield over 3 steps.

Scheme 7.31

---

\textsuperscript{419} Alcohol $538b$ is commercially available (Aldrich).

Chapter 7. Total synthesis of (+)-dactylolide

With both partners in hand, their coupling using the IMSC condensation was attempted (Table 7.3). Disappointingly, the desired product 777 was obtained so far in only 35% yield. However, many other conditions are still to be tested.

It appears that the competitive coordination of the Lewis acid to the PMB-oxygen atoms might be the reason for the poor yields of this reaction. It was previously shown in our laboratory by Dr. Leroy, that Bi(OTf)$_3$ was a good Lewis acid to overcome this problem. Unfortunately, we have not been able to test it in our condensation yet.

![Chemical structure](image1)

Table 7.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>L.A.</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$-OEt$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>-78°C (1h) to r.t.</td>
<td>deg.</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$-OEt$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>-78°C (2h) to 0°C</td>
<td>deg.</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$-OEt$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>-78°C (1h) to -40°C (1h) to -20°C</td>
<td>35$_a^a$</td>
</tr>
<tr>
<td>4</td>
<td>TMSOTf</td>
<td>CH$_2$Cl$_2$</td>
<td>-78°C (1h) to 0°C</td>
<td>deg.</td>
</tr>
<tr>
<td>5</td>
<td>TMSOTf</td>
<td>Et$_2$O</td>
<td>-78°C (1h) to 0°C</td>
<td>n.r.$_b^b$</td>
</tr>
</tbody>
</table>

$_a^a$ Product obtained as 2:1 mixture with desilylated product
$_b^b$ Only silylated alcohol 779 was obtained.

---

7.6 Synthesis of the eastern fragment

The retrosynthesis of the eastern fragment is depicted in Scheme 7.32. The key step involves again the opening of an epoxide opening by a Grignard reagent.

![Scheme 7.32](image)

The first approach towards epoxide 787 was based on the reaction of glycidol mesylate 789 with PTS‘Na’ (Scheme 7.33).\(^{422}\) Disappointingly, only traces of the desired product 787 were obtained. Unexpectedly, the bis sulfide, originating from a second addition of the PT thiolate to epoxide 787, 790 was formed as the major product.

In an attempted to avoid this undesired side reaction, non-basic Mitsunobu-substitution on glycidol 611 with PTSH, was attempted. Disappointingly, the desired epoxide 787 was obtained only in 14% yield along with 31% of sulfide 790.

---

These negative results, prompted us to modify our approach to sulfide 778. It was envisioned that by inverting the reaction sequence (introducing the olefinic chain before the sulfur group), might obtain the desired adduct more easily (Scheme 7.34). Thus, epichlorhydrin 791 was reacted with Grignard reagent 788, in the presence of CuCN, yielding chlorohidryn 792. The crude chlorohidryn 792 was mixed with solid KOH and the desired epoxide 793 was distilled off in a remarkable overall yield.
Chapter 7. Total synthesis of (+)-dactylolide

Opening of epoxide 793, followed by protection of the resulting alcohol and oxidation of the sulfide should afford to the desired sulfone 778.

7.7 **North, west, south and east fragments union**

Our first attempts to join all four fragments are shown in Scheme 7.35. It was envisioned that as a most convergent approach to (-)-694, the separate union of the northern and western subunits 775 and 776 and the southern and the eastern portions 777 and 778 should be accomplished (Scheme 7.35). The advanced fragments 794 and 795 would then be coupled via a Julia olefination. The subsequent metathesis reaction will generate the macrolactone.

Scheme 7.35
Chapter 7. Total synthesis of (+)-dactylolide

Taking advantage of the commercial availability of the acid 775 and its methyl ester derivative, we have decided to study not only the coupling of 776 with acid 775 but also with its methyl ester (Table 7.4). However, it was observed that neither Nolan’s carbene, \(^{423}\) nor base induced transesterification (Table 7.4, Entries 1 and 2) proceeded with satisfactory yields. Gratifyingly, a classical DCC-mediated coupling reaction provided the required ester in good yield (Table 7.4, Entry 3).

![Chemical structure](image)

**Table 7.4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>Carben catalyst, as Nolen’s procedure</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>n-BuLi (1.1 eq), THF, 24 h, r.t.</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>DCC (1.5 eq), DMAP (0.1 eq), CH₂Cl₂, r.t.</td>
<td>73-82(^{a})</td>
</tr>
</tbody>
</table>

\(^{a}\) Different scale from 0.05mmol to 1.0 mmol (3 attempts)

### 7.8 Conclusions and perspectives

In summary, we have proposed a short and convergent synthesis of (-) dactylolide 694. Our antithetic analysis divided molecule 694 into four fragments, north 775, west 776, south 777 and east 778. These would be united by a Kociensky-Julia olefination, a Julia olefination, an esterification and a final metathesis (Scheme 7.35).

---

Chapter 7. Total synthesis of (+)-dactylolide

So far, only the synthesis of the north and west fragments $775$ and $776$ has been accomplished. Their DCC-mediated coupling was also attempted and afforded the north-west subunit $794$ in 4 steps and 67.7% overall yield (3 steps and 68.3% overall yield in the longest linear sequence). The remaining fragments $777$ and $778$ are now under construction and the progress of the synthesis will be reported in the final version of the thesis.
Chapter 7. Total synthesis of (+)-dactylolide
8. Conclusions

The main objective of this Thesis was to develop a short, efficient and highly convergent synthesis of (+)-ambruticin 1. Our first approach towards this molecule failed. Finally, a novel disconnection of the molecule 1 into four fragments proved to be the most viable route (Scheme 8.1).

Since fragment 122 has already been prepared in our laboratory, our main synthetic efforts were focused on the assembly of the remaining three subunits: 182, 183 and 100 and their union. The synthesis of these three portions followed by their coupling afforded the eastern part 211 of ambruticin 1 in 25 steps and 5.9% overall yield (17 steps and 14.2% overall yield in the longest linear sequence) (Scheme 8.2).
To achieve this efficient synthesis, several novel modifications of standard reactions had to be performed.

First, a stable analog of CuCl, our precatalyst in the aerobic Cu(I)-promoted oxidation of alcohols, was introduced. It was shown that the CuCl(cod) complex is a shelf stable equivalent of CuCl. It is able to promote the oxidation reaction with the same yields though requires slightly longer reaction times (Table 2.8).

Additionally, the scope of the diastereoselective cyclopropanation of olefins was extended to 1,2,3-trisubstituted vinylboronates (Table 2.16).

More interestingly, we have developed the first chiral aldehyde-based Sakurai multicomponent reaction (Scheme 8.3). It was showed that the reaction proceeded in good to excellent yields and with complete diastereoccontrol in the case of secondary and tertiary silyl ethers.
Chapter 8. Conclusions

It was postulated that observed the diastereoselectivity originated from the addition of the allylsilane on the corresponding oxocarbenium ion, according to the Felkin-Anh transition state (Figure 8.1). This observation can be generalized for secondary and tertiary silyl ethers, but fails to provide an explanation in the case of primary silyl ethers. Even though we have performed several mechanistic studies, the precise reaction mechanism is still unclear.

During the synthesis of (+)-ambruticin 1, a novel modification of the classical Julia olefination method was introduced. By replacing the sulfone moiety with a sulfoxide, the equilibrium of the reaction between 494/495 and 510 was shifted towards the adduct 510. Furthermore, we have developed and optimized the conditions for the reductive-elimination of β-benzoyloxy sulfoxides 510 yielding the desired olefins 398. This overall sequence, consisting in three steps (addition, trapping with benzoyl chloride,
Chapter 8. Conclusions

Reductive-elimination furnishes the olefins 398 in good to acceptable yields and moderate to excellent E/Z selectivity (Scheme 8.4).

![Scheme 8.4](image)

Further mechanistic studies also proved that the reductive elimination was stereoselective but not stereospecific. Interestingly, the role of steric effects on the reaction’s selectivity was found to be important. This led us to propose an empirical selectivity model for the sulfoxide-modified Julia olefination (Figure 8.2).

![Figure 8.2](image)

This olefination method was used later on as a key step in the total synthesis of (+)-goniothalamin, (+)-goniothalamin oxide and (+)-kavain (Scheme 8.5).
In the context of the Julia olefination, we have also developed short and efficient accesses to sulfone-sulfide hybrids. The synthetic power of these doubly-functionalized synthons was then demonstrated using compound 184. By reacting 184 with benzaldehyde and cinnamaldehyde, under the standard Kociensky-Julia conditions, both enantiomers of 560 could be prepared in optically pure form by simply reversing the order of addition of the aldehydes (Scheme 8.6).

Finally, this newly developed method was also applied in the context of the synthesis of jerangolid D (617) (Scheme 8.7). Retrosynthetically, the molecule 617 was disconnected into three fragments: right (100), middle (685) and left (607b). Since the synthesis of subunits 100 and 685 has been previously established, only an efficient route to 607b had to be disclosed. Thus, several approaches towards 607b were examined and, in the best case, the precursor 615b was prepared in 5 steps and 34% overall yield (Scheme 8.8).
Coupling of the prepared fragments 607b, 685 and 100 then accomplished the first total synthesis of jerangolid D in 23 steps (9 steps in longest linear sequence) and 0.3% overall yield (9.3% yield in longest linear sequence). Starting from these building blocks, fragments 607b
Chapter 8. Conclusions

![Scheme 8.7]

Scheme 8.7

![Scheme 8.8]

Scheme 8.8
Chapter 8. Conclusions
9. Perspectives: Highlights

In this chapter, only the most important perspectives pertaining to each chapter will be overviewed and the obvious ones, such as to finish the total synthesis of (+)-ambruticin and (+)-dactylolide will not be mentioned.

Concerning the multicomponent Sakurai reaction, there is a wide range of variations to test. For example, the influence of an additional substituent on the aldehydic component, the replacement if the silyloxy moiety by a halide or an amine, and the use of ketones instead of aldehydes (Figure 9.1).

![Figure 9.1](image_url)

Additionally, further transformation of the initial condensation products and/or the dihydropyran derivatives should be exploited. Some examples of possible modifications are shown in Figure 9.2.

Taking into account the sulfoxide-modified Julia olefination, it might be interesting to investigate the influence of the EWG and EDG groups on the phenyl ring of the sulfoxide. These substituents might, not only change the reactivity of the anion generated α to the sulfoxide, but also strongly alter the reduction potential of the sulfoxide hence, making the reductive elimination an easier process. An example of this approach is depicted in Scheme 9.1.
Similarly the reduction potential of the $\beta$-benzyloxy sulfoxide might be successfully modified by introducing EDG or EWG on the phenyl ring of the acylating agent.

![Chemical structures](image)

**Figure 9.2**

Via this modification, several groups with different reduction potentials might be introduced in a molecule and, as a consequence, the selective reduction of one of them might be accomplished (Scheme 9.2).

Finally, since we have established short, efficient and general approaches to (+)-goniothalamin, (+)-kavain and jerangolid D, these synthetic routes might be used for the preparation of structural analogs of these natural products.

**Scheme 9.1**
Scheme 9.2
Chapter 9. Perspectives: High-lights
10. Experimental part

Routine nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN GEMINI-200 VXR-200 (\(^1\)H: 200 MHz and \(^{13}\)C: 50 MHz), a BRUCKER AC-250 (\(^1\)H: 250 MHz and \(^{13}\)C: 62.5 MHz), a VARIAN GEMINI-2000 (\(^1\)H: 300 MHz and \(^{13}\)C: 75 MHz) and a BRUCKER AC-300 Avance II (\(^1\)H: 300 MHz and \(^{13}\)C: 75 MHz). High field spectra were recorded on a BRUCKER AM-500 (\(^1\)H: 500 MHz and \(^{13}\)C: 125 MHz). \(^1\)H chemical shifts (\(\delta \) H) are reported in ppm downfield from internal tetramethylsilane or calibrated from CHCl\(_3\). \(^{13}\)C NMR spectra were recorded using CDCl\(_3\) as the internal standard.

Low resolution mass spectra were recorded using VARIAN MATT-44 and FINNIGAN MAT-TSQ 70 spectrometers.

Infra-red spectra (IR) were recorded, as KBr discs or thin films, on a PERKIN ELMER 681 spectrometer and a Shimadzu FTIR-8400S spectrometer and recorded in cm\(^{-1}\).

Elemental analyses were carried out at the university of Stuttgart, Germany.

Thin layer chromatography (TLC) were performed on TLC plastic sheets, Silica gel 60 F\(_{254}\) (MERCK and Aldrich). The plates were visualized using ultra-violet light (256 nm) and developed using KMnO\(_4\) and/or vanillin stain and/or I\(_2\)/SiO\(_2\) which were prepared according to the following procedures:

- **Potassium Permanganate**: This stain was prepared by dissolving 3 g of KMnO\(_4\) and 20 g of K\(_2\)CO\(_3\) in 5 mL of 5% NaOH and 300 mL of water.

- **Vanillin**: This stain was prepared by dissolving 2 g of vanillin in 100 mL of EtOH containing 1 mL of conc. H\(_2\)SO\(_4\). The plate was developed by heating.
Chapter 10. Experimental part

- **Ceric Ammonium Molybdate (CAM):** This stain is prepared by dissolving 2.5 g of \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\) and 1.0 g \(\text{Ce(SO}_4)_2\) in 90 mL of water and 10 mL of conc. \(\text{H}_2\text{SO}_4\). The plate is developed by heating on a hot plate. This stain chars blue and is good for polyhydroxylated compounds.

- **I\(_2\):** A jar of fine grade silica gel impregnated with iodine was used. The plate was immersed in the silica gel for a few seconds.

Column chromatographies were performed using MERCK silica gel 60 (230-400 mesh) under pressure with the stated solvents. All solvents were routinely distilled prior to use. Dry solvents were obtained by standard procedures according to D. D. Perrin and D. R. Perrin, *Purification of Laboratory Chemicals*. All compounds (Acros, Aldrich, Fluka, Lancaster and TCI) were used as received unless otherwise stated. All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated.

**Structure determination**

Structure determination was carried out with a help of 2D-COSY, HSQC, HMBS, 2D-NOESY, and/or n.O.e. diff. NMR spectroscopy experiments.

**General remarks**

- When the product was obtained as a mixture of two diastereoisomers, the signals for the minor isomer, if different from the major, are marked with \(^*\). *E.g.* ..., 1.23 (s, 1H, H-3), 1.26 (s, 1H, H-3\(^*\)). Only the characteristic peaks are marked with \(^*\).

- When a CH\(_2\) group, bearing two diastereotopic hydrogen atoms, is presented in the molecule, two different signals should be observed
in $^1$H-NMR spectra. To distinguish between them, the hydrogen atoms are described as e.g. H-1 and H-1'.

10.1 Sulphur-containing compounds

10.1.1 General procedure for sulphide synthesis

10.1.2 General procedure for sulfoxide synthesis
Chapter 10. Experimental part

10.1.3 General procedure for sulfone synthesis

\[
\begin{align*}
\text{MeO}_2C & \quad \text{O}_2S \quad \text{N} \quad \text{N} \quad \text{Ph} & \text{p. 413} \\
\text{HO} & \quad \text{SO}_2\text{Ph} & \text{p. 416} \\
\text{SO}_3\text{Ph} & \quad \text{OBz} & \text{p. 418} \\
\text{N} \quad \text{N} \quad \text{O}_2S \quad \text{Ph} & \quad \text{OTBS} & \text{p. 422} \\
\text{TBDPS} & \quad \text{SO}_3\text{Ph} & \text{p. 424} \\
\text{PTO}_2\text{S} & \quad \text{H} & \text{p. 425}
\end{align*}
\]

10.2 Transformations of alcohols

10.2.1 General procedure for mesylation of alcohols

\[
\begin{align*}
\text{MsO} & \quad \text{O}_2S \quad \text{N} \quad \text{N} \quad \text{Ph} & \text{p. 426} \\
\text{MeO}_2C & \quad \text{OMs} & \text{p. 428}
\end{align*}
\]
Chapter 10. Experimental part

10.2.2  General procedure for acylation of alcohols

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{p. 431} & \text{MeO} & \quad \text{p. 433} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{Br} \\
\text{O} & \quad \text{O} & \quad \text{OBn} & \quad \text{p. 434} \\
\text{O} & \quad \text{O} & \quad \text{OPMB} & \quad \text{p. 435} \\
\text{OPMB} & \quad \text{O} & \quad \text{SO}_2\text{Ph} & \quad \text{p. 436} \\
\end{align*}
\]

10.2.3  General procedure for oxidation of alcohols

\[
\begin{align*}
\text{O} & \quad \text{SPh} & \quad \text{p. 440} & \quad \text{O} & \quad \text{H} & \quad \text{p. 441} \\
\text{TBSO} & \quad \text{O} & \quad \text{p. 442} & \quad \text{O} & \quad \text{Ph}_2(\text{MeO})\text{C} & \quad \text{p. 443} \\
\end{align*}
\]

10.2.4

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{OBn} & \quad \text{p. 445} \\
\end{align*}
\]

10.2.5  General procedure for transacetalization

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{O} & \quad \text{OEt} & \quad \text{p. 448} & \quad \text{EtO}_2\text{C} & \quad \text{p. 449} \\
\end{align*}
\]
10.3 Olefination methods

10.3.1 General procedure for sulfoxide-modified Julia olefination

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
p. 452 & \quad \text{Ph} \\
\text{Me} & \quad \text{Me} \\
p. 453 & \quad \text{Me} \\
\text{Ph} & \quad \text{Ph} \\
p. 454 & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
p. 455 & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
p. 456 & \quad \text{Ph} \\
\text{OTBS} & \quad \text{OBz} \\
p. 457 & \quad \text{OTBS} \\
\text{MeO} & \quad \text{MeO} \\
p. 458 & \quad \text{MeO} \\
\text{Ph} & \quad \text{Ph} \\
p. 459 & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
p. 460 & \quad \text{Ph} \\
\end{align*}
\]
10.3.2 General procedure for Julia-Lythgoe olefination

10.3.3 General procedure for Kociensky-Julia olefination

10.3.4 General procedure for Wittig reaction

10.3.5 General procedure for alkylidation of esters

10.3.6 General procedure for metathesis reaction
Chapter 10. Experimental part

10.4 Protecting groups’ introduction and removal

10.4.1 General procedure for silicon protecting groups introduction and removal
Chapter 10. Experimental part

10.4.2 General procedure for benzyl group introduction and removal

10.4.3 General procedure for \( p \)-methoxy benzyl group introduction and removal

10.4.4 General procedure for protection and deprotection of diols

10.5 Carbonyl compounds

10.5.1 General procedure for ester-group reduction
Chapter 10. Experimental part

10.5.2 General procedure for esterification

$$\text{MeO}_2\text{C} \xrightarrow{\text{p. 542}} \text{CO}_2\text{Me}$$

10.4.3 General procedure for aldol condensation

$$\text{t-BuO \xrightarrow{\text{p. 544}} \text{t-BuO \xrightarrow{\text{p. 545}}}}$$

$$\text{MeO \xrightarrow{\text{p. 546}} }$$

10.4.4 General procedure for synthesis of Weinreb amides

$$\text{MeN \xrightarrow{\text{p. 548}} }$$

10.5.5 General procedure for synthesis of acetals

$$\text{OEt \xrightarrow{\text{p. 550}} }$$

10.5.6 α-Alkylation of esters

$$\text{N \xrightarrow{\text{p. 550}} }$$

10.6 Multicomponent Sakurai reaction

$$\text{OBn \xrightarrow{\text{p. 553}} \text{OTBS \xrightarrow{\text{p. 554}}}}$$
Chapter 10. Experimental part

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

TBDPSO

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS

OTBDPS
Chapter 10. Experimental part

10.7 Epoxides

10.7.1 General procedure for epoxide opening

\[
\text{NC} - \text{OH} \quad \text{OBn} \quad \text{p. 571}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 572}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 574}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 575}
\]

10.7.2 General procedure for epoxidation of olefins

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 576}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 577}
\]

10.8 Reformatsky-type reactions

10.1 Blaise reaction

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 581}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 582}
\]

10.2 Intramolecular Reformatsky-type cyclization

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 583}
\]

10.9 Allylation of nitriles

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 585}
\]

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{OBn} \quad \text{p. 586}
\]

10.10 Allylsilane synthesis

\[
\text{Br} \quad \text{SiCl}_3 \quad \text{p. 586}
\]

\[
\text{Br} \quad \text{SiMe}_3 \quad \text{p. 587}
\]
Chapter 10. Experimental part

10.11 Cyclopropanation of vinyl boronates

\[
\text{Ph}_2(\text{MeO})C\cdots\text{B} \text{OTBDPS} \quad \text{Ph}_2(\text{MeO})C\cdots\text{B} \text{OTBS}
\]

10.1 Sulphur-containing compounds

10.1.1 General procedure for sulphide synthesis

*Mitsunobu reaction.*

\[
\text{R-OH} + \text{HS-Ar} \xrightarrow{\text{DIAD, PPh}_3} \text{THF, 0°C to r.t.} \xrightarrow{\text{R-S-Ar}}
\]

A solution of alcohol (1.0 mmol, 1.0 eq), Ar-SH (1.2 mmol, 1.2 eq) and PPh\(_3\) (1.2 mmol, 1.2 eq) in THF (10 mL, 0.1 M) was cooled to 0°C and DIAD (1.2 mmol, d = 1.020 g·mL\(^{-1}\), 1.2 eq) was added within 15 min. Reaction mixture was allowed to warm to r.t. and stirred for 4 h.

---

Chapter 10. Experimental part

THF was evaporated under the reduced pressure and the crude reaction mixture was dissolved in Et₂O (8 mL) and kept for 4 h at –20°C. Precipitated P(O)Ph₃ was removed by filtration and filtrate was evaporated under reduced pressure. The residue was then purified by column chromatography on silica gel.

Method B: From alkyl halides or alkyl mesylates.

\[
R-X + HS-Ar \xrightarrow{\text{NaH, THF, 0°C to Δt}} R-S-Ar
\]

NaH (1.3 mmol, 60% suspension in mineral oil, 1.3 eq) was washed with n-pentane (2x10 mL) and then suspended in dry Et₂O (4 mL, 0.25 M). The suspension was cooled to 0°C and Ar-SH (1.2 mmol, 1.2 eq) was slowly added. The resulting mixture was stirred at 0°C for 30 min and alkyl bromide or mesylate (1.0 mmol, 1.0 eq) in dry Et₂O (2 mL) was slowly added over 5 min. The mixture was allowed to warm to r.t. and stirred for additional 20 h at r.t. or reflux. Saturated aqueous NaHCO₃ (10 mL) was added to quench the reaction and the resulting layers were separated. Aqueous layer was extracted with Et₂O (3x20 mL) and combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method C: From diphenyl disulphide.

\[
R-OH + PhS—SPh \xrightarrow{\text{Bu₃P, THF, 0°C to r.t.}} R—S—Ph
\]

\(^{425}\) Ph₃PO precipitation step might be skipped if small quantities (<1.0 mmol) of the alcohol are converted into the sulphide.
Chapter 10. Experimental part

To a solution of alcohol (1.0 mmol, 1.0 eq) and Ph₂S₂ (1.55 mmol, 1.55 eq) in THF (1.25 mL, 0.8 M), nBu₃P (1.54 mmol, d = 0.812 g mL⁻¹, 1.54 eq) was added at 0°C and the resulting mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel.

Method D: Via addition to olefins.⁴²⁶

A mixture of thiophenol (10.0 mmol, 1.0 eq), alkene (10.0 mmol, 1.0 eq) and 70% HClO₄ (2.5 mmol, 0.25 mmol) was heated at 100°C and stirred for 2.5 h. The reaction mixture was allowed to cool to r.t. and diluted with benzene (50 mL). The benzene solution was washed with 1.0 M aqueous NaOH (25 mL), H₂O (25 mL) and dried over MgSO₄. Benzene was evaporated and the residue was purified by distillation at reduced pressure.

**Methyl (2R)-2-methyl-3-[(1-phenyl-1H-1,2,3,4-tetrazol-5-yl)sulfanyl]propanoate**

Method A: Starting from alcohol (4.53 mmol). Purified by CC (φ 5.0 cm, 11 cm of SiO₂, 50 mL fractions; P.E. : EtAc = 10:1) to give 1.16 g (92%) of slightly yellow oil.

---

Chapter 10. Experimental part

**Method B:** Starting from the corresponding mesylate (90.0 mmol). Stirred at r.t. for 20h. Evaporation of the combined organic layers gave 24.0 g (96%) of slightly yellow oil, which was found to be sufficiently pure for the next step.

**Method A:** TLC (P.E.:EtAc = 1:1)  

**Method B:** TLC (P.E.:EtAc = 1:1)

![UV impurity, not identified](image)

![UV, KMnO₄, product](image)

![UV, KMnO₄, Ce-Mo system (blue spot)](image)

![UV, KMnO₄, sulfide](image)

![UV, KMnO₄, mesylate](image)

IR (NaCl, neat) $\nu$ (cm$^{-1}$): 3061 (m), 2952 (m), 1733 (s, C=O), 1610 (m), 1500 (s), 1459 (m), 1412 (m), 1193 (m), 761 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.35 (d, 3H, $^3J_{4,3}$ = 7.2 Hz, H-4), 3.11 (sextet, 1H, $^3J$ = 7.2 Hz H-3), 3.58 (d, 2H, $^3J_{5,3}$ = 7.2 Hz, H-5), 3.70 (s, 3H, H-1), 7.54-7.59 (m, 5H, Ar).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$(ppm): 17.4 (C-4), 35.9 (C-5), 39.9 (C-3), 52.4 (C-1), 124.0, 130.0, 133.5 (aromatic CH and Cq), 155.4 (C-6), 175.0 (C-2).

MS (ESI), $m/z$ (%): 278.4 (2) [M$^+$], 179.2 (29) [M$^+$+1], 219.1 (100) [M$^+$-CO$_2$Me], 201.1 (86) [M$^+$-Ph].

HRMS, $m/z$: calcd. (C$_{12}$H$_{14}$N$_4$O$_2$SNa) 301.0735; found 301.0735.
[α]_{D}^{20} = +38.1° (c = 1.49, CHCl₃).

(2R)-2-Methyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]propyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulfone

**Method A**: From alcohol (0.35 mmol). Stirred at r.t. for 2h. Purified by CC (ϕ 1.5 cm, 12 cm of SiO₂, 4 mL fractions; P.E.:EtAc = 3:1) to give 141 mg (91%) of slightly yellow very viscous oil.

**Method B**: From mesylate (20.7 mmol). Stirred at r.t. for 36 h at r.t. Residue was purified by CC (ϕ 6.5 cm, 10 cm of SiO₂, 50 mL fractions; P.E.:EtAc = 2:1→1:1) to give 7.0 g (82%) of very viscous yellow oil.

**Method A**: TLC (P.E.:EtAc = 1:1)  
**Method B**: TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3073 (w), 2962 (m), 2924 (m), 2854 (m), 1498 (s), 1339 (s), 1153 (s), 1024 (m), 764 (m).
Chapter 10. Experimental part

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.36 (d, 3H, $^3$J$_{3,3}$ = 6.6 Hz, H-4), 2.95 (m, 1H, H-3), 3.52 (dd, 1H, $^2$J$_{2,2'}$ = 13.4, $^3$J$_{2',3}$ = 6.7 Hz, H-2 partial overlap), 3.58 (dd, 1H, $^2$J$_{2,2'}$ = 13.8, $^3$J$_{2',3}$ = 6.2 Hz, H-2' partial overlap), 3.71 (dd, 1H, $^2$J$_{5,5'}$ = 14.8, $^3$J$_{5,3}$ = 7.7 Hz, H-5), 4.12 (dd, 1H, $^2$J$_{5',5}$ = 14.7, $^3$J$_{5',3}$ = 5.1 Hz, H-5'), 7.53-7.74 (m, 10H, Ar).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$(ppm): 19.7 (C-4), 29.3 (C-2), 38.7 (C-3), 60.6 (C-5), 124.1, 125.3, 129.8, 130.0, 130.5, 131.7, 133.7, 134.2 (aromatic CH and Cq), 156.7 (C-6), 159.7 (C-1).

MS (APCI), m/z (%): 442.9 (21) [M$^+$], 443.9 (6) [M$^+$+1], 444.9 (4) [M$^+$+2], 414.9 (14) [M$^+$-N$_2$], 296.9 (34) [M$^+$-PT], 233.0 (7) [M$^+$-SO$_2$PT], 163.1 (39) [M$^+$-SPT, -PhNH$_2$, -N$_2$], 149.1 (100) [M$^+$-SO$_2$PT], 119.1 (15) [M$^+$-PT, -SPT].

HRMS, m/z: calcd. (C$_{18}$H$_{18}$N$_8$O$_2$S$_2$Na) 465.0892; found 465.0892.

$\alpha$$_{20}^D$: +8.33° (c = 0.86, CHCl$_3$).

(2R)-Methyl 2-methyl-3-(phenylthio)propanoate

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{C}_6\text{H}_{10}\text{O}_3 & \quad \text{C}_8\text{H}_{14}\text{O}_2\text{S} \\
\text{Mol. Wt.:} & \quad 118.13 \quad \text{Mol. Wt.:} \quad 210.29
\end{align*}
\]

Method C: From alcohol (4.74 mmol). Purified by CC($\phi$ 4 cm, 9.5 cm of SiO$_2$, 20 mL fractions; P.E.:Et$_2$O = 20:1→4:1) to give 995 mg (quant.) of colourless oil.
TLC (5:1 = P.E.:Et$_2$O)

UV, KMnO$_4$, vanilline (red), PhSH

UV, KMnO$_4$, alcohol

IR (NaCl, neat) $\nu$(cm$^{-1}$): 3012 (w), 2976 (m), 2951 (m), 1732 (s), 1583 (w), 1480 (w), 1455 (w), 1211 (m), 1165 (m), 1025 (m).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.27 (3H, d, $^3J_{4,3} = 7.1$ Hz, H-4), 2.70 (1H, dqd, $^3J_{3,5'}, = 7.2$ Hz, $^3J_{3,4} = 7.1$ Hz, $^3J_{5,5'} = 7.0$ Hz, H-3), 2.93 (1H, dd, $^3J_{3,5} = 7.0$ Hz, $^2J_{5,3} = 13.4$ Hz, H-5), 3.27 (1H, dd, $^3J_{5,3} = 7.2$ Hz, $^2J_{5,5'} = 13.4$ Hz, H-5'), 7.20-7.41 (5H, m, aromatic CH).

$[\alpha]_{20}^D$: +74.6° (c = 1.20, CH$_2$Cl$_2$) [lit.$^{427}$ +64.3° (c = 1.59, CHCl$_3$).

CAS number: [165457-66-9]

(2$R$)-2-Methyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]propyl phenyl sulfone

Method B: Starting from mesylate (0.86 mmol). Stirred for 4 h at r.t. Purified by CC (φ 1.5 cm, 12 cm of SiO$_2$, 6 mL fractions; P.E.:EtAc = 2:1) to give 289 mg (90%) of very viscous yellow oil.

Chapter 10. Experimental part

**TLC (100% EtAc)**

\[
\begin{array}{c}
\text{IR (NaCl, neat) } \nu^1(\text{cm}^{-1}): 3067 (\text{w}), 2969 (\text{m}), 2926 (\text{m}), 2853 (\text{w}), 1654 \\
(\text{w}), 1596 (\text{w}), 1499 (\text{m}), 1447 (\text{w}), 1383 (\text{w}), 1305 (\text{s}), 1146 (\text{s}), 1086 \\
(\text{m}), 761 (\text{m}), 734 (\text{m}), 688 (\text{m}).
\end{array}
\]

\[
\begin{array}{c}
{^1}H\text{-NMR 300 MHz, CDCl}_3 \delta (\text{ppm}): 1.27 (\text{d, } 3H, {^3}J_{4,3} = 6.7 \text{ Hz, H-4}), 2.65 \\
(\text{m, } 1H, \text{ H-3}), 3.08 (\text{dd, } 1H, {^2}J_{5,5'} = 13.9, {^3}J_{5,3} = 7.2 \text{ Hz, H-5}), 3.36 (\text{dd,} \\
1H, {^2}J_{5',5} = 13.9, {^3}J_{5',3} = 4.8 \text{ Hz, H-5'}), 3.46 (\text{dd, } 1H, {^2}J_{2,2'} = 13.8, {^3}J_{2,3} = \\
6.7 \text{ Hz, H-2}), 4.52 (\text{dd, } 1H, {^2}J_{2',2} = 13.7, {^3}J_{2',3} = 6.3 \text{ Hz, H-2'}), 7.51-7.93 \\
(\text{m, } 10H, \text{ aromatic CH}).
\end{array}
\]

\[
\begin{array}{c}
{^{13}}C\text{-NMR (62.5 MHz, CDCl}_3 \delta (\text{ppm}): 19.8 (C-4), 29.4 (C-3), 39.3 (C-2), \\
60.7 (C-5), 124.0, 128.2, 129.5, 130.1, 133.7, 134.0, 139.6 (\text{aromatic CH} \\
and Cq), 153.8 (C-1).
\end{array}
\]

\[
\begin{array}{c}
\text{MS (APCI), m/z } (\%): 375.0 (100) \text{ [M$^+$]}, 376.0 (21) \text{ [M$^+$+1]}, 197.0 (32) \\
[M^+$-PTS], 143.0 (7) \text{ [PhS(OH)$_2^+$].}
\end{array}
\]

\[
\text{HRMS, m/z: calcd. (C$_{17}$H$_{18}$N$_4$O$_2$S$_2$Na) 397.0769; found 397.0771.}
\]

\[
[a]_{20}^{20} = -5.93^\circ (c = 1.32, \text{ CHCl}_3).
\]

**400**
Method B: Starting from mesylate (2.74 mmol). Refluxed for 4 h. Purified by CC (φ 3.5 cm, 10 cm of SiO₂, 20 mL fractions; P.E.:EtAc = 5:1) to give 906 mg (91%) of very viscous yellow oil.

TLC (P.E.:EtAc = 2:1)

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3064 (w), 2969 (m), 2926 (m), 2880 (w), 1475 (m), 1447 (m), 1427 (s), 1305 (s), 1085 (m), 756 (m), 728 (s), 595 (m).

¹H-NMR 300 MHz, CDCl₃ δ (ppm): 1.31 (d, 3H, ³J₄₋₃ = 6.7 Hz, H-4), 2.60 (m, 1H, H-3), 3.07 (dd, 1H, ³J₅₋₅' = 14.4, ³J₅₋₃ = 7.7 Hz, H-5), 3.39 (dd, 1H, ³J₂₋₂' = 13.4, ³J₂₋₃ = 13.4 Hz, H-2), 3.44-3.51 (m, 2H, H-2' and H-5'), 7.29-7.91 (m, 9H, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 19.8 (C-4), 29.5 (C-3), 39.4 (C-2), 60.8 (C-5), 121.2, 121.7, 124.6, 126.3, 128.1, 129.4, 133.8, 139.6 (aromatic CH and Cq), 153.0 (C-1).

MS (APCI), m/z (%): 364.0 (100) [M⁺], 365.0 (21) [M⁺ + H], 222.0 (4) [M⁺ - SO₂Ph], 197.0 (54) [M⁺ - BTS], 168.1 (7) [BT-SH + H⁺], 143.0 (11) [PhS(OH)⁺].

HRMS, m/z: calcd. (C₁₇H₁₇NNaO₂S₃Na) 386.0319; found 386.0314.

[α]²₀°D -20.2° (c = 2.11, CHCl₃).
Chapter 10. Experimental part

1-Cyclohexylethyl phenyl sulphide\(^{428}\)

\[
\begin{align*}
\text{C}_8\text{H}_{14} \quad \text{Mol. Wt.:} \quad 110.2 \\
\text{C}_{14}\text{H}_{20}\text{S} \quad \text{Mol. Wt.:} \quad 220.37 \\
\end{align*}
\]

*Method D*: Starting from vinyl cyclohexane (18.1 mmol). Distillation under reduced pressure afforded 3.47 g (87%) of colourless oil.

\[
\text{B.p.} = 224-225^\circ\text{C}/1.0 \text{mbar}
\]

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.18-1.82 (12H, m, H-2 to H-6), 1.42 (3H, d, \(^3J_{1,2} = 7.6\) Hz, H-1), 7.26-7.51 (5H, m, aromatic CH).

\(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) (ppm): 17.3 (C-1), 22.4 (C-5), 26.3 (C-6), 36.0 (C-4), 40.2 and 41.5 (C-2 and 3), 127.1, 130.2, 131.4, 133.3 (aromatic CH and Cq).

CAS number: [61836-05-3].

Isobutyl phenyl sulphide\(^{429}\)

\[
\begin{align*}
\text{C}_4\text{H}_9\text{Br} \quad \text{Mol. Wt.:} \quad 137.02 \\
\text{C}_{10}\text{H}_{14}\text{S} \quad \text{Mol. Wt.:} \quad 166.28 \\
\end{align*}
\]

*Method B*: Starting from alkyl bromide (14.6 mmol). Refluxed overnight. Distillation under reduced pressure yielded 2.13 g (88%) of colourless oil.

---


Chapter 10. Experimental part

B.p. = 130-131°C/1.0 mbar.

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ (ppm): 1.04 (d, 6H, $^3J_{1,2} = 6.6$ Hz, H-3), 1.87 (heptet, 1H, $^3J = 6.7$ Hz, H-2), 2.81 (d, 2H, $^3J_{1,2} = 6.8$ Hz, H-1), 7.10-7.40 (m, 5H, aromatic CH).

CAS number: [13307-61-4].

**Methyl (1-phenyl-1$H$-1,2,3,4-tetraazol-5-yl) sulphide**

Method B: Starting from 11.22 mmol of thiol. Stirred at r.t. overnight. After evaporation gave 2.14g (99%) of slightly yellow solid.

$^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ (ppm): 2.82 (s, 3H, H-1); 7.56 (m, 5H, aromatic H).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$ (ppm): 15.5 (C-1); 123.8, 130.0, 130.3 and 133.8 (aromatic CH and C$_q$), 155.1 (C-2).

MS (APCI), $m/z$ (%): 193.0 [M$^+$ + 1] (100), 165.1 (21), 150.1 (51), 118.1 (11).

CAS number: [1455-92-1].
Chapter 10. Experimental part

2-[(1-Phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]-1-ethanol

Method A: Starting from 10.0 mmol of diol. Stirred at r.t. for 2h. Purified by CC (φ 6.5 cm, 10 cm of SiO₂, 50 mL fractions; P.E.:EtAc=1:1) to give 1.81 g (82%) of slightly yellow crystals.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν (cm⁻¹): 3389 (broad), 3067 (m), 2937 (m), 2880 (m), 1499 (s), 1416 (m), 1388 (m), 1243 (m), 1070 (m), 1015 (m), 761 (m).

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 3.12 (broad s, 1H, H-1), 3.56 (t, 1H, 3J₂,₃ = 5.6 Hz, H-3), 4.06 (t, 1H, 3J₂,₃ = 5.6 Hz, H-2), 7.57-7.61 (m, 5H, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 36.1 (C-3), 61.5 (C-2), 124.3, 127.9, 131.7, 133.2 (aromatic CH and Cq), 154.6 (C-4).

MS (APCI), m/z (%): 222.9 (100) [M⁺], 194.92 (51) [M⁺ -N₂], 150.9 (6) [M⁺ -Ph].

HRMS, m/z: calcd. (C₉H₁₀N₄OSNa) 245.0473; found 245.0467.
Chapter 10. Experimental part

10.1.2 General procedure for sulfoxide synthesis

*Method A: mCPBA mediated oxidation.*

\[
\begin{align*}
 & \text{R-SPh} \xrightarrow{m\text{CPBA, CH}_2\text{Cl}_2, 0^\circ\text{C to r.t.}} \text{R-SOPh} \\
\end{align*}
\]

A solution of sulphide (1.0 mmol, 1.0 eq) in CH\textsubscript{2}Cl\textsubscript{2} (4.0 mL, 0.25 M) was cooled to 0°C and \textit{m}CPBA (1.01 mmol, 70% \textit{m}CPBA, 1.01 eq) was added in 5 portions. The resulting suspension was allowed to warm to r.t. and stirred for 3h. Saturated aqueous NaHCO\textsubscript{3} (4 mL) was added and the resulting layers were separated. Aqueous layer was extracted with Et\textsubscript{2}O (3x10 mL) and organic layers were combined, washed with H\textsubscript{2}O (5 mL), brine (5 mL), dried over MgSO\textsubscript{4} and evaporated under reduced pressure.

*Method B: MoO\textsubscript{2}(acac)\textsubscript{2}/tBuOOH system.*

\[
\begin{align*}
 & \text{R-SPh} \xrightarrow{\text{MoO}_2(\text{acac})_2, \text{TBHP, CH}_2\text{Cl}_2, \text{r.t.}} \text{R-SOPh} \\
\end{align*}
\]

A solution of sulphide (1.0 mmol, 1.0 eq) in CH\textsubscript{2}Cl\textsubscript{2} (2.2 mL, 0.5M) was degassed via freeze-pump-throw method (3x) and MoO\textsubscript{2}(acac)\textsubscript{2} (0.05 mmol, 0.05 eq) was added. Resulting mixture was cooled to 0°C and TBHP (1.0 mmol, 5.5M solution in dodecane, 2.2 eq) was added dropwise. An exothermic reaction occurred and resulting orange solution was stirred at r.t. for 30 min. Saturated aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (10 mL) was added and layers were separated. Aqueous layer was extracted with EtAc (3x20 mL) and combined organic layers were washed with H\textsubscript{2}O (10 mL), brine (10 mL), dried over MgSO\textsubscript{4} and evaporated under reduced pressure.

\[430\] Generally, 5 to 10% of sulfone along with desired sulfoxide is obtained. As a consequence, 5-10% of starting sulphide is recovered.
Chapter 10. Experimental part

Method C: Using H$_5$IO$_6$/FeCl$_3$-system.
A solution of sulphide (1.0 mmol, 1.0 eq) in CH$_3$CN (1.0 mL, not purified, p.a., 0.66 M) was stirred for 5 min at r.t. and FeCl$_3$ (0.03 mmol, 3 mol%) was added. After additional 5 min, H$_5$IO$_6$ (1.1 mmol, 1.1 eq) was added and resulting solution was stirred for 3 min. 10% aqueous solution of Na$_2$S$_2$O$_3$ (5 mL) was added and resulting mixture was extracted with CH$_2$Cl$_2$ (3x10 mL). Combined organic layers were washed with H$_2$O (5 mL), brine (5 mL), dried over MgSO$_4$ and evaporated under reduced pressure.

Isobutyl phenyl sulfoxide

Method A: Purified by CC ($\phi$ 1.5 cm, 14 cm of SiO$_2$, 5 mL fractions; P.E.:EtAc = 1:2) to give 182.2 mg (quant.) of slightly yellow oil.

Method C: Purified by CC ($\phi$ 1.5 cm, 14 cm of SiO$_2$, 5 mL fractions; P.E.:EtAc = 1:2) to give 182.1 mg (99%) of slightly yellow oil.

TLC (P.E.:EtAc = 1:2)

IR (NaCl, neat) $\nu$\(^{-1}\)(cm$^{-1}$): 3057, 2960, 2871, 1469, 1443, 1369, 1090, 1036, 998, 749, 691.
Chapter 10. Experimental part

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.07 (d, 3H, $^3J_{1,2} = 6.7$ Hz, H-1), 1.16 (d, 3H, $^3J_{1',2} = 6.7$ Hz, H-1'), 2.24 (m, 1H, H-2), 2.47 (dd, 1H, $^2J_{3,3'} = 12.4$ Hz, $^3J_{3,2} = 9.1$ Hz, H-3), 2.84 (dd, 1H, $^2J_{3',3} = 12.9$ Hz, $^3J_{3',2} = 4.8$ Hz, H-3'), 7.50-7.66 (m, 5H, Ar).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$ (ppm): 21.9 and 23.0 (C-1), 24.4 (C-2), 67.8 (C-3), 124.1, 129.5, 131.1, 144.8 (aromatic CH and Cq).

MS (Cl, CH$_3$/N$_2$O), $m/z$ (%): 182.9 (100) [M$^+$], 184.3 (32), 125.9 (43).

CAS number: [22456-89-9].

**Benzy] phenyl sulfoxide**

![Diagram of benzyl phenyl sulfoxide]

Method A: Starting from 4.99 mmol of sulphide. Purified by CC ($\phi$ 3.5 cm, 6 cm of SiO$_2$, 20 mL fractions; P.E.:EtAc = 1:2) to give 1.01 g (94%) of colourless crystals.

TLC (P.E.:EtAc = 1:1)

![TLC diagram](image)

IR (NaCl, neat) $\nu$ (cm$^{-1}$): 3082, 3069, 3031, 2987, 2966, 1471, 1443, 1358, 1092, 1035, 997, 749, 692.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 4.01 (d, 1H, $^2J_{1,1'} = 12.6$ Hz, H-1), 4.10 (d, 1H, $^2J_{1',1} = 12.9$ Hz, H-1'), 6.97-7.47 (m, 10H, Ar).
Chapter 10. Experimental part

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$(ppm): 63.7 (C-1), 124.6, 128.4, 128.6, 129.0, 129.3, 130.5, 131.3, 142.9 (aromatic CH and Cq).

MS (APCI), $m/z$ (%): 216.9 (54) [M$^+$], 91.0 (100).

CAS number: [210539-77-8].

1-Cyclohexylethyl phenyl sulfoxide

\[
\begin{array}{c}
\text{C}_{14}\text{H}_{20}\text{S} \\
\text{Mol. Wt.: 220.37}
\end{array}
\quad \begin{array}{c}
\text{C}_{14}\text{H}_{20}\text{OS} \\
\text{Mol. Wt.: 236.37}
\end{array}
\]

Method A: Starting from 9.08 mmol of sulphide. Purified by CC ($\phi$ 3.5 cm, 8 cm of SiO$_2$, 20 mL fractions; P.E.:EtAc = 1:2) to give 1.87 g (87%) of colourless crystals.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) $\nu$(cm$^{-1}$): 3081, 3061, 3028, 2967, 2912, 1472, 1442, 1360, 1091, 1031, 995, 748, 692.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.03-1.99 (m, 14H, H-1 and H-3 to 6), 2.81 (m, 1H, H-2), 7.36-7.63 (m, 5H, Ar).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$ (ppm): 21.7, 21.8 and 22.4 (C-1), 25.5, 26.2, 26.3, 26.5, 27.2, 27.9, 29.1, 31.3, 32.4, 55.2 and 55.3 (C-3), 61.4, 62.2 and 63.4 (C-2), 126.8, 129.7, 131.3, 141.7 (aromatic CH and Cq).
Chapter 10. Experimental part

MS (APCI), \( m/z \) (%): 237.2 (32) \([M^+1] \), 91.0 (100).
CAS number: [858658-48-7].

\( (2R,3E)-2\)-Methyl-6-(1,1,1-trimethylsilyl)-3-hexen-5-ynyl phenyl sulfoxide

\[
\begin{align*}
\text{C}_{16}H_{22}SSi \\
\text{Mol. Wt.: 274.5}
\end{align*}
\]

\[
\begin{align*}
\text{C}_{16}H_{22}OSSi \\
\text{Mol. Wt.: 290.5}
\end{align*}
\]

Method B: Starting from 1.82 mmol of sulphide. Purified by CC (\( \phi \) 2.5 cm, 14 cm of SiO\(_2\), 25 mL fractions; P.E.:Et\(_2\)O = 1:2) to give 510 mg (95%, \( E/Z = 6:1 \)) of slightly yellow oil.

Method C: Starting from 1.82 mmol of sulphide. Purified by CC (\( \phi \) 2.5 cm, 14 cm of SiO\(_2\), 25 mL fractions; P.E.:Et\(_2\)O = 1:2) to give 428 mg (81%, \( E/Z = 10:1 \)) of slightly yellow oil.

TLC (P.E.:Et\(_2\)O = 1:1)

Mixture of two diastereoisomers (\( d.r. = 2.3:1 \)).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 0.20 (s, 9H, H-1), 0.87 (d, 3H, \( ^3J_{12,6} = 6.7 \) Hz, H-12), 2.51-2.94 (m, 3H, H-6 and H-7), 5.72 (d, 1H, \( ^3J_{4,5} = 15.9 \) Hz, H-4), 6.16 (dd, 1H, \( ^3J_{5,6} = 15.9 \) Hz, \( ^3J_{5,6} = 8.1 \) Hz, H-5), 7.51-7.70 (m, 5H, Ar).
Chapter 10. Experimental part

Minor stereoisomer: \( ^1\text{H-NMR (300 MHz, CDCl}_3\) \( \delta\) (ppm): 0.18 (s, 9H, H-1\(^*\)), 1.17 (d, 3H, \(^3\)J\(_{1,2,6} = 6.7\) Hz, H-12\(^*\)), 2.51-2.94 (m, 3H, H-6 and H-7), 5.55 (d, 1H, \(^3\)J\(_{4,5} = 14.7\) Hz, H-4\(^*\)), 6.16 (dd, 1H, \(^3\)J\(_{5,6} = 15.9\) Hz, \(^3\)J\(_{5,6} = 8.1\) Hz, H-5), 7.51-7.70 (m, 5H, Ar).

\(^{13}\text{C-NMR (62.5 MHz, CDCl}_3\) \( \delta\) (ppm): -0.1 and 0.0 (C-1 and C-1\(^*\)), 18.7 and 20.3 (C-12 and C-12\(^*\)), 32.4 and 33.0 (C-6 and C-6\(^*\)), 65.0 and 65.1 (C-7 and C-7\(^*\)), 100.2, 101.3, 103.2 and 103.8 (C-2, C-2\(^*\), C-3 and C-3\(^*\)), 110.0 and 111.2 (C-4 and C-4\(^*\)), 146.3 and 147.0 (C-5 and C-5\(^*\)), 123.8, 123.9, 124.1, 129.2, 129.2, 129.3, 131.0, 131.1, 143.8 (aromatic CH and Cq).

\((2R)-3-[1-(\text{tert-Butyl})-1,1\text{-dimethylsilyl}]\text{oxy-2-methylpropyl phenyl sulfoxide}\)

\[
\begin{align*}
\text{TBSO} & \quad \text{SPh} \\
\text{C}_{16}\text{H}_{28}\text{OSSi} & \quad \text{Mol. Wt.: 296,54} \\
\text{IR (NaCl, neat)} & \quad \nu^{-1}(\text{cm}^{-1}): 3071, 2968, 2901, 1473, 1442. \\
\end{align*}
\]

Method A: Starting from 3.12 mmol of sulphide. Evaporation of the solvents yielded 973 mg (99%, d.r. = 1.24:1) of colourless oil.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) \( \nu^{-1}(\text{cm}^{-1}): 3071, 2968, 2901, 1473, 1442. \)

\(^1\text{H-NMR (300 MHz, CDCl}_3\) \( \delta\) (ppm): 0.02 and 0.05 (s, 3H, H-4), 0.87 (s, 9H, H-6), 1.06 (d, 3H, \(^3\)J\(_{7,2} = 7.0\) Hz, H-7), 2.23 (m, 1H, H-2), 2.69 (dd,
Chapter 10. Experimental part

1H, $^2J_{1,1'} = 13.2$ Hz, $^3J_{1,2} = 6.2$ Hz, H-1), 2.97 (dd, 1H, $^2J_{1',1} = 13.2$ Hz, $^3J_{1',2} = 4.1$ Hz, H-1'), 3.53 (dd, partial overlap, 1H, $^2J_{3,3'} = 9.9$ Hz, $^3J_{3,2} = 4.4$ Hz, H-3), 3.78 (dd, 1H, $^3J_{3,3'} = 10.3$ Hz, $^3J_{3',2} = 4.7$ Hz, H-3'), 7.46-7.67 (m, 5H, aromatic CH and Cq).

Minor stereoisomer: $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.03 and 0.06 (s, 3H, H-4*), 0.89 (s, 9H, H-6*), 1.15 (d, 3H, $^3J_{7,2} = 7.0$ Hz, H-7*), 2.23 (m, 1H, H-2), 2.55 (dd, 1H, $^2J_{1,1'} = 13.2$ Hz, $^3J_{1,2} = 9.4$ Hz, H-1*), 2.91 (dd, 1H, $^2J_{1',1} = 13.2$ Hz, $^3J_{1',2} = 8.2$ Hz, H-1'*), 3.52 (d, 2H, $^3J_{3,2} = 5.3$ Hz, H-3'), 7.46-7.67 (m, 5H, aromatic CH and Cq).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ (ppm): -5.3 and -5.2 (C-4), 16.4 and 17.5 (C-7 and C-7*), 18.5 and 18.5 (C-5 and C-5*), 26.1 (C-6), 31.8 (C-2), 62.3 and 62.7 (C-1 and C-1*), 66.1 and 67.5 (C-3 and C-3*), 124.1, 124.3, 125.2, 129.2, 129.3, 131.0, 131.1, 145.1 (aromatic CH and Cq).

MS (APCI), m/z (%): 131.1 (100) [M$^+$+1], 297.2 (15), 181.1 (52).

10.1.3 General procedure for sulfone synthesis

**Method A: $\text{(NH}_4\text{)}_6\text{Mo}_7\text{O}_{24} \cdot 4 \text{H}_2\text{O/H}_2\text{O}_2$ system.**

$\text{R-SO}_2\text{Ph} \xrightarrow{\text{($\text{NH}_4\text{)}_6\text{Mo}_7\text{O}_{24} \cdot 4 \text{H}_2\text{O}}\text{35% H}_2\text{O}_2 \text{EtOH, r.t.}} \text{R-SO}_2\text{Ph}$

To a solution of sulphide (1.0 mmol, 1.0 eq) in EtOH (5.0 mL, 0.2 M) cooled to 0°C, premixed bright yellow solution of molybdenate (0.20 mmol, 0.2 eq) in 35% aqueous solution of H$_2$O$_2$ (10.0 mmol, 10.0 eq) was added slowly over 5 min. The reaction mixture was allowed to warm up to r.t. and stirred for 6 h.

EtAc:H$_2$O = 1:1 (10 mL) was added and layers were separated. The aqueous layer was extracted with EtAc (3x5 mL). Combined organic layers were
washed with H₂O (3 mL), brine (3 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method B: MoO₂(acac)₂/tBuOOH system.**

\[
\begin{align*}
R\text{-SPh} & \xrightarrow{\text{MoO}_2\text{(acac)}_2/\text{TBHP, CH}_2\text{Cl}_2, \text{r.t.}} R\text{-SO}_2\text{Ph} \\
\end{align*}
\]

A solution of sulphide (1.0 mmol, 1.0 eq) in CH₂Cl₂ (2.2 mL, 0.5M) was degassed via freeze-pump-throw method (3x) and MoO₂(acac)₂ (0.05 mmol, 0.05 eq) was added. The resulting mixture was cooled to 0°C and TBHP (2.2 mmol, 5.5 M solution in dodecane, 2.2 eq) was added dropwise. An exothermic reaction occurred and resulting orange solution was stirred at r.t. for 4h. Saturated aqueous Na₂S₂O₃ (10 mL) was added and layers were separated. Aqueous layer was extracted with EtAc (3x20 mL) and collected organic layers were washed with H₂O (10 mL), brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method C: Starting from PhSO₂Na**

\[
\begin{align*}
\text{PhSO}_2\text{Na}^+ + R\text{-X} & \xrightarrow{\text{DMSO}} R\text{-SO}_2\text{Ph} \\
\end{align*}
\]

A solution of PhSO₂Na salt (1.0 mmol, 1.0 eq) in DMSO (2 mL, 0.2 M) was cooled to 0°C and alkyl halide (1.1 mmol, 1.1 eq) was added. The resulting suspension was stirred at r.t. for 4h and then diluted with ether (20 mL). Layers were separated and an aqueous layer was extracted with Et₂O (3x10 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method D: One-pot Mitsunobu substitution/sulphide oxidation method.**

\[
\begin{align*}
\text{R-OH} + \text{HS—Ar} & \xrightarrow{1) \text{DIAD, PPh₃}} \xrightarrow{2) \text{H}_2\text{O}_2/(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot4\text{H}_2\text{O}} \text{R—S—Ar} \\
\end{align*}
\]
A solution of alcohol (1.0 mmol, 1.0 eq), Ar-SH (1.2 mmol, 1.2 eq) and PPh₃ (1.2 mmol, 1.2 eq) in THF (10 mL, 0.1 M) was cooled to 0°C and DIAD (1.2 mmol, d = 1.020 g mL⁻¹, 1.2 eq) was added within 15 min. Reaction mixture was allowed to warm to r.t. and stirred for 4 h. 

EtOH (30 mL) was added and the resulting mixture was cooled to 0°C. To this mixture, a premixed bright yellow solution of molybdenate (0.20 mmol, 0.2 eq) in 35% aqueous solution of H₂O₂ (10.0 mmol, 10.0 eq) was added slowly over 5 min. The reaction mixture was allowed to warm up to r.t. and stirred for 12 h.

EtAc:H₂O = 1:1 (60 mL) was added and layers were separated. The aqueous layer was extracted with EtAc (3x40 mL). Combined organic layers were washed with H₂O (3 mL), brine (3 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Methyl (2R)-2-methyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfonyl]propanoate**

![Chemical Structure](image)

**Method A:** Residue was purified by CC (ϕ 3.5 cm, 11 cm of SiO₂, 10 mL fractions; P.E.:EtAc=5:1→1:1) to give 531 mg (95%) of slightly yellow oil.
Chapter 10. Experimental part

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν\(^{-1}\) (cm\(^{-1}\)):

- 3073 (m),
- 2957 (m),
- 2922 (m),
- 1499 (m),
- 1337 (m),
- 1152 (m),
- 1101 (m),
- 838 (m),
- 776 (m).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ (ppm):

- 1.44 (d, 3H, \(^3\)J\(_{4,3}\) = 7.7 Hz, H-4),
- 3.26 (dqd, 1H, \(^3\)J\(_{3,5'}\) = 8.6 Hz, \(^3\)J\(_{3,4}\) = 7.7 Hz, \(^3\)J\(_{3,5}\) = 4.8 Hz, H-3),
- 3.71 (s, 3H, H-1),
- 3.82 (dd, 1H, \(^2\)J\(_{5,5'}\) = 14.8 Hz, \(^3\)J\(_{5,3}\) = 4.3 Hz, H-5),
- 4.25 (dd, 1H, \(^2\)J\(_{5',5}\) = 14.8 Hz, \(^3\)J\(_{5',3}\) = 8.6 Hz, H-5'),
- 7.60-7.71 (m, 5H, aromatic CH).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) δ (ppm):

- 17.9 (C-4),
- 35.0 (C-3),
- 53.0 (C-1),
- 58.6 (C-5),
- 125.3, 129.9, 131.7, 133.0 (aromatic CH and Cq),
- 153.6 (C-6),
- 173.4 (C-2).

MS (APCI), m/z (%): 310.1 (13) [M\(^+\)], 279.2 (100) [M\(^+\) - OCH\(_3\)].

HRMS, m/z: calcd. for C\(_{12}\)H\(_{14}\)N\(_4\)O\(_4\)S [M+Na\(^+\)] 333.0628; found 333.0631.

[\(\alpha\)]\(_{20}^D\) +5.73° (c = 2.11, CHCl\(_3\)).

\(2R\)-2-Methyl-3-\{1-phenyl-1H-1,2,3,4-tetraazol-5-yl\}sulfonyl\}propan-1-ol

Chemical structures and reactions are shown in the image.
Method A: Starting from sulphide 15.3 mmol of sulphide. Stirred at r.t. for 12 h. Evaporation of solvents gave 4.32 g (99%) of product as yellow very viscous oil sufficiently pure for the next step.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3428 (s), 3073 (w), 2968 (m), 2935 (m), 2881 (m), 1498 (s), 1461 (m), 1338 (s), 1153 (s), 1042 (m), 764 (m).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) δ (ppm): 1.21 (d, 3H, \(^3\)J\(_{4,3} = 7.1\) Hz, H-4), 2.02 (broad s, 1H, H-1), 2.54 (m, 1H, H-3), 3.56 (dd, 1H, \(^2\)J\(_{5,5'} = 14.7\) Hz, \(^3\)J\(_{5,3} = 8.4\)Hz, H-5 (partial overlap)), 3.59 (dd, 1H, \(^2\)J\(_{2,3} = 11.6\) Hz, \(^3\)J\(_{2,3} = 6.7\), H-2 (partial overlap)), 3.80 (dd, 1H, \(^2\)J\(_{2',2} = 11.1\) Hz, \(^3\)J\(_{2',3} = 4.4\) Hz, H-2'), 4.12 (dd, 1H, \(^2\)J\(_{5,5'} = 14.7\) Hz, \(^3\)J\(_{5',3} = 5.5\) Hz,H-5'), 7.60-7.77 (m, 5H, Ar).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) δ (ppm): 16.2 (C-4), 37.0 (C-3), 58.3 (C-5), 64.8 (C-2), 125.2, 129.9, 131.7, 133.4 (aromatic CH and Cq), 155.6 (C-6).

MS (APCI), m/z (%): 282.8 (100) [M\(^+\)], 254.8 (65) [M\(^+\) -N\(_2\)], 146.8 (53) [PT], 118.8 (36).

HRMS, m/z: calcd.(C\(_{11}\)H\(_{14}\)N\(_4\)O\(_3\)SNa) 305.0684; found 305.0668.

[\(\alpha\)]\(_{D}^{20}\): -4.8° (c = 0.88, CHCl\(_3\)).
Chapter 10. Experimental part

(2R)-2-Methyl-3-(phenylsulfonyl)propan-1-ol

\[
\begin{align*}
\text{HO} & \quad \text{SPh} \\
\text{C}_{10}H_{14}O & \text{S} \\
\text{Mol. Wt.: 182.28} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{SO}_2\text{Ph} \\
\text{C}_{10}H_{14}O & \text{S} \\
\text{Mol. Wt.: 214.28} \\
\end{align*}
\]

**Method A**: Starting from 11.0 mmol of sulphide. Stirred at r.t. for 3 h. Evaporation of solvents gave 2.35 g (99%) of pale yellow oil.

**Method B**: Starting from 13.7 mmol of sulphide. Stirred at r.t. for 4 h. Evaporation of solvents gave 3.24 g (product contains dodecane) of pale yellow oil.

**Method A**: TLC (100% EtAc)  
**Method B**: TLC (100% EtAc)

IR (NaCl, neat) ν^1(cm^{-1}):3444 (m), 3064 (w), 2966 (w), 2932 (w), 2879 (w), 1447 (s), 1301 (s), 1290 (s), 1147 (s) 1084 (m), 1039 (m), 741 (m), 688 (m).

\(^1\)H-NMR (300 MHz, CDCl₃) δ (ppm): 1.11 (3H, d, \(^3\)J₄,₃ = 7.2 Hz, H-4), 1.80 (1H, broad s, H-1), 2.34 (1H, m, H-3), 2.98 (1H, dd, \(^2\)J₅,₅ = 14.4, \(^3\)J₅,₃ = 6.2 Hz, H-5), 3.37 (1H, dd, \(^2\)J₅',₅ = 14.4, \(^3\)J₅',₃ = 6.7 Hz, H-5'), 3.52 (1H, dd, \(^2\)J₂,₂ = 11.0, \(^3\)J₂,₃ = 6.7 Hz, H-2), 3.76 (1H, dd, \(^2\)J₂',₂ = 11.0, \(^3\)J₂',₃ = 4.3 Hz, H-2'), 7.56-7.96 (5H, m, aromatic CH).
Chapter 10. Experimental part

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$(ppm): 17.3 (C-4), 31.6 (C-3), 59.5 (C-5), 66.5 (C-2), 128.0, 129.6, 134.0, 140.4 (aromatic CH and C$_q$).

MS (Cl, CH$_4$/N$_2$O), m/z (%): 215.0 (57) [M$^+$], 216.6 (5) [M$^+$+H], 198.5 (12) [M$^+$-O], 197.0 (100) [M$^+$-O], 142.9 (35) [M$^+$+H-PhSO$_2$], 141.5 (15) [M$^+$-PhSO$_2$], 124.8 (17) [PhSO], 126.4 (6) [PhSOH], 77.9 (5) [Ph].

$\alpha$$^{20}_{D}$: -8.71° ($c$ = 1.32, CHCl$_3$) [lit. 431 -9.4° ($c$ = 0.96, CHCl$_3$)].

CAS number: [220018-33-7].

(2$R$,3$E$)-2-Methyl-6-(1,1,1-trimethylsilyl)-3-hexen-5-ynyl phenyl sulphide

![Diagram of the compound]

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$(ppm): 17.3 (C-4), 31.6 (C-3), 59.5 (C-5), 66.5 (C-2), 128.0, 129.6, 134.0, 140.4 (aromatic CH and C$_q$).

MS (Cl, CH$_4$/N$_2$O), m/z (%): 215.0 (57) [M$^+$], 216.6 (5) [M$^+$+H], 198.5 (12) [M$^+$-O], 197.0 (100) [M$^+$-O], 142.9 (35) [M$^+$+H-PhSO$_2$], 141.5 (15) [M$^+$-PhSO$_2$], 124.8 (17) [PhSO], 126.4 (6) [PhSOH], 77.9 (5) [Ph].

$\alpha$$^{20}_{D}$: -8.71° ($c$ = 1.32, CHCl$_3$) [lit. 431 -9.4° ($c$ = 0.96, CHCl$_3$)].

CAS number: [220018-33-7].

**Method A**: Starting from 11.0 mmol of sulphide. Stirred at r.t. for 2 h. Evaporation of solvents gave 3.37 g (99%) of colourless oil.

**Method B**: Starting from 0.6 mmol of sulphide. TBHP in toluene was used.432 Stirred at r.t. for 19h. Purified by CC($\phi$ 1.5cm; 10 cm of SiO$_2$, 10 mL fractions; P.E.:Et$_2$O = 2:1) yielded 147 mg (80%) of colourless oil.

TLC (EP:Et$_2$O = 1:1)


Chapter 10. Experimental part

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3061, 3031, 2982, 2945, 2801, 2125, 1722, 1643, 1581, 1493, 1452, 1387, 1042, 695.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 0.16 (s, 9H, H-1), 1.18 (d, 3H, ³J₁₂,₆ = 6.7 Hz, H-12), 2.85 (heptet, 1H, J = 6.7 Hz, H-6), 3.04 (dd, 1H, ²J₇,₇' = 14.3, ³J₇,₆ = 6.7 Hz, H-7), 3.14 (dd, 1H, ²J₇',₆ = 6.7 Hz, H-7'), 5.47 (dd, 1H, ²J₄,₅ = 15.8, ³J₄,₆ = 1.0 Hz, H-4), 5.98 (dd, 1H, ³J₅,₆ = 15.8, ³J₅,₆ = 7.5 Hz, H-5), 7.55-7.94 (m, 5H, H-9-11).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): -0.1 (C-1), 19.9 (C-12), 32.5 (C-6), 61.4 (C-7), 94.7 (C-2), 102.8 (C-3), 110.3 (C-4), 127.9, 129.2, 133.6, 139.5 (aromatic CH and Cq), 146.2 (C-5).

MS (CI, CH₄/N₂O), m/z (%): 307.9 [M⁺+2] (15), 107.1 [M⁺+1] (32), 214.9 (65), 125 (100).

[α]²⁰D: +50.2° (c = 1.2, CH₂Cl₂).

E.A. calc (C₁₆H₂₂O₂SSi) C 62.70%, H 7.24%; found C 62.98%, H 7.21%.

2-methyl-1-[2-methyl-1-(phenylsulfonyl)propyl]cyclohexyl benzoate

\[
\begin{align*}
\text{PhS}=\text{O} & \quad \text{MoO}_2(\text{acac})_2 \\
\text{OBz} & \quad \text{TBHP, CH}_2\text{Cl}_2, \text{r.t.}
\end{align*}
\]

Mol. Wt.: 398.56

**Method B:** Starting from 12.5 µmol of sulfoxide. Stirred at r.t. for 4h. Purified by column chromatography (φ 1.0 cm, 10 cm of SiO₂, 2.55 mL fractions; 1:1 = P.E.:EtAc) gave 5.1-5.2 mg (99%) of colourless oil.
Chapter 10. Experimental part

TLC (5:1=P.E.:EtAc)  TLC (10:1=P.E.:EtAc)

UV, KMnO₄  UV, KMnO₄
anti sulfoxide  anti sulfoxide

UV, KMnO₄  UV, KMnO₄
syn sulfoxide  syn sulfoxide

Syn-529 (at the C3-C4 bond)

^1^H NMR (300 MHz, CDCl₃) δ (ppm): 0.87 (dd, 3H, ^3^J₁,₂ = 6.8 Hz, ^2^J₁,₁' = 1.3 Hz, H-1), 0.99 (d, 3H, ^3^J₁₄,₅ = 7.0 Hz, H-14), 1.20 (dd, 3H, ^3^J₁,₂ = 6.7 Hz, ^2^J₁,₁' = 1.4 Hz, H-1'), 1.27-2.09 (m, 9H, H-5-9), 3.65 (m, 1H, H-2), 3.83 (d, 1H, ^3^J₁,₂ = 7.1 Hz, H-3), 7.14-8.25 (m, 10H, aromatic CH).

^1^C NMR (62.5 MHz, CDCl₃) δ (ppm): 16.4, 20.5, 23.3, 24.1, 24.9, 30.9, 34.2, 35.1, 39.2, 71.8 (C-3), 85.9 (C-4), 126.6-140.3 (aromatic CH and C₉), 167.1 (C-15).

MS (CI, CH₄/N₂O), m/z (%): 414.7 (100) [M⁺], 415.6 [M⁺+1] (22), 141.9 (34), 121.5 (56), 181.3 (28), 77.0 (15).

Anti-529 (at the C3-C4 bond)

^1^H NMR (300 MHz, CDCl₃) δ (ppm): 0.88 (dd, 3H, ^3^J₁,₂ = 6.8 Hz, ^2^J₁,₁' = 1.4 Hz, H-1), 1.01 (d, 3H, ^3^J₁₄,₅ = 7.0 Hz, H-14), 1.20 (dd, 3H, ^3^J₁,₂ = 6.7 Hz, ^2^J₁,₁' = 1.5 Hz, H-1'), 1.26-2.10 (m, 9H, H-5 to 9), 3.67 (m, 1H, H-2), 3.89 (d, 1H, ^3^J₁,₂ = 7.1 Hz, H-3), 7.14-8.25 (m, 10H, aromatic CH).

^1^C NMR (62.5 MHz, CDCl₃) δ (ppm): 16.3, 20.5, 23.8, 24.5, 24.9, 31.1, 34.2, 35.3, 39.2, 71.6 (C-3), 86.1 (C-4), 126.7-140.1 (aromatic CH and C₉), 167.2 (C-15).

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MS (CI, CH₄/N₂O), m/z (%): 414.7 (100) [M⁺], 415.6 [M⁺+1] (21), 141.9 (34), 121.5 (48), 181.3 (23), 77.0 (16).

(2S,3E)-2-Methyl-4-phenyl-3-butenyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulfone

\[
\text{PTOS}_{\text{Ph}} \quad \text{C}_{18}\text{H}_{18}\text{N}_{4}\text{O}_{2}\text{S} \\
\text{Mol. Wt.: 354.43}
\]

\[
\text{PTOS}_{\text{Ph}} \quad \text{C}_{18}\text{H}_{18}\text{N}_{4}\text{S} \\
\text{Mol. Wt.: 322.43}
\]

Method A: Starting from 0.18 mmol of sulphide. Stirred at r.t. for 12 h. Evaporation of solvents gave 63 mg (99%) of colourless oil.

TLC (EP:Et₂O = 1:1)

\[R_f = 0.25\]
\[R_f = 0.52\]

\[
\text{UV, KMnO}_4, \text{sulfone} \\
\text{UV, KMnO}_4, \text{sulfide}
\]

\[
\begin{align*}
&\text{1H-NMR (500 MHz, CDCl3) } \delta (\text{ppm): 1.34 (d, 3H, } J_{6,3} = 6.9 \text{ Hz, H-6), 3.19} \\
&\text{ (heptet, 1H, } J = 7.4 \text{ Hz, H-3), 3.74 (dd, 1H, } J_{4,4'} = 14.7 \text{ Hz, } J_{4,3} = 6.0 \\
&\text{ Hz, H-4), 4.08 (dd, 1H, } J_{4',4} = 14.7 \text{ Hz, } J_{4',3} = 7.8 \text{ Hz, H-4'), 6.00 (dd,} \\
&\text{ 1H, } J_{2,1} = 15.6 \text{ Hz, } J_{2,3} = 5.3 \text{ Hz, H-2), 6.39 (d, 1H, } J_{1,2} = 15.6 \text{ Hz, H-} \\
&\text{1), 7.24-7.70 (m, 5H, aromatic CH).}
\end{align*}
\]

\[
\text{13C-NMR (125 MHz, CDCl3) } \delta (\text{ppm): 20.7 (C-6), 33.1 (C-3), 61.6 (C-4),} \\
\text{130.6 (C-1), 136.3 (C-5), 131.6 (C-2), 125.4-131.4 (aromatic CH and Cq).}
\]

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Methyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulfone

Method A: Starting from 11.0 mmol of sulphide. Evaporation of solvents gave 2.37 g (96%) of yellow crystals.

\[\text{C}_8\text{H}_8\text{N}_4\text{O}_2\text{S}\]
Mol. Wt.: 224.24

\[\text{C}_8\text{H}_8\text{N}_4\text{S}\]
Mol. Wt.: 192.24

\[^1^H\text{-NMR}\ (250\text{ MHz, CDCl}_3 + \text{CD}_3\text{OD})\ \delta (ppm): 3.47\ (s, 3\text{H, H-1}); 7.45-7.55\ (m, 5\text{H, aromatic H}).\

\[^{13}\text{C-NMR}\ (62.5\text{ MHz, CDCl}_3)\ \delta (ppm): 43.5\ (\text{C-1}); 125.0, 129.6, 131.5\ \text{and}\ 132.8\ (\text{aromatic CH and C=q}), 154.1\ (\text{C-2}).\]

MS (APCI), m/z (%): 225.0 [M+ + 1] (100), 149.1 (64), 118.1 (87).

CAS number: [3206-44-8].

2-[(1-Phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfonyl]-1-ethanol

Method A: Starting from 3.03 mmol of sulphide. Evaporation of solvents under reduced pressure gave 647 mg (84%) of slightly yellow crystals.

\[\text{C}_9\text{H}_{10}\text{N}_4\text{O}_3\text{S}\]
Mol. Wt.: 254.27
TLC (100% EtAc)

\[
\begin{array}{c}
\text{Rf = 0.62} \\
\text{Rf = 0.11} \\
\text{Rf = 0.62}
\end{array}
\]

\[
\begin{array}{c}
\text{UV, KMnO}_4, \text{starting sulfide} \\
\text{UV, KMnO}_4, \text{product}
\end{array}
\]

\[^1\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta(\text{ppm}): 3.92 \text{ (t, 1H, } ^3J_{2,3} = 5.7 \text{ Hz, H-2)}, 4.24 \text{ (t, 1H, } ^3J_{3,2} = 5.6 \text{ Hz, H-3)}, 6.82 \text{ (broad s, 1H, H-1)}, 7.61-7.69 \text{ (m, 5H, aromatic CH).}
\]

\[^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta(\text{ppm): 56.4 \text{ (C-3), 59.0 \text{ (C-2), 125.6, 129.9, 131.7, 134.2 (aromatic CH and Cq), 154.5 \text{ (C-4).)}}
\]

\text{MS (APCI), } m/z \%: 255.0 \text{ (44) [M\textsuperscript+], 256.1 \text{ (9) [M\textsuperscript+} +\text{H}], 119.1 \text{ (17) [M\textsuperscript+ - Ph, N}_3\text{], 74.0 \text{ (100).}}
\]

\text{HRMS, } m/z: \text{ calcd. (C}_9\text{H}_10\text{N}_4\text{O}_3\text{SNa) 277.0371; found 277.0378.}
\]

\text{2-[1-(tert-butyl)-1,1-dimethylsilyloxyethyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulfone}

\[
\begin{array}{c}
\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_3\text{SSi} \quad \text{Mol. Wt.: 336.53} \\
\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_2\text{SSi} \quad \text{Mol. Wt.: 368.53}
\end{array}
\]

\text{Method A: Starting from 1.5 mmol of sulphide. Evaporation of the solvents yielded 547 mg (99\%) of colourless crystals.}
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IR (NaCl, neat) \(\nu^{-1}(\text{cm}^{-1})\): 3067, 2930, 2857, 1498, 1466, 1348.

\(^1\text{H-NMR}\) (300 MHz, \(\text{CDCl}_3\)) \(\delta\) (ppm): 0.1 (s, 6H, H-3), 0.91 (s, 9H, H-5), 3.9 (t, 2H, \(^3\text{J}_{1,2} = 5.7\) Hz, H-1), 4.19 (t, 2H, \(^3\text{J}_{2,1} = 5.7\) Hz, H-2), 7.59-7.73 (m, 5H, aromatic CH).

\(^{13}\text{C-NMR}\) (62.5 MHz, \(\text{CDCl}_3\)) \(\delta\) (ppm): -3.4 (C-3), 18.2 (C-4), 25.9 (C-5), 57.0 (C-2), 58.7 (C-1), 125.6, 129.9, 131.7 and 133.2 (aromatic CH and Cq), 142.2 (C-6).

MS (APCI), \(m/z\) (%): 369.0 (100) [\(\text{M}^+\)] , 370.0 (21) [\(\text{M}^+\)\(^2\)], 223.0 (18), 149.1 (18).

Elem. Anal.: calcd. (\(\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_3\text{SSi}\)) C, 48.49, H, 6.56, N, 15.20, S 8.70; found: C, 48.53, H, 6.51, N, 15.18, S, 8.73.

\((2\text{R})\)-3-[1-(\text{tert-Butyl})-1,1-dimethylsilyloxy-2-methylpropyl phenyl sulfone

\[
\begin{align*}
\text{TBSO} & \text{SPh} & \text{TBSO} & \text{SO}_2\text{Ph} \\
\text{C}_{16}\text{H}_{28}\text{OSSi} & \text{Mol. Wt.: 296.54} & \text{C}_{16}\text{H}_{28}\text{O}_3\text{SSi} & \text{Mol. Wt.: 328.54}
\end{align*}
\]

Method A: Starting from 3.6 mmol of sulphide. Evaporation of the solvents yielded 1.15 g (97%) of slightly yellow oil.

IR (NaCl, neat) \(\nu^{-1}(\text{cm}^{-1})\):3061, 2961, 2866, 1586, 1485, 1430, 1254.

\(^1\text{H-NMR}\) (300 MHz, \(\text{CDCl}_3\)) \(\delta\) (ppm): -0.02 and 0.00 (s, 3H, H-4), 0.85 (s, 9H, H-6), 1.07 (d, 3H, \(^3\text{J}_{7,2} = 6.6\) Hz, H-7), 2.18 (sextet, 1H, \(^3\text{J} = 7.8\) Hz, H-2), 2.87 (dd, 1H, \(^2\text{J}_{1,1'} = 14.4\) Hz, \(^3\text{J}_{1,2} = 8.1\) Hz, H-1), 3.36 (dd, 1H, \(^2\text{J}_{3,3'} = 9.6\) Hz, \(^3\text{J}_{3,2} = 6.3\) Hz, H-3), 3.42 (dd, 1H, \(^2\text{J}_{1',1} = 14.4\) Hz, \(^3\text{J}_{1',2} =

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4.5 Hz, H-1’), 3.54 (dd, 1H, $^2J_{3',3} = 10.2$ Hz, $^3J_{3',2} = 4.8$ Hz, H-3’), 7.55-7.94 (m, 5H, aromatic CH).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ (ppm): -4.9 and -4.8 (C-4), 17.4 (C-7), 19.2 (C-5), 26.4 (C-11), 32.3 (C-2), 59.5 (C-1), 70.0 (C-3), 128.4, 129.8, 134.0 and 140.5 (aromatic CH and Cq).

MS (APCI), m/z (%): 328.9 (100) [M$^+$], 329.3 (81) [M$^+$+1], 214.8 (34), 196.8 (76).

CAS number: [220018-34-8].

(2R)-3-[1-(tert-Butyl)-1,1-diphenylsilyl]oxy-2-methylpropyl phenyl sulfone

\[
\begin{array}{c}
\text{TBDPSO} \quad \text{SPh} \\
\text{C}_{26}H_{32}OSSi \\
\text{Mol. Wt.: 420.68}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{TBDPSO} \quad \text{SO}_2\text{Ph} \\
\text{C}_{26}H_{32}OSSi \\
\text{Mol. Wt.: 452.68}
\end{array}
\]

Method A: Starting from 0.4 mmol of sulphide. Evaporation of the solvents yielded 170 mg (94%) of colourless oil.

IR (NaCl, neat) ν$^1$(cm$^{-1}$):3061, 3064, 2961, 2866, 1586, 1485, 1430, 1254.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.05 (s, 9H, H-5), 1.24 (d, 3H, $^2J_{6,2} = 6.5$ Hz, H-6), 2.21 (m, 1H, H-2), 2.86 (dd, 1H, $^2J_{1.1} = 14.4$ Hz, $^3J_{1.2} = 8.0$ Hz, H-1), 3.39 (dd, 1H, $^2J_{3,3} = 9.9$ Hz, $^3J_{3,2} = 6.3$ Hz, H-3), 3.48 (dd, 1H, $^2J_{1',1} = 14.4$ Hz, $^3J_{1',2} = 4.7$ Hz, H-1’), 3.54 (dd, 1H, $^2J_{5,3} = 10.1$ Hz, $^3J_{5,2} = 4.9$ Hz, H-3’), 7.36-7.95 (m, 15H, aromatic CH).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ(ppm): 16.9 (C-6), 19.5 (C-4), 27.1 (C-5), 32.0 (C-2), 59.3 (C-1), 67.5 (C-3), 127.9-139.3 (aromatic CH and Cq).

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MS (APCI), m/z (%): 452.6 (3) [M⁺], 375.3 (100).
CAS number: [158812-78-3].

\((2S,3E)-4-[(2R,6R)-6-Ethyl-3,6-dihydro-2H-2-pyranyl]-2-methyl-3-pentenyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulfone\)

\[
\begin{align*}
\text{HO} & \quad \text{PTO}_2\text{S} \\
\text{C}_{14}\text{H}_{24}\text{O}_2 & \quad \text{Mol. Wt.: 224.34} \\
\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_3\text{S} & \quad \text{Mol. Wt.: 416.54}
\end{align*}
\]

\text{Method D: Starting from 0.11 mmol of alcohol. Purified by CC (φ1.5 cm, 10 cm of SiO}_2, 5 mL fractions; 5:1 = P.E.:EtAc) to give 38.9 mg (85%) of slightly yellow oil.}

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3082, 3061, 2962, 2867, 1584, 1484, 1433.

\(^1\)H-NMR (500 MHz, CDCl\(_3\)) δ (ppm): 0.90 (t, 3H, \(^3\)J\(_{11,10}\) = 7.3 Hz, H-11), 1.18 (d, 3H, \(^3\)J\(_{12,2}\) = 6.7 Hz, H-12), 1.54 (m, partial overlap, 1H, H-10), 1.56 (broad s, 3H, H-14), 1.60 (broad s, 3H, H-13), 1.78 (m, partial overlap, 1H, H-10'), 1.80 (m, partial overlap, 1H, H-6), 1.95 (m, 1H, H-6'), 3.29 (m, 1H, H-2), 3.60 (dd, 1H, \(^2\)J\(_{1,1'}\) = 14.4 Hz, \(^3\)J\(_{1,2}\) = 6.1 Hz, H-1), 3.72 (dd, 1H, \(^2\)J\(_{6,10}\) = 10.4 Hz, \(^3\)J\(_{6,10'}\) = 2.8 Hz, H-6), 3.78 (dd, 1H, \(^2\)J\(_{1',1}\) = 14.7 Hz, \(^3\)J\(_{1',2}\) = 7.6 Hz, H-1'), 4.08 (m, 1H, H-5), 5.20 (d, 1H, \(^3\)J\(_{5,2}\) = 9.5 Hz, H-3), 4.54 (m, 1H, H-7), 7.58-7.68 (m, 5H, aromatic CH).

\(^{13}\)C-NMR (62.5 MHz, CDCl\(_3\)) δ (ppm): 8.4 (C-11), 13.1 (C-13), 19.1 (C-14), 21.1 (C-12), 25.7 (C-10), 27.9 (C-2), 30.3 (C-6), 61.9 (C-1), 77.1 (C-5), 425
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78.2 (C-9), 120.8 (C-7), 125.4 (C-3), 125.5, 129.7, 131.7, 133.3 (aromatic CH and Cq), 135.3 (C-8), 138.5 (C-4), 154.2 (C-15).

MS (APCI), m/z (%): 416.9 (68) [M⁺], 398.9 (52), 282.2 (48), 189.1 (100).

HRMS, m/z: calcd. (C₂₁H₂₈N₄O₃SNa) 439.1780; found 439.1787.

10.2 Transformations of alcohols

10.2.1 General procedure for mesylation of alcohols

General procedure: A solution of alcohol (1.0 mmol, 1.0 eq) and Et₃N (3.0 mmol, d = 0.726g mL⁻¹, 3.0 eq) in THF or Et₂O (4.0 mL, 0.25M) was cooled to 0°C and MsCl (1.2 mmol, d = 1.480g mL⁻¹, 1.2 eq) was slowly added. The resulting mixture was stirred at 0°C for 30 min and H₂O (50 mL) was added. Resulting layers were separated and the aqueous phase was extracted with EtAc (3x10 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

(2R)-2-Methyl-3-[(1-phenyl-1H-1,2,3,4-tetrazol-5-yl)sulfonyl]propyl methanesulfonate

\[
\begin{align*}
\text{HO} & \quad \text{S}_2 \\
\text{O} & \quad \text{N} \quad \text{N} \\
\text{O} & \quad \text{Ph} \\
\text{C}_{11}H_{14}N_4O_3S & \quad \text{Mol. Wt.: 282.32} \\
\text{MsCl, TEA} & \quad \text{THF, 0°C to r.t.} \\
\end{align*}
\]

Starting from 16.1 mmol of alcohol. THF was used as a solvent. Evaporation of solvents under reduced pressure gave 5.8 g (quant.) of pale yellow oil, which was immediately used in the next step.
Chapter 10. Experimental part

TLC (P.E.:EtAc = 1:1)

UV, KMnO₄, product

UV, KMnO₄, alcohol

IR (NaCl, neat) ν¹(cm⁻¹): 3040 (w), 2977 (m), 2939 (m), 1655 (m), 1597 (m), 1498 (m), 1355 (s), 1176 (s), 1154 (m), 764 (m).

¹H-NMR (250 MHz, CDCl₃) δ(ppm): 1.29 (d, 3H, ³J₄,₃ = 6.7 Hz, H-4), 2.79 (m, 1H, H-3), 3.71 (dd, 1H, ²J₅,₅' = 15.1, ³J₅,₃ = 6.3 Hz, H-5), 3.98 (dd, 1H, ²J₅,₅ = 15.1, ³J₅',₃ = 6.4 Hz, H-5'), 4.20 (dd, 1H, ²J₂,₂ = 10.3, ³J₂',₃ = 5.6 Hz, H-2), 4.38 (dd, 1H, ²J₂',₂ = 10.3, ³J₂',₃ = 4.8 Hz, H-2'), 7.53-7.74 (m, 5H, Ar).

¹³C-NMR (62.5 MHz, CDCl₃) δ(ppm): 17.1 (C-4), 29.3 (C-3), 37.6 (C-1), 58.0 (C-5), 71.5 (C-2), 125.3, 129.9, 131.7, 133.1 (aromatic CH and Cq), 154.2 (C-6).

MS (APCI), m/z (%): 360.9 (96) [M⁺], 361.9 (14) [M⁺ +H], 237.1 (23) [M⁺ - PhNH₂, -N₂], 214.8 (9) [M⁺ -PT], 149.1 (100) [M⁺ -SO₂PT], 119.1 (15) [M⁺ -PT, -CH₃SO₃H].

HRMS, m/z: calcd. (C₁₂H₁₆N₄O₅S₂) 361.0640; found 361.0656.

(2R)-2-Methyl-3-(phenylsulfonyl)propyl methanesulfonate

Starting from 3.27 mmol of alcohol. THF used as a solvent. Stirred at 0°C (5 min), r.t. (1 h) and again 0°C (5 min). Evaporation of solvents under reduced
pressure gave 956 mg (quant.) of pale yellow oil, which was immediately used in the next step.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν\(_{\text{IR}}\) (cm\(^{-1}\)): 3063 (w), 3024 (w), 2976 (m), 2939 (m), 1619 (m), 1445 (m), 1355 (s), 1305 (s), 1175 (s), 1148 (s), 968 (m), 686 (m).

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) δ(ppm): 1.21 (d, 3H, \(^3\)J\(_{4,3}\) = 7.1 Hz, H-4), 2.59 (m, 1H, H-3), 2.98 (dd, 1H, \(^2\)J\(_{5,5'}\) = 14.3, \(^3\)J\(_{5,3}\) = 5.7 Hz, H-5), 3.05 (s, 3H, H-1), 3.29 (dd, 1H, \(^2\)J\(_{5,5'}\) = 14.3, \(^3\)J\(_{5,3}\) = 6.8 Hz, H-5'), 4.20 (dd, 1H, \(^2\)J\(_{2,2'}\) = 9.9, \(^3\)J\(_{2,3}\) = 5.2 Hz, H-2), 4.35 (dd, 1H, \(^2\)J\(_{2,2'}\) = 9.9, \(^3\)J\(_{2,3}\) = 4.8 Hz, H-2'), 7.57-7.95 (m, 5H, Ar).

\(^{13}\)C-NMR (62.5 MHz, CDCl\(_3\)) δ(ppm): 17.3 (C-4), 29.2 (C-3), 37.5 (C-1), 58.3 (C-5), 72.4 (C-2), 128.0, 129.7, 134.2, 139.2 (aromatic CH and Cq).

MS (ESI), m/z (%): 315.3 (100) [M\(^+\)+Na\(^+\)], 292.3 (15) [M\(^+\)], 197.1 (30) [M\(^+\)-SO\(_2\)CH\(_3\)].

Methyl (2S)-2-methyl-3-[(methylsulfonyl)oxy]propanoate

\[\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \]

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Starting from 90 mmol of alcohol (d = 1.066 g.mL⁻¹). Et₂O was used as a solvent. Stirred at 0°C (5 min), r.t. (30 min) and again 0°C (5 min). Evaporation of solvents under reduced pressure gave 17.66 g (quant.) of slightly yellow oil, which was used in the next step without any further purification.

TLC (P.E.:EtAc = 1:1)

1H-NMR (250 MHz, CDCl₃) δ(ppm): 1.28 (d, 3H, 3J₄,₃ = 7.1 Hz, H-4), 2.91 (m, 1H, H-3), 3.04 (s, 3H, H-6), 3.74 (s, 3H, H-1), 4.27 (dd, 1H, 2J₅,₅' = 9.9, 3J₅₃ = 5.2 Hz, H-5), 4.39 (dd, 1H, 2J₅₅' = 9.9, 3J₅₃ = 7.5 Hz, H-5').

13C-NMR (62.5 MHz, CDCl₃) δ(ppm): 13.8 (C-4), 37.5 (C-6), 39.5 (C-3), 52.4 (C-1), 70.6 (C-5), 173.6 (C-2).

CAS number: [142402-78-6].

10.2.2 General procedure for acylation of alcohols

Method A: Acylation using AcX/Et₃N system

A solution of alcohol (1.0 mmol, 1.0 eq) in CH₂Cl₂ (4 mL, 0.25 M) was cooled to 0°C and Et₃N (2.0 mmol, d = 0.726gmol⁻¹, 2.0 eq) was added. After 5 min at 0°C, acyl chloride or bromide (1.2 mmol, 1.2 eq) was added dropwise and the resulting slurry was stirred at 0°C for 1 h. CH₂Cl₂ (20 mL)
was added and the whole mixture was washed sequentially with 1.0 M aqueous solution of HCl (3x10 mL), saturated aqueous solution of NaHCO₃ (3x10 mL), brine (10 mL), dried over Na₂SO₄ and evaporated under reduced pressure.

**Method B: Base-induced trans esterification.**

\[
\begin{align*}
\text{OH} & \quad \text{R₁} \quad \text{R₂} \\
\text{R₂} \quad \text{OMe} & \quad \text{R₁} \quad \text{R₂} \\
\quad \text{nBuLi, Et₂O, r.t.} & \\
\quad \text{R₁} \quad \text{R₂} & \quad \text{R₁} \quad \text{R₂}
\end{align*}
\]

A solution of alcohol (1.0 mmol, 1.0 eq) in Et₂O (10 mL, 0.1 M) was cooled to 0°C and nBuLi (1.01 mmol, 1.6 M solution in hexane, 1.01 eq) was added. After 15 min at 0°C, ester (10 mL, 10 mL/mmol) was added. Resulting mixture was allowed to warm to r.t. and stirred for 15 h. Evaporation of the solvents yielded essentially pure product.

**Method C: Base-induced TMS-deprotection/trans esterification.**

\[
\begin{align*}
\text{OTMS} & \quad \text{R₁} \quad \text{R₂} \\
\text{R₂} \quad \text{OMe} & \quad \text{R₁} \quad \text{R₂} \\
\quad \text{MeLi, Et₂O, r.t.} & \\
\quad \text{R₁} \quad \text{R₂} & \quad \text{R₁} \quad \text{R₂}
\end{align*}
\]

A solution of TMS ether (1.0 mmol, 1.0 eq) in Et₂O (10 mL, 0.1 M) was cooled to 0°C and MeLi (1.01 mmol, 1.6 M solution in Et₂O, 1.01 eq) was added. The resulting slightly yellow mixture was stirred at 0°C for 5 min and then for 1 h at r.t. before being again cooled to 0°C. Ester (10 mL, 10 mL/mmol) was added and the resulting mixture was allowed to warm to r.t. and stirred for 15 h. Evaporation of the solvents yielded essentially pure product.
Method D: DCC-mediated esterification.

To a solution of alcohol (1.0 mmol, 1.0 eq), carboxylic acid (1.1 mmol, 1.1 eq) and DMAP (0.1 mmol, 10 mol%) in CH$_2$Cl$_2$ (10 mL, 0.1 M), DCC (1.2 mmol, 1.2 eq) was added in one portion and the resulting mixture was stirred at r.t. for 14h. Water (15 mL) was added and the resulting mixture was diluted with Et$_2$O (30 mL). Layers were separated and aqueous layer was extracted with Et$_2$O (3x20 mL). Combined organic layers were washed with brine (10 mL), dried over MgSO$_4$ and evaporated under reduced pressure.

**Ethyl 3-[(2-bromopropanoyl)oxy]butanoate**

Method A: Starting from 3.82 mmol of alcohol. Evaporation of solvents gave 1.02g (quant.) of slightly yellow oil. Product was sufficiently pure after the work-up.

TLC (1:1 = P.E.:EtAc)

\[ R_f = 0.71 \]

\[ R_f = 0.27 \]
Mixture of two diastereoisomers (d.r. = 1.02:1).

IR (NaCl, neat) ν\(^{-1}\) (cm\(^{-1}\)): 2982, 2936, 2900, 2868, 1732, 1445, 1225, 1309, 1221, 1188, 1163, 1053.

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.26 (t, 3H, \(^3\)\(J_{9,8}\) = 7.2 Hz, H-9), 1.35 (d, 3H, \(^3\)\(J_{4,3}\) = 6.4 Hz, H-4), 1.80 (d, 3H, \(^3\)\(J_{7,6}\) = 7.2 Hz, H-7), 2.54 (dd, 1H, \(^2\)\(J_{2,2'}\) = 15.6 Hz, \(^3\)\(J_{2,3}\) = 5.6 Hz, H-2), 2.67 (dd, 1H, \(^2\)\(J_{2,2'}\) = 15.6 Hz, \(^3\)\(J_{2,3}\) = 7.9 Hz, H-2'), 4.14 (q, 2H, \(^3\)\(J_{8,9}\) = 7.2 Hz, H-8), 4.32 (q, 2H, \(^3\)\(J_{6,7}\) = 7.2 Hz, H-6), 5.36 (m, 1H, H-3).

**Minor diastereoisomer:** \(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.27 (t, 3H, \(^3\)\(J_{9,8}\) = 7.2 Hz, H-9\(^*\)), 1.35 (d, 3H, \(^3\)\(J_{4,3}\) = 6.4 Hz, H-4\(^*\)), 1.81 (d, 3H, \(^3\)\(J_{7,6}\) = 7.2 Hz, H-7\(^*\)), 2.54 (dd, 1H, \(^2\)\(J_{2,2'}\) = 15.6 Hz, \(^3\)\(J_{2,3}\) = 5.6 Hz, H-2\(^*\)), 2.68 (dd, 1H, \(^2\)\(J_{2,2'}\) = 15.6 Hz, \(^3\)\(J_{2,3}\) = 7.9 Hz, H-2\(^*\)), 4.15 (q, 2H, \(^3\)\(J_{8,9}\) = 7.2 Hz, H-8\(^*\)), 4.32 (q, 2H, \(^3\)\(J_{6,7}\) = 7.2 Hz, H-6), 5.36 (m, 1H, H-3).

\(^{13}\)C-NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) (ppm): 14.3 (C-9), 19.6 and 19.8 (C-7 and C-7\(^*\)), 21.7 and 21.7 (C-4 and C-4\(^*\)), 40.4 and 40.5 (C-6 and C-6\(^*\)), 40.7 (C-2), 60.9 (C-8), 69.2 and 69.3 (C-3 and C-3\(^*\)), 169.5 and 169.5 (C-5 and C-5\(^*\)) and 170.1 and 170.1 (C-1 and C-1\(^*\)).

MS (APCI), \(m/z\) (%): 268.9 [M\(^+\), \(^{81}\)Br] (67), 266.9 [M\(^+\), \(^{79}\)Br] (65), 223.0 (31), 221.0 (31), 115.2 (100), 87.2 (32), 69.3 (34).

HRMS, \(m/z\): calcd. (C\(_9\)H\(_{15}\)O\(_4\)Br\(^+\)) 366.0154; found 366.0160.
(1R)-1-[(1-(tert-Butyl)-1,1-dimethylsilyl)oxyethyl]-3-methoxy-3-butenyl acrylate

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

Method B: Starting from 0.28 mmol of alcohol. Evaporation of the solvents yielded 69 mg (82%) of colourless oil.

Method C: Starting from 0.48 mmol of TMS ether. Evaporation of the solvents gave 133 mg (92%) of colourless oil.

Product was immediately used in the next metathesis step.

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{C}_{12}H_{26}O_3Si \]  
Mol. Wt.: 246.42

\[ \text{C}_{15}H_{34}O_3Si_2 \]  
Mol. Wt.: 318.6

\[ \text{C}_{15}H_{28}O_4Si \]  
Mol. Wt.: 300.47

\[ \text{OTMS} \]

\[ \text{OTBS} \]

\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{O} \]
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$^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$(ppm): -5.1 and -5.0 (C-6), 18.7 (C-7), 26.1 (C-8), 40.9 (C-3), 55.3 (C-12), 67.2 (C-5), 73.1 (C-4), 83.2 (C-1), 129.4 and 130.7 (C-10 and C-11), 160.6 (C-2), 166.0 (C-9).

(1R)-1-[(Benzyloxy)methyl]-3-butenyl acrylate

\[
\text{IR (NaCl, neat) $\nu$(cm$^{-1}$): 3061, 3029, 2962, 2928, 1724, 1445, 1339.}
\]

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$(ppm): 2.48 (m, 2H, H-6), 3.59 (d, 2H, $^3J_{6,7} = 4.8$ Hz, H-8), 4.52 and 4.59 (d, 1H, $^3J_{6,9} = 12.2$ Hz, H-9 and H-9'), 5.07-5.16 (m, 2H, H-4), 5.18 (pentet, 1H, $^3J = 6.6$ Hz, H-7), 5.74 (m, 1H, H-5), 5.82 (dd, 1H, $^3J_{5,2} = 6.7$ Hz, $^2J_{3,3'} = 1.4$ Hz, H-3), 6.15 (dd, 1H, $^3J_{2,3} = 17.3$ Hz, $^2J_{2,3} = 8.3$ Hz, H-2), 6.43 (dd, 1H, $^3J_{5,3} = 17.3$ Hz, $^2J_{5,3} = 1.6$ Hz, H-3'), 7.31-7.35 (m, 5H, aromatic CH).

Method A: Starting from 0.34 mmol of alcohol. Stirred at 0°C for 30 min. Purified by CC ($\phi$ 1.0 cm, 7 cm of SiO$_2$, 6 mL fractions; 5:1 = P.E.:EtAc) to give 68 mg (81%).

Method B: Starting from 1.20 mmol of alcohol. Purified by CC ($\phi$ 3.5 cm, 8 cm of SiO$_2$, 20 mL fractions; 5:1 = P.E.:EtAc) to give 278 mg (94%).
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$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$(ppm): 35.6 (C-6), 70.7 (C-7), 72.3 (C-9), 73.4 (C-8), 118.3 (C-4), 127.8, 127.9, 128.6, 128.7, 131.0, 133.3, 138.2 (aromatic CH and C$_q$, C-2, C-3 and C-5), 165.9 (C-1).

MS (APCI), $m/z$ (%): 246.9 [M$^+$+1] (100), 248.0 [M$^+$+2] (8), 157.1 (76), 129.1 (32), 91.0 (96).

[$\alpha$]$^D_{20}$: -1.69° ($c$ = 1.25, CHCl$_3$).

CAS number: [640298-47-1].

(1R)-1-[(4-Methoxybenzyl)oxy]methyl-3-butenyl acrylate

![Chemical structure]

$Method A$: Starting from 0.51 mmol of alcohol. Stirred at 0°C for 30 min. Purified by CC ($\phi$ 1.0 cm, 7 cm of SiO$_2$, 6 mL fractions; 5:1 = P.E.:EtAc) to give 129 mg (90%).

$Method B$: Starting from 0.25 mmol of alcohol. Purified by CC ($\phi$ 1.5 cm, 8 cm of SiO$_2$, 10 mL fractions; 5:1 = P.E.:EtAc) to give 63 mg (91%).

IR (NaCl, neat) $\nu$(cm$^{-1}$): 3062, 3031, 2975, 2930, 1722, 1447, 1341.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$(ppm): 2.45 (m, H-6), 3.56 (d, 2H, $^3J_{8,7} = 5.0$ Hz, H-8), 3.82 (s, 3H, H-14), 4.46 and 4.53 (d, 1H, $^3J_{9,9'} = 11.7$ Hz, H-9 and H-9'), 5.08-5.12 (m, 2H, H-4), 5.19 (pentet, 1H, $^3J = 5.0$ Hz, H-7), 5.75 (m, 1H, H-5), 5.84 (dd, 1H, $^3J_{J,3} = 8.2$ Hz, $^2J_{3,3'} = 1.6$ Hz, H-3), 6.15
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(dd, 1H, $^3J_{2,3} = 17.3$ Hz, $^3J_{2,3'} = 10.4$ Hz, H-2), 6.43 (dd, 1H, $^3J_{3',3} = 17.3$ Hz, $^2J_{3'3} = 1.6$ Hz, H-3'), 6.90 (d, 2H, $^3J_{12,11} = 8.6$ Hz, H-12), 7.26 (d, 2H, $^3J_{11,12} = 8.6$ Hz, H-11).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 35.7 (C-6), 55.5 (C-14), 70.3 (C-7), 72.3 (C-9), 73.0 (C-8), 114.0 (C-12), 118.3 (C-2), 129.5 (C-11), 130.0 (C-10), 130.1 (C-3), 133.4 (C-4), 159.5 (C-13), 165.9 (C-1).

MS (Cl, CH$_4$), m/z (%): 276.2 [M$^+$] (14), 277.2 [M$^+$+1] (4), 258.2 (9), 241.2 (27), 104.0 (13), 121.1 (100).

[$\alpha$]$^D_{20}$: -0.63° (c = 1.44, CHCl$_3$).

HRMS, m/z: calcd. (C$_{16}$H$_{20}$O$_4$) 276.1326; found 276.1321.

(1S)-1-[(4-Methoxybenzyl)oxy]methyl-3-(phenylsulfonyl)butyl (2E,4E)-2,4-hexadienoate

Method D: Starting from 1.2 mmol of alcohol. Purification by CC ($\phi$ 3.5 cm, 7 cm of SiO$_2$, 15 mL fractions; 5:1→1:1 = P.E.:EtAc) gave 451 mg (82%) of thick oil.
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TLC (P.E.:EtAc = 1:1)

\[ R_f = 0.15 \]
\[ R_f = 0.72 \]
\[ R_f = 0.58 \]

UV, KMnO\textsubscript{4}, alcohol

UV, KMnO\textsubscript{4}, ester

\[
\begin{align*}
\text{SO}_2\text{Ph} \\
\text{MeO} \\
\end{align*}
\]

Mixture of two diastereoisomers (d.r. = 1.54:1).

IR (NaCl, neat) \(\nu\) (cm\textsuperscript{-1}): 3088, 3083, 3061, 2995, 2970, 1718, 1604, 1448.

\(^1\)H-NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm):

1.27 (d, 3H, \(^3\)J\textsubscript{1,2} = 6.9 Hz, H-1), 1.68-1.81 (m, 1H, H-3), 1.88 (t, 3H, \(^3\)J = 5.1 Hz, H-17), 2.35-2.43 (m, 1H, H-3'), 3.10 (m, 1H, H-2), 3.44-3.82 (m, 2H, H-5), 3.81 (s, 3H, H-11), 4.38-4.49 (m, 2H, H-6), 5.12 (m, partial overlap, 1H, H-4), 5.73 (d, 1H, \(^3\)J\textsubscript{13,14} = 15.2 Hz, H-13), 6.13-6.23 (m, 2H, H-15 and H-16), 6.87 (d, 2H, \(^3\)J\textsubscript{8,9} = 8.3 Hz, H-9), 7.20 (d, 2H, \(^3\)J\textsubscript{8,9} = 8.3 Hz, H-8), 7.24 (m, partial overlap, 1H, H-14), 7.53-7.87 (m, 5H, aromatic CH).

Minor diastereoisomer: H-NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm):

1.30 (d, 3H, \(^3\)J\textsubscript{1,2} = 6.4 Hz, H-1*), 1.68-1.81 (m, 1H, H-3), 1.88 (t, 3H, \(^3\)J = 5.1 Hz, H-17), 2.35-2.43 (m, 1H, H-3'), 3.10 (m, 1H, H-2), 3.30 (m, 1H, H-2*), 3.44-3.82 (m, 2H, H-5), 3.82 (s, 3H, H-11*), 4.38-4.49 (m, 2H, H-6), 5.17 (m, partial overlap, 1H, H-4*), 5.74 (d, 1H, \(^3\)J\textsubscript{13*,14*} = 15.6 Hz, H-13*), 6.13-6.23 (m, 2H, H-15 and H-16), 6.88 (d, 2H, \(^3\)J\textsubscript{8,9} = 8.3 Hz, H-9*), 7.21 (d, 2H, \(^3\)J\textsubscript{8,9} = 8.3 Hz, H-8*), 7.24 (m, partial overlap, 1H, H-14), 7.53-7.87 (m, 5H, aromatic CH).

\(^13\)C-NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm):

13.4 and 14.8 (C-1 and C-1*), 18.9 and 18.9 (C-17 and C-17*), 31.2 and 31.7 (C-3 and C-3*), 68.9 and 71.0 (C-5 and C-5*), 70.6 and 70.9 (C-4 and C-4*), 73.1 (C-6), 114.0 and

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114.1 (C-9 and C-9'), 118.4 and 118.6 (C-13 and C-13'), 129.3-137.1 (aromatic CH and C_q), 133.9 and 133.9 (C-15 and C-15'), 140.3 and 140.5 (C-14 and C-14'), 159.5 (C-10), 166.5 and 166.8 (C-12 and C-12').

MS (Cl, CH₄), m/z (%): 458.7 [M⁺] (11), 441.1 (93), 338.8 (59), 241.2 (100), 227.0 (67), 187.1 (61), 121.1 (88), 95.0 (27).

HRMS, m/z: calcd. (C_{25}H_{30}O_{6}SNa) 481.1661; found 481.1665.

10.2.3 General procedure for oxidation of alcohols

**Method A: Aerobic Cu(I)/O₂ oxidation.**

1,10-phenanthroline (180 mg, 1 mmol, 5 mol%) followed by solid CuCl(cod)⁴³⁴ (207 mg, 1 mmol, 5 mol%) were added to 200 mL anhydrous FC₆H₅. The suspension had been stirred for 5 min at room temperature and alcohol (3.65 g, 20 mmol) was added followed by solid KOtBu (112 mg, 1 mmol, 5 mol%). The resulting yellowish solution was stirred at room temperature for 10 min before NMI (120 mg, 1.4 mmol, 7 mol%) and DBAD (230 mg, 1 mmol, 5 mol%) were added. The reaction mixture was heated at reflux under a gentle stream of O₂ for 9h. After the reaction mixture was cooled to 20°C, celigel (4 g, 80/20 w/w mixture of celite and silica gel) was added and stirring was continued for 2 min. The solid residue was removed by filtration and washed with ether (200 mL). Solvents were evaporated under reduced pressure to yield pure aldehyde.

**Method B: Swern oxidation**

To a cold (-60°C) solution of oxalyl chloride (1.5 mmol, 1.5 eq) in CH₂Cl₂ (1.0 mL), a solution of DMSO (2.0 mmol, 2.0 eq) in CH₂Cl₂ (1.0 mL) was

added. After 15 min, alcohol (1.0 mmol, 1.0 eq) in CH₂Cl₂ (0.5 mL) was added. After additional 30 min, Et₃N (5.0 mmol, 5.0 eq) was added. After an additional 15 min at -60°C, the reaction mixture was allowed to warm to r.t. over 1h. Water (1 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3x15 mL) and the combined organic layers were washed with water (5 mL) and brine (10 mL), then dried over MgSO₄. After filtration, the organic phase was concentrated under reduced pressure.

Method C: Dess-Martin oxidation
To a cold (0°C) suspension of alcohol (1.0 mmol) and dry NaHCO₃ (4 mmol) in CH₂Cl₂ (5 mL, 0.2M), a Dess-Martin reagent (1.2 mmol) was added and the resulting mixture was allowed to warm to r.t. After 30 min (for primary alcohols) or 3h (for secondary alcohols), the suspension was filtered through Celite® and filter cake was washed with Et₂O (3x10 mL). Combined organic layers were then evaporated under reduced pressure.

Method D: Oxidation using PCC/AcONa system.
To a vigorously stirred solution of PCC (60 mmol) and AcO⁻Na⁺ (60 mmol) in CH₂Cl₂ (60 mL, 1.0M), alcohol (10 mmol) was added and stirred for 4 h at r.t.. Reaction was diluted with Et₂O (200 mL) and filtered through silica gel (φ 10 cm, 2 cm layer). Filter cake was washed with Et₂O (2x75 mL) and combined filtrates were evaporated under reduced pressure.

Method E: Oxidation of primary alcohols by TEMPO/NCS system.
A solution of alcohol (1.0 mmol), Tempo (0.1 mmol, 10 mol%) and tetrabutylammonium chloride (0.1 mmol, 10 mol%) in CH₂Cl₂/buffer (pH = 8.6) (20 mL) was vigorously stirred at r.t. and NCS (1.2 mmol) was
added in one portion. After 4 h at r.t., layers were separated and aqueous phase was extracted with CH₂Cl₂ (3x10 mL). Combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated under reduced pressure to give slightly yellow foam.

**(2R)-2-Methyl-3-(phenylsulfanyl)propanal**

\[
\begin{align*}
\text{HO} & \quad \text{SPh} \\
\text{C}_{10} \text{H}_{14} \text{OS} & \quad \text{C}_{10} \text{H}_{12} \text{OS}
\end{align*}
\]

Method A: Refluxed for 9h. Evaporation afforded 3.07g (85%) of slightly yellow liquid.

TLC (P.E.:Et₂O = 5:1)

\[
R_f = 0.09
\]

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3054, 2961, 2925, 2801, 2714, 1719, 1581, 1479, 1455, 1381, 1375, 1019, 927, 691.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 1.28 (d, 3H, ³J₇,₂ = 7.2 Hz, H-8), 2.79 (sextet, 1H, ³J = 7.2 Hz, H-2), 3.09 (dd, 1H, ³J₃,₃ = 13.4, ³J₃,₂ = 7.2 Hz, H-3), 3.48 (dd, 1H, ²J₃,₂ = 13.4, ³J₃,₃ = 7.2 Hz, H-'3'), 7.36-7.56 (m, 5H, aromatic CH), 9.85 (d, 1H, ³J₁,₂ = 1.5Hz, H-1).

MS (Cl, CH₄/N₂O), m/z (%): 181.2 [M⁺+1] (24), 123.1 (100).
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$[\alpha]_{D}^{20} +2.6^\circ (c = 2.4, \text{CHCl}_3)$ [lit.$^{435} +2.3^\circ (c = 2.4, \text{CCl}_4)$].

CAS number: [221372-46-9].

1-[(2R, 6R)-6-Ethyl-5-methyl-3,6-dihydro-2H-2-pyran]-1-ethanone

Method C: Starting from 2.64 mmol of alcohol. Purified by CC ($\phi$ 3.5 cm, 12 cm of SiO$_2$, 20 mL fractions; 10:1 = P.E.:Et$_2$O) yielded 422 mg (95%) of colourless oil.

TLC (4:1 = P.E.:Et$_2$O)

IR (NaCl, neat) $\nu$(cm$^{-1}$): 2966, 2936, 2879, 1721, 1435, 1352, 1229, 1116, 1058, 927.

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.94 (t, 3H, $^3J_{9,8} = 6.5$ Hz, H-9), 1.54 (octet, 1H, $^3J = 7.3$ Hz, H-8), 1.60 (q, 3H, $^4J = 1.2$ Hz, H-10), 1.80 (d pentet, 1H, $^2J_{8,8} = 10.8$ Hz, $^3J = 3.5$ Hz, H-8$'$), 2.01-2.14 (m, 2H, H-4), 2.24 (s, 3H, H-1), 3.91 (dd, 1H, $^3J_{7,8} = 10.0$ Hz, $^3J_{7,8} = 4.4$ Hz, H-7), 4.09 (m, 1H, H-3), 5.56 (broad dt, 1H, $^3J = 3.8$ Hz, $^3J = 1.5$ Hz, H-5).

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\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): 8.3 (C-9), 18.9 (C-10), 25.6 (C-1), 25.7 (C-8), 27.3 (C-4), 78.3 (C-7), 78.8 (C-3), 119.6 (C-5), 135.6 (C-6), 210.0 (C-2).

MS (Cl, CH\(_4\)), \(m/z\) (%): 169.3 [M\(^{+}\)+1] (100), 151.0 (67), 135.8 (32), 109.1 (63), 95.1 (83).

\([\alpha]\)\(^{20}\)D: +181° (c = 0.257, CDCl\(_3\)) [lit.\(^{436}\) +172° (c = 0.248, CDCl\(_3\))].

CAS number: [393530-60-4].

3-[(1-(tert-butyl)-1,1-dimethylsilyl)oxypropanal

```
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<th>TBSO</th>
<th>OH</th>
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<tr>
<td>C(<em>9)H(</em>{22})O(_2)Si</td>
<td>Mol. Wt.: 190,36</td>
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</tbody>
</table>
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\[\text{PCC, AcONa} \rightarrow \]

```
<table>
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<th>TBSO</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(<em>9)H(</em>{20})O(_2)Si</td>
<td>Mol. Wt.: 188,34</td>
</tr>
</tbody>
</table>
```

*Method D*: Resulting yellow-orange oil was purified by CC (\(\phi\) 3.5 cm, 11 cm of SiO\(_2\), 50 mL fractions; 5:1 to 2:1 = P.E.:Et\(_2\)O) to give 1.75 g (93%) of colourless oil.

TLC (2:1 = P.E.:Et\(_2\)O)

```
<table>
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</thead>
<tbody>
<tr>
<td>alcohol, KMnO(_4)</td>
</tr>
</tbody>
</table>
```

\(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 0.07 (s, 6H, H-4), 0.88 (s, 9H, H-6), 2.60 (td, 2H, \(^3\)\(J\)\(_{2,3}\) = 6.0 Hz, \(^3\)\(J\)\(_{2,1}\) = 2.1 Hz, H-2), 3.99 (t, 2H, \(^3\)\(J\)\(_{3,2}\) = 6.0 Hz, H-3), 9.80 (t, 2H, \(^3\)\(J\)\(_{1,2}\) = 2.1 Hz, H-1).

---

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\[ ^{13}\text{C-NMR (125 MHz, CDCl}_3 \text{)} \delta (\text{ppm}): -5.9 \text{ (C-4), 18.4 (C-5), 26.0 (C-6), 46.7 (C-2), 57.5 (C-3), 202.3 (C-1).} \]

MS \((\text{CI, CH}_4 \text{)} \), \(m/Z\) (%): \(188.9 [M^+] (87), 187.1 (100), 146.9 (55), 145.0 (24), 89.0 (14), 57.0 (12).\)

CAS number: [89922-82-7].

\((E)-3-(4R,5R)-4,5\text{-Di[methoxy(diphenyl)methyl]-1,3,2-dioxaborolan-2-yl-2-propenal}\)

\begin{align*}
\text{Ph}_2\text{(MeO)C} & \text{O} \quad \text{C}_{33}\text{H}_{33}\text{BO}_5 \quad \text{Mol. Wt.: 520.42} \\
\text{Ph}_2\text{(MeO)C} & \text{O} \quad \text{C}_{33}\text{H}_{31}\text{BO}_5 \quad \text{Mol. Wt.: 518.41}
\end{align*}

\text{Method E: Essentially pure product was obtained after the work-up. IMPORTANT: product is not stable and is recommended to use it immediately after the isolation. No data about its stability at -20°C are available.}

\[ ^1\text{H-NMR (500 MHz, CDCl}_3 \text{)} \delta (\text{ppm}): 3.09 (\text{s, 6H, H-7}), 5.33 (\text{s, 2H, H-5}), 6.29 (\text{d, 1H, } ^3\text{J}_{1,2} = 18.0 \text{ Hz, H-1}), 6.42 (\text{dd, 1H, } ^3\text{J}_{2,1} = 18.0 \text{ Hz, } ^3\text{J}_{2,3} = 7.7 \text{ Hz, H-2}), 7.34-7.41 (\text{m, 20H, aromatic CH}), 9.46 (\text{d, 1H, } ^3\text{J}_{3,2} = 7.7 \text{ Hz, H-3}). \]

\[ ^{13}\text{C-NMR (125 MHz, CDCl}_3 \text{)} \delta (\text{ppm}): 53.2 \text{ (C-7), 77.3 (C-5), 82.6 (C-6), 126.6-140.7 \text{ (C-1 and aromatic CH and } C_\text{q}), 146.0 \text{ (C-2), 194.3 (C-3).} \]
10.2.4 General procedure for lactone formation

Method A: Cyclization in basic conditions

A solution of β-keto ester (1.0 mmol, 1.0 eq) in MeOH (5 mL, 0.2 M) was stirred at r.t. and dry K$_2$CO$_3$ (2.0 mmol, 2.0 eq) was added in one portion. The resulting mixture was stirred at r.t. for 2.5h and then evaporated under reduced pressure to dryness. The residue was suspended in acetone (5 mL, 0.2 M) and Me$_2$SO$_4$ (2.0 mmol, d = 1.333 g.mL$^{-1}$, 2.0 eq) was added. After being stirred for 14h, the mixture was diluted with EtAc (60 mL) and washed with 0.5 M aqueous HCl (20 mL). Aqueous layer was back extracted with EtAc (2x10 mL) and combined organic layers were dried over Na$_2$SO$_4$ and evaporated under reduced pressure.

Method B: Acid catalyzed cyclization

A solution of β-keto ester (1.0 mmol, 1.0 eq) in CH$_2$Cl$_2$ (10 mL, 0.1 M) was cooled to 0°C and TFA (1.5 mmol, d = 1.535 g.cm$^{-3}$, 1.5 eq) was added dropwise. Resulting mixture was stirred at 0°C for 5 min and then for 12h at r.t. The resulting solution was evaporated under reduced pressure and the crude was dissolved in acetone (5 mL, 0.2 M). K$_2$CO$_3$ (3 mmol, 3.0 eq) followed by Me$_2$SO$_4$ (2.0 mmol, d = 1.333 g.cm$^{-3}$, 2.0 eq) was added. After being stirred for 12h, the resulting mixture was diluted with EtAc (60 mL)
and washed with 0.5 M aqueous HCl (20 mL). Aqueous layer was back extracted with EtAc (2x10 mL) and combined organic layers were dried over Na$_2$SO$_4$ and evaporated under reduced pressure.

(6$R$)-6-[(Benzyloxy)methyl]-4-methoxy-5,6-dihydro-2H-2-pyranone

Method A: Starting from 0.36 mmol of methyl ester. Purified by CC ($\phi$ 1.5 cm, 8 cm of SiO$_2$, 5 mL fractions; 100:1→5:1→1:1 = P.E.:EtAc) to give 46.5 mg (52%) of slightly yellow oil.

Method B: Starting from 0.16 mmol of tert-butyl ester. Purified by CC ($\phi$ 1.5 cm, 9 cm of SiO$_2$, 6 mL fractions; 100:1→5:1→1:1 = P.E.:EtAc) to yield 15.5 mg (39%) of slightly yellow oil.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) $\nu$ (cm$^{-1}$): 3031, 2962, 2925, 1738, 1580, 1471, 692.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 2.40 (dd, 1H, $^2J_{4,4'} = 17.3$ Hz, $^3J_{4,4} = 4.1$ Hz, H-4), 2.74 (ddd, 1H, $^2J_{4',4} = 17.3$ Hz, $^3J_{4',5} = 12.0$ Hz, $^4J_{4',2} = 1.5$ Hz, H-4$'$), 3.71 (d, partial overlap, 2H, $^1J_{6,5} = 4.7$ Hz, H-6), 3.75 (s, 3H, H-8), 2.40 (dq, partial overlap, 1H, $^1J_{5,4'} = 12.0$ Hz, $^3J = 4.7$ Hz, H-5), 445
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4.61 (d, 2H, $^4J = 1.5$ Hz, H-7), 5.15 (d, 1H, $^4J_{2,4'} = 1.5$ Hz, H-2), 7.30-7.36 (m, 5H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 30.0 (C-4), 56.3 (C-8), 70.8 (C-5), 73.9 (C-6), 74.8 (C-7), 90.4 (C-2), 127.9, 128.1, 128.7 and 137.8 (aromatic CH and C$_q$), 166.9 (C-3), 172.9 (C-1).

MS (Cl, CH$_4$/N$_2$O), m/z (%): 249.1 [M$^+$+H] (57), 250.1 (9), 92.2 (12), 91.6 (100).

$[\alpha]_{20}^D$: +102.5° ($c = 1.4$, CH$_2$Cl$_2$) [lit. $^{437}$ +105° ($c = 1.5$, CH$_2$Cl$_2$)].

CAS number: [296785-14-3]

$(6R)$-6-[(Benzyloxy)methyl]-4-methoxy-3-methyl-5,6-dihydro-$2H$-2-pyranone

Method A: Starting from 1.93 mmol of methyl ester. Purified by CC (φ 3.5 cm, 11 cm of SiO$_2$, 20 mL fractions; 100:1→5:1→1:1 = P.E.:EtAc) to give 314 mg (62%) of slightly yellow oil.

Method B: Starting from 0.67 mmol of tert-butyl ester. Purified by CC (φ 1.5 cm, 14 cm of SiO$_2$, 10 mL fractions; 100:1→5:1→1:1 = P.E.:EtAc) to give 73.8 mg (42%) of slightly yellow oil.

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TLC (P.E.:EtAc = 1:1)

[Rf = 0.26, Rf = 0.48, UV, KMnO₄, β-ketoester, UV, KMnO₄, lactone]

IR (NaCl, neat) ν(cm⁻¹): 3032, 2972, 2927, 1742, 1581, 1469, 691.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 1.78 (s, 3H, H-8), 2.52-2.70 (m, 2H, H-4 and H-4’), 3.69 (dd, partial overlap, 1H, ³J₆,₆’ = 10.2 Hz, 1H, ³J₆,₅ = 5.6 Hz, H-6), 3.74 (dd, partial overlap, 1H, ³J₆’,₆ = 10.2 Hz, 1H, ³J₆’,₅ = 4.4 Hz, H-6’), 3.78 (s, 3H, H-9), 4.49 (sextet, 1H, ³J = 5.3 Hz, H-5), 4.60 (d, 2H, ³J = 3.2 Hz, H-7), 7.30-7.39 (m, 5H, aromatic CH).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 9.1 (C-8), 26.4 (C-4), 55.7 (C-9), 71.0 (C-5), 73.5 (C-6), 74.0 (C-7), 103.4 (C-2), 128.0, 128.1, 128.7 and 137.8 (aromatic CH and Cq), 165.6 (C-3), 168.2 (C-1).

MS (CI, CH₄/N₂O), m/z (%): 263.0 [M⁺+H] (100), 253.1 (14), 91.0 (77).

HRMS, m/z: calcd. (C₁₅H₁₈NaO) 285.1103; found 285.1096.

[α]²⁰D: +112.3°(c = 1.54, CH₂Cl₂).

10.2.5 General procedure for transacetylation

![Diagram of reaction]

A solution of alcohol (1.0 mmol, 1.0 eq), acetal (10.0 mmol, 10.0 eq) and PPTSA (0.1 mmol, 10 mol%) in toluene (40 mL, 0.025M) was vigorously stirred at r.t. and reduced pressure (50-55 mbar) for 24h. Saturated solution
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of NaHCO₃ (10 mL) was then added and the layers were separated. Aqueous layer was extracted with Et₂O (2x40 mL). Combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and evaporated.

**Methyl (3R)-4-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-3-[1-ethoxyallyl]oxy]butanoate**

Starting from 0.4 mmol of alcohol. Purification by CC (φ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; 10:1:0.1 = P.E.:Et₂O:Et₃N) gave 89.0 mg (67%) of colourless oil along with 41 mg (31%) of starting alcohol.

TLC (EP:Et₂O = 10:1)

Since both diastereoisomers are presented in ~1:1 ratio, all signals are presented twice with 0.002-0.03 ppm (¹H-NMR) difference.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 0.11 (s, 6H, H-5), 0.90 (s, 9H, H-7), 1.24 and 1.24 (t, 3H, ³J₁₂,₁₁ = 7.0 Hz, H-12), 2.25-2.75 (m, 2H, H-2), 3.35-3.85 (m, 4H, H-11 and H-4), 3.69 and 3.68 (s, 3H, H-13), 4.07-4.15 (m, 1H, H-3), 5.01 and 5.01 (t, 1H, ³J₁₃,₁₁ = 4.3 Hz, H-8), 5.25-5.47 (m, 2H, H-10), 5.76-5.89 (m, 1H, H-9).
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$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): -5.3 and -5.2 (C-5), 15.4 and 15.4 (C-12), 18.4 and 18.5 (C-6), 26.0 and 26.1 (C-7), 37.8 and 37.9 (C-2), 51.7 (C-13), 61.2 and 61.5 (C-11), 65.1 and 65.4 (C-4), 73.5 and 73.5 (C-3), 102.3 and 102.8 (C-8), 118.3 and 118.4 (C-10), 135.7 and 135.9 (C-9), 172.3 and 172.4 (C-1).

MS (Cl, CH$_4$/N$_2$O), $m/z$ (%): 333.3 [M$^+$+H] (3), 287.3 (21), 288.5 (6), 149.2 (9), 101.1 (19), 85.1 (100).

HRMS, $m/z$: calcd. (C$_{16}$H$_{32}$O$_5$SiNa) 355.1917; found 355.1924.

**Ethyl 3-[(1-methoxyallyl)oxy]butanoate**

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{OH} \\
\text{C}_6\text{H}_{12}\text{O}_3 & \quad \text{Mol. Wt.: 132.16} \\
\rightarrow & \\
\text{EtO}_2\text{C} & \quad \text{OMe} \\
\text{C}_{10}\text{H}_{18}\text{O}_4 & \quad \text{Mol. Wt.: 202.25}
\end{align*}
\]

Starting from 2.3 mmol of alcohol. Purification by CC ($\phi$ 3.5 cm, 10 cm of SiO$_2$, 20 mL fractions; 2:1:0.1 = P.E.:Et$_2$O:Et$_3$N) gave 330 mg (71%) of colourless oil.

TLC (EP:Et$_2$O = 1:1)

Since both diastereoisomers are presented in ~1:1 ratio, all signals are presented twice with 0.002-0.03 ppm ($^1$H-NMR) difference.
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$^{1}$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.19-1.28 (m, 6H, H-4 and H-10), 2.34-2.67 (m, 2H, H-2), 3.26 and 3.27 (s, 3H, H-8), 4.06-4.20 (m, 3H, H-3 and H-9), 4.89 and 4.90 (t, 1H, $^3J = 4.8$ Hz, H-5), 5.22-5.40 (m, 2H, H-7), 5.69-5.87 (m, 1H, H-6).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 14.3 (C-10), 20.6 and 21.6 (C-4), 42.5 and 42.7 (C-2), 52.1 and 52.4 (C-8), 60.5 (C-9), 69.1 and 70.6 (C-3), 101.3 and 102.7 (C-5), 118.5 and 118.6 (C-7), 135.2 and 135.5 (C-6), 171.4 and 171.5 (C-1).

MS (CI, CH$_4$/N$_2$O), m/z (%): 203.0 [M$^+$+H] (2), 187.1 (2), 171.0 (100), 115.0 (53), 85.8 (25), 83.8 (36), 71.0 (16).

10.3 Olefination methods

10.3.1 General procedure for sulfoxide-modified Julia olefination

\[
\begin{align*}
\text{Coupling step:} & \quad \text{A solution of sulfoxide (1.0 mmol) in dry THF (10 mL, 0.1 M sol.) was cooled to } -78^\circ\text{C} \text{ and LDA (550 } \mu \text{L, 1.1 mmol) was added dropwise. The colour of the mixture changed from slightly yellow to orange/red. After stirring at } -78^\circ\text{C for 30 min, the aldehyde/ketone (1.05} \\
& \quad \text{mol) was added dropwise. The colour of the mixture changed from slightly yellow to orange/red. After stirring at } -78^\circ\text{C for 30 min, the aldehyde/ketone (1.05}}
\end{align*}
\]
mmol), dissolved in dry THF (0.5 mL), was added dropwise and the mixture
was stirred for an additional 2 h at –78°C. Benzoyl chloride (1.5 mmol) in
dry THF (0.5 mL) was then added, the resulting mixture was stirred for 30
min at –78°C and then allowed to warm to r.t. over 1 h. After an additional
30 min at r.t., Me₂N(CH₂)₃OH (1.55 mmol) was added and the resulting
suspension was stirred for 10 min at r.t. The suspension was then diluted
with Et₂O:H₂O = 1:1 (10 mL) and the layers were separated. The aqueous
layer was extracted with Et₂O (3×10 mL) and the combined organic layers
were washed with 1.0 M aq. HCl (10 mL), H₂O (10 mL) and brine (10 mL),
dried over MgSO₄ and evaporated under reduced pressure to give the crude
product, which was used without additional purification in the subsequent
step.

Reductive elimination: To a solution of SmI₂ (35 mL, 0.1 M in THF, 3.5 eq),
HMPA (613 μL, 3.5 eq) was added and the mixture was cooled to –78°C.
The crude coupled product (1.0 mmol) in dry THF (0.5 mL) was added
dropwise and the resulting mixture was stirred at –78°C for an additional 30
min. Then, aqueous NH₄Cl (20 mL) was added and the whole was allowed
to warm to r.t. The layers were separated and the aqueous phase was
extracted with Et₂O (3×20 mL). The pooled organic layers were washed with
10% aq. Na₂S₂O₃ (20 mL), H₂O (20 mL), brine (20 mL), dried over MgSO₄
and evaporated under the reduced pressure. The crude product was then
purified by chromatography on silicagel.

---

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1-[(E)-4-Phenyl-1-butenyl]benzene

Purified by column chromatography (ϕ 2.5 cm, 11 cm of SiO², 5 mL fractions; P.E.:Et₂O = 30:1) to give 139.6 mg (67%, E/Z = >99:1) of desired olefin.

\[
\begin{array}{c}
\text{Ph} \\
1 \\
2 \\
3 \\
4 \\
\text{Ph}
\end{array}
\]

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3080, 3059, 3025, 2924, 2854, 1601, 1578, 1496, 1476, 1452, 1439, 1070, 1023, 963, 908, 735, 689.

\(^1\)H-NMR (250 MHz, CDCl₃) δ (ppm): 2.56 (m, 2H, H-3), 2.83 (m, 2H, H-4), 6.29 (dt, 1H, \(^3\)J₂,₁ = 15.9 Hz, \(^3\)J₁,₂ = 5.6 Hz, H-2), 6.45 (d, 1H, \(^3\)J₁,₂ = 15.9 Hz, H-1), 7-23-7.57 (m, 10H, aromatic CH).

\(^13\)C-NMR (50 MHz, CDCl₃) δ (ppm): 35.0 (C-3), 36.1 (C-4), 127.7 (C-2), 129.3 (C-1), 126.1-131.8 (aromatic CH and Cₘ).

MS (APCI), \(m/z\) (%): 207.5 (26) [M⁺-H], 141.1 (100), 109.1 (75).

CAS number: [27066-35-9].

1-[(E)-3-Methyl-1-butenyl]benzene

Purified by column chromatography (ϕ 2.5 cm, 11 cm of SiO², 5 mL fractions; 100% n-pentane) to give 102.4 mg (70%, E/Z = 76:24) of colourless oil.

\[
\begin{array}{c}
\text{Ph} \\
1 \\
2 \\
3 \\
4 \\
\text{Ph}
\end{array}
\]

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3082, 3063, 2963, 2926, 2866, 1655, 1593, 1493, 1462, 1446, 1147, 1111, 965, 745, 691.

(E) olefin

\(^1\)H-NMR (300 MHz, CDCl₃) δ (ppm): 1.10 (d, 9H, \(^3\)J₁,₂ = 6.7 Hz, H-1\text{trans}), 2.48 (sextet, 1H, \(^3\)J = 6.7 Hz, H-2\text{trans}), 6.21 (dd, 1H, \(^3\)J₃,₄ = 16.3 Hz, \(^3\)J₃,₂

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= 6.7 Hz, H-3\textsuperscript{trans}, 6.35 (d, 1H, \textsuperscript{3}J_{4,3} = 16.3 Hz, H-4\textsuperscript{trans}), 7.17-7.39 (m, 5H, aromatic CH).

\textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm): 22.7 (C-1\textsuperscript{trans}), 31.7 (C-2\textsuperscript{trans}), 127.0 (C-4\textsuperscript{trans}), 128.8 (C-3\textsuperscript{trans}), 126.2-131.3 (aromatic CH and C\textsubscript{q}).

\textit{(Z) olefin}

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm): 1.06 (d, 9H, \textsuperscript{3}J_{1,2} = 6.7 Hz, H-1\textsuperscript{cis}), 2.96 (m, 1H, H-2\textsuperscript{cis}), 5.49 (dd, 1H, \textsuperscript{3}J_{3,4} = 10.1 Hz, \textsuperscript{3}J_{3,2} = 11.5 Hz, H-3\textsuperscript{cis}), 6.31 (d, 1H, \textsuperscript{3}J_{4,3} = 10.1 Hz, H-4\textsuperscript{cis}), 7.17-7.39 (m, 5H, aromatic CH).

\textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm): 23.4 (C-1\textsuperscript{cis}), 27.6 (C-2\textsuperscript{cis}), 128.4 (C-4\textsuperscript{cis}), 138.2 (C-3\textsuperscript{cis}), 126.2-131.3 (aromatic CH and C\textsubscript{q}).

MS (Cl, CH\textsubscript{4}/N\textsubscript{2}O), \(m/z\) (%): 147.0 (100) [M\textsuperscript{+}+1], 91.1 (31).

CAS number: [15325-61-8].

\textbf{(E)-5-Methyl-1-phenyl-3-hexene}

Purified by column chromatography (\(\phi\) 2.5 cm, 11 cm of SiO\textsubscript{2}, 5 mL fractions; 100\% n-pentane) to give 120.3 mg (69\%, \(E/Z = 94:6\)) of colourless oil.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure}
\end{center}

IR (NaCl, neat) \(\nu^{-1}(\text{cm}^{-1})\): 3085, 3063, 3027, 2959, 2925, 2868, 1604, 1496, 1454, 1380, 1362, 1260, 1100, 1029, 969, 803, 745, 697.

\textit{(E) olefin}

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm): 0.97 (d, 9H, \textsuperscript{3}J_{1,2} = 6.7 Hz, H-1\textsuperscript{trans}), 2.29 (m, 1H, partial overlap, H-2), 2.32 (m, 1H, partial overlap, H-5), 2.69 (dd, \textsuperscript{3}J_{6,5} = 8.1 Hz, \textsuperscript{3}J_{6,5'} = 6.7 Hz, Hz, H-6), 5.42 (m, 2H, H-3 and 4), 7.19-7.32 (m, 5H, aromatic CH).
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$^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ (ppm): 23.8 (C-1$_{\text{trans}}$), 31.2 (C-2), 34.7 (C-5), 36.5 (C-6), 125.9 (C-4), 138.5 (C-3), 126.4-142.4 (aromatic CH and C$_q$).

(Z) olefin

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 0.90 (d, 9H, $^3J_{1,2} = 6.7$ Hz, H-1$_{\text{cis}}$), 2.29 (m, 1H, partial overlap, H-2), 2.32 (m, 1H, partial overlap, H-5), 2.69 (dd, $^3J_{6,5} = 8.1$ Hz, $^3J_{6,5'} = 6.7$ Hz, Hz, H-6), 5.42 (m, 2H, H-3 and 4), 7.19-7.32 (m, 5H, aromatic CH).

$^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ (ppm): 29.9 (C-1$_{\text{cis}}$), 31.2 (C-2), 34.7 (C-5), 36.5 (C-6), 125.9 (C-4), 138.5 (C-3), 126.4-142.4 (aromatic CH and C$_q$).

MS (CI, CH$_4$/N$_2$O), $m/z$ (%): 175.0 (77) [M$^+$+1], 176.1 (7) [M$^+$+2], 173.4 (26), 133.0 (27), 119.0 (100), 104.7 (84), 90.9 (71).

CAS number: [96025-23-9].

1-[(E)-2,3-Dimethyl-1-butenyl]benzene

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO$_2$, 5 mL fractions; 100% n-pentane) to give 91.4 mg (57%, $E/Z = 91:9$) of colourless oil.

\[
\begin{align*}
\text{IR (NaCl, neat) } & \nu^{-1}(\text{cm}^{-1}) : 3079, 3057, 3021, 2963, 2932, 2868, 1645, 1597, 1489, 1456, 1435, 1373, 1111, 1074, 1028, 908, 732, 698. \\
\end{align*}
\]

(E) olefin

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.13 (d, 9H, $^3J_{1,2} = 6.7$ Hz, H-1$_{\text{trans}}$), 1.84 (d, 3H, $^4J_{5,4} = 1.4$ Hz, H-5), 2.44 (heptet, 1H, $J = 6.7$ Hz, H-2), 6.30 (broad s, H-4$_{\text{trans}}$), 7.17-7.35 (m, 5H, aromatic CH).

(Z) olefin

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1H-NMR (300 MHz, CDCl₃) δ (ppm): 1.05 (d, 9H, 3J₁,₂ = 6.7 Hz, H-1\(^\text{cis}\)), 1.84 (d, 3H, 4J₃,₄ = 1.4 Hz, H-5), 2.44 (heptet, 1H, J = 6.7 Hz, H-2), 6.22 (broad s, 1H, H-4\(^\text{cis}\)), 7.17-7.35 (m, 5H, aromatic CH).

13C-NMR (62.5 MHz, CDCl₃) δ (ppm): 15.3 (C-5), 21.7 (C-1), 37.9 (C-2), 122.8 (C-4), 145.0 (C-3), 124.4-139.0 (aromatic CH and C₉).

MS (CI, CH₄/N₂O), m/z (%): 161.0 (54) [M⁺+1], 159.9 (33) [M⁺-1], 145.0 (29), 119.0 (21), 104.6 (41), 85.8 (65), 83.8 (100).

CAS number: [70975-43-8].

1-[(E)-1,3-Dimethyl-1-butenyl]benzene

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 102.6 mg (64%, E/Z = 74:26) of colourless oil.

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3082, 3061, 3021, 2957, 2926, 2868, 1597, 1493, 1468, 1446, 1383, 1157, 1111, 1028, 991, 755, 698.

(E) olefin

1H-NMR (300 MHz, CDCl₃) δ (ppm): 1.06 (d, 9H, 3J₁,₂ = 6.7 Hz, H-1\(^\text{trans}\)), 2.06 (d, 3H, 4J₃,₅ = 1.4 Hz, H-5\(^\text{trans}\)), 2.70 (m, 1H, H-2), 5.62 (dd, 1H, 3J₁,₂ = 9.3 Hz, 4J₃,₅ = 1.2 Hz, H-3\(^\text{trans}\)), 7.18-7.42 (m, 5H, aromatic CH).

13C-NMR (62.5 MHz, CDCl₃) δ (ppm): 15.9 (C-5\(^\text{trans}\)), 23.2 (C-1\(^\text{trans}\)), 28.1 (C-2), 125.9-143.7 (aromatic CH and C₉, C-3 and C-4).

(Z) olefin

1H-NMR (300 MHz, CDCl₃) δ (ppm): 0.94 (d, 9H, 3J₁,₂ = 6.7 Hz, H-1\(^\text{cis}\)), 2.01 (d, 3H, 4J₃,₅ = 1.5 Hz, H-5\(^\text{cis}\)), 2.70 (m, 1H, H-2), 5.27 (dd, 1H, 3J₁,₂ = 10.2 Hz, 4J₃,₅ = 1.5 Hz, H-3\(^\text{cis}\)), 7.18-7.42 (m, 5H, aromatic CH).
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$^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 23.6 (\text{C-1}^{\text{cis}}), 25.9 (\text{C-5}^{\text{cis}}), 28.1 (\text{C-2}), 125.9-143.7 (\text{aromatic CH and C} \varepsilon, \text{C-3 and C-4}).$

MS (CI, CH$_4$/N$_2$O), $m/z$ (%): 162.1 (13) [M$^{+2}$], 161.0 (96) [M$^{+1}$], 160.0 (35) [M$^{-1}$], 159.0 (26), 145.0 (56), 133.0 (36), 110.9 (38), 104.9 (100), 83.3 (26).

CAS number: [70303-26-3].

1-[(E)-2-Phenyl-1-propenyl]benzene

Purified by column chromatography ($\phi$ 2.5 cm, 11 cm of SiO$_2$, 5 mL fractions; 100% n-pentane) to give 98 mg (51%, E/Z = 76:24) of colourless oil.

[(E) olefin]

$^{1}\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 2.35 (\text{d}, 3\text{H}, ^{4}J_{3,1} = 1.4 \text{ Hz, H-3}^{\text{trans}}), 6.91 (\text{d}, 1\text{H}, ^{4}J_{1,3} = 1.4 \text{ Hz, H-1}^{\text{trans}}), 7.23-7.61 (\text{m}, 10\text{H}, \text{aromatic CH}).$

$^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 17.7 (\text{C-3}^{\text{trans}}), 126.2-144.2 (\text{aromatic CH and C} \varepsilon, \text{C-1 and C-2}).$

[(Z) olefin]

$^{1}\text{H-NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 2.27 (\text{d}, 3\text{H}, ^{4}J_{3,1} = 1.4 \text{ Hz, H-3}^{\text{cis}}), 6.54 (\text{broad s, 1H, H-1}^{\text{cis}}), 7.23-7.61 (\text{m}, 10\text{H}, \text{aromatic CH}).$

$^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 27.3 (\text{C-3}^{\text{cis}}), 126.2-144.2 (\text{aromatic CH and C} \varepsilon, \text{C-1 and C-2}).$

MS (CI, CH$_4$/N$_2$O), $m/z$ (%): 194.7 (100) [M$^{+}$], 196.2 (12) [M$^{+2}$], 110.9 (12), 83.8 (14).
CAS number: [833-81-8].

1-[(E)-2-Methyl-4-phenyl-1-butenyl]benzene

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 158 mg (71%, E/Z = 52:48) of colourless oil.

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3079, 3058, 3023, 2926, 2854, 1599, 1577, 1497, 1435, 739, 697.

(E) olefin

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 1.92 (d, 3H, ⁴J₅,₁ = 1.2 Hz, H-5trans), 2.53 (m, 2H, H-3), 2.84 (m, 2H, H-4), 6.27 (broad s, 1H, H-1trans), 7.13-7.54 (m, 10H, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 18.2 (C-5trans), 34.7 (C-3trans), 34.9 (C-4), 126.0 (C-1trans), 126.1-144.1 (aromatic CH and C₉ and C-2).

(Z) olefin

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 1.95 (d, 3H, ⁴J₅,₁ = 1.2 Hz, H-5cis), 2.53 (m, 2H, H-3), 2.84 (m, 2H, H-4), 6.34 (broad s, 1H, H-1cis), 7.13-7.54 (m, 10H, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 24.4 (C-5cis), 34.7 (C-3cis), 34.9 (C-4), 126.0 (C-1cis), 126.1-144.1 (aromatic CH and C₉ and C-2).

MS (APCI), m/z (%): 222.1 (3) [M⁺], 221.2 (5), 220.2 (19), 219.2 (100), 149.1 (18).

CAS number: [54130-64-2].
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*(E)-3,5-Dimethyl-1-phenyl-3-hexene*

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 119 mg (63%, E/Z = 68:32) of colourless oil.

\[
\text{IR (NaCl, neat) } \nu (\text{cm}^{-1}): 3082, 3036, 3026, 2955, 2927, 2866, 1603, 1495, 1453, 1382, 1360, 1100, 1077, 1030, 847, 743, 697.
\]

*(E) olefin*  
\[1^1\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta \text{ (ppm)}: 0.92 (d, 6H, }^3\text{J}_{1,2} = 6.7 \text{ Hz, H-1}^{\text{trans}}, 1.68 (d, 3H, }^4\text{J}_{7,3} = 1.4 \text{ Hz, H-7}^{\text{trans}}, 2.31 (m, 2H, H-5), 2.47 (m, 1H, H-2), 2.72 (m, 2H, H-6), 4.97 (m, 1H, H-3), 7.18-7.32 (m, 5H, aromatic CH).\]

\[1^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta \text{ (ppm)}: 16.3 \text{ (C-7}^{\text{trans}}\text{), 23.3 \text{ (C-1}^{\text{trans}}\text{), 27.3 \text{ (C-2}^{\text{trans}}\text{), 35.0 \text{ (C-6), 41.8 \text{ (C-5}^{\text{trans}}\text{), 133.3 \text{ (C-3}^{\text{trans}}\text{), 134.2 \text{ (C-4}^{\text{trans}}\text{, 125.8-142.7 (aromatic CH and C}_q\text{).}}\]

*(Z) olefin*  
\[1^1\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta \text{ (ppm)}: 0.85 (d, 6H, }^3\text{J}_{1,2} = 6.7 \text{ Hz, H-1}^{\text{cis}}, 1.74 (d, 3H, }^4\text{J}_{7,3} = 1.3 \text{ Hz, H-7}^{\text{cis}}, 2.31 (m, 2H, H-5), 2.47 (m, 1H, H-2), 2.72 (m, 2H, H-6), 4.97 (m, 1H, H-3), 7.18-7.32 (m, 5H, aromatic CH).\]

\[1^{13}\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta \text{ (ppm)}: 23.6 \text{ (C-1}^{\text{cis}}\text{), 25.2 \text{ (C-7}^{\text{cis}}\text{), 29.9 \text{ (C-2}^{\text{cis}}\text{), 34.4 \text{ (C-5}^{\text{cis}}\text{), 35.0 \text{ (C-6), 132.1 \text{ (C-4}^{\text{cis}}\text{, 125.8-142.7 (aromatic CH and C}_q\text{ and C-3}^{\text{cis}}\text{).}}\]

MS (Cl, CH₄/N₂O), \text{m/z (％): 189.0 (100) [M}^{\text{+1}}, 119.0 (13), 105.0 (33), 91.0 (14).}

CAS number: [858658-47-6].
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1-Methyl-2-[(E)-2-methylpropylidene]cyclohexane

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO₂; 5 mL fractions; 100% n-pentane) to give 97 mg (64%, E/Z = 88:12) of colourless oil.

IR (NaCl, neat) ν<sup>1</sup>(cm⁻¹): 3023 (w), 2951 (m), 2929 (m), 2861 (w), 1601 (w), 1497 (w), 1458 (w).

(E) olefin

<sup>1</sup>H-NMR (300 MHz, CDCl₃) δ (ppm): 0.90 (m, 3H, H-10<sup>trans</sup>), 0.97 (dd, 6H,<br>³J<sub>1,2</sub> = 6.7 Hz, ³J<sub>1,1'</sub> = 1.4 Hz, H-1<sup>trans</sup>), 1.22-2.14 (m, 9H, H-5 to 9), 2.50 (m, 1H, H-2<sup>trans</sup>), 4.86 (d, 1H, ³J<sub>3,2</sub> = 9.1 Hz, H-3<sup>trans</sup>).

<sup>13</sup>C-NMR (62.5 MHz, CDCl₃) δ (ppm): 18.3 (C-10<sup>trans</sup>), 22.9 (C-1<sup>trans</sup>), 26.2, 27.3, 27.7, 28.0, 30.3, 30.8, 33.4, 34.5, 35.3, 36.1, 37.4, 126.6 (C-3<sup>trans</sup>), 137.3 (C-4<sup>trans</sup>).

(Z) olefin

<sup>1</sup>H-NMR (300 MHz, CDCl₃) δ (ppm): 0.91 (dd, 6H, ³J<sub>1,2</sub> = 6.7 Hz, ³J<sub>1,1'</sub> = 1.4 Hz, H-1<sup>cis</sup>), 1.01 (m, 3H, H-10<sup>cis</sup>), 1.22-2.14 (m, 9H, H-5 to 9), 2.56 (m, 1H, H-2<sup>cis</sup>), 5.06 (t, 1H, ³J<sub>3,2</sub> = 7.2 Hz, H-3<sup>cis</sup>).

<sup>13</sup>C-NMR (62.5 MHz, CDCl₃) δ (ppm): 19.0 (C-10<sup>cis</sup>), 23.4 (C-1<sup>cis</sup>), 26.2, 27.3, 27.7, 28.0, 30.3, 30.8, 33.4, 34.5, 35.3, 36.1, 37.4, 129.1 (C-3<sup>cis</sup>), 139.2 (C-4<sup>cis</sup>).

Elem. Anal. (C<sub>14</sub>H<sub>24</sub>): calcd. C, 86.76, H, 13.24; found: C, 86.80, H, 13.27.
Chapter 10. Experimental part

(E)-3,5-Dimethyl-1-phenyl-3-hexene

Purified by column chromatography (Φ 2.5 cm, 11 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 110 mg (63%, E/Z = 68:32) of colourless oil.

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 3082 (w), 3063 (w), 3026 (w), 2955 (m), 2927 (m), 2866 (w), 1603 (w), 1496 (w), 1453 (w), 743 (m), 697 (m).

(E) olefin

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 0.92 (d, 6H, J₂,₁ = 6.7 Hz, H₁trans), 1.67 (s, 3H, H₁₁trans), 2.22-2.75 (m, 5H, H₂, H₅ and H₆), 4.95 (m, 1H, H₃trans), 7.18-7.32 (5H, m, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 23.6 (C₁₁cis), 27.3 (C₁trans), 27.3 (C₂trans), 35.0 (C₆), 41.8 (C₅trans), 125.8-142.7 (aromatic CH and C₉), 132.1 (C₄), 133.3 (C₃trans).

(Z) olefin

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 0.86 (d, 6H, J₂,₁ = 6.7 Hz, H₁cis), 1.73 (s, 3H, H₁₁cis), 2.22-2.75 (m, 5H, H₂, H₅ and H₆), 4.98 (m, 1H, H₃cis), 7.18-7.32 (5H, m, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 23.6 (C₁₁cis), 25.2 (C₁cis), 29.9 (C₂cis), 34.4 (C₅cis), 35.0 (C₆), 125.8-142.7 (aromatic CH and C₉), 132.1 (C₄), 134.2 (C₃cis).

MS (CI, CH₄/N₂O), m/z (%): 189.1 (46) [M⁺], 187.2 (29), 133.0 (63), 131.0 (32), 119.0 (100), 104.8 (93), 90.9 (41).
1-(1-Cyclohexylethylidene)cyclohexane

Purified by column chromatography (ϕ 2.5 cm, 10 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 63 mg (33%) of colourless oil.

IR (NaCl, neat) υᵣ(cm⁻¹): 3025 (w), 2958 (m), 2924 (m), 2867 (w), 1601 (w), 1498 (w), 1451 (w).

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 0.82-0.99 (m, 6H), 1.21 (m, 10H), 1.59 (s, 3H, H-10), 1.52-2.38 (m, 5H, H-4 and H-7).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 17.1 (C-10), 25.7, 26.6, 27.1, 27.7, 28.9, 30.1, 30.7, 35.1, 41.2 (C-4), 125.3 (C-6), 136.1 (C-5).


1-[(E)-1,2,3-Trimethyl-1-butenyl]cyclohexane

Purified by column chromatography (ϕ 2.5 cm, 9 cm of SiO₂, 5 mL fractions; 100% n-pentane) to give 52 mg (29%, E/Z = 97:3) of colourless oil.

IR (NaCl, neat) υᵣ(cm⁻¹): 3024 (w), 2951 (m), 2931 (m), 2862 (w), 1599 (w), 1499 (w), 1444 (w).
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**(E) olefin**

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.82-1.39 (m, 10H, H-1, H-2 and H-3), 0.92 (d, 6H, $^3$J$_{2,1}$ = 6.7 Hz, H-8), 1.57 (s, 3H, H-10$^{trans}$), 1.59 (s, 3H, H-9$^{trans}$), 1.71 (m, 1H, H-7), 1.86 (m, 1H, H-4).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ(ppm): 18.2 (C-10$^{trans}$), 18.6 (C-9$^{trans}$), 21.1 and 21.3 (C-8), 26.5, 26.7, 31.1 and 31.2 (C-7), 35.6 (C-3), 40.1 and 40.2 (C-4), 134.5 (C-5$^{trans}$), 138.7 (C-6$^{trans}$).

**(Z) olefin**

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.82-1.39 (m, 10H, H-1, H-2 and H-3), 0.92 (d, 6H, $^3$J$_{2,1}$ = 6.7 Hz, H-8), 1.39 (s, 3H, H-10$^{cis}$), 1.46 (s, 3H, H-9$^{cis}$), 1.71 (m, 1H, H-7), 1.86 (m, 1H, H-4).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ(ppm): 16.4 (C-10$^{cis}$), 16.9 (C-9$^{cis}$), 21.1 and 21.3 (C-8), 26.5, 26.7, 31.1 and 31.2 (C-7), 35.6 (C-3), 40.1 and 40.2 (C-4), 123.1 (C-5$^{cis}$), 127.4 (C-6$^{cis}$).

Elem. Anal. (C$_{13}$H$_{24}$): calcd. C, 86.59, H, 13.41; found: C, 86.64, H, 13.36.

1-[(E)-1,2-Dimethyl-4-phenyl-1-butenyl]cyclohexane

Purified by column chromatography (φ 2.5 cm, 12 cm of SiO$_2$, 5 mL fractions; 100% n-pentane) to give 76 mg (32%, $E/Z = 91:9$) of colourless oil.

IR (NaCl, neat) ν$^{-1}$(cm$^{-1}$): 3067 (m), 3026 (w), 2959 (m), 2926 (m), 2868 (w), 1603 (w), 1500 (w), 1449 (w).

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(E) olefin

$^1$H-NMR (250 MHz, CDCl$_3$) δ (ppm): 0.72-1.39 (m, 10H, H-1, H-2 and H-3), 1.59 (s, 1H, H-14$^{trans}$), 1.68 (s, 1H, H-13$^{trans}$), 1.86 (m, 2H, H-7), 2.28 (m, 1H, H-4), 2.70 (m, 2H, H-8), 7.18-7.31 (m, 5H, H-10, H-11 and H-12).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ (ppm): 14.7 (C-14$^{trans}$), 18.2 (C-13$^{trans}$), 26.6, 26.9, 33.6, 34.7, 36.2, 41.4 (C-4), 124.3 (C-6$^{trans}$), 137.4 (C-5$^{trans}$), 126.3-141.2 (aromatic C and C$_q$).

(E) olefin

$^1$H-NMR (250 MHz, CDCl$_3$) δ (ppm): 0.72-1.39 (m, 10H, H-1, H-2 and H-3), 1.41 (s, 1H, H-13$^{cis}$), 1.61 (s, 1H, H-14$^{cis}$), 1.86 (m, 2H, H-7), 2.28 (m, 1H, H-4), 2.70 (m, 2H, H-8), 7.18-7.31 (m, 5H, H-10, H-11 and H-12).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ (ppm): 16.3 (C-13$^{cis}$), 17.9 (C-14$^{cis}$), 26.6, 26.9, 33.6, 34.7, 36.2, 41.4 (C-4), 116.2 (C-6$^{cis}$), 125.2 (C-5$^{cis}$), 126.3-141.2 (aromatic C and C$_q$).

1-(2-Cyclopentenylidemethyl)benzene

Purified by column chromatography (φ 2.5 cm, 11 cm of SiO$_2$, 5 mL fractions; 100% n-pentane) to give 106 mg (68%, $E/Z = 65:35$) of 6c as a colourless oil.

IR (NaCl, neat) ν$^1$(cm$^{-1}$): 3084 (w), 3072 (w), 3021 (w), 2954 (m), 2923 (m), 2868 (w), 1602 (w), 1495 (w), 1454 (w), 742 (m), 699 (m).
Chapter 10. Experimental part

\((E)\) olefin

\(^1\)H NMR (250 MHz, CDCl\(_3\)): 1.71-1.83 (m, 2H, H-9), 2.20-2.31 (m, 2H, H-10), 6.22 (m, 1H, H-7\(^{\text{trans}}\)), 6.49-6.52 (m, 1H, H-8), 6.52 (broad s, 1H, H-5\(^{\text{trans}}\)), 7.02-7.68 (m, 5H, aromatic CH).

\(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): 28.3 (C-10\(^{\text{trans}}\)), 30.4 (C-9\(^{\text{trans}}\)), 132.4 (C-5\(^{\text{trans}}\)), 27.3 (C-2\(^{\text{trans}}\)), 123.5-137.2 (aromatic CH and \(\text{C}_q\)), 132.7 (C-7\(^{\text{trans}}\)), 134.5 (C-7\(^{\text{cis}}\)), 143.2 (C-8).

\((Z)\) olefin

\(^1\)H NMR (250 MHz, CDCl\(_3\)): 1.71-1.83 (m, 2H, H-9), 2.20-2.31 (m, 2H, H-10), 6.19 (broad s, 1H, H-5\(^{\text{cis}}\)), 6.49-6.52 (m, 1H, H-8), 7.25 (broad s, H-7\(^{\text{cis}}\)), 7.02-7.68 (m, 5H, aromatic CH).

\(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)): 30.5 (C-9\(^{\text{cis}}\)), 37.2 (C-10\(^{\text{cis}}\)), 117.2 (C-5\(^{\text{cis}}\)), 123.5-137.2 (aromatic CH and \(\text{C}_q\)), 134.5 (C-7\(^{\text{cis}}\)), 143.2 (C-8).

MS (Cl, CH\(_4\)/N\(_2\)O), \(m/z\) (%): 156.11 (100) [M\(^+\)], 157.25 [M\(^+\)+1] (23), 79.2 (26), 77.5 (16).

Elem. Anal. (C\(_{12}\)H\(_{12}\)): calcd. C, 92.26; found: C, 92.34; H, 7.66.

3-[\((E)\)-2-Methylpropylidene]-1-cyclopentene

Purified by column chromatography (\(\phi\) 2.5 cm, 11 cm of SiO\(_2\), 5 mL fractions; 100\% \(n\)-pentane) to give 77 mg (63\%, \(E/Z = 68:32\)) of \(6h\) as a colourless oil.

IR (NaCl, neat): 3058 (w), 2957 (m), 2862 (w), 1604 (w), 1494 (w), 1453 (w).
**Chapter 10. Experimental part**

*(E) olefin*

$^1$H NMR (250 MHz, CDCl$_3$): 0.95 (dd, 6H, $^3$$J_{1,2}$ = 6.7 Hz, $^3$$J_{1,1'}$ = 1.4 Hz, H-$^1$trans), 1.52-1.74 (m, 2H, H-7), 1.98-2.09 (m, 2H, H-8), 2.61 (m, 1H, H-$^2$trans), 5.17 (d, 1H, $^3$$J_{3,2}$ = 9.1 Hz, H-3trans), 6.28 (broad s, 1H, H-5trans), 6.78 (m, 1H, H-6).

$^{13}$C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 23.2 (C-$^1$trans), 28.3 (C-$^2$trans), 29.2 (C-$^8$trans), 31.9 (C-7), 134.2 (C-5trans), 135.9 (C-4trans), 137.2 (C-$^3$cis), 138.2 (C-$^3$trans), 140.6 (C-6).

*(Z) olefin*

$^1$H NMR (250 MHz, CDCl$_3$): 0.92 (dd, 6H, $^3$$J_{1,2}$ = 6.7 Hz, $^3$$J_{1,1'}$ = 1.4 Hz, H-$^1$cis), 1.52-1.74 (m, 2H, H-7), 1.98-2.09 (m, 2H, H-8), 2.36 (m, 1H, H-$^2$cis), 5.44 (d, 1H, $^3$$J_{3,2}$ = 10.1 Hz, H-3cis), 6.78 (m, 1H, H-6), 7.35 (m, 1H, H-5cis).

$^{13}$C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 21.4 (C-$^1$cis), 30.3 (C-2cis), 31.9 (C-7), 36.2 (C-$^8$cis), 134.3 (C-4cis), 134.5 (C-5cis), 137.2 (C-3cis), 140.6 (C-6).

MS (CI, CH$_4$/N$_2$O), m/z (%): 122.19 (100) [M$^+$], 95.7 (15), 79.7 (39), 51.3 (8).


1-(tert-Butyl)-1,1-dimethylsilyl [(E)-2,4-dimethyl-2-pentenyl] ether

Purified by column chromatography (ϕ 2.5 cm, 11 cm of SiO$_2$, 5 mL fractions; 100% n-pentane) to give 117 mg (51%, $E$/Z = 79:21) of 6i as a colourless oil.
Chapter 10. Experimental part

(E) olefin

$^1$H-NMR (250 MHz, CDCl$_3$): 0.03 (s, 6H, SiMe$_2$Bu'), 0.91 (s, 9H, SiMe$_2$Bu'), 0.96 (dd, 6H, $^3$$J_{1,2}$ = 6.7 Hz, $^3$$J_{1,1'}$ = 1.4 Hz, H-$^1_{trans}$), 1.67 (m, 1H, H-$^6_{trans}$), 2.49 (m, 1H, H-$^2_{trans}$), 4.01-4.12 (m, 2H, H-5), 4.76 (d, 1H, $^3$$J_{2,3}$ = 9.5 Hz, H-$^3_{trans}$).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$): -3.2 (SiMe$_2$Bu'), 14.0 (C-$^6_{trans}$), 18.7, 23.2 (C-$^1_{trans}$), 24.1 (C-$^2_{trans}$), 26.2 (SiMe$_2$Bu'), 64.2 (C-$^5_{trans}$), 132.3 (C-$^4_{trans}$), 138.9 (C-$^3_{trans}$).

(Z) olefin:

$^1$H-NMR (250 MHz, CDCl$_3$): 0.03 (s, 6H, SiMe$_2$Bu'), 0.91 (s, 9H, SiMe$_2$Bu'), 0.92 (dd, 6H, $^3$$J_{1,2}$ = 6.7 Hz, $^3$$J_{1,1'}$ = 1.5 Hz, H-$^1_{cis}$), 1.67 (m, 1H, H-$^6_{trans}$), 2.49 (m, 1H, H-$^2_{trans}$), 4.01-4.12 (m, 2H, H-5), 5.11 (d, 1H, $^3$$J_{2,3}$ = 9.3 Hz, H-$^3_{cis}$).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$): -3.2 (SiMe$_2$Bu'), 18.7, 21.4 (C-$^6_{cis}$), 22.9 (C-$^1_{cis}$), 26.2 (SiMe$_2$Bu'), 28.1 (C-$^2_{cis}$), 70.2 (C-$^5_{cis}$), 132.1 (C-$^4_{cis}$), 148.8 (C-$^3_{cis}$).

MS (CI, CH$_4$/N$_2$O), m/z (%): 128.45 (67) [M$^+$], 114.6 (100), 97.9 (65), 77.2 (15), 55.2 (12).

Elem. Anal. (C$_{13}$H$_{26}$O$\text{Si}$): calcd. C, 68.35, H, 12.35; found: C, 68.51, H, 12.23.

2-Methyl-1-[2-methyl-1-(phenylsulfinyl)propyl]cyclohexyl benzoate

Sulfoxides 523 were prepared according to the standard coupling procedure. The crude mixture was purified by repetitive (7x) column chromatography ($\phi$ 2.5 cm, 11 cm of SiO$_2$, 5 mL fractions; 20:1 = P.E.:Et$_2$O) to give four diastereoisomers more polar-syn-523 (11 mg), less polar-syn-523 (15 mg), more polar-anti-523 (25 mg) and more polar-anti-523 (28 mg).
TLC (5:1 = P.E.:EtAc)

More polar syn-523

$^1$H NMR (300 MHz, CDCl$_3$): 0.86 (dd, 3H, $^3J_{1,2} = 6.5$ Hz, $^2J_{1,1'} = 1.4$ Hz, one of H-1), 1.06 (d, 3H, $^3J_{14,5} = 7.2$ Hz, H-14), 1.21 (dd, 3H, $^3J_{1,2} = 6.8$ Hz, $^2J_{1,1'} = 1.3$ Hz, the other H-1), 1.17-2.27 (m, 10H, H-2, 5-9), 3.89 (d, 1H, $^3J_{3,2} = 7.0$ Hz, H-3), 7.11-8.24 (m, 10H, aromatic CH).

$^{13}$C NMR (75 MHz, CDCl$_3$): 13.5, 20.3, 21.8, 22.9, 24.3, 29.2, 31.8, 32.8, 36.2, 71.9 (C-3), 76.8 (C-4), 124.3-147.9 (aromatic CH and C$_q$), 166.2 (C-15).

MS (Cl, CH$_4$/N$_2$O), m/z (%): 586.46 (67) [M$^+$], 587.67 [M$^{+1}$] (34), 121 (100), 181.3 (43), 96.9 (15), 77.3 (20).

HRMS, m/z: calcd. 398.1916; found 398.1924.

Less polar syn-523

$^1$H NMR (300 MHz, CDCl$_3$): 0.86 (dd, 3H, $^3J_{1,2} = 6.5$ Hz, $^2J_{1,1'} = 1.4$ Hz, one of H-1), 1.07 (d, 3H, $^3J_{14,5} = 7.2$ Hz, H-14), 1.20 (dd, 3H, $^3J_{1,2} = 6.8$ Hz, $^2J_{1,1'} = 1.2$ Hz, the other H-1), 1.17-2.28 (m, 10H, H-2, 5-9), 4.12 (d, 1H, $^3J_{3,2} = 7.1$ Hz, H-3), 7.10-8.25 (m, 10H, aromatic CH).

$^{13}$C NMR (75 MHz, CDCl$_3$): 13.6, 20.3, 21.8, 22.9, 24.4, 29.3, 31.8, 32.8, 36.2, 71.4 (C-3), 76.5 (C-4), 124.1-147.9 (aromatic CH and C$_q$), 166.1 (C-15).
Chapter 10. Experimental part

MS (Cl, CH₄/N₂O), m/z (%): 586.4 (63) [M⁺], 587.6 [M⁺+1] (33), 121.4 (100), 181.3 (38), 96.9 (19), 77.3 (21).

HRMS, m/z: calcd. 398.1916; found 398.1918.

More polar anti-523

¹H NMR (300 MHz, CDCl₃): 0.87 (dd, 3H, 3J₁,₂ = 6.5 Hz, 2J₁₁ = 1.3 Hz, one of H-1), 1.07 (d, 3H, 3J₁₄,₅ = 7.2 Hz, H-14), 1.21 (dd, 3H, 3J₁₂ = 6.8 Hz, 2J₁₁ = 1.3 Hz, the other H-1), 1.17-2.25 (m, 10H, H-2, 5-9), 4.26 (d, 1H, 3J₃₂ = 6.9 Hz, H-3), 7.11-8.24 (m, 10H, aromatic CH).

¹³C NMR (75 MHz, CDCl₃): 13.4, 20.5, 21.8, 22.8, 24.8, 29.3, 31.8, 32.8, 36.3, 72.3 (C-3), 77.1 (C-4), 124.5-147.9 (aromatic CH and C₉), 165.1 (C-15).

MS (Cl, CH₄/N₂O), m/z (%): 586.6 (78) [M⁺], 587.9 [M⁺+1] (40), 122.4 (100), 181.9 (43), 97.0 (17), 77.4 (21).

HRMS, m/z: calcd. 398.1916; found 398.1910.

Less polar anti-523

¹H NMR (300 MHz, CDCl₃): 0.87 (dd, 3H, 3J₁,₂ = 6.5 Hz, 2J₁₁ = 1.3 Hz, one of H-1), 1.07 (d, 3H, 3J₁₄,₅ = 7.1 Hz, H-14), 1.21 (dd, 3H, 3J₁₂ = 6.9 Hz, 2J₁₁ = 1.3 Hz, the other H-1), 1.17-2.25 (m, 10H, H-2, 5-9), 4.36 (d, 1H, 3J₃₂ = 7.1 Hz, H-3), 7.14-8.25 (m, 10H, aromatic CH).

¹³C NMR (75 MHz, CDCl₃): 13.4, 20.4, 21.8, 22.9, 24.8, 29.3, 31.7, 32.8, 36.8, 72.1 (C-3), 76.7 (C-4), 124.7-147.7 (aromatic CH and C₉), 164.9 (C-15).

MS (Cl, CH₄/N₂O), m/z (%): 586.4 (45) [M⁺], 587.6 [M⁺+1] (23), 121.7 (100), 182.1 (43), 96.7 (24), 77.0 (16).

HRMS, m/z: calcd. 398.1916; found 398.1907.


Chapter 10. Experimental part

(R)-(+)−goniothalamin

\[
\begin{align*}
\text{Swern oxidation} & \quad \text{sulfoxide-modified Julia olefination} \\
\text{Mol. Wt.: 128,13} & \quad \text{Mol. Wt.: 126,11}
\end{align*}
\]

Starting from 1.17 mmol of alcohol. Oxidation of alcohol, see chapter 10.2.4 method B. Aldehyde used immediately in the next step. Purified by column chromatography (ϕ 3.5 cm, 9.5 cm of SiO₂, 10 mL fractions, P.E.:EtAc = 3:1) to give 173.3 mg (78%, E/Z = >95:1) of colourless crystals.

TLC (1:1 = P.E.:EtAc)

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<thead>
<tr>
<th>1H-NMR</th>
<th>Synthetic (300 MHz) [ppm]</th>
<th>Natural (300 MHz) [ppm]</th>
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<tr>
<td>H-4</td>
<td>2.56 (m, 2H)</td>
<td>2.54 (m, 2H)</td>
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<tr>
<td>H-5</td>
<td>5.12 (dq, ( J_{5,6} = 6.5 ) Hz, ( J_{5,4} = 1.2 ) Hz)</td>
<td>5.10 (dq, 1H, ( J = 7 ) and 1 Hz)</td>
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<td>H-2</td>
<td>6.10 (dt, 1H, ( J_{2,3} = 9.7 ) Hz, ( J_{2,4} = 1.7 ) Hz)</td>
<td>6.09 (dt, 1H, ( J = 10 ) and 4 Hz)</td>
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<tr>
<td>H-6</td>
<td>6.29 (dd, 1H, ( J_{6,7} = 16.1 ) Hz)</td>
<td>6.27 (dd, 1H, ( J = 16 ))</td>
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Chapter 10. Experimental part

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<th>Hz, $J_{6,5} = 6.5$ Hz) and 6 Hz)</th>
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<td>6.74 (d, 1H, $J_{7,6} = 15.8$ Hz)</td>
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<td>H-3</td>
<td>6.94 (dt, 1H, $J_{3,2} = 9.7$ Hz, $J_{3,4} = 4.4$ Hz)</td>
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<td>6.73 (d, 1H, 16Hz)</td>
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<td>C-5</td>
<td>78.1</td>
<td>77.9</td>
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<td>C-2</td>
<td>121.9</td>
<td>121.5</td>
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<td>C-6</td>
<td>125.8</td>
<td>125.6</td>
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<tr>
<td>C-7</td>
<td>133.3</td>
<td>133.1</td>
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<td>C-3</td>
<td>144.8</td>
<td>144.7</td>
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<tr>
<td>Aromatic CH and Cq</td>
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<td>133.3 and 136.0</td>
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<tr>
<td>C-1</td>
<td>164.1</td>
<td>163.9</td>
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</table>

M.p. = 82-83°C; lit. 81-82°C$^{440}$ or 85°C.$^{441}$

IR (KBr) $\nu$ (cm$^{-1}$): 3056 (m), 3026 (m), 2928 (m), 1722 (s, C=O), 1609 (m), 1249 (m), 813 (m), 701 (m).

MS (APCI), $m/z$ (%): 201.0 (39) [M$^+$H], 183.1 (100), 155.2 (66), 130.1 (41).

$^{440}$ de Fátima, A.; Pilli, R. A. ARKIVOC 2003, 10, 118.

[α]_{20}^{D} = +169.8° (c 1.45, CHCl₃); lit. \cite{441} [α]_{25}^{D} = +170.3° (c 1.38, CHCl₃).

CAS number: [17303-67-2].

(R)-(+)–Kavain

Starting from 0.67 mmol of alcohol. Oxidation of alcohol, see chapter 10.2.4 method B. Aldehyde used immediately in the next step. Purified by column chromatography (φ 3.5 cm, 9.5 cm of SiO₂, 10 mL fractions, P.E.:EtAc = 2:1) to give 100 mg (65%, E/Z = >95:1) of colourless crystals.

TLC (1:1 = P.E.:EtAc)

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<th>H-NMR</th>
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<th>Natural (300 MHz)</th>
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<tr>
<td>H-4</td>
<td>2.53 (dd, 1H, (^{2} J_{4,4'} = 17.1) Hz, (^{3} J_{4,5} = 4.6) Hz)</td>
<td>2.55 (dd, 1H, (J = 17.1) Hz)</td>
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<td>2.68 (dd, 1H, (^{2} J_{4',4} = 17.1) Hz)</td>
<td>2.67 (dd, 1H, (J = 17.1) Hz)</td>
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<td>H-4'</td>
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Chapter 10. Experimental part

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<th>Synthetic (75 MHz) [ppm]</th>
<th>Natural (75 MHz) [ppm]</th>
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<td>H-8</td>
<td>3.77 (s, 3H)</td>
<td>3.77 (s, 3H)</td>
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<tr>
<td>H-5</td>
<td>5.03-5.11 (m, 1H)</td>
<td>5.02-5.11 (m, 1H)</td>
</tr>
<tr>
<td>H-2</td>
<td>5.21 (s, 1H)</td>
<td>5.20 (s, 1H)</td>
</tr>
<tr>
<td>H-6</td>
<td>6.29 (dd, 1H, $J_{6,7} = 16.1$ Hz, $J_{6,5} = 6.3$ Hz)</td>
<td>6.26 (dd, 1H, $J = 16.0$ and $6.2$ Hz)</td>
</tr>
<tr>
<td>H-7</td>
<td>6.73 (d, 1H, $J_{7,6} = 16.0$ Hz)</td>
<td>6.74 (d, 1H, 16.0 Hz)</td>
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<tr>
<td>Aromatic CH</td>
<td>7.28-7.41 (m, 5H)</td>
<td>7.27-7.40 (m, 5H)</td>
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<th>Synthetic (75 MHz) [ppm]</th>
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<td>C-3</td>
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<td>127.0, 128.8, 129.2, 136.3</td>
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<tr>
<td>Aromatic CH and Cq</td>
<td>136.3</td>
<td>127.1-136.2</td>
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<td>172.6</td>
<td>172.7</td>
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</table>

M.p. = 113-114°C; lit. 112-113°C or 105-106°C.

---

IR (KBr) \( \nu (\text{cm}^{-1}) \): 3063, 2967, 1703, 1626, 1394, 1248, 1233, 1063, 1024, 971, 747, 693.  

\([\alpha]^{20}_D = +120.3^\circ \ (c \ 1.02, \text{EtOH})\); lit. \([\alpha]^{25}_D = +124.3^\circ \ (c \ 1.00, \text{EtOH})\) or \([\alpha]^{25}_D = +105^\circ \ (c \ 1.00, \text{EtOH})\).  

CAS number: [19902-88-6].

### 10.3.2 General procedure for Julia-Lythgoe olefination

A solution of sulfone (1.0 mmol) in toluene (5 mL) was refluxed for 15 min and then evaporated to dryness (twice repeated).

**Coupling step:** A solution of sulfone (1.0 mmol) in dry THF (10 mL, 0.1 M) was cooled to –78°C and \(n\)-BuLi (1.1 mmol, 1.6 M solution in hexane) was added dropwise. The colour of the mixture changed from slightly yellow to orange. After stirring at –78°C for 30 min, the aldehyde or ketone (1.05 mmol) in dry THF (0.5 mL) was added dropwise and the mixture was stirred for additional 2 h at –78°C. Benzoyl chloride (1.5 mmol) in dry THF (0.5 mL) was then added, the resulting mixture was stirred for 30 min at –78°C and then allowed to warm to r.t. over 1 h. After additional 30 min at r.t., \(\text{Me}_2\text{N(CH}_2\text{)}_3\text{OH} \) (1.55 mmol) was added and the resulting suspension was stirred for 10 min at r.t. The suspension was then diluted with Et\(_2\)O:H\(_2\)O = 1:1 (10 mL) and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (3x10 mL) and the combined organic layers were washed with 1.0
Chapter 10. Experimental part

M aqueous solution of HCl (10 mL), H₂O (10 mL) and brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure to give the crude product, which was used without additional purification in the subsequent step.

Reductive elimination: To a solution of SmI₂ (35 mL, 0.1 M in THF, 3.5 eq), HMPA (613 μL, 3.5 eq) was added and the mixture was cooled to −78°C. The crude coupled product (1.0 mmol) in dry THF (0.5 mL) was added dropwise and the resulting mixture was stirred at −78°C for 30 min. Then, aqueous solution of NH₄Cl (20 mL) was added and the whole mixture was allowed to warm to r.t. The layers were separated and the aqueous phase was extracted with Et₂O (3x20 mL). The pooled organic layers were washed with 10% aqueous solution of Na₂S₂O₃ (20 mL), H₂O (20 mL), brine (20 mL), dried over MgSO₄ and evaporated under the reduced pressure. The crude product was purified by chromatography on silicagel.

\[
\text{(3E,5R,6E)-7-[(2R,6R)-6-Ethyl-5-methyl-3,6-dihydro-2H-2-pyranyl]-5-methyl-3,6-octadien-1-ynyl(trimethyl)silane}
\]

Starting from 52 μmol of sulfone. Purified by CC (φ 1.0 cm, 9 cm of SiO₂, P.E.:Et₂O = 10:1) to give 4.8 mg (29%) of colourless oil.
Chapter 10. Experimental part

TLC (10:1 = P.E.:Et₂O)

IR (NaCl, neat): 3064, 2958, 2862, 2146, 1654, 1608, 1495, 1457.

\(^1\)H NMR (300 MHz, CDCl₃): 0.19 (s, 9H, H-1), 0.90 (t, 3H, \(^3\)J\(_{15,14}\) = 7.7 Hz, H-15), 1.09 (d, 3H, \(^3\)J\(_{16,6}\) = 6.7 Hz, H-16), 1.55 (q, 1H, \(^3\)J\(_{14,15}\) = 7.2 Hz, H-14), 1.60 (broad s, 3H, H-18), 1.65 (broad s, 3H, H-17), 1.73-1.82 (m, 1H, H-14'), 1.82-1.92 (m, 1H, H-10), 2.06-2.15 (m, 1H, H-10'), 3.13-3.22 (m, 1H, H-6), 3.86 (dd, 1H, \(^3\)J\(_{9,10}\) = 10.5 Hz, \(^3\)J\(_{9,10'}\) = 2.7 Hz, H-9), 4.09 (broad s, 1H, H-13), 5.23 (d, 1H, \(^3\)J\(_{7,6}\) = 9.0 Hz, H-7), 5.46 (dd, 1H, \(^3\)J\(_{4,5}\) = 15.9 Hz, \(^4\)J\(_{4,6}\) = 1.5 Hz, H-4), 5.57 (broad d, 1H, \(^3\)J\(_{11,10}\) = 5.7 Hz, H-11), 6.16 (dd, 1H, \(^3\)J\(_{5,4}\) = 16.2 Hz, \(^3\)J\(_{5,6}\) = 6.6 Hz, H-5).

\(^13\)C NMR (125 MHz, CDCl₃) \(\delta\) (ppm): 0.1 (C-1), 8.3 (C-15), 12.5 (C-17), 19.0 (C-18), 20.3 (C-16), 25.7 (C-14), 30.2 (C-10), 35.5 (C-6), 77.7 (C-9), 77.8 (C-13), 93.2 (C-2), 104.2 (C-3), 107.5 (C-4), 120.7 (C-11), 127.2 (C-7), 135.0 (C-12), 136.7 (C-8), 149.5 (C-5).

MS (CI, CH₄/N₂O), \(m/z\) (%): 316.4 (25) [M⁺], 301.3 (100), 191 (25), 113 (47), 96 (65).

[\(\alpha\)]\(^{20}\)_D: +84.5° (c = 1.02, CHCl₃).

HRMS, \(m/z\): calcd. (C\(_{20}\)H\(_{32}\)OSiNa) 339.2120; found 339.2124.
Chapter 10. Experimental part

\[(2R,6R)-2-[E]-1,3-Dimethyl-1-butenyl]-6-ethyl-5-methyl-3,6-dihydro-2H-pyran\]

\[
\begin{array}{c}
\text{SO}_2\text{Ph} \quad + \quad \text{C}_9\text{H}_8\text{O}_2\text{S} \\
\text{C}_{10}\text{H}_{14}\text{O}_2\text{S} \quad \text{Mol. Wt.: 198.28} \\
\end{array}
\]

Starting from 88 μmol of sulfone. Purified by CC (φ 1.5 cm, 12 cm of SiO₂, P.E.:Et₂O = 10:1→5:1→2:1) to give 6.3 mg (34%) of colourless oil.

TLC (20:1 = P.E.:Et₂O)

IR (NaCl, neat): 3061, 2958, 2862, 1604, 1495, 1452.

\(^1\)H NMR (300 MHz, CDCl₃): 0.86-0.98 (m, 9H, H-1, H-1' and H-11), 1.53 (1H, q, \[^3\]J_{10,11} = 7.2 Hz, H-10), 1.60 (s, 3H, H-12), 1.66 (s, 3H, H-13), 1.78 (ddd, 1H, \[^2\]J_{10',10} = 14.4 Hz, \[^3\]J_{10',11} = 7.2 Hz, \[^3\]J_{10',9} = 3.8 Hz, H-10'), 1.86 (broad d, \[^2\]J_{6,6'} = 13.5 Hz, H-6), 2.13 (broad dd, \[^3\]J_{6,6'} = 16.5 Hz, \[^3\]J_{6',4} = 16.5 Hz, H-6'), 2.54 (appear to be dq, \[^3\]J_{2,3} = 9.0 Hz, \[^3\]J_{2,1} = 6.6 Hz, H-2), 3.81 (dd, 1H, \[^3\]J_{5,6'} = 10.5 Hz, J = 2.9 Hz, H-5), 5.57 (d, 1H, \[^3\]J_{7,6'} = 6.2 Hz, H-7).

\(^{13}\)C NMR (125 MHz, CDCl₃) δ(ppm): 8.5 (C-11), 12.4 (C-13), 19.2 (C-12), 23.2 (C-1), 25.9 (C-10), 26.9 (C-2), 30.3 (C-6), 78.1 and 78.1 (C-2 and C-6), 121.2 (C-7), 133.1 (C-3), 133.8 and 135.3 (C-8 and C-4).
MS (Cl, CH₄/N₂O), m/z (%): 209.1 (37) [M⁺+1], 207.2 (45), 191 (100), 113 (54), 96 (71).

ε²₀D: +106.32° (c = 0.99, CHCl₃).

HRMS, m/z: calcd. (C₁₄H₂₄ONa) 231.1725; found 231.1718.

10.3.3 General procedure for Kociensky-Julia olefination

Method A: Using KHMDS/THF system

A solution of sulfone (1.0 mmol, 1.0 eq) and aldehyde (1.1 mmol, 1.1 eq) in THF (10 mL, 0.1 M) was cooled to -78°C and KHMDS (1.2 mmol, 0.5 M solution in toluene, 1.2 eq) was added dropwise. The resulting mixture was stirred at -78°C for 30 min and then was allowed to warm to r.t over 1.5h. After additional 30 min, saturated aqueous solution of NH₄Cl (10 mL) was added. Layers were separated and aqueous layer was extracted with Et₂O (3x10 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method B: Using LiHMDS/toluene system

A solution of sulfone (1.0 mmol, 1.0 eq) and aldehyde (1.1 mmol, 1.1 eq) in toluene (10 mL, 0.1 M) was cooled to -70°C and LiHMDS (1.2 mmol, 1.0 M solution in hexane, 1.2 eq) was added dropwise. The resulting mixture was stirred at -70°C for 30 min and then was allowed to warm to r.t over 1.5h. After additional 30 min, saturated aqueous solution of NH₄Cl (10 mL) was added. Layers were separated and aqueous layer was extracted with Et₂O (3x10 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.
Chapter 10. Experimental part

(2S,3E)-2-Methyl-4-phenyl-3-butenyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulphide

Method A: Starting from 0.07 mmol of sulphide. Purified by CC (ϕ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; P.E.:Et₂O = 5:1) to give 21.4 mg (95%, E/Z = >95:1, 98:1 based on ¹³C spectra) of yellow oil.

Method B: Starting from 0.07 mmol of sulphide. Purified by CC (ϕ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; P.E.:Et₂O = 5:1) to give 7.7 mg (34%, E/Z = 54:46) of colourless crystals.

TLC (EP:Et₂O = 2:1)

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3062, 3032, 2987, 2963, 2925, 1642, 1581, 1492, 1447, 1382, 1023, 693.

¹H-NMR (500 MHz, CDCl₃) δ(ppm): 1.34 (d, 3H, ³J₆,₃ = 6.9 Hz, H-6), 2.80 (heptet, 1H, J = 6.9 Hz, H-3), 3.41 (m, 2H, H-4), 5.92 (dd, 1H, ³J₂,₁ = 15.6 Hz, ¹J₂,₃ = 5.4 Hz, H-2), 6.41 (d, 1H, ¹J₁,₂ = 15.6 Hz, H-1), 7.21-7.49 (m, 5H, aromatic CH).

¹³C-NMR (125 MHz, CDCl₃) δ(ppm): 20.7 (C-6), 32.4 (C-3), 42.6 (C-4), 125.4-146.1 (aromatic CH and Cq, C-1, C-2 and C-5).
MS (Cl, CH,N2O), m/z (%): 323.6 [M+] (100), 324.5 [M+1] (45), 325.2 (19).

[α]20D: -11.6°(c = 2.90, CHCl3).

HRMS, m/z: calcd. (C18H18N4SNa) 345.1150; found 345.1155.

(2S,3E,5E)-2-Methyl-6-phenyl-3,5-hexadienyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulphide

Method A: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO2, 7 mL fractions; P.E.:Et2O = 5:1) to give 19.8 mg (81%, E/Z = >95:1, 99:1 based on 13C spectra) of colourless crystals.

Method B: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO2, 7 mL fractions; P.E.:Et2O = 5:1) to give 13.9 mg (57%, E/Z = 57:43) of colourless crystals.

TLC (EP:Et2O = 2:1)

IR (NaCl, neat) ν̈(cm−1): 3060, 3032, 3028, 2989, 2987, 2961, 2925, 1640, 1583, 1491, 1452, 1374, 1013, 692.
Chapter 10. Experimental part

**(E) olefin**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$(ppm): 1.23 (d, 3H, $^3J_{8,5} = 6.8$ Hz, H-8$^{\text{trans}}$), 2.80 (m, 1H, H-5); 3.46 (m, 2H, H-6), 5.72 (dd, 1H, $^3J_{4,3} = 15.2$ Hz, $^3J_{4,5} = 7.9$ Hz, H-4$^{\text{trans}}$), 6.27 (dd, 1H, $^3J_{3,4} = 15.2$ Hz, $^3J_{3,2} = 10.4$ Hz, H-3$^{\text{trans}}$), 6.50 (d, 1H, $^3J_{1,2} = 15.7$ Hz, H-1$^{\text{trans}}$), 6.73 (dd, 1H, $^3J_{2,1} = 15.8$ Hz, $^3J_{2,3} = 10.4$ Hz, H-2$^{\text{trans}}$), 7.22-7.61 (m, 10H, aromatic CH).

$^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$(ppm): 20.0 (C-8), 37.0 (C-6), 38.2 (C-5$^{\text{cis}}$), 124.1-142.3 (aromatic CH and Cq, C-1 to C-4 and C-7).

**(Z) olefin**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$(ppm): 1.30 (d, 3H, $^3J_{8,5} = 6.8$ Hz, H-8$^{\text{cis}}$), 2.80 (m, 1H, H-5); 3.46 (m, 2H, H-6), 6.07 (dd, 1H, $^3J_{4,5} = 7.5$ Hz, $^3J_{4,3} = 6.0$ Hz, H-4$^{\text{cis}}$), 6.12 (dd, 1H, $^3J_{2,1} = 15.8$ Hz, $^3J_{2,3} = 7.9$ Hz, H-2$^{\text{cis}}$), 6.36 (d, 1H, $^3J_{3,4} = 6.2$ Hz, H-3$^{\text{cis}}$), 6.43 (d, 1H, $^3J_{1,2} = 15.8$ Hz, H-1$^{\text{cis}}$), 7.22-7.61 (m, 10H, aromatic CH).

$^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$(ppm): 20.0 (C-8), 37.0 (C-6), 38.2 (C-5$^{\text{cis}}$), 124.1-142.3 (aromatic CH and Cq, C-1 to C-4 and C-7).

MS (APCI), $m/z$ (%): 349.0 [M$^+$+1] (100), 350.0 (18), 351.0 (4), 171.17 (57), 129.2 (16), 91.1 (14).

[$\alpha$]$^\text{D}_20$: -11.2°(c = 0.25, CHCl$_3$).

HRMS, $m/z$: calcd. (C$_{20}$H$_{22}$N$_4$SNa) 371.1306; found 371.1297.

**(2S,3E)-2-Methyl-6-phenyl-3-hexenyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulphide**

![](image.png)

Mol. Wt.: 442.52

![image.png](image.png)

Mol. Wt.: 350.48
Chapter 10. Experimental part

Method A: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; P.E.:Et₂O = 5:1) to give 22.8 mg (93%, E/Z = 83:17) of colourless crystals.

Method B: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; P.E.:Et₂O = 5:1) to give 5.4 mg (22%, E/Z = 69:31) of colourless crystals.

TLC (EP:Et₂O = 2:1)

\[ R_f = 0.31 \quad R_f = 0.53 \]

UV, KMnO₄, olefin

UV, KMnO₄, aldehyde

IR (NaCl, neat) \( \nu^{-1}(\text{cm}^{-1}) \): 3063, 3031, 2982, 2960, 2923, 1641, 1584, 1492, 1449, 1373, 1011, 693.

(E) olefin

\(^1\)H-NMR (500 MHz, CDCl₃) \( \delta \) (ppm): 1.13 (d, 3H, \(^3\)J₈,₅ = 6.8 Hz, H-8\(^\text{trans}\)), 2.63-2.78 (m, 7H, H-1, H-2, H-5 and H-6), 5.35 (dd, 1H, \(^3\)J₄,₃ = 15.3 Hz, \(^3\)J₄,₅ = 7.6 Hz, H-4\(^\text{trans}\)), 5.54 (dt, 1H, \(^3\)J₃,₄ = 15.4 Hz, \(^3\)J₃,₂ = 6.8 Hz, H-3\(^\text{trans}\)), 7.12-7.58 (m, 10H, aromatic CH).

\(^1\)C-NMR (125 MHz, CDCl₃) \( \delta \) (ppm): 22.6 (C-8\(^\text{trans}\)), 29.9 (C-2\(^\text{trans}\)), 36.0 (C-6\(^\text{trans}\)), 36.7 (C-1), 40.3 (C-5), 126.0-147.5 (aromatic CH and Cq, C-3, C-4 and C-7).

(Z) olefin

\(^1\)H-NMR (500 MHz, CDCl₃) \( \delta \) (ppm): 0.99 (d, 3H, \(^3\)J₈,₅ = 6.7 Hz, H-8\(^\text{cis}\)), 2.63-2.78 (m, 7H, H-1, H-2, H-5 and H-6), 5.02 (t, 1H, \(^3\)J = 5.2 Hz, H-
Chapter 10. Experimental part

4<sup>cis</sup>, 5.19 (ddd, 1H, <sup>3</sup>J<sub>3,2</sub> = 10.1 Hz, <sup>3</sup>J<sub>3,2'</sub> = 6.1 Hz, <sup>3</sup>J<sub>3,4</sub> = 5.2 Hz, H-3<sup>cis</sup>), 7.12-7.58 (m, 10H, aromatic CH).

<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ (ppm): 20.2 (C-2<sup>cis</sup>), 22.8 (C-8<sup>cis</sup>), 34.5 (C-6<sup>cis</sup>), 36.7 (C-1), 40.3 (C-5), 126.0-147.5 (aromatic CH and Cq, C-3, C-4 and C-7).

MS (APCI), <em>m/z</em> (%): 351.0 [M<sup>+1</sup>] (100), 352.0 (54), 353.0 (22), 323 (22), 282.2 (19), 249.1 (14).

<sup>[α]</sup><sub>D</sub>: −8.3°(<em>c</em> = 0.29, CHCl<sub>3</sub>).

HRMS, <em>m/z</em>: calcd. (C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>S<sub>Na</sub>) 373.1463; found 373.1459.

(2S,3E)-2-Methyl-3-heptenyl (1-phenyl-1H-1,2,3,4-tetraazol-5-yl) sulphide

Method A: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO<sub>2</sub>, 7 mL fractions; P.E.:Et<sub>2</sub>O = 5:1) to give 15.7 mg (78%, <i>E</i>/<i>Z</i> = 82:18) of colourless crystals.

Method B: Starting from 0.07 mmol of sulphide. Purified by CC (φ 1.5 cm, 11 cm of SiO<sub>2</sub>, 7 mL fractions; P.E.:Et<sub>2</sub>O = 5:1) to give 4.2 mg (21%, <i>E</i>/<i>Z</i> = 73:28) of colourless soil.
Chapter 10. Experimental part

TLC (EP:Et₂O = 2:1)

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3061, 2989, 2963, 1640, 1581, 1492, 1453, 1371, 1111, 692.

(E) olefin

¹H-NMR (500 MHz, CDCl₃) δ (ppm): 0.87 (t, 3H, 3J₁,₂ = 6.7 Hz, H-1), 1.15 (d, 3H, 3J₈,₅ = 6.7 Hz, H-9trans), 1.35 (m, 2H, H-2), 1.95 (m, 2H, H-3trans), 2.61 (heptet, 1H, 3J = 6.7Hz, H-5); 3.35-3.43 (m, 2H, H-1, H-7), 5.33 (dd, 1H, 3J₄₅ = 15.3 Hz, 3J₅₆ = 7.7 Hz, 4J₃₅ = 6.7 Hz, H-5trans), 5.33 (dd, 1H, 3J₄₅ = 15.3 Hz, 3J₃₅ = 6.7 Hz, 4J₄₆ = 0.6 Hz, H-4trans), 7.51-7.60 (m, 5H, aromatic CH).

¹³C-NMR (125 MHz, CDCl₃) δ(ppm): 13.8 (C-1), 20.2 (C-9trans), 22.6 (C-2), 34.7 (C-3trans), 36.8 (C-7trans), 40.4 (C-6), 119.4-142.1 (aromatic CH and Cq, C-4, C-5 and C-8).

(Z) olefin

¹H-NMR (500 MHz, CDCl₃) δ (ppm): 0.87 (t, 3H, 3J₁,₂ = 6.7 Hz, H-1), 1.01 (d, 3H, 3J₈,₅ = 6.8 Hz, H-9cis), 1.35 (m, 2H, H-2), 1.72 (m, 2H, H-3cis), 2.61 (heptet, 1H, 3J = 6.7Hz, H-5); 3.35-3.43 (m, 2H, H-1, H-7), 5.02 (t, 1H, 3J = 5.1 Hz, H-5cis), 5.19 (dd, 1H, 3J₄₅ = 10.8 Hz, 3J₄₃ = 5.9 Hz, 3J₃₅ = 4.6 Hz, H-4cis), 7.51-7.60 (m, 5H, aromatic CH).
Chapter 10. Experimental part

$^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$(ppm): 13.8 (C-1), 19.0 (C-9$^{cis}$), 22.6 (C-2), 31.3 (C-3$^{cis}$), 32.1 (C-7$^{cis}$), 40.4 (C-6), 119.4-142.1 (aromatic CH and Cq, C-4, C-5 and C-8).

MS (APCI), $m/z$: 289.1 [M$^+$+1] (100), 290.1 (19), 291.1 (5).

[$\alpha$]$^D_{20}$: -6.5°($c = 0.31$, CHCl$_3$).

HRMS, $m/z$: calcd. (C$_{15}$H$_{20}$N$_4$SNa) 311.1306; found 311.1312.

(1$^E$,3$^E$,5$^R$,6$^E$)-5-Methyl-1,7-diphenyl-1,3,6-heptatriene

Method A: Starting from 0.17 mmol of sulphide. Purified by CC ($\phi$ 1.5 cm, 9 cm of SiO$_2$, 7 mL fractions; P.E.:Et$_2$O = 10:1) to give 41.6 mg (94%, E/Z = 86:14) of slightly yellow oil.

TLC (EP:Et$_2$O = 3:1)

IR (NaCl, neat) $\nu$-1(cm$^{-1}$): 3082, 3063, 3031, 3022, 2989, 2963, 1641, 1585, 1492, 1455, 1372, 1067, 697.

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 1.18 (d, 3H, $^3J_{8,5} = 6.0$ Hz, H-8$^{cis}$), 1.27 (d, 3H, $^3J_{8,5} = 6.9$ Hz, H-8$^{trans}$), 3.16 (sextet, 1H, $^3J = 6.9$ Hz, H-5$^{cis}$), 3.65 (sextet, 1H, $^3J = 9.2$ Hz, H-5$^{trans}$), 5.45 (t, 1H, $^3J = 10.1$ Hz, H-4$^{cis}$), 5.87 (dd, 1H, $^3J_{6,7} = 15.2$ Hz, $^3J_{6,5} = 6.9$ Hz, H-6$^{trans}$), 6.21 (dd, 1H,
3J_{4,3} = 16.0 Hz, 3J_{4,5} = 6.9 Hz, H-4^{\text{trans}}, 6.28 (dd, 1H, 3J_{3,4} = 15.1 Hz, 3J_{3,2} = 10.6 Hz, H-2^{\text{trans}}), 6.42 (d, 1H, 3J_{7,6} = 15.6 Hz, H-7^{\text{trans}}), 6.51 (d, 1H, 3J_{1,2} = 15.6 Hz, H-1^{\text{trans}}), 6.81 (dd, 1H, 3J_{2,1} = 15.6 Hz, 3J_{2,3} = 10.6 Hz, H-2^{\text{trans}}), 7.21-7.45 (m, 10H, aromatic CH).

13C-NMR (125 MHz, CDCl3) δ (ppm): 20.4 (C-8^{\text{trans}}), 21.2 (C-8^{\text{cis}}), 40.1 (C-5^{\text{trans}}), 41.2 (C-5^{\text{cis}}), 126.3-139.0 (aromatic CH and Cq, C-1 to C-4 and C-6 and C-7).

MS (APCI), m/z (%): 259.2 [M^-1] (100), 260.2 [M^-] (26), 261.2 [M^+1] (56), 219.3 (39), 180.9 (37), 157.2 (57).

[α]_{20}^D: +10.2°(c = 0.58, CHCl3).

HRMS, m/z: calcd. (C15H20N4SNa) 283.1463; found 283.1470.

(1E,3E,5S,6E)-5-Methyl-1,7-diphenyl-1,3,6-heptatriene

**Method A:** Starting from 0.11 mmol of sulphide. Purified by CC (ϕ 1.5 cm, 9 cm of SiO2, 7 mL fractions; P.E.:Et2O = 20:1) to give 26.1 mg (91%, E/Z = 85:15) of slightly yellow oil.

TLC (EP:Et2O = 3:1)
Chapter 10. Experimental part

IR (NaCl, neat) $\nu$ (cm$^{-1}$): 3082, 3063, 3031, 3022, 2989, 2963, 1641, 1585, 1492, 1455, 1372, 1067, 697.

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 1.27 (d, 3H, $^3J_{8,5} = 6.9$ Hz, H-8), 3.16 (sextet, 1H, $^3J_{5} = 6.9$ Hz, H-5), 5.87 (dd, 1H, $^3J_{6,7} = 15.2$ Hz, $^3J_{6,5} = 6.9$ Hz, H-6), 6.21 (dd, 1H, $^3J_{4,3} = 16.0$ Hz, $^3J_{4,5} = 6.9$ Hz, H-4), 6.28 (dd, 1H, $^3J_{3,4} = 15.1$ Hz, $^3J_{3,2} = 10.6$ Hz, H-3), 6.42 (d, 1H, $^3J_{7,6} = 15.6$ Hz, H-7), 6.51 (d, 1H, $^3J_{1,2} = 15.6$ Hz, H-1), 6.81 (dd, 1H, $^3J_{2,1} = 15.6$ Hz, $^3J_{2,3} = 10.6$ Hz, H-2), 7.21-7.43 (m, 10H, aromatic CH).

$^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ (ppm): 20.4 (C-8$_{trans}$), 21.2 (C-8$_{cis}$), 40.1 (C-5$_{trans}$), 41.2 (C-5$_{cis}$), 126.3-139.0 (aromatic CH and C$_q$, C-1 to C-4 and C-6 and C-7).

MS (APCI), $m/z$ (%): 259.2 [M+-1] (100), 260.2 [M$^+$] (28), 261.2 [M$^{++}$+1] (54), 193.4 (42), 180.9 (38), 157.2 (55).

$[\alpha]_{D}^{20}$: $-9.1^\circ$ (c = 0.51, CHCl$_3$).

Methyl (E)-7-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-5-heptenoate

\[ \text{O} \text{CO}_2\text{Me} \longrightarrow \text{TBSO} \text{CO}_2\text{Me} \]

\[ \text{C}_6\text{H}_{10}\text{O}_3 \quad \text{Mol. Wt.: 130.14} \]

\[ \text{C}_{14}\text{H}_{28}\text{O}_3\text{Si} \quad \text{Mol. Wt.: 272.46} \]

Method A: Starting from 0.1 mmol of sulfone. Purification by CC ($\phi$1.5 cm, 10 cm of SiO$_2$, 5 mL fractions; 9:1 = P.E.:Et$_2$O) yielded 20.1 mg (75%, E/Z = 20:1) of colourless oil.

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Chapter 10. Experimental part

TLC (9:1 = P.E.:Et₂O)

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 2952, 2929, 2855, 1741, 1456, 1438.

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 0.07 (s, 6H, H-8), 0.91 (s, 9H, H-10), 1.7-1.75 (m, 2H, H-3), 2.04-2.09 (m, 2H, H-4), 2.32 (t, 2H, J₂,₃ = 7.5 Hz, H-2), 3.67 (s, 3H, H-11), 4.11-4.22 (m, 2H, H-7), 5.52-5.57 (m, 2H, H-5 and H-6).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): -2.6 (C-8), 18.2 (C-9), 23.7 (C-3), 25.3 (C-10), 26.9 (C-5), 31.2 (C-2), 52.3 (C-11), 62.7 (C-7), 131.7 (C-6), 136.8 (C-6), 172.8 (C-1).

MS (APCI), m/z (%): 272.8 [M⁺] (64), 140.9 (100), 109.0 (19), 80.9 (51).

HRMS, m/z: calcd. (C₁₄H₂₈O₃SiNa) 295.1705; found 295.1698.

(4R,5R)-2-[(1E)-1,3-Butadienyl]-4,5-di[3methoxy(diphenyl)methyl]-1,3,2- dioxaborolane

Method A: Starting from 0.11 mmol of sulfone. Purification by CC (φ1.5 cm, 10 cm of SiO₂, 5 mL fractions; 10:1 = P.E.:Et₂O) yielded 48.9 mg (86%) of colourless foam.
Chapter 10. Experimental part

TLC (5:1 = P.E.:Et₂O)

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3069, 2952, 2929, 1648, 1438.

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) δ (ppm): 2.99 (s, 6H, H-7), 5.11-5.23 (m, 3H, H-4 and H-1), 6.21 (dt, 1H, \(^3\)\(J_{3,4}\) = 17.0 Hz, \(^3\)\(J\) = 9.9 Hz, H-3), 6.56 (dd, 1H, \(^3\)\(J_{2,1}\) = 17.4 Hz, \(^3\)\(J_{2,3}\) = 7.1 Hz, H-2), 7.24-7.37 (m, 20H, aromatic CH).

\(^13\)C-NMR (62.5 MHz, CDCl\(_3\)) δ (ppm): 53.7 (C-7), 78.2 (C-5), 83.4 (C-6), 104.2 (C-1), 115.4 (C-4), 127.3-144.2 (C-2, C-3 and aromatic CH and C\(_q\)).

Elem. Anal. (C\(_{34}\)H\(_{33}\)BO\(_4\)): calcd. C, 79.07, H, 6.44; found: C, 79.15; H, 6.40. \([\alpha]\)\(^{20}\)\(^D\) = -83.4°(c = 0.92, CHCl\(_3\)).
Chapter 10. Experimental part

Jerangolid D

Starting from 8.9 μmol of sulfone. Oxidation of alcohol (1.2 eq, 10.2 μmol), see chapter 10.2.4 method B. Aldehyde used immediately in the next step. Purified by preparative TLC (SiO₂, P.E.:Et₂O = 10:1) to give 0.9 mg (28%, E/Z >95:1) of colourless crystals.

Starting from 8.9 μmol of sulfone. Oxidation of alcohol (1.2 eq, 10.2 μmol), see chapter 10.2.4 method B. Aldehyde used immediately in the next step. Purified by preparative TLC (SiO₂, P.E.:Et₂O = 10:1) to give 0.9 mg (28%, E/Z >95:1) of colourless crystals.

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1H-NMR

Intensity

Natural (400 MHz, CD₃OD)

[ppm]

[ppm]

---

### Chapter 10. Experimental part

| H-17 | 3H | 0.90 (td, \( J = 7.3 \) Hz and 3.7 Hz) | 0.94 (dd, \( J = 7.3 \) Hz and 7.4 Hz) |
| H-20 | 3H | 1.18 (d, \( J = 6.7 \) Hz) | 1.14 (d, \( J = 6.8 \) Hz) |
| H-16 | 1H | 1.56 (m) | 1.58 (m) |
| H-22 | 3H | 1.60 (broad m) | 1.64 (m) |
| H-21 | 3H | 1.63 (broad d, \( J = 1.2 \) Hz) | 1.64 (d, \( J = 1.1 \) Hz) |
| H-18 | 3H | 1.79 (broad d, \( J = 0.9 \) Hz) | 1.75 (broad s) |
| H-16' | 1H | 1.80 (m) | 1.81 (m) |
| H-12 | 1H | 1.83 (m) | 1.95 (m) |
| H-12' | 1H | 1.99 (m) | 2.14 (m) |
| H-4 | 1H | 2.54 (dd, \( J = 17.0 \) Hz and 4.0 Hz) | 2.88 (ddd, \( J = 17.3 \) Hz, 4.0 Hz and 0.7 Hz) |
| H-4' | 1H | 2.81 (ddq, \( J = 17.0 \) Hz, 12.3 Hz and 2.0 Hz) | 2.67 (ddq, \( J = 17.4 \) Hz, 11.4 Hz and 2.0 Hz) |
| H-8 | 1H | 3.28 (m) | 3.23 (m) |
| H-11 | 1H | 3.72 (dd, \( J = 10.4 \) Hz and 2.8 Hz) | 3.88 (dd, \( J = 10.3 \) and 3.2 Hz) |
| H-19 | 3H | 3.82 (s) | 3.88 (s) |
| H-15 | 1H | 4.08 (broad s) | 4.13 (broad s) |
| H-5 | 1H | 4.89 (m) | 4.85 (m) |
| H-9 | 1H | 5.20 (dq, \( J = 9.5 \) Hz and 1.1 Hz) | 5.33 (ddq, \( J = 9.1 \) Hz, 1.2 Hz and 1.1 Hz) |
Chapter 10. Experimental part

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10.3.4 General procedure for Wittig reaction

*General method:* To a colourless suspension of phosphonium salt (1.2 mmol, 1.2 eq) in THF (4 mL, 0.2M), nBuLi (1.21 mmol, 1.63 M in hexane, 1.21 eq) was added at -78°C within 30 sec and the resulting brown mixture was stirred for 30 min at -78°C. Aldehyde (1.0 mmol, 1.0 eq) in THF (1.0 mL) was added and the whole reaction mixture was stored in the freezer at -20°C for 19h. Saturated aqueous NH₄Cl (10 mL) was added. The aqueous layer was separated and extracted with Et₂O (3x10 mL). Combined organic layers were washed with H₂O (5 mL), brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

(2R,3E)-2-Methyl-6-(1,1,1-trimethylsilyl)-3-hexen-5-ynyl phenyl sulphide

\[
\begin{align*}
\text{O} & \quad \text{SPh} \\
\text{C}_{10}\text{H}_{12}\text{OS} & \quad \text{Mol. Wt.: 180.27} \\
\end{align*}
\]

\[
\begin{align*}
\text{TMS} & \quad \text{Br} \\
\text{PPh₃} & \quad \text{n-BuLi, THF, -20°C} \\
\end{align*}
\]
Starting from 0.99 mmol of aldehyde. Purified by CC (φ 1.5 cm, 11 cm of SiO₂, 10 mL fractions; P.E.:Et₂O = 20:1) to give 198 mg (72%) of yellow oil (E/Z = 6:1).

TLC (EP:Et₂O = 5:1)

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3062, 2978, 2961, 2925, 2724, 1641, 1584, 1492, 1452, 1375, 1013, 692.

¹H-NMR (300 MHz, CDCl₃) δ(ppm): 0.17 (s, 9H, H-1(Z)), 0.20 (s, 9H, H-1); 1.14 (d, 3H, J₁₂,₆ = 6.7 Hz, H-12), 2.48 (heptet, 1H, J = 7.2 Hz, H-6), 2.83 (dd, 1H, J₇',₇ = 12.9, J₇,₆ = 7.2 Hz, H-7), 2.95 (dd, 1H, J₇,₇ = 12.9, J₇',₆ = 6.7 Hz, H-7'), 5.52 (d, 1H, J₄,₅ = 10.5 Hz, H-4(Z)), 5.55 (dd, 1H, J₄,₅ = 15.8, J₄,₆ = 1.0 Hz, H-4), 5.80 (dd, 1H, J₅,₄ = 10.5, J₅,₆ = 9.6 Hz, H-5(Z)), 6.17 (dd, 1H, J₅,₄ = 15.8, J₅,₆ = 7.6 Hz, H-5), 7.15-7.34 (m, 5H, H-9-11).

¹³C-NMR (62.5 MHz, CDCl₃) δ(ppm): 0.02 (C-1), 19.2 (C-12), 37.0 (C-6), 40.1 (C-7), 93.8 (C-2), 103.5 (C-3), 109.6 (C-4), 125.7-136.2 (aromatic CH and Cq), 149.0 (C-5).

MS (CI, CH₄/N₂O), m/z (%): 276.2 [M⁺+2] (13), 274.9 [M⁺+1] (24), 259.1 (100).

[α]²⁰D: +74.2°(c = 1.1, CHCl₃).

E.A. calc for C 70.01%, H 8.08%; found C 69.98%, H 7.92%.
Chapter 10. Experimental part

### 10.3.5 General procedure for alkylation of esters

**Method A: Tebbe reagent.**

\[
\begin{align*}
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 \\
&\text{Tebbe reagent} \quad \text{THF} \\
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 
\end{align*}
\]

A solution of ester (1.0 mmol, 1.0 eq) in THF (2.0 mL, 0.5M) was cooled to -78°C and Tebbe reagent (1.2 mmol, 0.5M solution in toluene, 1.2 eq) was slowly added. After 15 min, the mixture was allowed to warm to r.t. and stirred for 1.5h. Et₂O (10 mL) was added and the resulting solution was cooled to 0°C. 1.0M aqueous solution of NaOH (10 drops) was added and resulting suspension was stirred at r.t. for 10 min. Filtration over basic alumina followed by solvents evaporation then yielded yellow oil.

**Method B: Petasis reagent.**

\[
\begin{align*}
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 \\
&\text{C}_{2}\text{TiMe}_{2} \quad \text{toluene} \\
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 
\end{align*}
\]

To Petasis reagent (3.0 mmol, 0.5 M solution in toluene, 3.0 eq), a solution of ester (1.0 mmol, 1.0 eq) in toluene (0.5 mL) was added and the resulting red solution was stirred at 65°C for 6h. Petroleum ether (25 mL) was added and the resulting mixture was filtered over basic alumina. Filter cake was washed with petroleum ether (2x10 mL) and combined filtrates were evaporated under reduced pressure.

**Method C: Takai-Utimoto reaction.**

\[
\begin{align*}
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 \\
&\text{Takai-Utimoto} \quad \text{THF} \\
&\text{R}^1\text{CH}_{2}\text{OCH}_2\text{R}^2 
\end{align*}
\]

TiCl₄ (4.0 mmol, d = 1.720 g.cm⁻³, 4.0 eq) was added to THF (3.3 mL, 0.3M) at 0°C. Resulting bright yellow suspension was stirred at 0°C for 10
min and TMEDA (8.0 mmol, d = 0.775 g.cm⁻³, 8.0 eq) was added dropwise. The mixture changed colour to orange and was stirred at 0°C for additional 20 min. Preactivated Zn dust (9.0 mmol, 9.0 eq, Zn-dust was washed sequentially with 5% aqueous HCl, H₂O, EtOH, Et₂O and then dried under high vacuum) and PbCl₂ (0.03 mmol, 3 mol%) were added in one portion. Grey-blue mixture was then stirred at r.t. for 40 min (after 40 min the colour of mixture remains deep blue). Reaction mixture was again cooled to 0°C and a solution of ester (1.0 mmol, 1.0 eq) and CH₂Br₂ (2.2 mmol, 2.2 eq) in THF (0.5 mL) was added dropwise. After 48h at r.t., the mixture was again cooled to 0°C and saturated aqueous K₂CO₃ (0.5 mL) was added. After 15 min, resulting thick suspension was poured to Et₂O (20 mL) and the resulting suspension was filtered over basic alumina. Glassware was washed with Et₂O (2x 10 mL) and organic washings were also filtered over basic alumina. Evaporation of combined organic layers afforded white precipitate which was washed with P.E. (3x10 mL). Combined organic layers were filtered over basic alumina and evaporated.

Method D: Takai-Utimoto reaction – Roush modification.

\[ \text{R}^1\text{O} + \text{R}^2\text{O} \xrightarrow{Takai-Utimoto} \text{CH}_2\text{Cl}_2 \]

A CH₂Cl₂ (100 mL, 0.01M) was cooled to 0°C and TiCl₄ (16.0 mmol, 16.0 eq) was slowly added. THF (100 mmol, d = 0.889 g.cm⁻³, 100 eq) was added over 30 min and resulting yellow solution was stirred at 0°C for additional 10 min. TMEDA (100 mmol, d = 0.775 g.cm⁻³, 100 eq) was then added dropwise over 50 min. Cooling bath was removed and after additional 30 min of stirring at r.t., Zn (36.0 mmol, 36 eq) and PbCl₂ (2.0 mmol, 2.0 eq) were added. After 1h, the mixture turned from green to blue and a solution
of ester (1.0 mmol, 1.0 eq) and CH₂Br₂ (16.0 mmol, 16 eq) in CH₂Cl₂ (2 mL) were added. The resulting mixture was refluxed for 3h and then cooled to 0°C. Saturated aqueous solution of K₂CO₃ (2 mL) was added and the resulting slurry was stirred for next 15 min at r.t and then poured into Et₂O (150 mL). Heterogeneous mixture was then filtered over basic alumina. Filter cake was washed with Et₂O (3x50 mL) and collected filtrates were evaporated under reduced pressure. Solid obtained by evaporation was washed with P.E. (4x100 mL) and then again filtered over basic alumina. Filtrates evaporation afforded the pure olefin.

\[
(3\text{-Ethoxy-1-methyl-3-butenyl}o\text{xy})(\text{trimethyl})\text{silane}
\]

\[
\text{UV, KMnO}_4, \text{olefin} \\
\text{KMnO}_4, \text{ester}
\]

**Method A**: Starting from 0.46 mmol of ester. After evaporation of the solvents, reaction yielded 50 mg (45%) of colourless oil.

**Method B**: Starting from 1.12 mmol of ester. After evaporation of the solvents, reaction yielded 67 mg (30%) of colourless oil.

**Method C**: Starting from 10.0 mmol of ester. After evaporation of the solvents, reaction yielded 1.54g (76%) of colourless oil.

TLC (4:1 = P.E.:Et₂O)

- UV
- KMnO₄, olefin
- KMnO₄, ester

IR (NaCl, neat) ν⁻¹(cm⁻¹): 2970, 2930, 1655, 1445, 1250, 840.
Chapter 10. Experimental part

$^1$H-NMR (250 MHz, CD$_2$Cl$_2$) δ (ppm): 0.10 (s, 9H, H-6), 1.15 (d, 3H, $^3$J$_{3,4}$ = 6.0 Hz, H-5), 1.29 (t, 3H, $^3$J$_{8,7}$ = 7.2 Hz, H-8), 2.13 (dd, 1H, $^2$J$_{3,3'}$ = 13.5 Hz, $^3$J$_{1,4}$ = 5.6 Hz, H-3), 2.26 (dd, 1H, $^2$J$_{3',3}$ = 13.5, $^3$J$_{3',4}$ = 7.2 Hz, H-3'), 3.68 (q, 2H, $^3$J$_{7,8}$ = 7.2 Hz, H-7), 3.87 (q, 2H, $^3$J$_{1,4}$ = 1.2 Hz, H-4), 4.04 (sextet d, 1H, $^3$J = 5.9Hz, $^4$J$_{4,1}$ = 1.2 Hz, H-4).

$^{13}$C-NMR (125 MHz, CD$_2$Cl$_2$) δ (ppm): 0.3 (C-6), 14.7 (C-8), 23.9 (C-5), 46.0 (C-3), 62.7 (C-7), 66.7 (C-4), 82.9 (C-1), 160.6 (C-2).

MS (Cl, CH$_3$/N$_2$O), m/z (%):203.2 [M$^+$+1] (5), 116.9 (14), 103.0 (100).

HRMS, m/z: calcd. (C$_{10}$H$_{22}$NO$_2$Si) 202.1389; found 202.1392.

tert-Butyl(2$^R$)-4-methoxy-2-[(1,1,1-trimethylsilyl)oxy]-4-pentenyl oxy)dimethylsilane

Method C: Starting from 0.31 mmol of ester. Reaction yielded 50 mg (51%) of colourless oil.

Method D: Starting from 0.58 mmol of ester. Reaction yielded 170 mg (92%) of colourless oil.

$^1$H-NMR (500 MHz, CD$_2$Cl$_2$) δ (ppm): 0.05 and 0.06 (s, 3H, H-6), 0.07 (s, 9H, H-9), 0.89 (s, 9H, H-8), 2.06 (dd, 1H, $^2$J$_{3,3'}$ = 13.9 Hz, $^3$J$_{3,4}$ = 8.1 Hz, H-3), 2.33 (dd, 1H, $^2$J$_{3',3}$ = 13.9 Hz, $^3$J$_{3',4}$ = 4.6 Hz, H-3'), 3.45 (dd, 1H, $^2$J$_{5,5'}$ = 10.2 Hz, $^3$J$_{5,4}$ = 5.4 Hz, H-5), 3.48 (dd, partial overlap, 1H, $^2$J$_{5,5'}$ = 10.2 Hz, $^3$J$_{5,4}$ = 5.7 Hz, H-5'), 3.50 (s, 3H, H-10), 3.89 (m, partial
Chapter 10. Experimental part

overlap, 1H, H-4), 3.88 (d, 1H, J = 1.8 Hz, H-1), 3.91 (d, 1H, J = 1.7 Hz, H-1’).

$^{13}$C-NMR (125 MHz, CD$_2$Cl$_2$) δ(ppm): -5.2 and -5.1 (C-6), 0.4 (C-9), 18.8
(C-7), 26.3 (C-8), 40.7 (C-3), 55.1 (C-10), 68.1 (C-5), 71.7 (C-4), 82.9
(C-1), 161.7 (C-2).

[$\alpha$]$^D_{20}$: +2.11°(c = 1.61, CHCl$_3$).

MS and HRMS are measured for the product of enol ether hydrolysis:

$^{13}$C-NMR (125 MHz, CD$_2$Cl$_2$) δ(ppm): -5.2 and -5.1 (C-6), 0.4 (C-9), 18.8
(C-7), 26.3 (C-8), 40.7 (C-3), 55.1 (C-10), 68.1 (C-5), 71.7 (C-4), 82.9
(C-1), 161.7 (C-2).

[$\alpha$]$^D_{20}$: +2.11°(c = 1.61, CHCl$_3$).

MS and HRMS are measured for the product of enol ether hydrolysis:

MS (APCI), m/z (%): 304.9 [M$^+$] (100), 282.2 (39), 258.1 (72), 229.1 (35),
215.0 (32).

HRMS, m/z: calcd. (C$_{14}$H$_{32}$O$_3$Si$_2$Na) 327.1788; found 327.1784.

10.3.6 General procedure for metathesis reaction

*Method A: Standard metathesis protocol.*

A solution of substrate (1.0 mmol, 1.0 eq) in CH$_2$Cl$_2$ (20 mL, 0.05 M) was
gently refluxed and GC-1 (0.05 mmol, 5 mol%) in CH$_2$Cl$_2$ (1 mL) was
added dropwise. After being refluxed for 15 h, the solvent was evaporated
and the residue was purified by column chromatography on silica gel.

*Method B: The use of Ti(OPr$^t$)$_4$ in the context of metathesis.*

To a solution of substrate (1.0 mmol, 1.0 eq) in CH$_2$Cl$_2$ (20 mL, 0.05M),
Ti(OPr$^t$)$_4$ (0.3 mmol, 0.3 eq) was added and the resulting mixture was
refluxed for 15 min. A solution of GC-1 (0.1 mmol, 10 mol%) in CH$_2$Cl$_2$ (2
mL) was then added dropwise to the refluxing mixture. After being refluxed
for 15h, the solvent was evaporated and the residue was purified by column chromatography on silica gel.

\((6R)-6\text{-}[(\text{benzyloxy})\text{methyl}]\text{-}5,6\text{-}\text{dihydro-2H-2-pyranone}\)

\[
\begin{align*}
\text{C}_{15}\text{H}_{14}\text{O}_{3} & \quad \text{Mol. Wt.: 246.3} \\
\text{C}_{15}\text{H}_{18}\text{O}_{3} & \quad \text{Mol. Wt.: 246.3}
\end{align*}
\]

*Method A*: Starting from 0.21 mmol of substrate. Purification by CC (ϕ1.5 cm, 9 cm of SiO\(_2\), 7 mL fractions; P.E.:EtAc = 3:1) yielded 21 mg (45%) of colourless oil.

*Method B*: Starting from 0.12 mmol of substrate. Purification by CC (ϕ1.0 cm, 8 cm of SiO\(_2\), 5 mL fractions; P.E.:EtAc = 3:1) yielded 24 mg (92%) of colourless oil.

TLC (1:1 = P.E.:EtAc)

\[R_f = 0.31\]

IR (NaCl, neat) \(\nu^1(\text{cm}^{-1})\): 3061, 3030, 2913, 2868, 1724, 1385, 1247.

\(^1\text{H}-\text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta(\text{ppm}): 2.39 \text{ (dddd, 1H, } ^2J_{4,4'} = 18.5 \text{ Hz, } ^3J_{4,3} = 6.8 \text{ Hz, } ^3J_{4,5} = 4.2 \text{ Hz, } ^3J_{4,2} = 1.0 \text{ Hz, H-4)}, 2.63 \text{ (ddt, 1H, } ^2J_{4',4} = 18.5 \text{ Hz, } ^3J_{4',3} = 11.4 \text{ Hz, } ^3J = 2.6 \text{ Hz, H-4'}), 3.69 \text{ (d, 2H, } ^3J = 4.7 \text{ Hz, H-6)}, 4.57 \text{ (m, overlapped, 1H, H-5)}, 4.60 \text{ (d, 2H, } ^3J = 1.0 \text{ Hz, H-7)}, 6.01 \text{ (ddd, 1H, } ^3J_{2,3} = 9.8 \text{ Hz, } ^3J_{2,4} = 2.6 \text{ Hz, } ^3J_{2,4} = 1.0 \text{ Hz, H-2}), 6.90 \text{ (ddd, 1H, } ^3J_{3,2} =
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9.7 Hz, $^3 J_{3,4} = 5.9$ Hz, $^3 J_{3,4'} = 2.5$ Hz, H-3), 7.32-7.36 (m, 5H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ(ppm): 26.3 (C-4), 70.9 (C-6), 73.7 (C-7), 76.7 (C-5), 121.3 (C-2), 127.8, 128.0, 128.6, 137.8 (aromatic CH and C$_q$), 145.2 (C-3), 163.8 (C-1).

MS (CI, CH$_4$/N$_2$O), $m/z$ (%): 218.9 [M$^{+1}$] (56), 219.9 [M$^{+2}$] (7), 181.1 (23), 91.0 (100).

$\alpha^D_{20}$: -116.3°(c = 1.25, CHCl$_3$).

CAS number: [120996-46-5].

(6R)-6-[(4-Methoxybenzyl)oxy]methyl-5,6-dihydro-2H-2-pyranone

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{molecule}};
\end{tikzpicture}
\end{center}

Method B: Starting from 0.11 mmol of substrate. Purification by CC ($\phi$1.0 cm, 8 cm of SiO$_2$, 5 mL fractions; P.E.:EtAc = 3:1) yielded 21.2 mg (78%) of colourless oil.

TLC (1:1 = P.E.:EtAc)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{tlc}};
\end{tikzpicture}
\end{center}

IR (NaCl, neat) ν (cm$^{-1}$): 3060, 3031, 2912, 2868, 1723, 1384, 1248.

500
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\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm): 2.33 (dtd, 1H, \(2^J_{J,4} = 17.3\) Hz, \(3^J = 4.4\) Hz, \(3^J_{J,2} = 1.2\) Hz, H-4), 2.53 (ddt, 1H, \(2^J_{J',4} = 17.3\) Hz, \(3^J_{J',3} = 11.4\) Hz, \(3^J = 1.2\) Hz, H-4'), 3.64 (d, 2H, \(3^J = 4.7\) Hz, H-6), 3.78 (s, 3H, H-12), 4.57 (m, overlapped, 1H, H-5), 4.51 (s, 2H, H-7), 6.01 (ddd, 1H, \(3^J_{J,2,4} = 10.0\) Hz, \(3^J_{J,2,4} = 1.0\) Hz, H-2), 6.88 (d, 2H, \(3^J_{J,10,9} = 8.5\) Hz, H-10), 6.90 (m, overlapped, 1H, H-3), 7.24 (d, 2H, \(3^J_{J,10} = 8.5\) Hz, H-9).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): 26.3 (C-4), 55.4 (C-12), 70.6 (C-6), 73.6 (C-7), 76.7 (C-5), 113.9 (C-10), 121.2 (C-2), 129.5 (C-9), 129.8 (C-8), 145.2 (C-3), 159.4 (C-11), 163.9 (C-1).

MS (APCI), \(m/z\) (%): 249.3 \([M^+1]\) (92), 250.3 \([M^+2]\) (11), 135.1 (24), 121.1 (100).

\([\alpha]\)^{20}_D: -1.47\(^\circ\) (c = 0.09, CHCl\(_3\)).

HRMS, \(m/z\): calcd. (C\(_{14}\)H\(_{16}\)O\(_4\)Na) 271.0946; found 271.0951.

\((2R,6R)\) and \((2S,6R)\)-2-[(1S)-1-(Benzyloxy)ethyl]-6-ethyl-5-methyl-3,6-dihydro-2\(H\)-pyran

Method A: Starting from 69.3\(\mu\)mol of substrate. Purified by CC (ϕ1.0 cm, 9 cm of SiO\(_2\), 5 mL fractions; P.E.:EtAc = 50:1→20:1) to give 10 mg (50%) of \((2R,6R)\)-diastereoisomer and 10 mg (50%) of \((2S,6R)\)-diastereoisomer in form of colourless oil.
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\[ \text{Ph} \]

O

H

H

3

4

5

6

7

8

9

10

11

\[ \text{H-NMR (300 MHz, CDCl}_3\text{)} \delta (ppm): 0.93 (t, 3H, }^3J_{9,8} = 7.2 \text{ Hz, H-9), 1.25 (d, 3H, }^3J_{1,2} = 6.3 \text{ Hz, H-1), 1.49 (ddq, 1H, }^2J_{8,8'} = 14.4 \text{ Hz, }^3J_{8,7} = 7.2 \text{ Hz, }^3J_{6,9} = 7.2 \text{ Hz, H-8), 1.60 (broad s, 3H, H-11), 1.78 (dqd, 1H, }^2J_{8,8} = 14.4 \text{ Hz, }^3J_{8,9} = 7.8 \text{ Hz, }^3J_{8,7} = 3.9 \text{ Hz, H-8'), 2.08 (broad s, 2H, H-4), 3.45 (m, 1H, H-3), 3.55 (dq, 1H, }^2J_{2,3} = 6.2 \text{ Hz, }^3J_{2,1} = 6.2 \text{ Hz, H-2), 4.02 (broad s, 1H, H-7), 4.62 (d, 1H, }^2J_{10,10'} = 13.2 \text{ Hz, H-10), 4.67 (d, 1H, }^2J_{10,10'} = 13.2 \text{ Hz, H-10'), 5.57 (broad s, 1H, H-5), 7.25-7.38 (m, 5H, aromatic CH).} \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta (ppm): 8.8 (C-9), 16.6 (C-1), 19.0 (C-11), 25.8 (C-8), 27.2 (C-4), 71.3 (C-10), 76.9 (C-2), 77.2 (C-7), 78.3 (C-3), 120.5 (C-5), 135.2 (C-6), 127.3, 127.6, 128.2, 139.0 (aromatic CH and Cq).} \]

\[ [\alpha]^{20}_D: +101.2^\circ (c = 1.01, \text{CHCl}_3). \]

HRMS, \( m/z \): calcd. (C\(_{17}\)H\(_{25}\)O) 261.1855; found 261.1847.

Stereochemistry established with the help of NOEsy experiments using various mixing times (0.1, 0.25, 0.50 and 0.75 ms). Following n.O.e. interactions were observed.

The second diastereoisomer.
Chapter 10. Experimental part

$\textbf{1H-NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm})$: 1.05 (t, 3H, $^3J_{9,8} = 7.2$ Hz, H-9), 1.20 (d, 3H, $^3J_{1,2} = 6.3$ Hz, H-1), 1.59 (broad dq, 2H, $^3J_{8,7} = 7.5$ Hz, $^3J_{8,9} = 7.5$ Hz, H-8), 1.63 (broad s, 3H, H-11), 1.85 (broad d, 1H, $^2J_{4,4'} = 16.8$ Hz, H-4), 2.12 (ddq, 1H, $^2J_{4',4} = 16.8$ Hz, $^3J_{4,3} = 10.5$ Hz, $^3J = 2.7$ Hz, H-4’), 3.52 (dq, 1H, $^3J_{2,3} = 6.3$ Hz, $^1J_{2,1} = 6.3$ Hz, H-2), 3.62 (ddd, 1H, $^3J_{3,4'} = 9.6$ Hz, $^3J_{3,2} = 5.4$ Hz, $^3J_{3,4} = 3.9$ Hz, H-3), 3.89 (d, 1H, $^3J_{7,8} = 6.9$ Hz, H-7), 4.64 (d, 1H, $^2J_{10,10'} = 12.3$ Hz, H-10), 4.69 (d, 1H, $^2J_{10,10'} = 12.3$ Hz, H-10’), 5.46 (broad d, 1H, $^3J_{3,2} = 3.9$ Hz, H-5), 7.25-7.39 (m, 5H, aromatic CH).

$\textbf{13C-NMR (75 MHz, CDCl}_3\text{)} \delta (\text{ppm})$: 8.8 (C-9), 16.6 (C-1), 19.0 (C-11), 25.8 (C-8), 27.2 (C-4), 71.3 (C-10), 76.9 (C-2), 77.2 (C-7), 78.3 (C-3), 120.5 (C-5), 135.2 (C-6), 127.3, 127.7, 128.1, 139.0 (aromatic CH and Cq).

$[\alpha]^{20}_D$: +84.2° (c = 0.93, CHCl3).

HRMS, $m/z$: calcd. (C17H25O) 261.1855; found 261.1847.

Stereochemistry established with the help of NOEsy experiments using various mixing times (0.1, 0.25, 0.50 and 0.75 ms). Following n.O.e. interactions were observed.
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1-(tert-Butyl)-1,1-dimethylsilyl (1R)-1-[(2R,6R)-6-ethyl-5-methyl-3,6-dihydro-2H-2-pyranyl]ethyl ether

Method A: Starting from 19.2 mmol of substrate. Purified by CC (ϕ 7.5 cm, 9 cm of SiO₂, 50 mL fractions; P.E.:Et₂O = 100:1→50:1) to give 5.28 g (97%) of colourless oil.

1H-NMR (300 MHz, CDCl₃) δ (ppm): 0.06 and 0.07 (s, 3H, H-10), 0.89 (s, 9H, H-12), 0.92 (t, partial overlap, 3H, J₉,₈ = 7.3 Hz, H-9), 1.19 (d, 3H, J₁,₂ = 6.2 Hz, H-1), 1.37-1.52 (m, 1H, H-8), 1.59 (broad s, 3H, H-13), 1.68-1.79 (m, 1H, H-8'), 1.98-2.04 (m, 2H, H-4), 3.20 (dd, 1H, J₇,₈ = 13.8 Hz, J₇,₈' = 5.3 Hz, H-7), 3.73 (pentet, 1H, J = 6.2 Hz, H-2), 3.97 (m, 1H, H-3), 5.56 (m, 1H, H-5).

13C-NMR (75 MHz, CDCl₃) δ (ppm): -4.7 and -4.4 (C-10), 9.0 (C-9), 18.6 (C-11), 18.9 (C-13), 20.9 (C-1), 25.8 (C-8), 25.9 (C-12), 27.3 (C-4), 71.2 (C-2), 78.2 (C-7), 78.6 (C-3), 120.8 (C-5), 135.3 (C-6).

MS (APCI), m/z (%): 285.1 [M+1] (42), 286.1 [M+2] (8), 267.1 (49), 107.1 (21), 72.9 (100).

[α]²⁰°D: +91.3° (c = 1.01, CHCl₃).
HRMS, m/z: calcd. (C_{16}H_{32}O_{2}SiNa) 307.2069; found 307.2071.

1-(tert-Butyl)-1,1-diphenylsilyl 1-[(2R,6R)-6-ethyl-5-methyl-3,6-dihydro-2H-2-pyranyl]ethyl ether

**Method A**: Purified by CC (φ 1.0 cm, 9 cm of SiO_{2}, 5 mL fractions; P.E.:Et_{2}O = 100:1 → 50:1) to give 392 mg (96%) of colourless oil.

{1H-NMR (300 MHz, CDCl_{3}) δ(ppm): 0.97 (s, 9H, H-12), 0.93 (t, partial overlap, 3H, \(^3J_{9,8} = 7.2\) Hz, H-9), 1.19 (d, 3H, \(^3J_{1,2} = 6.2\) Hz, H-1), 1.36-1.53 (m, 1H, H-8), 1.59 (broad s, 3H, H-10), 1.67-1.78 (m, 1H, H-8\(^\prime\)), 1.97-2.05 (m, 2H, H-4), 3.21 (dd, 1H, \(^3J_{7,8} = 13.7\) Hz, \(^3J_{7,8\prime} = 5.4\) Hz, H-7), 3.72 (pentet, 1H, \(^3J = 6.2\) Hz, H-2), 3.96 (m, 1H, H-3), 5.56 (m, 1H, H-5), 7.35-7.71 (m, 10H, aromatic CH).

{13C-NMR (75 MHz, CDCl_{3}) δ(ppm): 9.1 (C-9), 18.7 (C-11), 18.9 (C-10), 21.0 (C-1), 25.7 (C-8), 27.4 (C-12), 27.4 (C-4), 71.6 (C-2), 78.3 (C-7), 78.5 (C-3), 120.9 (C-5), 135.4 (C-6), 128.7-134.1 (aromatic CH and C_4).

MS (APCI), m/z (%): 409.3 [M+1] (36), 266.4 (43), 108.2 (32), 73.0 (100).

[\[\alpha\]_D]^{20}_{D} = +72.3°(c = 1.00, CHCl_{3}).

HRMS, m/z: calcd. (C_{26}H_{36}O_{2}SiNa) 431.2382; found 431.2387.
Chapter 10. Experimental part

Stereochemistry established with the help of NOEsy experiments using various mixing times (0.1, 0.25, 0.50 and 0.75 ms). Following n.O.e. interactions were observed.

\[
\begin{align*}
\text{TBDPSO} & \quad \text{R}^2 = \text{CH} (\text{OTBDPS}) \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

1-(\text{tert-Butyl})-1,1-diphenylsilyl 1-[(2R,3S,6R)-6-ethyl-3,5-dimethyl-3,6-dihydro-2H-2-pyranyl]ethyl ether

\[
\begin{align*}
\text{TBDPSO} & \quad \text{GC-1} \\
\text{C}_{27}\text{H}_{38}\text{O}_{2}\text{Si} & \quad \text{Mol. Wt.: 450,73} \\
\end{align*}
\]

\[
\begin{align*}
\text{TBDPSO} & \quad \text{GC-1} \\
\text{C}_{27}\text{H}_{38}\text{O}_{2}\text{Si} & \quad \text{Mol. Wt.: 422,67} \\
\end{align*}
\]

\textit{Method A}: Starting from 0.5 mmol of substrate. Purified by CC (φ1.0 cm, 8 cm of SiO\textsubscript{2}, 5 mL fractions; P.E.:Et\textsubscript{2}O = 100:1→50:1) to give 192 mg (91%) of colourless oil.

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta \text{(ppm): 0.97} & \text{ (s, 9H, H-13), 0.93} \text{ (t, partial overlap, 3H,} \text{J}_{9,8} = 7.2 \text{ Hz, H-9), 1.19} \text{ (d, 3H,} \text{J}_{1,2} = 6.2 \text{ Hz, H-1), 1.23} \text{ (d, 3H,} \text{J}_{10,4} = 6.3 \text{ Hz, H-10), 1.36-1.53} \text{ (m, 1H, H-8), 1.59} \text{ (broad s, 3H, H-11), 1.67-1.79} \text{ (m, 1H, H-8'), 2.45} \text{ (pentet, 1H,} \text{J} = 6.3 \text{ Hz, H-4), 3.22} \text{ (s, 2H,} \text{J} = 7.2 \text{ Hz, H-6).}
\end{align*}
\]

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(dd, 1H, \(^3J_{7,8} = 13.7\) Hz, \(^3J_{7,8'} = 5.4\) Hz, H-7), 3.73 (pentet, 1H, \(^3J = 6.2\) Hz, H-2), 3.95 (t, 1H, \(^3J = 6.4\) Hz, H-3), 5.57 (m, 1H, H-5), 7.35-7.71 (m, 10H, aromatic CH).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): 9.1 (C-9), 18.7 (C-12), 18.9 (C-11), 19.4 (C-10), 21.0 (C-1), 25.8 (C-8), 27.6 (C-13), 33.6 (C-4), 71.5 (C-2), 79.2 (C-7), 80.4 (C-3), 121.1 (C-5), 136.3 (C-6), 129.2-133.8 (aromatic CH and C\(_q\)).

MS (APCI), \(m/z\) (%): 423.5 \([M^++1]\) (56), 270.1 (76), 109.1 (25), 72.9 (100). \([\alpha]^{20}_D: +69.5^\circ (c = 0.91, \text{CHCl}_3)\).

HRMS, \(m/z\): calcd. (C\(_{27}\)H\(_{38}\)O\(_2\)SiNa) 445.2539; found 445.2543.

Stereochemistry established on the bases of the observed n.O.e. effect.

10.4 Protecting groups’ introduction and removal

10.4.1 General procedure for silicon protecting groups introduction and removal

Method A: Protection of alcohols with TMS group.

A solution of alcohol (1.0 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (10 mL, 0.1 M) was cooled to 0°C and Et\(_3\)N (4.0 mmol, \(d = 0.720\) g.mL\(^{-1}\), 4.0 eq) was slowly added. After 5 min, TMSCl (1.5 mmol, \(d = 0.856\) g.mL\(^{-1}\), 1.5 eq) was added dropwise and the resulting mixture was stirred at r.t. for 5h. Saturated aqueous solution of NaHCO\(_3\) (10 mL) was added and layers were separated.
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Aqueous layer was extracted with CH₂Cl₂ (3x10 mL) and combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method B: MeLi-based selective TMS group deprotection.**

\[
\text{OTBS} \quad \text{R} \quad \text{OTMS} \quad \xrightarrow{\text{MeLi}} \quad \text{R} \quad \text{OH}
\]

To a cold (0°C) solution of trimethyl silyl ether (1.0 mmol, 1. eq) in THF (10 mL, 0.1 M), MeLi (1.1 mmol, 1.6 M solution in Et₂O, 1.1 eq) was added dropwise and the resulting slightly yellow solution was allowed to warm to r.t. After 1h at r.t., saturated aqueous solution of NaHCO₃ (5 mL) was added and the whole mixture was extracted with CH₂Cl₂ (3x20 mL). Combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated in vacuum to give essentially pure monodeprotected alcohol.

**Method C: Monoprotection of 1,2-diols with TBS group.**

\[
\text{R} \quad \text{OH} \quad \text{OH} \quad \xrightarrow{\text{TBSCI, Et₃N, cat. DMAP, CH₂Cl₂}} \quad \text{R} \quad \text{OH} \quad \text{OTBS}
\]

A solution of a diol (1.0 mmol, 1.0 eq) and DMAP (0.05 mmol, 5 mol%) in CH₂Cl₂ (2 mL, 0.5 M) was cooled to 0°C and Et₃N (1.4 mmol, 1.4 eq) was added. After 5 min, TBSCI (1.25 mmol, 1.25 eq) in CH₂Cl₂ (0.5 mL) was added dropwise and the resulting mixture was stirred at r.t. for 19h. Saturated aqueous solution of NaHCO₃ (5 mL) was added and layers were separated. Aqueous layer was extracted with CH₂Cl₂ (3x10 mL) and combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method D: Protection of sensitive alcohols with TBSCI/imidazol system.**
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A solution of alcohol (1.0 mmol, 1.0 eq) and imidazol (1.5 mmol, 1.5 eq) in CH₂Cl₂ (10 mL, 0.1 M) was cooled to 0°C and TBSCI (1.1 mmol, 1.1 eq) in CH₂Cl₂ (2 mL, 0.5 M) was added dropwise over 1h. The resulting solution was allowed to warm to r.t. overnight. Saturated aqueous solution of NaHCO₃ (5 mL) was added and layers were separated. Aqueous layer was extracted with CH₂Cl₂ (3x15 mL) and combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method E: Protection of alcohols with TBSCI or TBDPS/imidazol system.
A solution of alcohol (1.0 mmol) and imidazol (2.0 mmol) in dry DMF (2 mL, 0.5 M) was cooled to 0°C and TBDPSCl (1.2 mmol, d = 1.057 g.cm⁻³) was added within 30 min. The resulting mixture was allowed to warm to r.t. and stirred for 12h. After re-cooling to 0°C and saturated aqueous solution of NaHCO₃ (5 mL) was added and the whole was extracted with P.E. (3x20 mL). Combined organic layers were washed with water (10 mL), brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method F: Deprotection using TBS or TBDPS group.
A solution of alcohol (1.0 mmol) in THF (5 mL, 0.2 M) was cooled to 0°C and TBAF (2.0 mmol, 1.0 M solution in THF) was added. Resulting brown solution was stirred at r.t. for 3h and then diluted with a mixture of Et₂O:H₂O = 1:1 (20 mL). Resulting layers were separated and aqueous phase was extracted with Et₂O (3x10 mL). Combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method G: Monoprotection of diols using TBSCI/NaH system.
To a solution of diol (10.0 mmol) in THF (10 mL, 1.0M), NaH (9.9 mmol, 60% suspension in mineral oil) was added in several portions at 0°C. The resulting mixture was allowed to warm to r.t. and stirred for 45 min. TBSCI (10.0 mmol) in THF (10 mL) was added via a cannula. After 4h (determined by TLC), H₂O (10 mL) was added and layers were separated. Aqueous layer was extracted with Et₂O (3x10 mL) and combined organic layers were washed with saturated aqueous solution of NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure.

Method H: Deprotection of TBS ethers presented on the cyclopropane ring. Alkenylboronic ester (1.0 mol) was dissolved in EtOH (10 mL, 0.1M), concentrated HCl (166 μL, 166 μL/mmol) in EtOH (2.5 mL, 0.07M) was slowly added, and the solution was stirred at r.t. for 2 h. The mixture was diluted with Et₂O:H₂O = 1:1 (50 mL), the aqueous layer was extracted with Et₂O (3x30 mL), and the combined organic layer was washed with saturated aqueous NaHCO₃. After being dried over MgSO₄, the mixture was filtered, the solvent evaporated, and the crude product subjected to flash column chromatography.

\[ \text{(2R)-1-[(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxy-4-penten-2-ol} \]

Method B: Starting from 0.36 mmol of TMS ether. Reaction yielded 74 mg (85%) of slightly yellow oil.
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TLC (20:1 = P.E.:Et₂O)

IR (NaCl, neat) ν⁻¹ (cm⁻¹): 2970, 2930, 2870, 1652, 1447, 1250, 841.

¹H-NMR (500 MHz, CD₂Cl₂) δ (ppm): 0.06 (s, 6H, H-6), 0.90 (s, 9H, H-8), 2.22 (dd, 1H, ²J₃,₃' = 13.9 Hz, ³J₃,₄ = 7.3 Hz, H-3), 2.27 (dd, 1H, ²J₃',₃ = 14.0 Hz, ³J₃',₄ = 5.5 Hz, H-3'), 2.45 (broad s, 1H, H-9), 3.47 (dd, 1H, ²J₅,₅' = 10.3 Hz, ³J₅,₄ = 6.6 Hz, H-5), 3.52 (s, 3H, H-10), 3.59 (dd, 1H, ²J₅',₅ = 10.3 Hz, ³J₅',₄ = 4.4 Hz, H-4'), 3.80 (pentet, 1H, ³J = 5.9 Hz, H-4), 3.94 (d, 1H, J = 1.8 Hz, H-1), 3.96 (d, 1H, J = 1.8 Hz, H-1').

¹³C-NMR (125 MHz, CD₂Cl₂) δ (ppm): -5.2 (C-6), 18.7 (C-7), 26.2 (C-8), 39.5 (C-3), 55.3 (C-10), 67.1 (C-5), 10.5 (C-4), 83.0 (C-1), 161.6 (C-2).

MS (Cl, CH₃/N₂O), m/z (%): 247.5 [M⁺] (10), 147.2 (100).

HRMS, m/z: calcd. (C₁₂H₂₆O₃SiNa) 269.1549; found 269.1543.

**Methyl (3R)-4-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-3-hydroxybutanoate**

**Method C:** Starting from 33.4 mmol of diol. Purification by CC (φ 7.5 cm, 11 cm of SiO₂, 50 mL fractions; 8:1 = P.E.:EtAc) yielded 7.38g (91%) of colourless oil.
Chapter 10. Experimental part

TLC (4:1 = P.E.:EtAc)

\[ R_f = 0.43 \]

\[ R_f = 0.02 \]

1

\[ \text{UV, KMnO}_4, \text{TBS ether} \]

\[ \text{UV, KMnO}_4, \text{diol} \]

Product obtained as a 16:1 mixture of primary:secondary TBS-ether.

IR (NaCl, neat) \( \nu \) (cm\(^{-1}\)): 2982, 2931, 1731.

\[^1\text{H-NMR (500 MHz, CD}_2\text{Cl}_2) \delta \) (ppm): \( 0.07 \) and \( 0.09 \) (s, \( 3\text{H, H-5} \)), \( 0.90 \) (s, \( 9\text{H, H-7} \)), \( 2.50 \) (dd, \( 1\text{H, }^2J_{2,2'} = 16.0 \text{ Hz, }^2J_{2,3} = 7.6 \text{ Hz, H-2} \)), \( 2.54 \) (dd, \( 1\text{H, }^2J_{2,2'} = 16.0 \text{ Hz, }^3J_{2',3} = 5.1 \text{ Hz, H-2'} \)), \( 2.87 \) (d, \( 1\text{H, }^3J_{6,3} = 2.6 \text{ Hz, H-8} \)), \( 3.57 \) (dd, \( 1\text{H, }^2J_{4,4'} = 10.0 \text{ Hz, }^3J_{4,3} = 5.7 \text{ Hz, H-4} \)), \( 3.64 \) (dd, \( 1\text{H, }^2J_{4',4} = 10.0 \text{ Hz, }^3J_{4',3} = 4.8 \text{ Hz, H-4'} \)), \( 3.71 \) (s, \( 3\text{H, H-9} \)), \( 4.08 \) (m, \( 1\text{H, H-3} \)).

\[^{13}\text{C-NMR (125 MHz, CD}_2\text{Cl}_2) \delta \) (ppm): \( -2.3 \) (C-5), \( 18.5 \) (C-6), \( 25.9 \) (C-7), \( 38.0 \) (C-2), \( 52.0 \) (C-9), \( 66.3 \) (C-4), \( 68.7 \) (C-3), \( 172.8 \) (C-1).

MS (CI, CH\(_4\)/N\(_2\))O, \( m/z \) (%): \( 249.0 \) [M\(^{+}\)+1] (100), \( 217.1 \) (76), \( 117.0 \) (29).

\([\alpha]^{20}_D: +7.38^\circ (c = 1.91, \text{CHCl}_3)\).

CAS number: [374681-00-2].

Methyl \( (3R)-4-[1-(\text{tert-butyl})-1,1-dimethylsilyl]oxy-3-][(1,1,1-trimethylsilyl)oxy]butanoate

\[
\text{MeO}_2\text{C} \quad \begin{array}{c}
\text{OH} \\
\text{OTBS}
\end{array}
\rightarrow
\text{MeO}_2\text{C} \quad \begin{array}{c}
\text{OTMS} \\
\text{OTBS}
\end{array}
\]

\text{C}_{11}\text{H}_{24}\text{O}_{4}\text{Si}
\text{Mol. Wt.: 248,39}

\text{C}_{14}\text{H}_{32}\text{O}_{4}\text{Si}_2
\text{Mol. Wt.: 320,57}
Chapter 10. Experimental part

*Method A*: Starting from 2.02 mmol of alcohol. Purification by CC (ϕ 3.5 cm, 10 cm of SiO₂, 20 mL fractions; 8:1 = P.E.:Et₂O) gave 304 mg (95%) of colourless oil.

TLC (4:1 = P.E.:Et₂O)

![TLC diagram](image)

IR (NaCl, neat) ν¹(cm⁻¹): 2981, 2931, 2882, 1731.

¹H-NMR (500 MHz, CD₂Cl₂) δ (ppm): 0.05 and 0.06 (s, 3H, H-5), 0.11 (s, 9H, H-8), 0.89 (s, 9H, H-7), 2.38 (dd, 1H, ²J₂,₂' = 14.9 Hz, ³J₂,₃ = 8.3 Hz, H-2), 2.63 (dd, 1H, ²J₂',₂ = 15.0 Hz, ³J₂',₃ = 4.2 Hz, H-2'), 3.43 (dd, 1H, ²J₄,₄' = 10.0 Hz, ³J₄,₃ = 6.8 Hz, H-4), 3.58 (dd, 1H, ²J₄',₄ = 10.0 Hz, ³J₄',₃ = 5.5 Hz, H-4'), 3.68 (s, 3H, H-9), 4.15 (m, 1H, H-3).

¹³C-NMR (125 MHz, CD₂Cl₂) δ (ppm): -5.1 and 5.2 (C-5), 0.4 (C-8), 18.6 (C-6), 26.1 (C-7), 40.1 (C-2), 51.7 (C-9), 67.3 (C-4), 70.5 (C-3), 172.5 (C-1).

MS (APCI), m/z (%): 320.9 [M⁺] (43), 290.0 (21), 289.0 (100), 199.1 (25), 85.0 (26).


HRMS, m/z: calcd. (C₁₄H₃₂O₆Si₂Na) 343.1737; found 343.1752.
Chapter 10. Experimental part

**1-(tert-Butyl)-1,1-dimethylsilyl [(2R)oxiran-2-ylmethyl] ether**

![Chemical structure](image)

**Method D:** Starting from 20.0 mmol of glycidol. Purified by CC(φ5.5 cm, 9 cm of SiO₂, 50 mL fractions; 10:1 = P.E.:Et₂O) yielded 3.73 g (99%) of colourless oil.

TLC (5:1 = P.E.:Et₂O)

- TLC: Rf = 0.40
- KMnO₄, epoxide
- KMnO₄, glycidol

**¹H-NMR (250 MHz, CDCl₃) δ (ppm):** 0.08 (s, 6H, H-4), 0.90 (s, 9H, H-6), 2.64 (dd, 1H, ₊J₁₁ = 6.2 Hz, ₊J₁₂ = 2.9 Hz, H-1), 2.77 (dd, 1H, ₊J₁₁ = 6.2 Hz, ₊J₁₂ = 5.2 Hz, H-1'), 3.09 (m, 1H, H-2), 3.66 (dd, 1H, ₊J₃₃ = 14.7 Hz, ₊J₃₂ = 5.7 Hz, H-3), 3.86 (dd, 1H, ₊J₃₃ = 14.3 Hz, ₊J₃₂ = 3.8 Hz, H-3')

**¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm):** -2.4 (C-4), 18.6 (C-5), 26.1 (C-6), 44.7 (C-1), 52.6 (C-2), 63.9 (C-3).

**MS (APCI), m/z (%):** 188.9 [M⁺]+ (16), 171.9 (12), 170.9 (100).

[α]₀²⁰⁰: +2.4º (c = 2.01, CHCl₃).

CAS number: [124150-87-4].
Chapter 10. Experimental part

**Ethyl 3-[(1,1,1-trimethylsilyl)oxy]butanoate**

Method A: Starting from 3.2 mmol of alcohol. Evaporation of the solvents yielded 654 mg (quant.) of colourless oil.

TLC (4:1 = P.E.:EtO)

IR (NaCl, neat) ν (cm⁻¹): 2983, 2963, 2905, 1737, 1659, 1643, 1251.

¹H-NMR (250 MHz, CD₂Cl₂) δ (ppm): 0.11 (s, 9H, H-7), 1.20 (d, 3H, J = 6.3 Hz, H-4), 2.36 (dd, 1H, J₂,₂' = 14.7 Hz, J₂,₃ = 5.6 Hz, H-2), 2.48 (dd, 1H, J₂',₂ = 14.7 Hz, J₂',₃ = 7.9 Hz, H-2’), 4.12 (qd, 2H, J₅,₆ = 7.2 Hz, J₅,₆ = 3.2 Hz, H-5), 4.26 (m, 1H, H-3)

¹³C-NMR (125 MHz, CD₂Cl₂) δ (ppm): 0.3 (C-7), 14.4 (C-6), 24.1 (C-4), 45.1 (C-2), 60.5 (C-5), 65.9 (C-3), 171.8 (C-1).

MS (APCI), m/z (%): 205.0 [M⁺+1] (44), 116.9 (74), 104.9 (31), 72.9 (100).

CAS number: [55816-59-6].
Chapter 10. Experimental part

**1,1-Dimethyl-1-phenylsilyl [(2R)-2-methyl-3-(phenylsulfanyl)propyl] ether**

![Chemical Structure](image)

**Method A**: Starting from 0.5 mmol of alcohol. Purified by CC(1.5 cm, 12 cm of SiO₂, 7 mL fractions; 10:1 = P.E.:Et₂O) to give 152 mg (96%) of colourless oil.

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3086, 2958, 2869, 1585, 1480, 1427, 1252.

¹H-NMR (250 MHz, CD₂Cl₂) δ(ppm): 0.36 (s, 6H, H-4), 0.99 (d, 3H, 3 J = 7.2 Hz, H-5), 1.92 (sextet, 1H, 3 J = 6.0 Hz, H-2), 2.68 (dd, 1H, 2 J₁,₁' = 12.9 Hz, 3 J₁,₂ = 7.5 Hz, H-1), 3.13 (dd, 1H, 2 J₁,₁ = 12.9 Hz, 3 J₁,₂ = 5.7 Hz, H-1'), 3.51 (dd, 1H, 2 J₃₃' = 9.9 Hz, 3 J₁',₂ = 6.3 Hz, H-3), 3.57 (dd, 1H, 2 J₃₃ = 10.2 Hz, 3 J₃',₂ = 5.7 Hz, H-3'), 7.13-7.57 (m, 10H, aromatic CH).

¹³C-NMR (125 MHz, CD₂Cl₂) δ(ppm): -1.1 (C-4), 17.0 (C-5), 36.3 (C-2), 37.5 (C-1), 67.2 (C-3), 126.0-138.3 (aromatic CH and Cq).

MS (APCI), m/z (%): 317.1 [M⁺+1] (7), 255.1 (7), 239.1 (100).

**1-(tert-Butyl)-1,1-dimethylsilyl [(2R)-2-methyl-3-(phenylsulfanyl)propyl] ether**

![Chemical Structure](image)
Method E: Starting from 1.6 mmol of alcohol. Purified by CC(φ2.5 cm, 12 cm of SiO₂, 10 mL fractions; 10:1 = P.E.:Et₂O) to give 446 mg (94%) of colourless oil.

IR (NaCl, neat) ν⁻¹(cm⁻¹): 3083, 2953, 2926, 2857, 1582, 1473, 1428, 1254.

¹H-NMR (300 MHz, CD₂Cl₂) δ(ppm): 0.04 (s, 6H, H-4), 0.88 (s, 9H, H-6), 0.99 (d, 3H, ³J₁₂ = 6.6 Hz, H-7), 1.88 (sextet, 1H, ³J = 6.9 Hz, H-2), 2.67 (dd, 1H, ³J₁₂ = 12.9 Hz, ³J₁₂ = 7.5 Hz, H-1), 3.15 (dd, 1H, ³J₄₂ = 12.9 Hz, ³J₄₂ = 5.7 Hz, H-1'), 3.48 (dd, 1H, ³J₃₃ = 9.6 Hz, ³J₃₃ = 4.8 Hz, H-3'), 7.10-7.34 (m, 5H, aromatic CH).

¹³C-NMR (75 MHz, CD₂Cl₂) δ(ppm): -4.7 and -4.7 (C-4), 17.0 (C-7), 19.0 (C-5), 26.6 (C-6), 36.5 (C-1), 37.5 (C-2), 67.3 (C-3), 125.9-137.9 (aromatic CH and Cq).

MS (APCI), m/z (%): 296.9 [M⁺] (24), 165.0 (100), 123.0 (53).

CAS number: [189223-93-6].

1-(tert-Butyl)-1,1-diphenylsilyl [(2R)-2-methyl-3-(phenylsulfanyl)propyl] ether

Method E: Starting from 0.5 mmol of alcohol. Purified by CC(φ2.5 cm, 12 cm of SiO₂, 10 mL fractions; 10:1 = P.E.:Et₂O) to give 202 mg (96%) of colourless oil.
**Chapter 10. Experimental part**

**IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)):** 3083, 3062, 2954, 2927, 2853, 1579, 1474, 1435, 1256.

**\(^1\)H-NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\)(ppm):** 0.99 (d, 3H, \(^3J\_\text{H-H} = 6.6\) Hz, H-6), 1.1.08 (s, 9H, H-5), 1.87 (sextet, 1H, \(^3J\_\text{H-H} = 4.0\) Hz, H-2), 2.72 (dd, 1H, \(^2J\_\text{H-H} = 12.9\) Hz, \(^3J\_\text{H-H} = 7.7\) Hz, H-1), 3.29 (dd, 1H, \(^2J\_\text{H-H} = 12.9\) Hz, \(^3J\_\text{H-H} = 5.3\) Hz, H-1'), 3.56 (dd, 1H, \(^2J\_\text{H-H} = 10.1\) Hz, \(^3J\_\text{H-H} = 6.7\) Hz, H-3), 3.67 (dd, 1H, \(^2J\_\text{H-H} = 10.1\) Hz, \(^3J\_\text{H-H} = 4.8\) Hz, H-3'), 7.15-7.67 (m, 15H, aromatic CH).

**\(^{13}\)C-NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\)(ppm):** 16.4 (C-6), 19.1 (C-4), 26.4 (C-5), 36.4 (C-1), 38.1 (C-2), 67.9 (C-3), 125.9-137.9 (aromatic CH and C\(_\text{q}\)).

**MS (APCI), \(m/z\) (%):** 420.3 [M\(^+\)] (4), 363.3 (81), 343.3 (100).

**CAS number:** [189223-93-6].

**(S)-Ethyl 2-\textit{tert}-butyldiphenylsilyloxypropionate**

\[
\begin{align*}
\text{HO} & \quad \text{CO}_2\text{Et} \\
\text{C}_8\text{H}_{15}\text{O}_3 & \quad \text{Mol. Wt.:} 118.13
\end{align*}
\]

\[
\begin{align*}
\text{TBDPSCI, Imidazol} & \quad \text{DMF, 0°C -> rt, 12h} \\
\text{HO} & \quad \text{CO}_2\text{Et} \\
\text{C}_8\text{H}_{15}\text{O}_3 & \quad \text{Mol. Wt.:} 356.53
\end{align*}
\]

**Method E:** Starting from 74.5 mmol of alcohol. Purified by CC (ϕ 6.5 cm, 11 cm of SiO\(_2\), 50 mL fractions; EP:Et\(_2\)O=25:1→10:1) to give 22.88 g (86%) of slightly yellow oil.
Chapter 10. Experimental part

TLC (EP:Et₂O=25:1)

\[
\begin{align*}
R_f &= 0.69 \quad UV, \text{KMnO}_4, \text{silicon impurities (nonidentified)} \\
R_f &= 0.13 \quad UV, \text{KMnO}_4, \text{product} \\
R_f &= 0.65 \quad UV, \text{KMnO}_4, \text{starting alcohol}
\end{align*}
\]

\(^1\)H-NMR (300 MHz, CDCl₃) \(\delta (\text{ppm})\): 1.10 (s, 9H, SiC(CH₃)₃), 1.11 (t, 3H, \(J_{\text{CH}_3-\text{CH}_2} = 7.2 \text{ Hz}, \text{OCH}_2\text{CH}_3\)), 1.38 (d, 3H, \(J_{\text{CH}_3-\text{CH}} = 6.9 \text{ Hz}, \text{CHCH}_3\)), 4.03 (q, 1H, \(J_{\text{CH}-\text{CH}_3} = 6.9 \text{ Hz}, \text{CHCH}_3\)), 7.34-7.71 (m, 10H, Ar).

\(^{13}\)C-NMR (75 MHz, CDCl₃) \(\delta (\text{ppm})\): 14.4 (OCH₂CH₃), 19.5 (SiCMe₃), 21.6 (CH₂CH₃), 27.1 (SiC(CH₃)₃), 60.8 (OCH₂CH₃), 69.2 (CH₃), 127.7-136.0 (aromatic CH and Cq), 173.8 (CO₂Et).

CAS number: [87681-25-2].

**Method A:** Starting from 80.5 mmol of alcohol. Purified by CC (φ 5.5 cm, 75 g of SiO₂, 50 mL fractions; EP:Et₂O=30:1) to give\(^445\) 13.4 g (97%) of colourless oil.

\(^{445}\) The solvent was removed under atmospheric pressure
Chapter 10. Experimental part

TLC (EP:Et₂O=30:1)

\[ R_f = 0.57 \]
\[ R_f = 0.04 \]

vaniline (dark blue), product

\[ \text{KMnO}_4, \text{starting alcohol} \]

\[ \text{Me}_3\text{SiO} \]

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 0.11 \text{ (s, 9H, H-7), 0.85 (t, 3H, } J_{5,4} = 7.2 \text{ Hz, H-5), 1.51 (2H, qd, } J_{4,5} = 7.2, J_{4,3} = 7.0 \text{ Hz, H-4), 1.68 (3H, s, H-6), 3.93 (1H, t, } J_{3,4} = 6.6 \text{ Hz, H-3), 4.77 and 4.87 (Broad s, 1H, H-1).} \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta (\text{ppm}): \]

CAS number: [125637-07-2].

1,1-Dimethylallyl (1,1,1-trimethylsilyl) ether

\[ \text{Method A: Starting from 11.6 mmol of alcohol. Purified by CC (φ 4.5 cm, 11 cm of SiO}_2\text{, 20 mL fractions; P.E.:Et}_2\text{O = 25:1) to give 1.52 g (83%) of colourless oil (IMPORTANT: compound is volatile).} \]

\[ \text{1H-NMR (250 MHz, CDCl}_3\text{)} \delta (\text{ppm): 0.13 \text{ (s, 9H, H-7), 1.32 (s, 6H, H-4), 4.94 (dd, } J_{1,2} = 10.7, J_{1,1'} = 1.6 \text{ Hz, H-1-cis), 5.14 (dd, } J_{1',2} = 17.4, J_{1',1} = 1.6 \text{ Hz, H-1-trans), 5.96 (dd, } J_{2,1'} = 17.0 \text{ Hz, } J_{2,1} = 10.7 \text{ Hz, H-2).} \]

\[ \text{13C-NMR (62.5 MHz, CDCl}_3\text{)} \delta (\text{ppm): 2.8 (C-5), 30.3 (C-4), 75.3 (C-3), 110.8 (C-1), 147.0 (C-2).} \]
Chapter 10. Experimental part

MS (CI, CH₄/N₂O), m/z (%): 159.1 [M⁺+1] (39), 157.0 (44), 143.0 (100), 85.7 (54), 83.8 (69).
CAS number: [19916-99-5].

2-Methylallyl (1,1,1-trimethylsilyl) ether

\[
\text{C}_7\text{H}_{16}\text{O} \quad \text{Mol. Wt.: 144.29} \\
\text{C}_4\text{H}_8\text{O} \quad \text{Mol. Wt.: 72.11}
\]

Method A: Starting from 11.9 mmol of alcohol. Purified by CC (ϕ 3.5 cm, 8 cm of SiO₂, 15 mL fractions; P.E.:Et₂O = 25:1) to give 1.45 g (85%) of colourless oil (IMPORTANT: compound is volatile).

\[\text{H-NMR (250 MHz, CDCl}_3\text{)} \delta\text{ (ppm): 0.14 (s, 9H, H-7), 1.72 (s, 3H, H-4), 4.02 (s, H-3), 4.83 (broad s, 1H, H-1), 4.98 (broad s, 1H, H-1').}\]

\[\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta\text{ (ppm): -0.3 (C-5), 19.2 (C-4), 66.7 (C-3), 111.0 (C-1), 144.7 (C-2).}\]

MS (CI, CH₄/N₂O), m/z (%): 145.0 [M⁺+1] (77), 129.0 (66), 101.9 (47), 83.9 (100), 59.1 (88).
CAS number: [25195-89-5].

1-Methyl-3-butenyl (1,1,1-trimethylsilyl) ether

\[
\text{C}_8\text{H}_{18}\text{O} \quad \text{Mol. Wt.: 158.31} \\
\text{C}_5\text{H}_{10}\text{O} \quad \text{Mol. Wt.: 86.13}
\]

1-H-NMR (250 MHz, CDCl₃) δ(ppm): 0.14 (s, 9H, H-7), 1.72 (s, 3H, H-4), 4.02 (s, H-3), 4.83 (broad s, 1H, H-1), 4.98 (broad s, 1H, H-1').

\[\text{C-NMR (62.5 MHz, CDCl}_3\text{)} \delta\text{ (ppm): -0.3 (C-5), 19.2 (C-4), 66.7 (C-3), 111.0 (C-1), 144.7 (C-2).}\]

MS (CI, CH₄/N₂O), m/z (%): 145.0 [M⁺+1] (77), 129.0 (66), 101.9 (47), 83.9 (100), 59.1 (88).
CAS number: [25195-89-5].
Chapter 10. Experimental part

Method A: Starting from 9.7 mmol of alcohol. Purified by CC (ϕ 3.5 cm, 7 cm of SiO₂, 15 mL fractions; P.E.:Et₂O = 25:1) to give 1.32 g (86%) of colourless oil.

\[ \begin{array}{c}
\text{OSiMe}_3 \\
\text{1H-NMR (250 MHz, CDCl}_3\text{)} \delta (ppm): 0.12 (s, 9H, H-6), 1.15 (d, 3H, \text{ }^{3}J_{5,4} = 6.0 \text{ Hz, H-5}), 2.09-2.27 (m, 2H, H-3), 3.82 (sextet, 1H, \text{ }^{3}J_{5,4} = 6.3 \text{ Hz, H-4}), 5.03 (d, 1H, \text{ }^{3}J_{1,2} = 10.3 \text{ Hz, H-1}), 5.04 (d, 1H, \text{ }^{3}J_{1',2} = 17.0 \text{ Hz, H-1'}), 5.76 (m, 1H, H-2).
\end{array} \]

\[ \begin{array}{c}
\text{13C-NMR (62.5 MHz, CDCl}_3\text{)} \delta (ppm): 0.4 (C-6), 23.7 (C-5), 44.3 (C-3), 68.5 (C-4), 116.8 (C-1), 135.8 (C-2).
\end{array} \]

MS (CI, CH₄/N₂O), m/z (%): 159.1 [M⁺+1] (25), 143.1 (99), 117.0 (100), 83.9 (24), 69.0 (42).

CAS number: [103303-96-4].

1-(3-Butenyl)-4-pentenyl (1,1,1-trimethylsilyl) ether

Method A: Starting from 7.13 mmol of alcohol. Purified by CC (ϕ 3.5 cm, 7 cm of SiO₂, 15 mL fractions; P.E.:Et₂O = 25:1) to give 1.33 g (88%) of colourless oil.

\[ \begin{array}{c}
\text{OSiMe}_3 \\
\text{1H-NMR (250 MHz, CDCl}_3\text{)} \delta (ppm): 0.13 (s, 9H, H-6), 1.49-1.58 (m, 2H, H-4), 2.00-2.16 (m, 2H, H-3), 3.68 (pentet, 1H, \text{ }^{3}J = 6.0 \text{ Hz, H-5}), 4.97
\end{array} \]

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Chapter 10. Experimental part

(dd, 1H, $^3J_{1,2} = 11.5$ Hz, $^3J_{1,1'} = 1.2$ Hz, H-1), 5.03 (dd, 1H, $^3J_{1,2} = 17.0$ Hz, $^3J_{1',2} = 1.2$ Hz, H-1').

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ(ppm): 0.7 (C-6), 30.0 (C-4), 36.9 (C-3), 71.7 (C-5), 114.6 (C-1), 138.9 (C-2).

MS (CI, CH$_4$/N$_2$O), m/z (%): 213.1 [M$+1$] (27), 197.1 (84), 157.0 (100), 123.1 (47), 83.8 (32), 59.0 (34).

HRMS, m/z: calcd. (C$_{12}$H$_{24}$OSiNa) 235.1494; found 25.1501.

(1$R$)-1-[(2$R,6R$)-6-Ethyl-5-methyl-3,6-dihydro-2$H$-2-pyranyl]ethan-1-ol

Method F: Starting from 15.0 mmol of silyl ether. Purified by CC ($\phi$ 7.5 cm, 9 cm of SiO$_2$, 50 mL fractions; P.E.:Et$_2$O = 10:1→5:1) to give 2.07 g (81%) of colourless oil (colourless crystals at -20°C).

TLC (5:1 = P.E.:Et$_2$O)

$^1$H-NMR (300 MHz, CDCl$_3$) δ(ppm): 0.88 (t, 3H, $^3J_{9,8} = 7.3$ Hz, H-9), 1.14 (d, 3H, $^3J_{1,2} = 6.5$ Hz, H-1), 1.50 (heptet, 1H, $^3J = 7.1$ Hz, H-8), 1.58 (broad t, 3H, $^4J = 1.2$ Hz, H-11), 1.69-1.87 (m, 2H, H-8' and H-4), 2.08-2.20 (m, 1H, H-4’), 2.28 (broad s, 1H, H-10), 3.41 (dt, 1H, $^3J = 10.8$ Hz,
Chapter 10. Experimental part

$^{3}J = 3.2$ Hz, H-7), 3.90 (qd, 1H, $^{3}J_{2,1} = 6.5$ Hz, $^{3}J_{2,3} = 3.5$ Hz, H-2), 4.07 (m, 1H, H-3), 5.56 (broad d, 1H, $^{3}J = 5.9$ Hz, H-5).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) $\delta$(ppm): 8.6 (C-9), 17.7 (C-11), 19.1 (C-1), 24.5 (C-8), 25.8 (C-4), 69.3 (C-2), 76.3 (C-7), 78.3 (C-3), 120.6 (C-5), 135.2 (C-6).

MS (APCI), $m/z$ (%): 171.0 [M$^{+}+1$] (100), 153.1 (83), 135.1 (42), 109.1 (62), 95.1 (79).

$[\alpha]_{D}^{20}$: $+103.4^{\circ}$ (c = 1.31, CHCl$_3$).

CAS number: [863895-02-7].

3-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-1-propanol$^{446}$

Method G: Starting from 359.7 mmol of diol. The crude product was purified by CC ($\phi$ 8.5 cm, 12 cm of SiO$_2$, 50 mL fractions; 3:1→1:1 = P.E.:Et$_2$O) to give (67.9g, 99%) of colourless oil.

TLC (2:1 = P.E.:Et$_2$O)

\[ \text{product, KMnO}_4 \]

$^{446}$ Org. Lett. 2004, 6, 1939.
Chapter 10. Experimental part

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm): 0.08 (s, 6H, H-5), 0.91 (s, 9H, H-7), 1.79 (quintet, 2H, \(^3J_{J,2}\) and 4 = 5.7 Hz, H-3), 2.61 (t, 1H, \(^3J_{J,1}\) = 5.4, H-1), 3.81 (q, 2H, \(^3J_{J,2,3}\) and 1 = 5.4, H-2), 3.85 (t, 2H, \(^3J = 5.7\), H-4).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): -5.8 (C-5), 18.4 (C-7), 25.8 (C-6), 34.6 (C-3), 61.8 (C-2), 62.5 (C-4).

CAS number: [73842-99-6].

\((E)-3-(4R,5R)-4,5-Di[\text{methoxy(diphenyl)methyl}]\text{-}1,3,2\text{-dioxaborolan-2-yl-2-propen-1-ol}\)

Method H: Starting from 12.4 mmol of diol. The crude product was purified by CC (φ 8.5 cm, 12 cm of SiO\(_2\), 50 mL fractions; 10:1 → 3:1 = P.E.:Et\(_2\)O) to give (67.9g, 74%) of colourless oil.

\(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.21 (t, 1H, \(^3J_{J,3}\) = 6.0 Hz, H-4), 2.97 (s, 6H, H-6), 4.04 (ddd, 2H, \(^3J = 6.0\) Hz, \(^3J = 4.2\) Hz, \(^3J_{J,4,3}\) = 2.1 Hz, H-3), 5.28 (dt, \(^3J_{J,1,2}\) = 18.1 Hz, \(^4J_{J,1}\) = 1.9 Hz, H-1), 5.33 (s, 2H, H-5), 6.30 (dt, \(^3J_{J,2,1}\) = 18.1 Hz, \(^3J_{J,2,3}\) = 4.2 Hz, H-2), 7.21-7.36 (m, 20H, aromatic CH).

\(^13\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) (ppm): 51.8 (C-7), 64.5 (C-3), 77.7 (C-5), 83.4 (C-6), 116.2 (C-1), 127.2, 127.3, 127.5, 127.8, 128.4, 129.7, 141.1, 141.3 (aromatic CH and C\(_3\)), 151.3 (C-2).
Chapter 10. Experimental part

\[ \alpha \]_{D}^{20}: -85.1^\circ (c = 1.0, \text{CHCl}_3) ; \text{lit.}^447\ -85.8 (c = 1.0, \text{CHCl}_3).

CAS number: [251956-33-9].

10.4.2 General procedure for benzyl group introduction and removal

**Method A: FeCl₃ mediated benzyl group deprotection.**

A solution of benzyl ether (1.0 mmol, 1.0 eq) in CH₂Cl₂ (10 mL, 0.1M) was stirred at r.t. and FeCl₃ (3.3 mmol, 3.3 eq) was added in one portion. The resulting suspension was stirred at r.t. for 10 min and H₂O (5 mL) was added. The resulting suspension was diluted with CH₂Cl₂ (80 mL) and layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3x20 mL) and combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and evaporated under reduced pressure.

**Method B: BCl₃ mediated benzyl group deprotection.**

A solution of benzyl ether (1.0 mmol, 1.0 eq) in CH₂Cl₂ (10 mL, 0.1M) was cooled to -78°C and BCl₃ (2.0 mmol, 2.0 eq) was added dropwise. After 2h at -78°C, saturated solution of NaHCO₃ (5 mL) was added and the resulting slurry was allowed to warm to r.t. Layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3x20 mL). Combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and evaporated under reduced pressure.

**Method C: Monobenzylation of 1,2-diols.**

\[ \text{R-OH} \rightarrow 1) \text{Bu}_3\text{SnO} \rightarrow \text{R-OH} \rightarrow 2) \text{BnBr, TBAI} \rightarrow \text{R-OBn} \]

Chapter 10. Experimental part

A solution of diol (1.0 mmol, 1.0 eq) and Bu₃SnO (1.1 mmol, 1.1 eq) in benzene (3.3 mL, 0.33 M) was refluxed for 16h. Water was continuously removed using Dean-Stark trap. After 16h, the mixture was cooled to r.t. and TBAI (1.1 mmol, 1.1 eq) followed by BnBr (2.5 mmol, 2.5 eq) were added. The resulting thick solution was refluxed for additional 4h. After cooling to r.t., benzene was removed under reduced pressure and the resulting oil was purified by column chromatography on silica gel.

**Benzyl (3R)-4-(benzyloxy)-3-hydroxybutanoate**

![Chemical Structure](image)

**Method C**: Starting from 12.6 mmol of diol. 4.0 equivalents of BnBr were used. Purification by CC (φ5 cm, 8 cm of SiO₂, 20 mL fractions; 5:1→3:1 = P.E.:EtAc) gave 2.76g (73%) of colourless oil.

TLC (P.E.:EtAc = 2:1)

![TLC Image]

1H-NMR (300 MHz, CDCl₃) δ(ppm): 2.62 (d, 2H, ³J₂,₃ = 6.2 Hz, H-2), 3.18 (d, 1H, ³J₆,₃ = 4.4 Hz, H-6), 3.49 (dd, 1H, ²J₄,₄' = 9.7 Hz, ³J₄,₃ = 5.9 Hz, H-4), 3.53 (dd, 1H, ²J₄',₄ = 9.7 Hz, ³J₄',₃ = 4.7 Hz, H-4'), 4.29 (pentet, 1H, ³J = 4.7 Hz, H-3), 4.56 (s, 2H, H-5), 5.16 (s, 2H, H-7), 7.33-7.38 (m, 10H, aromatic CH).
Chapter 10. Experimental part

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 38.4 (C-2), 66.5 (C-7), 67.2 (C-3), 73.2 (C-5), 73.4 (C-4), 127.8, 127.8, 128.3, 128.4, 128.5, 128.6, 135.7, 137.9 (aromatic CH and C$_q$), 171.9 (C-1).

MS (APCI), $m$/z (%): 300.8 [M$^+$] (23), 301.9 (5), 181.1 (100), 91.0 (52).

CAS number: [261159-55-1].

(6R)-6-(hydroxymethyl)-4-methoxy-5,6-dihydro-2H-2-pyranone

\[
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{MeO} \\
\text{C}_6\text{H}_{10}\text{O}_4 \\
\text{Mol. Wt.: 248,27}
\end{array}
\quad
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{OH} \\
\text{C}_7\text{H}_{10}\text{O}_4 \\
\text{Mol. Wt.: 158,15}
\end{array}
\]

Method A: Starting from 0.21 mmol of benzyl ether. Purified by CC ($\phi$ 1.0 cm, 8 cm of SiO$_2$, 7 mL fractions; 100% EtAc) to give 22.3 mg (67%) of colourless crystals.

TLC (100% EtAc)

\[
\begin{array}{c}
R_f = 0.79
\end{array}
\quad
\begin{array}{c}
UV, KMnO_4, benzyl ether
\end{array}
\]

\[
\begin{array}{c}
R_f = 0.79
\end{array}
\quad
\begin{array}{c}
UV, KMnO_4, alcohol
\end{array}
\]

IR (NaCl, neat) $\nu$ (cm$^{-1}$): 3457, 3283, 2977, 2965, 2927, 2724, 1739, 1739, 1491.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 2.28 (dd, 2H, $^2J_{4,4'} = 17.0$ Hz, $^3J_{4,5} = 3.8$ Hz, H-4 and overlapped H-7), 2.80 (ddd, 1H, $^2J_{4',4} = 17.0$ Hz, $^3J_{4',5} = 12.6$ Hz, $^4J_{4',4} = 1.4$ Hz, H-4$'$), 3.74 (broad dd, partial overlap, 1H, $^2J_{6,6'} = 11.7$ Hz, $^3J_{6,5} = 4.4$ Hz, H-6), 3.77 (s, 3H, H-8), 3.91 (broad d, 1H, $^2J_{6,6'} = 3.91$ Hz), 4.58 (s, 1H, H-3), 6.80 (d, 1H, H-2).
11.7 Hz, H-6'), 4.52 (dq, 1H, J5,6' = 12.6 Hz, J = 4.1 Hz, H-5), 5.16 (d, 1H, J = 1.8 Hz, H-2).

13C-NMR (75 MHz, CDCl3) δ(ppm): 29.1 (C-4), 56.4 (C-8), 63.9 (C-6), 76.5 (C-5), 90.2 (C-2), 167.0 (C-3), 173.2 (C-1).

MS (APCI), m/z (%): 159.0 [M+1] (100), 160.0 [M+2] (7), 141.0 (28), 113.1 (27).

[a]20 D: +187.3° (c = 0.95, CHCl3).

E.A. (C7H10O4): calcd. C 53.16%, H 6.37%; found C 53.10%, H 6.40%.

(6R)-6-(Hydroxymethyl)-4-methoxy-3-methyl-5,6-dihydro-2H-2-pyranone

\[ \text{C}_{15} \text{H}_{18} \text{O}_{4} \quad \text{Mol. Wt.: 262.3} \]
\[ \text{C}_{10} \text{H}_{12} \text{O}_{4} \quad \text{Mol. Wt.: 172.18} \]

Method A: Starting from 0.21 mmol of benzyl ether. Purified by CC (φ 1.0 cm, 8 cm of SiO2, 6 mL fractions; 100% EtAc) to give 25.7 mg (71%) of colourless crystals.

TLC (100% EtAc)

IR (NaCl, neat) ν -1 (cm⁻¹): 3450, 3026, 2978, 2964, 2929, 1743, 1492.
Chapter 10. Experimental part

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.79 (d, 3H, $^4J = 0.9$ Hz, H-8), 2.20 (broad s, 1H, H-7), 2.53 (dd, 1H, $^3J_{4,4'} = 17.0$ Hz, $^3J_{4,5} = 4.0$ Hz, H-4), 2.81 (ddd, 1H, $^3J_{4,4} = 16.8$ Hz, $^3J_{5,5} = 13.8$ Hz, $^4J = 2.0$ Hz, H-4$'$), 3.74 (dd, 1H, $^3J_{6,6} = 12.0$ Hz, $^3J_{6,5} = 4.4$ Hz, H-6), 3.82 (s, 3H, H-9), 3.94 (dd, 1H, $^3J_{5,5} = 4.1$ Hz, H-6$'$), 4.42 (dq, 1H, $^3J_{5,4} = 12.3$ Hz, $^4J = 4.1$ Hz, H-5).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 9.1 (C-8), 25.4 (C-4), 55.7 (C-9), 64.0 (C-6), 75.1 (C-5), 103.2 (C-2), 165.8 (C-3), 168.3 (C-1).

MS (APCI), $m/z$ (%): 173.0 [M$^{+}+1$] (100), 174.0 [M$^{+}+2$] (8), 155.0 (21), 127.1 (20).

[$\alpha$]$^2$D: +192° ($c = 1.00$, CHCl$_3$).

E.A. (C$_{8}$H$_{12}$O$_{4}$) calcd. C 55.81%, H 7.02%; found C 55.85%, H 7.04%.

(6R)-6-(Hydroxymethyl)-5,6-dihydro-2H-2-pyranone

![Chemical Structure]

Method A: Starting from 0.87 mmol of benzyl ether. Purified by CC ($\phi$ 1.5 cm, 14 cm of SiO$_2$, 10 mL fractions; 100% EtAc) to give 89 mg (80%) of colourless solid.

Method B: Starting from 0.52 mmol of benzyl ether. Purified by CC ($\phi$ 1.5 cm, 8 cm of SiO$_2$, 10 mL fractions; 100% EtAc) to give 55 mg (83%) of colourless solid.
Chapter 10. Experimental part

TLC (100% EtAc)

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\))): 3398, 3032, 2977, 2959, 2930, 1699, 1493.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ(ppm): 1.97 (broad s, 1H, H-7), 2.30 (ddddd, 1H, \(^2\)J\(_{4,4'}\) = 18.5 Hz, \(^3\)J\(_{4,4',3}\) = 6.2 Hz, \(^3\)J\(_{4,4',5}\) = 4.1 Hz, \(^3\)J\(_{4,2}\) = 1.0 Hz, H-4), 2.63 (ddt, 1H, \(^2\)J\(_{4,4'}\) = 18.5 Hz, \(^3\)J\(_{4,4',3}\) = 9.8 Hz, \(^3\)J\(_{4,2}\) = 2.5 Hz, H-4'), 3.76 (dd, 1H, \(^2\)J\(_{6,6'}\) = 12.5 Hz, \(^3\)J\(_{6,6',5}\) = 4.8 Hz, H-6), 3.91 (dd, 1H, \(^2\)J\(_{6,6'}\) = 12.5 Hz, \(^3\)J\(_{6,6',5}\) = 9.8 Hz, H-6'), 4.57 (tt, 1H, \(^3\)J\(_{6,5}\) = 8.2 Hz, \(^3\)J\(_{4,2}\) = 4.0 Hz, H-5), 6.05 (ddd, 1H, \(^3\)J\(_{3,3}\) = 9.8 Hz, \(^3\)J\(_{2,4}\) = 2.9 Hz, \(^3\)J\(_{2,4}\) = 1.0 Hz, H-2), 6.95 (ddd, 1H, \(^3\)J\(_{3,4}\) = 9.7 Hz, \(^3\)J\(_{3,4}\) = 6.2 Hz, \(^3\)J\(_{3,4}\) = 2.3 Hz, H-3).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) δ(ppm): 25.4 (C-4), 63.9 (C-6), 78.6 (C-5), 121.0 (C-2), 145.7 (C-3), 164.2 (C-1).

MS (APCI), m/z (%): 129.0 [M\(^{+1}\)] (76), 130 [M\(^{+2}\)] (3), 102.1 (100), 91.0 (26), 85.0 (21), 83.0 (31).

\([\alpha]\)\(^{20}\)_D: +175.7°(c = 1.01, CHCl\(_3\)).

CAS number: [109519-21-3].

10.4.3 General procedure for \(p\)-methoxy benzyl group introduction and removal

**Method A: PMB-group introduction.**

A solution of NaH (1.2 mmol, 60% suspension in mineral oil, 1.2 eq) in DMF (2 mL, 0.5 M) was cooled to 0°C and alcohol (1.0 mmol, 1.0 eq) was
added. After 5 min, Bu₄NI (0.05 mmol, 5 mol%) followed by PMBCl (2.0 mmol, d = 1.155 g.mL⁻¹, 2.0 eq) was added. The resulting mixture was allowed to warm to r.t. and stirred for 5h. Saturated aqueous solution of NaHCO₃ (1 mL) was added carefully and the whole mixture was diluted with brine (10 mL) and extracted with CH₂Cl₂ (3x15 mL). Combined organic layers were dried over MgSO₄ and evaporated to dryness. Residue was purified by column chromatography on silica gel.

2-[(4-Methoxybenzyl)oxy]methylxirane

\[
\begin{align*}
\text{C}_3\text{H}_6\text{O}_2 & \quad \text{Mol. Wt.: 74.08} \\
\text{C}_{11}\text{H}_{14}\text{O}_3 & \quad \text{Mol. Wt.: 194.23}
\end{align*}
\]

Method A: Starting from 40.0 mmol of glycidol. Purified by CC(φ5.5 cm, 8 cm of SiO₂, 50 mL fractions; 2:1 = P.E.:EtAc) yielded 6.70 g (86%) of colourless oil.

TLC (1:1 = P.E.:EtAc)

\[R_f = 0.49\]

\[
\begin{align*}
\text{UV, KMnO}_4, \text{epoxide} \\
\end{align*}
\]

\[
\begin{align*}
\text{1H-NMR (250 MHz, CDCl}_3\}) \delta (ppm): 2.62 & \quad (\text{dd, 1H, } ^2J_{1,1'} = 5.7 \text{ Hz, } ^3J_{1,2} = 2.3 \text{ Hz, H-1}), 2.80 & \quad (\text{t, 1H, } J = 6.2 \text{ Hz, H-1'}), 3.19 & \quad (\text{sextet, 1H, } ^2J = 6.2 \text{ Hz, H-2}), 3.42 & \quad (\text{dd, 1H, } ^2J_{3,3'} = 13.3 \text{ Hz, } ^3J_{3,2} = 6.7 \text{ Hz, H-3}), 3.74 & \quad (\text{dd, 1H, } ^3J_{3,3'} = 13.3 \text{ Hz, } ^3J_{3,2} = 3.3 \text{ Hz, H-3'}), 3.82 & \quad (\text{s, 3H, H-9}), 4.79 & \quad \text{and 4.56 (d, 1H,}
\end{align*}
\]
10. Experimental part

$^{3}J_{4,4'} = 13.8$ Hz, H-4 and H4'), 6.89 (dd, 1H, $^{3}J_{3,6} = 7.6$ Hz, $^{3}J = 2.4$ Hz, H-7), 7.29 (dd, 1H, $^{3}J_{6,7} = 7.6$ Hz, $^{3}J = 2.9$ Hz, H-6).

$^{13}$C-NMR (62.5 MHz, CDCl$_3$) δ (ppm): 44.5 (C-1), 51.1 (C-2), 55.5 (C-9), 70.7 (C-3), 73.2 (C-4), 114.0 (C-7), 129.6 (C-6), 130.4 (C-5), 159.5 (C-8).

MS (APCI), m/z (%): 195.2 [M++1] (73), 196.1 [M++2] (27), 137.0 (100), 121.0 (47).

(2R)-2-[(4-methoxybenzyl)oxy]methyloxirane
$[\alpha]_{D}^{20}: +1.88^\circ$ (c = 2.40, CHCl$_3$).
CAS number: [134733-19-0].

(2S)-2-[(4-methoxybenzyl)oxy]methyloxirane
$[\alpha]_{D}^{20}: -1.63^\circ$ (c = 2.09, CHCl$_3$).
CAS number: [144069-33-0].

10.4.4 General procedure for protection and deprotection of diols

To a solution of a 1,2-diol (1.0 mmol, 1.0 eq) in a mixture of 2,2-dimethoxypropane (0.26 mL) and acetone (1.4 mL) pre-cooled to 0°C, pTSA.H$_2$O (70.9 mg, 0.38 mmol, 0.1 eq) was added and the resulting solution was stirred at 0°C for 1 h. Saturated aqueous solution of NaHCO$_3$ (2 mL) was added to stop the reaction and the resulting biphasic system was allowed to warm to r.t. Layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3x10 mL). Combined organic layers were dried over MgSO$_4$ and evaporated.
Chapter 10. Experimental part

**Methyl 2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate**

\[
\begin{align*}
\text{C}_8\text{H}_{14}\text{O}_4 & \quad \text{Mol. Wt.: 174.19} \\
\text{C}_5\text{H}_{10}\text{O}_4 & \quad \text{Mol. Wt.: 134.13}
\end{align*}
\]

Starting from 3.7 mmol of diol. After evaporation, resulting thick oil was placed under the high-vacuum to give 617 mg (95%) of colourless oil sufficiently pure for the next step.

**TLC** (1:1 = P.E.:Et\(_2\)O)

\[
R_f = 0.30
\]

**1H-NMR** (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.35 and 1.41 (two s, 6H, H-7 and 7'), 2.52 (dd, 1H, 2\(\_2'\) = 16.1 Hz, 3\(\_2'\) = 7.4 Hz, H-2), 2.71 (dd, 1H, 2\(\_2'\) = 15.6 Hz, 3\(\_2'\) = 3.9 Hz, H-2'), 3.64 (dd, 1H, 2\(\_4'\) = 8.7 Hz, 3\(\_4'\) = 6.4 Hz, H-4), 3.69 (s, 3H, H-5), 4.15 (dd, 1H, 2\(\_4'\) = 8.3 Hz, 3\(\_4'\) = 6.0 Hz, H-4'), 4.47 (quintet, 1H, 3\(\_3\) = 6.4 Hz, H-3).

**13C-NMR** (125 MHz, CDCl\(_3\)) \(\delta\) (ppm): 25.7 and 27.1 (C-7 and 7'), 38.9 (C-2), 52.0 (C-5), 69.3 (C-4), 72.2 (C-3), 109.4 (C-6), 171.3 (C-1).

**MS** (APCI), \(m/z\) (%): 174.1 [M'] (100), 172.1 [M' + H] (4), 107.1 (19), 79.9 (25).

\([\alpha]^{20}_D\): -8.93°(c = 2.00, CHCl\(_3\)).

10.5 Carbonyl compounds

10.5.1 General procedure for ester-group reduction

A solution of ester (1.0 mmol, 1.0 eq) in dry CH$_2$Cl$_2$ (10 mL, 0.1 M) was cooled to -78°C and DIBAL-H (1.0 mmol, d = 0.798 g.mL$^{-1}$, 2.1 eq) was added within 15 min. Reaction mixture was allowed to warm to r.t. and stirred there for 4 h and again cooled to -78°C. 1.0M aqueous solution of HCl (10 mL) was carefully added. Layers were separated and the aqueous layer was extracted with EtAc (3x20 mL). Combined organic layers were washed with H$_2$O (5 mL), brine (5 mL), dried over MgSO$_4$, filtrated and evaporated under reduced pressure.

Method B: DIBAL-H-mediated ester-to-aldehyde transformation.
A solution of ester (1.0 mmol, 1.0 mmol) in dry CH$_2$Cl$_2$ (10 mL, 0.1 M) was cooled to -78°C and DIBAL-H (1.1 mmol, 1.0 M solution in CH$_2$Cl$_2$, 1.1 eq) was added within 15 min. The resulting mixture was stirred for additional 1h at -77°C and 1.0 M aqueous solution of HCl (5 mL) was added. The resulting mixture was allowed to warm to r.t. Layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x20 mL). Combined organic layers were washed with water (10 mL), brine (10 mL), dried over MgSO$_4$ and evaporated under reduced pressure from the cold bath.

Method C: Selective reduction of $\alpha$-hydroxy esters to 1,2-diols.
A solution of hydroxyester (1.0 mmol, 1.0 eq) in dry THF (4 mL, 0.25 M) was stirred at r.t. and BH$_3$. SMe$_2$ complex (1.03 mmol, 10.0 M solution in SMe$_2$, 1.03 eq.,) was slowly added. After 1 h the H$_2$ evolution ceased and the resulting solution was cooled to 0°C. After additional 5 min., NaBH$_4$ (0.05 mmol, 5 mol%) was added in one portion. Reaction mixture was stirred at 0°C for 30 min and then at r.t. for 1 h, before it was again cooled to 0°C. MeOH (0.33 mL, 3.0 M) was carefully added and immediately followed by $p$TSA (0.05 mmol, 5 mol%). After additional 15 min at 0°C, the mixture was slowly warm to r.t. and stirred there for 30 min. Solvents were evaporated and the residue was partitioned between MeOH/benzene = 1:1 (10 mL) mixture and solvents were again evaporated. This was twice repeated. Finally, benzene (25 mL) was added and evaporated (twice repeated).

(2$R$)-2-Methyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfanyl]propan-1-ol

---

For small scale reactions (0.1-10 mmol), DIBAL-H solution in CH$_2$Cl$_2$ or toluene might be used. For bigger scale synthesis, a pure DIBAL-H is recommended.
Chapter 10. Experimental part

Method A. Starting from 44.9 mmol of ester. Stirred at -78°C (30’) and r.t. (4h). Purified by CC (φ 11.0 cm, 12 cm of SiO2, 50 mL fractions; P.E.:EtAc = 3:1→1:3) to give 10.1g (90%) of slightly yellow oil.

TLC (P.E.:EtAc = 1:1)

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3350 (m), 2961 (m), 2931 (m), 1597 (m), 1500 (m), 1387 (m), 909 (m), 732 (m).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ(ppm): 1.04 (d, 3H, \(^3\)J\(_{4,3}\) = 6.6 Hz, H-4), 2.18 (m, 1H, H-3), 3.47 (d, 2H, \(^3\)J\(_{5,3}\) = 5.7 Hz, H-5), 3.49 (dd, 1H, \(^2\)J\(_{2,2'}\) = 11.4, \(^3\)J\(_{2,3}\) = 6.6 Hz, H-2), 3.64 (dd, 1H, \(^2\)J\(_{2',2}\) = 11.4, \(^3\)J\(_{2',3}\) = 4.2 Hz, H-2’), 3.79 (broad s, 1H, H-1), 7.56-7.59 (m, 5H, Ar).

\(^1\)C-NMR (75 MHz, CDCl\(_3\)) δ(ppm): 16.2 (C-4), 36.4 (C-5), 37.0 (C-3), 64.8 (C-2), 124.0, 129.9, 130.4, 133.5 (aromatic CH and Cq), 155.5 (C-6).

MS (ESI), m/z (%): 251.1 (6) [M\(^{+}\) +H], 207.9 (28) [M\(^{+}\) -HN\(_3\)], 151.1 (100) [M\(^{+}\) -SCN, N\(_3\)], 119.0 (57) [M\(^{+}\) -PhOH, N\(_3\)], 105.0 (8) [M\(^{+}\) - PT].

HRMS, m/z: calcd. for C\(_{11}\)H\(_{14}\)N\(_4\)O\(_5\) [M+Na\(^{+}\)] 273.0781; found 273.0775.

[\(\alpha\)]\(_{D}\)^{20}: -78.7° (c = 2.1, CHCl\(_3\)).

CAS number: [101212-36-6].


\(^{450}\) Other reducing reagents, as LiAlH\(_4\), cannot be used for the ester reduction, because resulting alcohol is sticking to it (or its salts) and the yield is dropping down dramatically (10-15%).
Method A: Starting from 0.95 mmol of ester. DIBAL-H solution in toluene (1.5 M) was used. Stirred at -78°C (10 min) and at r.t. (1h). Purified by CC (φ 1.5 cm, 11 cm of SiO₂, 10 mL fractions; P.E.:Et₂O = 2:1) to give 181 mg (quant.) of colourless oil.

TLC (1:1 = P.E.:Et₂O)

\[ \text{UV, KMnO}_4 \text{, sulfid} \]

\[ \text{UV, KMnO}_4 \text{, vanilline (red), PhSH} \]

\[ ^1H-\text{NMR (300 MHz, CDCl}_3 \text{)} \delta (\text{ppm}): 1.05 (3H, d, }^3J_{4,3} = 6.6 \text{ Hz, H-4), 1.79 (1H, broad s, H-1), 1.96 (1H, octet, }^J = 6.6 \text{ Hz, H-3), 2.85 (1H, dd, }^3J_{5,3} = 7.2 \text{ Hz, }^2J_{5,5} = 12.9 \text{ Hz, H-5), 3.07 (1H, dd, }^3J_{5',3} = 6.6 \text{ Hz, }^2J_{5',5} = 12.9 \text{ Hz, H-5'), 3.62 (2H, m, CH-2, 7.15-7.41 (5H, m, aromatic CH).} \]

MS (CI, CH₄/N₂O), m/z (%): 183 (72) [M⁺+H], 123 (67), 109 (100), 77 (54). 

\[ [\alpha]^{20}_D: -20.9^\circ (c = 1.05, \text{CH}_2\text{Cl}_2) \text{[lit.}^{451} -19.9^\circ (c 1.4, \text{CH}_2\text{Cl}_2). \]

CAS number: [101212-36-6].

---

Chapter 10. Experimental part

(2R)-2-methyl-3-[(1-phenyl-1H-1,2,3,4-tetraazol-5-yl)sulfonyl]propan-1-ol

\[
\begin{align*}
\text{C}_{12}H_{14}N_{4}O_{3}S & \quad \text{Mol. Wt.: 310.33} \\
\text{C}_{11}H_{14}N_{4}O_{3}S & \quad \text{Mol. Wt.: 282.32}
\end{align*}
\]

**Method A:** Starting from 3.22 mmol of ester. Stirred at -78°C (5'), r.t. (4h) and again -78°C (5'). Purified by CC (\(\phi = 2.5 \text{ cm}, 12 \text{ cm of SiO}_2, 6 \text{ mL fractions; P.E.:EtAc}=3:1\rightarrow100\%\)) to give 773 mg (85%) of yellow very viscous oil.

TLC (P.E.:EtAc = 1:1)

Experimental data, see p. 414.

Methyl (3R)-3,4-dihydroxybutanoate

\[
\begin{align*}
\text{C}_{6}H_{10}O_{5} & \quad \text{Mol. Wt.: 162.14} \\
\text{C}_{5}H_{10}O_{4} & \quad \text{Mol. Wt.: 134.13}
\end{align*}
\]

**Method C:** Starting from 6.17 mmol of diester. Residue was purified by CC (\(\phi = 3.5 \text{ cm}, 11 \text{ cm of SiO}_2, 20 \text{ mL fraction; 100\% EtAc}\)) to give 786 mg (95%) of colourless oil.
Chapter 10. Experimental part

TLC (100% EtAc)

![TLC Diagram]

\[ R_f = 0.23 \]

1H-NMR (250 MHz, CDCl3) \( \delta \) (ppm): 2.50 (1H, dd, \( ^2J_{2,2'} = 16.3 \text{ Hz}, ^3J_{2,3} = 5.2 \text{ Hz}, \text{H-2})\), 2.2.57 (1H, dd, \( ^2J_{2',2} = 16.3 \text{ Hz}, ^3J_{2',3} = 8.1 \text{ Hz}, \text{H-2'})\), 3.53 (dd, 1H, \( ^2J_{4,4'} = 11.5 \text{ Hz}, ^3J_{4,3} = 6.4 \text{ Hz}, \text{H-4})\), 3.69 (dd, 1H, \( ^2J_{4',4} = 11.5 \text{ Hz}, ^3J_{4',3} = 3.6 \text{ Hz}, \text{H-4'})\), 3.72 (s, 3H, H-6).

13C-NMR (62.5 MHz, CDCl3) \( \delta \) (ppm): 37.6 (C-2), 52.2 (C-6), 65.9 (C-4), 68.6 (C-3), 173.1 (C-1).

MS (APCI), \( m/z \) (%): 134.9 (56) [M^+1], 117.0 (36), 103.0 (80), 91.0 (100), 84.9 (21).

\( [\alpha]_{D}^{20} = +13.8^{\circ} \) (c = 2.27, CHCl3) [lit.\(^452 \) +13.7° (c = 1.2, CH3OH).

CAS number: [114819-45-3].

(S)-2-tert-Butyldiphenylsilyloxypropionaldehyde

\[
\begin{array}{c}
\text{TBDPSO}^+\text{CO}_2\text{Et} \\
\text{C}_{21}\text{H}_{28}\text{O}_3\text{Si} \\
\text{Mol. Wt.: 356.53}
\end{array}
\]

\[
\text{DIBAL-H} \rightarrow
\begin{array}{c}
\text{TBDPSO}^+\text{CHO} \\
\text{C}_{19}\text{H}_{24}\text{O}_2\text{Si} \\
\text{Mol. Wt.: 312.48}
\end{array}
\]

Method B: Starting from 28.0 mmol of ester. Purified by CC (φ 6.5 cm, 12 cm of SiO₂, 50 mL fractions; EP:Et₂O=35:1) to give 8.2 g (93%) of clear oil.

Chapter 10. Experimental part

TLC (EP:Et₂O=20:1)

- Rf = 0.30
- Rf = 0.15

UV, KMnO₄, vaniline (dark pink), aldehyde
UV, KMnO₄, ester

1H-NMR (200 MHz, CDCl₃) δ (ppm): 1.12 (s, 9H, SiC(CH₃)₃), 1.23 (d, 3H, JCH₃-CH = 6.9 Hz, CHCH₃), 4.10 (q, 1H, JCH-CH₃ = 6.9 Hz, CHCH₃), 7.36-7.71 (m, 10H, Ar), 9.66 (d, 1H, JCOH-CH=1.1 Hz, CHO)

[α][D]: -22.0° (c = 10.5, CH₂Cl₂).
CAS number: [87696-33-1].

10.5.2 General procedure for esterification

*Method A: AcCl/ROH-mediated esterification.*

MeOH (1 mL, 1.0M) was cooled to 0°C and acyl chloride (0.8 mmol, 0.8 eq) was added dropwise. Cooling bath was removed and the resulting mixture was stirred at r.t. for 10 min. Acid (1.0 mmol, 1.0 eq) was added (dropwise or portion-wise) and the reaction mixture was stirred at r.t. for 26h. Volatile organic solvents were evaporated under the reduced pressure and resulting crude was purified by CC or distillation.
Chapter 10. Experimental part

**Dimethyl (2R)-2-hydroxybutanedioate**

![Structural formula](image_url)

**Method A**: Starting from 37.3 mmol of diacid. Purification by CC (ϕ 7.5 cm, 8 cm of SiO₂, 50 mL fractions; 95:5 = CH₂Cl₂:MeOH) gave 5.68 g (94%) of colourless oil.

TLC (100% EtAc)

\[ \text{KMnO}_4, \text{diester} \]

\[ \text{1H-NMR} (250 \text{ MHz, CDCl}_3) \delta (\text{ppm}): 2.77 (1\text{H, dd, }^2J_{2,2'} = 16.3 \text{ Hz, }^3J_{2,3} = 5.9 \text{ Hz, H-2}), 2.86 (1\text{H, dd, }^2J_{2',2} = 16.6 \text{ Hz, }^3J_{2',3} = 4.4 \text{ Hz, H-2'}), 3.35 \text{ (broad d, 1H, }^3J_{6,3} = 4.0 \text{ Hz, H-6), 3.70 and 3.79 (s, 3H, H-5 and H-7), 4.50 (broad pentet, 1H, } J = 5.1 \text{ Hz, H-3).} \]

\[ \text{13C-NMR} (62.5 \text{ MHz, CDCl}_3) \delta (\text{ppm}): 38.6 (\text{C-2}), 52.2 \text{ and 53.0 (C-5 and C-7), 67.4 (C-3), 171.2 and 173.9 (C-1 and C-4).} \]

MS (APCI), \( m/z \) (%): 162.9 (100) [M⁺+1], 130.8 (34), 113.0 (37), 103.0 (87), 70.9 (26).

\[ [\alpha]_{D}^{20}: +2.21^\circ (c = 2.62, \text{CHCl}_3) \text{ [lit.}^{453} +6.6^\circ \text{ (neat).} \]

CAS number: [70681-41-3].

---

453 Aldrich catalogue.
10.5.3 General procedure for aldol condensation

Method A: Starting from Weinreb amide.

A solution of LDA (0.8 mL, 1.6 mmol, 1.6 eq, 2.0 M solution in THF) in THF (10 mL, 0.1 M) was cooled to -78°C and ester (1.5 mmol, 1.5 eq) in THF (0.5 mL) was added dropwise. After 1h, amide (1.0 mmol, 1.0 eq) in THF (0.5 mL) was added. The resulting mixture was stirred at -78°C for indicated time and saturated aqueous solution of NH₄Cl (5 mL) was added. The temperature was allowed to remote to r.t. and the resulting layers were separated. The aqueous layer was extracted by Et₂O (3x10 mL). Combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

Method B: Starting from esters.

A solution of LDA (4.1 mmol, 2.0M solution in THF, 4.1 eq) in THF (5 mL, 0.2M) was cooled to -40°C and ester (1.0 mmol, 1.0 eq) in THF (0.5 mL) was added. The resulting mixture was stirred at -40°C for 5 min and at -20°C for additional 2h. The reaction was quenched by AcOH:H₂O = 1:3 (5 mL) mixture and the whole solution was diluted with Et₂O:H₂O = 1:1 (30 mL). Layers were separated and the aqueous layer was extracted with Et₂O (3x30 mL). Combined organic layers were washed with saturated aqueous solution of NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄ and evaporated in vacuum.
Chapter 10. Experimental part

**tert-Butyl 4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxobutanoate**

Stirred at -78°C for 6 h. Purified by CC (φ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; 10:1 to 1:1 = P.E.:EtAc) furnished 222 mg (86%) of colourless oil. TLC (1:1 = P.E.:EtAc)

Presented also in its enol form (ketoester:enol form = 85:15).

**1H-NMR** (500 MHz, CDCl₃) δ(ppm): 1.35 (s, 3H, H-8), 1.41 (s, 3H, H-8’), 1.49 (s, 9H, H-10), 2.73 (dd, 1H, 1J₄₄’ = 16.9 Hz, 2J₄₄’ = 7.0 Hz, H-4), 2.73 (dd, 1H, 1J₄₄’ = 17.2 Hz, 2J₄₄’ = 5.9 Hz, H-4’), 3.39 (d, 1H, 1J₂₂’ = 16.9 Hz, H-2), 3.41 (d, 1H, 1J₂₂’ = 17.0 Hz, H-2’), 3.57 (dd, 1H, 1J₆₆’ = 8.4 Hz, 2J₆₆’ = 6.6 Hz, H-6), 4.19 (dd, 1H, 1J₆₆’ = 8.1 Hz, 2J₆₆’ = 10.3 Hz, H-6’), 4.48 (pentet, 1H, 1J = 6.6 Hz, H-5).

**13C-NMR** (125 MHz, CDCl₃) δ(ppm): 25.6 (C-8), 27.0 (C-8’), 28.2 (C-10), 47.3 (C-4), 51.2 (C-2), 69.5 (C-6), 71.6 (C-5), 82.1 (C-9), 109.2 (C-7), 166.3 (C-1), 201.4 (C-3).

**MS** (CI, CH₄), m/Z (%): 259.2 [M⁺ +1] (3), 243.1 (5), 203.0 (46), 183.0 (24), 144.9 (99), 126.9 (34), 101.2 (23), 85.1 (100), 83.8 (31), 60.8 (23), 59.0 (67), 57.1 (51).
Chapter 10. Experimental part

**tert-Butyl 4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-3-oxobutanoate**

Stirred at -78°C for 8 h. Purified by CC (ϕ 1.5 cm, 11 cm of SiO₂, 7 mL fractions; 10:1 to 1:1 = P.E.:EtAc) furnished 224 mg (89%) of colourless oil. Desired β-ketoester was obtained as a mixture of two diastereoisomers in 1.3:1 ratio.

TLC (1:1 = P.E.:EtAc)

Presented also in its enol form (ketoester:enol form = 91:9).

**1H-NMR (500 MHz, CDCl₃) δ (ppm):**

- **Minor diastereoisomer:** 1.30 (d, 3H, \(^3J_{11,2} = 3.7\) Hz, H-11\(^*\)), 1.35 (s, 6H, H-8\(*\)), 1.41 (s, 3H, H-8\(*\)), 1.46 (s, 18H, H-10), 2.76 (dd, 1H, \(^2J_{4,4} = 17.2\) Hz, \(^3J_{4,5} = 7.7\) Hz, H-4\(*\)), 4.08 (dd, 1H, \(^2J_{4,4} = 17.2\) Hz, \(^3J_{4,5} = 7.7\) Hz, H-4\(*\)).
Chapter 10. Experimental part

\[ \begin{align*}
{^1}H, & \quad {^2}J_{4',4} = 17.3 \text{ Hz}, \quad {^3}J_{4',5} = 5.2 \text{ Hz}, \quad \text{H-4'}^*, \quad 3.45 \text{ (pentet, 2H, } \text{H-6'})^*, \quad 3.55 \text{ (m, 2H, H-6'^*}, \quad 4.20 \text{ (m, 2H, H-6'^*)}, \quad 4.48 \text{ (m, 2H, H-5'^*).}

{^{13}}C-NMR (125 MHz, CDCl}_3 \delta (ppm): 12.6 \text{ and 12.7 (C-11), 25.6 and 25.6 (C-8), 27.1 and 27.1 (C-8'), 28.1 (C-10), 45.7 and 46.1 (C-4), 54.3 and 54.4 (C-2), 69.6 and 69.6 (C-6), 71.7 and 71.9 (C-5), 82.3 (C-9), 109.0 \text{ and 109.1 (C-7), 169.6 and 169.7 (C-1), 204.3 (C-3).}

MS (CI, CH}_4, \quad m/Z \%: 273.2 [M^+ +1] (5), 257.1 (3), 217.1 (41), 197.1 (27), 159.0 (100), 141.0 (38), 100.9 (10), 58.9 (31).

Methyl 2-methyl-3-oxopentanoate

Obtained as a product of the methyl propionate self condensation.

TLC (1:1 = P.E.:EtAc)

Presented also in its enol form (ketoester:enol form = 87:13).

\[ \begin{align*}
{^1}H-NMR (500 MHz, CDCl}_3 \delta (ppm): & \quad 1.07 \text{ (d, 3H, } {^3}J_{5,4} = 7.4 \text{ Hz, H-5)}, \quad 1.34 \quad \text{ (d, 3H, } {^3}J_{7,2} = 6.9 \text{ Hz, H-7)}, \quad 2.54 \text{ (m, 1H, H-4)}, \quad 2.61 \text{ (m, 1H, H-4'^*)}, \quad 3.54 \quad \text{ (q, 1H, } {^3}J_{2,7} = 7.3 \text{ Hz, H-2)}, \quad 3.73 \text{ (s, 3H, H-6).}

{^{13}}C-NMR (125 MHz, CDCl}_3 \delta (ppm): 7.9 \text{ (C-5), 13.1 (C-7), 34.9 (C-4), 52.0 (C-2), 52.6 (C-6), 171.4 (C-1), 206.7 (C-3).}

MS (CI, CH}_4, \quad m/Z \%: 145.0 [M^+ +1] (21), 113.0 (26), 57.1 (100).
Chapter 10. Experimental part

**tert-Butyl (5R)-6-(benzyloxy)-5-hydroxy-3-oxohexanoate**

\[
\begin{align*}
\text{C}_{17}H_{20}O_4 & \quad \text{Mol. Wt.: 300.35} \\
\text{t-BuO} & \quad \text{O} \\
\text{OH} & \quad \text{OBn} \\
\text{BnO} & \quad \text{O}
\end{align*}
\]

**Method B**: Starting from 0.17 mmol of ester. Purification by CC (φ1.5 cm, 9 cm of SiO₂, 6 mL fractions; 2:1 = P.E.:EtAc) yielded 42.6 mg (77%) of colourless oil. Additionally 3.1 mg (6%) of starting ester was recuperated.

TLC (1:1 = P.E.:EtAc)

\[ R_f = 0.48 \]

UV, KMnO₄, vanilline (brown);

UV, KMnO₄, vanilline (blue);

β-ketoester

Presented also in its enol form (ketoester:enol form* = ~1:1).

\[ ^1H\text{-NMR (300 MHz, CDCl}_3\text{)} \delta(\text{ppm}): 1.47 \text{ (s, 9H, H-10)}, 2.61 \text{ (d, 1H, } J_{4,3} = 6.3 \text{ Hz, H-4)}, 2.76 \text{ (d, 1H, } J_{4',3} = 6.2 \text{ Hz, H-4')}, 2.93 \text{ and 2.99 (two broad s, partial overlap, 2H, H-8 and H-8')}, 2.60 \text{ (s, 2H, H-2)}, 3.44-3.55 \text{ (m, 2H, H-6)}, 4.30 \text{ (m, 1H, H-5)}, 4.55 \text{ and 4.56 (s, 2H, H-7 and H-7*)}, 5.15 \text{ (s, 1H, H-2')}, 7.33-7.37 \text{ (m, 5H, aromatic CH).}
\]

\[ ^{13}C\text{-NMR (125 MHz, CDCl}_3\text{)} \delta(\text{ppm}): 28.1 \text{ (C-10)}, 38.5 \text{ and 46.4 (C-4), 51.4 (C-2), 66.7 (C-5'), 66.9 (C-6), 67.4 (C-5), 73.3 (C-6*), 73.6 (C-7), 82.4 (C-9), 127.9, 128.7, 130.2, 138.0 (aromatic CH and C_q), 166.4 (C-1'), 172.1 (C-1), 203.2 (C-3).
\]

MS (APCI), \( m/Z \text{ (%): 308.3 [M'] (9), 313.0 (34), 217.1 (26), 181.1 (49), 91.0 (100).} \)
10.5.4 General procedure for synthesis of Weinreb amides

A suspension of ester (1.0 mmol, 1.0 eq) and amine (1.25 mmol, 1.25 eq) in THF (3.3 mL, 0.3 M) was cooled to -20°C and iso-propyl magnesium bromide (2.06 mmol, 2.06 eq, 2.0 M solution in Et₂O) was added. The resulting mixture was stirred at -10°C for 1h and saturated aqueous solution of NH₄Cl (2 mL) was added. After warming to r.t., brine (2 mL) was added and the layers were separated. Aqueous layer was extracted with Et₂O (3x10 mL) and combined organic layers were dried over MgSO₄ and evaporated under reduced pressure.

N-methoxy-N-methyl-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)acetamide

Starting from 10.0 mmol of ester. Purification by CC (φ 3.5 cm, 12 cm of SiO₂, 20 mL fractions; 2:1 to 1:1 = P.E.:EtAc) provided 1.93g (95%) of colourless oil.
Chapter 10. Experimental part

TLC (1:1 = P.E.:EtAc)

\[ R_f = 0.54 \]
\[ R_f = 0.19 \]

\begin{align*}
\text{ester, KMnO}_4 \\
\text{product, KMnO}_4
\end{align*}

\[ \text{Me} \]

\[ \text{OMe} \]

\[ 1 \]
\[ 2 \]
\[ 3 \]
\[ 4 \]
\[ 5 \]
\[ 6' \]
\[ 6 \]
\[ 7 \]
\[ 8 \]

\[ 1^\text{H}-\text{NMR (500 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 1.37 \text{ and } 1.43 \text{ (two s, 6H, H-6 and 6')}, \\
2.56 \text{ (dd, 1H, } ^2J_{2,2'} = 16.1 \text{ Hz, } ^3J_{2,3} = 7.8 \text{ Hz, H-2)}, 3.00 \text{ (dd, 1H, } ^2J_{2',2} = 16.1 \text{ Hz, } ^3J_{2',3} = 5.1 \text{ Hz, H-2'}), 3.18 \text{ (s, 3H, H-7)}, 3.65 \text{ (dd, 1H, } ^2J_{4',4} = 8.3 \text{ Hz, } ^3J_{4,3} = 6.9 \text{ Hz, H-4}), 3.70 \text{ (s, 3H, H-8)}, 4.23 \text{ (dd, 1H, } ^2J_{4,4'} = 8.3 \text{ Hz, } ^3J_{4',3} = 6.0 \text{ Hz, H-4'}), 4.47 \text{ (quintet, 1H, } ^3J = 6.0 \text{ Hz, H-3}).
\]

\[ 13^\text{C}-\text{NMR (125 MHz, CDCl}_3\text{)} \delta (\text{ppm}): 25.6 \text{ and } 27.1 \text{ (C-6 and 6')}, 32.1 \text{ (C-7), 36.9 (C-2), 61.5 (C-8), 69.9 (C-4), 72.5 (C-3), 109.0 (C-5), 171.6 (C-1)}.
\]

\[ \text{MS (APCI), } m/Z (\%) : \text{ 203.9 [M+] (5), 147.0 (9), 146.0 (100), 128.1 (10), 85.0 (4).} \]

\[ [\alpha]_{20}^\text{D} = -21.3^\circ \text{ (c = 1.20, CHCl}_3\text{).} \]

\text{CAS number: } [148933-43-1].

### 10.5.5 General procedure for synthesis of acetals

\[ \text{HC(OEt)}_3 \]

\[ \text{NH}_2\text{NO}_3, \text{EtOH} \]

\[ \text{HC(OEt)}_3 \]

A warm solution of \( \text{NH}_2\text{NO}_3 \) (0.04 mmol, 4 mol%) in EtOH (1 ml, 1.0 M to acrolein) was added to a mixture of acrolein (1.0 mmol, 1.0 eq) and \( \text{HC(OEt)}_3 \) and the resulting mixture was allowed to react at room temperature for 12 hours. The light-red solution was then filtered and
Chapter 10. Experimental part

Na₂CO₃ (5g, 5g/mmol) was added. This mixture was then fractionally distilled using a good column.

3,3-diethoxy-2-methyl-1-propene

\[
\text{\begin{align*}
\text{C}_4\text{H}_6\text{O} & \rightarrow \text{C}_8\text{H}_{16}\text{O}_2
\end{align*}}
\]

Starting from 100 mmol of methacrolein. Distilled under atmospheric pressure (b.p. = 132-135°C) yielded 11.0 g (76%) of colourless liquid.

\[
\begin{align*}
\text{\textit{H}} & \text{NMR (500 MHz, CDCl}_3\text{)} \delta \text{ (ppm): } 1.23 \ (\text{t, } 6\text{H, }^{3}J_{6,5} = 7.1 \text{ Hz, H-6}), 1.74 \\
& \quad \ (\text{s, } 3\text{H, H-4}), 3.41-3.66 \ (\text{m, } 4\text{H, H-5}), 4.69 \ (\text{s, } 1\text{H, H-1}), 4.99 \ (\text{d, } 1\text{H, }^{1}J = \\
& \quad \ 1.5 \text{ Hz, H-3}), 5.10 \ (\text{t, } 1\text{H, }^{1}J = 0.9 \text{ Hz, H-3'}). \\
\text{\textit{C}} & \text{-NMR (125 MHz, CDCl}_3\text{)} \delta \text{ (ppm): } 15.3 \ (\text{C-6}), 17.2 \ (\text{C-4}), 61.8 \ (\text{C-5}), \\
& \quad 104.1 \ (\text{C-1}), 113.8 \ (\text{C-3}), 142.6 \ (\text{C-2}).
\end{align*}
\]

CAS number: [23553-27-7].

10.5.6 α−Alkylation of esters

Methyl 2-cyanopropanoate

\[
\text{\begin{align*}
\text{C}_4\text{H}_5\text{NO}_2 & \rightarrow \text{C}_5\text{H}_7\text{NO}_2
\end{align*}}
\]
Chapter 10. Experimental part

A suspension of NaH (1.05 mmol, 60% suspension in mineral oil, 1.05 eq) in THF (10 mL, 0.1M) was cooled to 0°C and MeOH (0.05 mmol, 5 mol%), followed by cyanoacetate (1.0 mmol, d = 1.123 g.cm\(^{-3}\), 1.0 eq), was slowly added. After 30 min at 0°C, a solution of MeI (1.0 mmol, d = 2.28 g.mL\(^{-1}\), 1.0 eq) in THF (2 mL) was added dropwise and the resulting mixture was stirred at 0°C for 4h. Water (5 mL) was added and layers were separated. The aqueous layer was extracted with Et\(_2\)O (3x10 mL) and combined organic layers were washed with brine (10 mL), dried over MgSO\(_4\) and evaporated under reduced pressure. The residue was purified by CC (φ1.5 cm, 10 cm of SiO\(_2\), 7 mL fractions; 5:1 = P.E.:EtAc) to give 81 mg (72%) of colourless oil.

TLC (2:1 = P.E.:EtAc)

\[ \begin{array}{cccc}
R_f &=& 0.46 \\
R_f &=& 0.36 \\
R_f &=& 0.23 \\
\end{array} \]

IR (NaCl, neat) \(\nu^{-1}(\text{cm}^{-1})\): 2956, 2254, 1752, 1458, 1437.

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta(\text{ppm})\): 1.61 (d, 3H, \(^3J_{2,5}\) = 7.5 Hz, H-5), 3.57 (q, 1H, \(^3J_{2,5}\) = 7.5 Hz, H-2), 3.83 (s, 3H, H-4).

\(^13\)C-NMR (62.5 MHz, CDCl\(_3\)) \(\delta(\text{ppm})\): 14.3 (C-5), 31.2 (C-2), 52.4 (C-4), 115.2 (C-1), 167.1 (C-3).

CAS number: [14618-77-0].
Chapter 10. Experimental part

10.6 Multicomponent Sakurai reaction

Method A: Starting from benzyl protected aldehyde.
A solution of aldehyde (1.0 mmol, 1.0 eq), silyl enol ether (1.07, 1.07 eq) and allylsilane (1.1 mmol, d = 0.719 g.mL⁻¹, 1.1 eq) in dry CH₂Cl₂ (10 mL, 0.1 M) was cooled to -78°C and TMSOTf (0.1 mmol, d = 1.182 g.mL⁻¹, 0.1 eq) was added. The reaction mixture was stirred -78°C for 4h. Saturated aqueous solution of NaHCO₃ (5 mL) was added and the whole mixture was extracted with CH₂Cl₂ (3x20 mL). Combined organic layers were washed with water (5 mL), brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure to give colourless oil.

Method B: Starting from TBS protected aldehyde.
A solution of aldehyde (1.0 mmol, 1.0 eq) and silyl enol ether (1.07, 1.07 eq) in CH₂Cl₂ (2 mL, 0.5M) was cooled to -78°C and precooled (-78°C) solution of allylsilane (1.1 mmol, d = 0.719 g.mL⁻¹, 1.1 eq) and TMSOTf (0.1 mmol, d = 1.182 g.mL⁻¹, 10 mol%) in CH₂Cl₂ (0.5 mL) was added. The reaction mixture was stirred for 48h at -78°C and then was allowed to warm to 0°C over 2h. Hüning base (Et₂PrN) (0.2 mmol, 20 mol%) was added. The resulting solution was allowed to warm to r.t. and the solvent was distilled off under atmospheric pressure.

Method C: Starting from TBDPS protected aldehyde.
A solution of aldehyde (1.0 mmol, 1.0 eq) and silyl enol ether (1.07, 1.07 eq) in CH₂Cl₂ (2 mL, 0.5M) was cooled to -78°C and precooled (-78°C) solution of allylsilane (1.1 mmol, d = 0.719 g.mL⁻¹, 1.1 eq) and TMSOTf (0.1 mmol, d = 1.182 g.mL⁻¹, 10 mol%) in CH₂Cl₂ (0.5 mL) was added. The reaction
mixture was stirred for 5h at –78°C and then was allowed to warm to 0°C over 1h. Hüning base (Et$_2$Pr$i$N) (0.2 mmol, 20 mol%) was added. The resulting solution was allowed to warm to r.t. and the solvent was distilled off under atmospheric pressure.

(4$R$,5$S$)-5-(Benzyloxy)-4-[(1$R$)-1-ethyl-2-methyl-2-propenyl]oxy-1-hexene

![Chemical structure](attachment:image.png)

Method A: Starting from 0.44 mmol of aldehyde. Purified by CC (φ 1.0 cm, 12 cm of SiO$_2$, 5 mL fractions; P.E.:Et$_3$P = 50:1→4:1) to give 23 mg (18%, d.r. = 1.1) of colourless oil.

$^{1}$H-NMR (300 MHz, CDCl$_3$) δ(ppm): 0.84 (t, 3H, $^3$J$_{6,5}$ = 7.2 Hz, H-6), 1.15 (d, 3H, $^3$J$_{1,2}$ = 6.2 Hz, H-1), 1.22 (d, 3H, $^3$J$_{1,2}$ = 6.2 Hz, H-1*), 1.42-1.54 (m, 2H, H-5), 1.62 and 1.66 (s, 3H, H-12), 2.16-2.49 (m, 2H, H-7), 3.39-3.44 (m, 1H, H-4), 3.49-3.69 (m, 3H, H-3, H-3* and H-4*), 3.65 and 3.87 (t, 1H, $^2$J$_{13,13'}$ = 7.2 Hz, H-13 and H-13*), 4.71-5.03 (m, 4H, H-11 and H-9), 5.61-5.92 (m, 1H, H-8), 7.18-7.39 (m, 5H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ(ppm): 8.2 and 8.4 (C-6), 15.3 and 16.7 (C-1), 17.1 and 17.2 (C-12), 26.2 and 26.4 (C-5), 36.3 and 36.7 (C-7), 70.8 and
70.9 (C-13), 69.2 and 74.7 (C-2), 79.3 and 80.4 (C-4), 84.6 and 85.9 (C-3), 111.4 and 112.3 (C-11), 114.3 and 114.9 (C-9), 136.9 and 137.5 (C-8), 143.7 and 143.9 (C-10), 127.4-139.3 (aromatic CH and C₉).

MS (APCI), m/z (%): 289.6 (100) [M++1], 213.0 (39), 181.1 (21), 163.1 (51).

HRMS, m/z: calcd. (C₁₉H₂₉O ++H+) 289.2168; found 289.2170.

tert-Butyl[(1S,2R)-2-[(1R)-1-ethyl-2-methyl-2-propenyl]oxy-1-methyl-4-pentenyl]oxy]dimethylsilane

Method B: Starting from 42.0 mmol of aldehyde. Purified by CC (φ 9.5 cm, 12 cm of SiO₂, 50 mL fractions; P.E.:CH₂Cl₂ = 20:1→10:1→5:1) to give 9.56 g (80%) of colourless oil.

TLC (4:1 = P.E.:CH₂Cl₂)

1H-NMR (300 MHz, CDCl₃) δ(ppm): 0.06 (s, 6H, H-13), 0.82-0.92 (m, 12H, H-6 and H-15), 1.15 (d, 3H, J₁,₂ = 6.7 Hz, H-1), 1.40-1.61 (m, 2H, H-5), 1.65 (broad s, 3H, H-12), 2.10-2.23 (m, 2H, H-7), 3.35 (m, 1H, H-4),
3.82 (m, 1H, H-2), 3.94 (t, 1H, $^3J = 6.5$ Hz, H-3), 4.86 and 4.89 (broad s, 1H, H-11), 4.98-5.06 (m, 2H, H-9), 5.75-5.86 (m, 1H, H-8).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ(ppm): -4.6 and -4.4 (C-13), 10.3 (C-6), 16.6 (C-12), 18.1 (C-14), 18.4 (C-1), 26.0 (C-15), 26.2 (C-5), 36.7 (C-7), 70.5 (C-2), 80.3 (C-4), 85.4 (C-3), 113.7 (C-11), 116.2 (C-9), 135.8 (C-C-8), 144.9 (C-10).

MS (APCI), $m/z$ (%): 313.0 (100) [M$^{++}$+1], 295.1 (37), 213.0 (46), 181.1 (45), 163.1 (54).

HRMS, $m/z$: calcd. (C$_{18}$H$_{36}$O$_2$SiNa) 335.2382; found 335.2392.

$[\alpha]_{D}^20$: +46.2°(c = 1.02, CHCl$_3$).

**tert-Butyl[(1S,2R)-2-[(1R)-1-ethyl-2-methyl-2-propenyl]oxy-1-methyl-4-pentenyl]oxy]diphenylsilane**

![Reaction Scheme](image)

**Method C**: Starting from 9.0 mmol of aldehyde. Purified by CC (φ 3.5 cm, 12 cm of SiO$_2$, 20 mL fractions; P.E.:CH$_2$Cl$_2 = 20:1 \rightarrow 10:1 \rightarrow 5:1$) to give 3.18 g (81%) of colourless oil.
Chapter 10. Experimental part

TLC (3:1 = P.E:CH₂Cl₂)

UV, KMnO₄, vanilline (light blue), silylenol ether

UV, KMnO₄, vanilline (deeph blue), adduct

$^{1}$H-NMR (300 MHz, CDCl₃) δ(ppm): 0.83 (t, 3H, $^3$$J_{6,5}$ = 7.2 Hz, H-6), 1.04 (s, 9H, H-14), 1.16 (d, 3H, $^3$$J_{1,2}$ = 6.7 Hz, H-1), 1.41-1.62 (m, 2H, H-5), 1.64 (broad s, 3H, H-12), 2.10-2.24 (m, 2H, H-7), 3.34 (m, 1H, H-4), 3.81 (m, 1H, H-2), 3.95 (m, 1H, $^3$$J$ = 6.6 Hz, H-3), 4.86 and 4.88 (broad s, 1H, H-11), 4.98-5.07 (m, 2H, H-9), 5.75-5.86 (m, 1H, H-8), 7.31-73 (m, 10H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl₃) δ(ppm): 10.4 (C-6), 16.7 (C-12), 18.7 (C-13), 18.5 (C-1), 27.7 (C-14), 26.2 (C-5), 36.9 (C-7), 70.4 (C-2), 80.2 (C-4), 85.5 (C-3), 113.7 (C-11), 116.3 (C-9), 135.9 (C-8), 144.8 (C-10), 129.3-137.3 (aromatic CH and C₆).

MS (APCI), m/z (%): 437.6 (100) [M⁺+1], 214.0 (46), 181.1 (47), 163.1 (47), 91.0 (67).

HRMS, m/z: calcld. (C₂₈H₄₀O₂SiNa) 459.2695; found 459.2700.

$[\alpha]_{D}^{20}$: +58.7°(c = 1.02, CHCl₃).
Chapter 10. Experimental part

**tert-Butyl**[(1R,2S)-2-[(1S)-1-ethyl-2-methyl-2-propenyl]oxy-1-methyl-4-pentenyl]oxy|diphenylsilane

\[
\text{OTBDPS} + \text{TMS} \rightarrow \text{OTBDPS}
\]

\[
\text{C}_9\text{H}_{20}\text{OSi} \quad \text{Mol. Wt.: 172,34}
\]

\[
\text{C}_9\text{H}_{20}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 188,34}
\]

\[
\text{C}_{28}\text{H}_{40}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 436,7}
\]

**Method C**: Purified by CC (ϕ 1.5 cm, 12 cm of SiO\(_2\), 5 mL fractions; P.E.: CH\(_2\)Cl\(_2\) = 20:1 → 10:1 → 5:1) to give 332 mg (76%) of colourless oil. 
\([\alpha]^{20}_D = -64.7^\circ (c = 1.03, \text{CHCl}_3)\).

**tert-Butyl**[(1S,2R)-2-[(1S)-1-ethyl-2-methyl-2-propenyl]oxy-1-methyl-4-pentenyl]oxy|diphenylsilane

\[
\text{OTBDPS} + \text{TMS} \rightarrow \text{OTBDPS}
\]

\[
\text{C}_9\text{H}_{20}\text{OSi} \quad \text{Mol. Wt.: 172,34}
\]

\[
\text{C}_9\text{H}_{20}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 188,34}
\]

\[
\text{C}_{28}\text{H}_{40}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 436,7}
\]

**Method C**: Starting from 1.4 mmol of aldehyde. Purified by CC (ϕ 3.5 cm, 12 cm of SiO\(_2\), 10 mL fractions; P.E.: CH\(_2\)Cl\(_2\) = 20:1 → 10:1 → 5:1) to give 501 mg (82%) of colourless oil.
Chapter 10. Experimental part

TLC (3:1 = P.E:CH₂Cl₂)

\[ \text{UV, KMnO}_4, \text{vanilline (light blue), silylenol ether} \]

\[ \text{UV, KMnO}_4, \text{vanilline (deep blue), adduct} \]

\[ ^1\text{H-NMR (300 MHz, CDCl₃)} \delta (\text{ppm}): 0.74 (t, 3H, } ^3J_{6,5} = 7.2 \text{ Hz, H-6), 1.02-1.15 (m, 12H, H-1 and H-14), 1.42-1.67 (m, 2H, H-5), 1.64 \text{ (broad s, 3H, H-12), 2.04-2.20 (m, 2H, H-7), 3.12 (t, 1H, } ^3J = 6.5 \text{ Hz, H-3), 3.23 (dt, 1H, } ^3J = 8.2 \text{ Hz, } ^3J = 3.4 \text{ Hz, H-4), 3.94 (m, 1H, H-2), 4.49 \text{ and 4.77 (broad s, 1H, H-11), 4.89-5.13 (m, 2H, H-9), 5.76-5.94 (m, 1H, H-8), 7.33-77 (m, 10H, aromatic CH).} \]

\[ ^{13}\text{C-NMR (75 MHz, CDCl₃)} \delta (\text{ppm}): 8.8 \text{ (C-6), 16.5 (C-12), 18.6 (C-13), 19.1 (C-1), 26.1 (C-5), 27.9 (C-14), 36.3 (C-7), 70.8 (C-2), 82.3 (C-4), 85.4 (C-3), 113.6 (C-11), 116.3 (C-9), 136.0 (C-C-8), 144.9 (C-10), 129.1-137.4 \text{ (aromatic CH and Cq).} \]

MS (APCI), \textit{m/z} (%): 437.6 (100) [M⁺+1], 214.0 (46), 181.1 (47), 163.1 (47), 91.0 (67).

HRMS, \textit{m/z}: calcd. (C₂₈H₄₀O₂SiNa) 459.2695; found 459.2697.

\([\alpha]^{20}_D: +30.4°(c = 0.98, \text{CHCl}_3).\]
**Chapter 10. Experimental part**

*tert*-Butyl[(1R,2S)-2-[(1R)-1-ethyl-2-methyl-2-propenyl]oxy-1-methyl-4-pentenyl]oxy|diphenylsilane

\[
\text{OTBDPS} + \text{OTMS} \xrightarrow{C_6H_{14}Si} \text{OTBDPS} \quad \text{Mol. Wt.: 114,26} \\
\text{C}_9\text{H}_{20}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 188,34} \\
\text{C}_{20}\text{H}_{40}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 436,7}
\]

*Method C*: Purified by CC (φ 3.5 cm, 12 cm of SiO₂, 5 mL fractions; P.E.:CH₂Cl₂ = 20:1→10:1→5:1) to give 328 mg (75%) of colourless oil. 

\([\alpha]^{20}_D: -34.3° (c = 1.00, \text{CHCl}_3)\).

*tert*-Butyl [(1S,2R) and (1S,2S)-1-methyl-2-(3-phenylpropoxy)-4-pentenyl]oxy|diphenylsilane

\[
\text{OTBDPS} + \text{OTMS} \xrightarrow{C_6H_{14}Si} \text{OTBDPS} \quad \text{Mol. Wt.: 114,26} \\
\text{C}_9\text{H}_{20}\text{O}_2\text{Si} \quad \text{Mol. Wt.: 188,34} \\
\text{Ph} \quad \text{Mol. Wt.: 208,37} \\
\text{Ph} \quad \text{Mol. Wt.: 472,73}
\]

*Method C*: Purified by CC (φ 1.5 cm, 10 cm of SiO₂, 6 mL fractions; P.E.:Et₂O = 50:1→25:1) to give 411 mg (87%) of colourless oil.

TLC (20:1 = P.E.:Et₂O)

- **R₁ = 0.58**
  - UV, KMnO₄, vaniline (purple), product
- **R₂ = 0.28**
  - UV, KMnO₄, vaniline (pink), aldehyde

---

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Chapter 10. Experimental part

Mixture of two diastereoisomers at the C-3 position (d.r. = 1.2:1)

IR (NaCl, neat) $\nu$(cm$^{-1}$):3071, 3027, 2931, 2857, 1641, 1589, 1428, 1110.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.01-1.11 (m, 12H, H-1 and H-11),
1.68 and 1.89 (pentet, 2H, $^3J = 5.6$ Hz, H-5), 2.11-2.38 (m, 2H, H-7), 2.54 and 2.70 (t, 2H, $^3J = 6.1$ Hz, H-6), 3.05-3.36 (m, 2H, H-4 and H-4$^\star$), 2.48 (m, 1H, H-2), 3.67 (t, 1H, $^3J = 6.4$ Hz, H-3), 3.81-3.92 (m, 1H, H-2$^\star$),
3.98 (pentet, $^3J = 4.6$ Hz, H-3), 4.97-5.17 (m, 2H, H-9), 5.68-5.98 (m, 1H, H-8), 7.11-7.79 (m, 15H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): 18.9 (C-10), 19.6 and 23.0 (C-1), 27.4 (C-11), 32.0, 32.3, 32.6, 32.9 and 34.6 (C-5, C-6 and C-7), 70.5 (C-4), 73.8 (C-2), 77.2 (C-2), 82.8 (C-3), 84.2 (C-3), 116.4 and 117.1 (C-9), 134.9 and 136.1 (C-8), 129.1-134.6 (aromatic CH and C$_q$).

MS (APCI), m/z (%): 473.4 (4) [M$^+$+1], 395.0 (72), 349.0 (100), 297.0 (18), 251.0 (32).

HRMS, m/z: calcd. (C$_{31}$H$_{40}$O$_2$SiNa) 495.2695; found 495.2699.

tert-Butyl ((1S,2R) and (1S,2S)-1-methyl-2-[(2-methylallyl)oxy]-4-pentenyloxy)diphenylsilane

Method C: Purified by CC ($\phi$ 1.5 cm, 10 cm of SiO$_2$, 6 mL fractions; P.E.:Et$_2$O = 50:1→25:1) to give 411 mg (87%) of colourless oil.

Mol. Wt.: 114,26

Mol. Wt.: 188,34

Mol. Wt.: 144,29

Mol. Wt.: 408,65

Mol. Wt.: 114,26

Mol. Wt.: 408,65

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TLC (50:1 = P.E.:Et₂O)

- Rf = 0.66
- Rf = 0.41
- Rf = 0.17

Mixture of two diastereoisomers at the C-3 position (d.r. = 1.5:1)

IR (NaCl, neat) ν (cm⁻¹): 3070, 3029, 2931, 2861, 1640, 1588, 1429, 1110.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 0.97 (d, 3H, 3J₁,₂ = 6.9 Hz, H-1), 1.06 (s, 9H, H-12), 1.72 (broad s, 3H, H-10), 2.02-2.18 (m, 2H, H-7), 3.47-3.72 (m, 2H, H-2 and H-3), 4.02 (s, 2H, H-4), 5.85-5.11 (m, 4H, H6 and H-9), 5.67-5.91 (m, 1H, H-8), 7.36-7.77 (m, 10H, aromatic CH).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 16.2 (C-10), 18.4 and 10.3 (C-1), 19.5 (C-11), 27.2 (C-12), 35.1 and 36.8 (C-7), 66.7 (C-4), 71.5 and 72.8 (C-2), 75.2 and 77.4 (C-3), 110.2 (C-6), 116.4 and 116.9 (C-9), 127.4-139.1 (C-8, C-5 and aromatic CH and C₉).

MS (APCI), m/z (%): 408.7 (35) [M⁺], 375.27 (48), 255.3 (100).

HRMS, m/z: calcd. (C₂₆H₃₆O₂SiNa) 431.2382; found 431.2385.

**tert-Butyl[[(1S,2R)-1-methyl-2-[(1S) and (1R)-1-methyl-3-butenyl]oxy-4-pentenyl]oxy]diphenylsilane**

![Diagram](image-url)
Chapter 10. Experimental part

Method C: Purified by CC (ϕ 1.5 cm, 10 cm of SiO₂, 6 mL fractions; P.E.:Et₂O = 100:1→50:1) to give 359 mg (85%) of colourless oil.

TLC (50:1 = P.E.:Et₂O)

Rf = 0.65
Rf = 0.50
Rf = 0.17

UV, KMnO₄, vaniline (pink), aldehyde
UV, KMnO₄, vaniline (blue), silyl ether
UV, KMnO₄, vaniline (blue), product

Mixture of two diastereoisomers at the C-4 position (d.r. = 1.02:1)
IR (NaCl, neat) ν(cm⁻¹): 3068, 3031, 2974, 2965, 2861, 1641, 1587, 1431.

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 0.85-0.97 (m, 15H, H-1, H-11 and H-13), 2.04-2.30 (m, 4H, H-5 and H-8), 3.48-3.80 (m, 3H, H-2, H-3 and H-4), 4.98-5.11 (m, 4H, H-7 and H-10), 5.62-5.87 (m, 2H, H-6 and H-7), 7.39-7.72 (m, 10H, aromatic CH).

¹³C-NMR (62.5 MHz, CDCl₃) δ (ppm): 18.7 (C-1), 19.1 (C-12), 22.9 (C-11), 27.2 (C-12), 35.0 (C-8), 38.3 (C-5), 71.8 and 73.0 (C-4), 75.2 (C-2), 77.4 (C-3), 116.1 (C-7), 116.9 (C-10), 125.9-137.1 (C-6, C-9 and aromatic CH and Cq).

MS (CI, CH₄/N₂O), m/z (%): 442.9 (67) [M⁺], 375.2 (100), 329.2 (12).
HRMS, m/z: calcd. (C₂₇H₃₈O₂SiNa) 445.2539; found 445.2542.
Chapter 10. Experimental part

\[((1S,2R)-2-(1-(3-butenyl)-4-pentenyl)oxy-1-methyl-4-pentenyl)oxy)(tert-
butyl)diphenylsilane

Method C: Purified by CC (ϕ 1.5 cm, 10 cm of SiO₂, 6 mL fractions; P.E.:Et₂O = 100:1→50:1) to give 343 mg (72%) of colourless oil. TLC (50:1 = P.E.:Et₂O)

\[1H\text{-NMR (300 MHz, CDCl}_3\text{)} \delta (ppm): 1.08 (s, 9H, H-13), 1.13 (d, 3H, }^3J_{1,2} = 5.7 \text{ Hz, H-1), 1.22-1.38 (m, 2H, H-5), 1.51-1.64 (m, 2H, H-5'), 1.90-2.27 (m, 4H, H-6 and H-9), 3.13 (dt, 1H, }^1J = 10.5 \text{ Hz, }^3J_{1,2} = 2.9 \text{ Hz, H-4), 3.36 (td, 1H, }^3J = 6.4 \text{ Hz, }^3J = 2.9 \text{ Hz, H-2), 3.61 (t, 1H, }^3J = 5.7 \text{ Hz, H-3), 4.82-5.14 (m, 6H, H-7 and H-10), 5.60-5.91 (m, 3H, H-7 and H-10), 7.35-7.71 (m, 10H, aromatic CH).}

\[1^3C\text{-NMR (75 MHz, CDCl}_3\text{)} \delta (ppm): 16.8 (C-1), 19.2 (C-12), 27.2 (C-12), 29.9 and 30.0 (C-6), 34.1 and 34.3 (C-5), 36.3 (C-9), 72.1 (C-4), 76.6 (C-2), 81.2 (C-3), 114.2 and 114.3 (C-8), 116.4 (C-11), 128.4-139.3 (C-7, C-10 and aromatic CH and C_6).}
MS (CI, CH₄/N₂O), m/z (%): 477.3 (28) [M+1], 453.1 (21), 339.1 (57), 189.1 (100), 149.1 (63), 123.0 (35).

HRMS, m/z: calcd. (C₃₁H₄₄O₂SiNa) 499.3008; found 499.3002.

[α]²₀: +49.2°(c = 0.99, CHCl₃).

**tert-Butyl((1S,2R)-2-[(1,1-dimethylallyl)oxy]-1-methyl-4-pentenyloxy) diphenylsilane**

![Chemical Structure](image)

**Method C:** Purified by CC (ϕ 1.5 cm, 10 cm of SiO₂, 6 mL fractions; P.E.:Et₂O = 100:1 → 50:1) to give 283 mg (67%) of colourless oil.

**TLC (50:1 = P.E.:Et₂O)**

<table>
<thead>
<tr>
<th>Rf</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.81</td>
<td>UV, KMnO₄ (blue), product</td>
</tr>
<tr>
<td>0.61</td>
<td>UV, KMnO₄ (blue), silyl ether</td>
</tr>
<tr>
<td>0.17</td>
<td>UV, KMnO₄ (pink), aldehyde</td>
</tr>
</tbody>
</table>

¹H-NMR (300 MHz, CDCl₃) δ(ppm): 1.02 (d, partial overlap 3H, ³J₁,₂ = 5.7 Hz, H-1), 1.05-1.18 (m, 15H, H-10 and H-12), 2.24-2.29 (m, 2H, H-7), 3.82 (m, 1H, H-2), 3.95 (td, 1H, ³J₁ = 6.2 Hz, ³J₂ = 1.5 Hz, H-3), 4.82-5.16 (m, 4H, H-6 and H-9), 5.65-5.93 (m, 2H, H-5 and H-8), 7.36-7.72 (m, 10H, aromatic CH).
\[ ^{13}\text{C-NMR} \ (75 \text{ MHz, CDCl}_3) \delta \text{ (ppm): } 19.2 \text{ (C-11), } 19.3 \text{ (C-1), } 27.3 \text{ (C-12), } 38.2 \text{ (C-7), } 67.1 \text{ (C-4), } 77.3 \text{ (C-2), } 84.5 \text{ (C-3), } 114.2 \text{ (C-6), } 116.3 \text{ (C-9), } 127.4-137.2 \text{ (C-5, C-8 and aromatic CH and C=O).} \]

MS (Cl, CH\textsubscript{4}/N\textsubscript{2}O), \( m/z \) (%): 423.4 (100) \([\text{M}^+1]\), 339.5 (61), 190.1 (87), 149.1 (44), 119.0 (45).

HRMS, \( m/z \) : calcd. \( (\text{C}_{27}\text{H}_{38}\text{O}_2\text{SiNa}) \) 445.2539; found 445.2542.

\([\alpha]^{20}_D: +38.1^\circ\) \((c = 0.99, \text{CHCl}_3)\).

\textit{tert-}butyl\[(1\text{S,2R}) \text{ and } (1\text{S,2S})-2-\text{(cyclohexyloxy)-1-methyl-4-pentenyl}]\oxydiphenylsilane

\begin{align*}
\text{OTBDPS} \quad + \quad \text{TMSO} \quad \xrightarrow{} \quad \text{TBDPS} \\
\text{C}_{19}\text{H}_{24}\text{O}_2\text{Si} \quad \text{Mol. Wt.: } 312.46 \\
\text{C}_{9}\text{H}_{20}\text{OSi} \quad \text{Mol. Wt.: } 172.34
\end{align*}

\text{C}_{28}\text{H}_{40}\text{O}_2\text{Si} \quad \text{Mol. Wt.: } 436.7

\text{M}ethod \ C: \text{ Purified by CC (}\phi \ 1.5 \text{ cm, } 10 \text{ cm of SiO}_2, \ 6 \text{ mL fractions; P.E.:Et}_2\text{O } = 100:1\rightarrow 50:1\text{) to give 387 mg (89\%) of colourless oil.}

TLC (50:1 = P.E.:Et\textsubscript{2}O)

\begin{align*}
\text{R}_f = 0.82 & \quad \text{UV, KMnO}_4, \text{vaniline (blue), product} \\
\text{R}_f = 0.64 & \quad \text{UV, KMnO}_4, \text{vaniline (blue), silyl ether} \\
\text{R}_f = 0.17 & \quad \text{UV, KMnO}_4, \text{vaniline (pink), aldehyde}
\end{align*}

A mixture of two epimers at C4 position \((d.r. = 8:1)\). * represents the minor stereoisomer.
Chapter 10. Experimental part

$^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 0.89-1.75 (m, 10H, H-5, H-6 and H-7), 1.07 (s, 9H, H-12), 1.11 (d, 3H, $^3$J$_{1,2}$ = 6.2 Hz, H-1), 2.04-2.27 (m, 2H, H-8), 3.11 (dt, 1H, $^3$J = 10.1 Hz, $^3$J = 3.8 Hz, H-4*), 3.39 (pentet, 1H, $^3$J = 4.8 Hz, H-4), 3.45-3.57 (m, 2H, H-2 and H-2*), 3.77-3.88 (m, 2H, H-3 and H-3*), 4.94-5.12 (m, 2H, H-10), 5.49-5.90 (m, 1H, H-9), 7.36-7.78 (m, 10H, aromatic CH).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm): 18.5 (C-11), 19.2 (C-1), 23.2 (C-6) 25.7 (C-7), 27.4 (C-12), 31.4 (C-5), 34.1 (C-8), 74.2 (C-4), 80.2 (C-2), 85.4 (C-3), 116.6 (C-10), 127.9-136.3 (C-9 and aromatic CH and Cq).

MS (CI, CH$_4$/N$_2$O), $m/z$ (%): 438.4 (100) [M$^{+1}$], 345.2 (24), 190.1 (36), 150.3 (25), 119.0 (28).

HRMS, $m/z$: calcd. (C$_{28}$H$_{40}$O$_2$SiNa) 459.2695; found 459.2699.

**tert-Butyl[((1S,2R,3R)-2-[(1R)-1-ethyl-2-methyl-2-propenyl]oxy-1,3-dimethyl-4-pentenyl]oxy]diphenylsilane**

\[ \begin{array}{c}
\text{TBDPSO} \\
\text{C$_{29}$H$_{42}$O$_2$Si} \\
\text{Mol. Wt.: 450.73}
\end{array} \]

\[ \begin{array}{c}
\text{C$_{29}$H$_{42}$O$_2$Si} \\
\text{Mol. Wt.: 450.73}
\end{array} \]

**Method C**: Purified by CC (φ 1.5 cm, 10 cm of SiO$_2$, 5 mL fractions; P.E.:Et$_2$O = 100:1→50:1) to give 198 mg (44%) of colourless oil.
Chapter 10. Experimental part

TLC (50:1 = P.E:Et₂O)

\[ R_f = 0.17 \]
\[ R_f = 0.84 \]
\[ R_f = 0.69 \]

UV, KMnO₄, vaniline (pink), aldehyde

UV, KMnO₄, vaniline (blue), product

UV, KMnO₄, vaniline (pink), aldehyde

\[ ^1\text{H-NMR (300 MHz, CDCl}_3\text{) } \delta \text{ (ppm): 0.83 (t, 3H, } ^3\text{J}_{6,5} = 7.2 \text{ Hz, H-6), 1.06 (s, 9H, H-14), 1.17 (d, 3H, } ^3\text{J}_{1,2} = 6.7 \text{ Hz, H-1), 1.15 (d, 3H, } ^3\text{J}_{0,7} = 6.1 \text{ Hz, H-1), 1.40-1.63 (m, 2H, H-5), 1.63 \text{ (broad s, 3H, H-13), 2.87-2.93 (m, 1H, H-7), 3.35 (m, 1H, H-4), 3.83 (m, 1H, H-2), 3.98 (t, 1H, } ^3\text{J} = 6.4 \text{ Hz, H-3), 4.87 and 4.88 (broad s, 1H, H-11), 4.99-5.09 (m, 2H, H-9), 5.75-5.89 (m, 1H, H-8), 7.31-73 (m, 10H, aromatic CH).} \]

\[ ^13\text{C-NMR (75 MHz, CDCl}_3\text{) } \delta \text{ (ppm): 10.7 (C-6), 16.8 (C-12), 18.7 (C-14), 18.6 (C-1), 27.7 (C-15), 26.3 (C-5), 38.7 (C-7), 71.4 (C-2), 80.5 (C-4), 86.4 (C-3), 113.8 (C-12), 116.4 (C-9), 134.7 (C-8), 144.7 (C-11), 129.2-137.5 (aromatic CH and C_q).} \]

MS (APCI), \( m/z \) (%): 451.4 (100) [M⁺+1], 329.0 (72), 181.1 (100), 118.8 (67), 90.9 (67).

HRMS, \( m/z \): calcd. (C₂₈H₄₀O₂SiNa) 473.2852; found 473.2856.

\[ [\alpha]_{D}^{20} +39.4° (c = 0.93, \text{CHCl}_3). \]
Chapter 10. Experimental part

**tert-Butyl\([(1S,2R)-2-\{1R\}-1-ethyl-2-methyl-2-propenyl\}oxy-1,4-dimethyl-4-pentenyl]oxy\]diphenylsilane**

![Chemical structure diagram]

Method C: Purified by CC (φ 1.0 cm, 11 cm of SiO₂, 5 mL fractions; P.E.:CH₂Cl₂ = 20:1→10:1→5:1) to give 356 mg (79%) of colourless oil. TLC (3:1 = P.E.:CH₂Cl₂)

1H-NMR (300 MHz, CDCl₃) δ (ppm): 0.84 (t, 3H, \(^3J_{6,5} = 7.2\) Hz, H-6), 1.05 (s, 9H, H-14), 1.18 (d, 3H, \(^3J_{1,2} = 6.7\) Hz, H-1), 1.41-1.62 (m, 2H, H-5), 1.52 (broad s, 3H, H-15), 1.65 (broad s, 3H, H-12), 2.11-2.27 (m, 2H, H-7), 3.35 (m, 1H, H-4), 3.80 (m, 1H, H-2), 3.94 (t, 1H, \(^3J = 6.7\) Hz, H-3), 4.47 and 4.48 (broad s, 1H, H-9), 4.87 and 4.89 (broad s, 1H, H-11), 7.35-7.5 (m, 10H, aromatic CH).

13C-NMR (75 MHz, CDCl₃) δ (ppm): 10.5 (C-6), 16.6 (C-12), 18.6 (C-1), 18.9 (C-13), 27.5 (C-14), 26.1 (C-5), 40.8 (C-7), 71.3 (C-2), 80.5 (C-4), 85.7 (C-3), 113.7 (C-11), 114.2 (C-9), 142.7 (C-8), 144.8 (C-10), 129.5-137.4 (aromatic CH and C=).
Chapter 10. Experimental part

MS (APCI), \( m/z \) (%): 451.5 (100) [M\(^{+1}\)], 214.0 (52), 180.9 (39), 163.0 (34), 90.9 (74).

HRMS, \( m/z \): calcd. (C\(_{29}\)H\(_{42}\)O\(_2\)SiNa) 473.2852; found 473.2850.

\([\alpha]\)\(^{20}\): +63.2°(c = 1.02, CHCl\(_3\)).

**tert-Butyl((1S,2R) and (1S,2S)-1,4-dimethyl-2-[(1,1,1-trimethylsilyl)oxy]-4-pentyloxy)diphenylsilane**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{SiMe}_3 & \quad \text{Si} \\
\text{Ph} & \quad \text{Ph} \\
1 & \quad 2 \quad 3 \\
4 & \quad 5 \quad 6 \\
7 & \quad 8 \\
\end{align*}
\]

Obtained, in some cases, as a side product during the Sakurai multicomponent reaction. Generally, it is formed when the reaction is performed at higher temperature than -78°C (from -50°C).

IR (NaCl, neat) \( \nu (\text{cm}^{-1}) \): 3070, 3048, 2955, 2931, 2893, 1640, 1589, 1472, 1427, 1250, 1110.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm): 0.09 (s, 9H, H-9), 0.98 (d, 3H, \( ^3J_{1,2} = 6.3 \) Hz, H-1), 1.07 (s, 9H, H-8), 2.09-2.19 (m, 1H, H-4), 2.17-2.27 (m, 2H, H-4\(^\prime\)), 2.53-1.61 (m, 1H, H-4\(^\prime\)), 3.50-3.79 (m, 2H, H-2 and H-3), 4.98-5.11 (m, 2H, H-6), 5.68-5.83 (m, 1H, H-5), 7.35-7.72 (m, 10H, aromatic CH).
Chapter 10. Experimental part

$^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (ppm): -0.5 (C-9), 19.7 (C-1), 19.9 (C-7), 27.4 (C-8), 38.4 (C-4), 71.8 (C-2’), 72.9 (C-2), 75.1 (C-3’), 77.6 (C-3), 116.3 (C-6’), 117.2 (C-6), 127.2-137.2 (C-5 and aromatic CH and C$q$).

MS (APCI), $m/z$ (%): 427.2 (16) [M$^+$+1], 349.0 (82), 282.9 (42), 252.9 (77), 238.8 (100), 196.8 (52), 163.0 (33).

10.7 Epoxides

10.7.1 General procedure for epoxide opening

Method A: Et$_2$AlCN-mediated epoxide opening.

A solution of epoxide (1.0 mmol, 1.0 eq) in benzene (5 mL, 0.2M) was cooled to 0°C and Et$_2$AlCN (1.01 mmol, 1.0M solution in toluene, 1.01 eq) was added dropwise. The resulting mixture was allowed to warm to r.t. After 1h at r.t., Et$_2$O (20 mL) was added and the reaction mixture was again cooled to 0°C. After additional 5 min, 10% solution of H$_2$SO$_4$ (10 mL) was carefully added. (ATTENTION: During the addition of H$_2$SO$_4$, HCN is generated, thus reaction mixture was connected with 50% aqueous KOH solution and argon was bubbled through the reaction mixture for 10 min). The resulting layers were separated and aqueous layer was extracted with Et$_2$O (3x20 mL). Combined organic layers were washed with brine (10 mL), dried over MgSO$_4$ and evaporated under reduced pressure.

Method B: Cu(I)-mediated epoxide opening.

Method B: Cu(I)-mediated epoxide opening.
Chapter 10. Experimental part

A suspension of epoxide (1.0 mmol, 1.0 eq) and CuBr•SMe₂ (41 mg, 0.2 mmol, 0.2 eq) in dry THF (10 mL, 0.1 M) was cooled to -20°C and Grignard reagent (1.5 mmol, 1.5 eq) was added dropwise. The slightly yellow suspension changed to dark brown solution during the addition. After 1 h at -20°C, the reaction was quenched by addition of saturated aqueous solution of NH₄Cl (5 mL) and resulting layers were separated. Aqueous layer was extracted with Et₂O (3x10 mL). Combined organic layers were washed with brine (5 mL), dried over MgSO₄ and evaporated under reduced pressure.

**Method C: Epoxide opening with alkyl phenyl sulfones**

\[
\begin{align*}
\text{R}^1\text{CH}_2\text{SO}_2\text{Ph} + \text{R}^1\text{CH}_2\text{SO}_2\text{Ph} & \xrightarrow{n\text{BuLi}} \text{R}^1\text{CH}_2\text{SO}_2\text{Ph} + \text{R}^1\text{CH}_2\text{SO}_2\text{Ph} \\
\text{THF/HMPA} = 10:1 & \text{at } -78°C
\end{align*}
\]

A solution of sulfone (3.0 mmol) in THF/HMPA = 10:1 (10 mL) was cooled to -78°C and nBuLi (3.2 mmol, 1.6 M solution in hexane) was added dropwise. After 30 min at -78°C, epoxide (1.0 mmol) in THF (0.5 mmol) was added. The reaction mixture was stirred at -78°C for 1 h and then was allowed to warm to r.t. over 3h. Saturated aqueous solution of NH₄Cl (5 mL) was added and the layers were separated. Aqueous layer was extracted with EtAc (3x15 mL) and combined organic layers were washed with brine (10 mL), dried over MgSO₄ and evaporated under reduced pressure.

**(3R)-4-(Benzyloxy)-3-hydroxybutanenitrile**

\[
\begin{align*}
\text{C}_{11}\text{H}_{13}\text{NO}_2 & \xrightarrow{\text{O}} \text{C}_{10}\text{H}_{12}\text{O}_2 \\
\text{Mol. Wt.: 191.23} & \text{Mol. Wt.: 164.2}
\end{align*}
\]

**Method A**: Starting from 2.0 mmol of epoxide. Solvent evaporation yielded 382 mg (99%) of colourless oil.
Chapter 10. Experimental part

TLC (1:1 = P.E.:EtAc)

Rf = 0.52

UV, KMnO₄, vanilline (yellow), nitrile

\[
\begin{align*}
\text{NC} & \quad \text{OH} \\
2 & \quad 3 \\
4 & \quad 5 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \\
1 & \quad 6 \\
\end{align*}
\]

\[\delta \text{ (ppm): } 1.72 \text{ (broad s, } 1\text{H, } H-6), 2.58 \text{ (dd, } 1\text{H}, 2J_{4,4'} = 13.2 \text{ Hz, } 3J_{4,3} = 6.2 \text{ Hz, H-4}), 2.65 \text{ (dd, } 1\text{H, } 2J_{4,4'} = 13.2 \text{ Hz, } 3J_{4',3} = 6.2 \text{ Hz, H-4'}), 3.58 \text{ (dd, } 1\text{H, } 2J_{2,2'} = 9.7 \text{ Hz, } 3J_{2,3} = 5.9 \text{ Hz, H-2), 3.60 \text{ (dd, } 1\text{H, } 2J_{2,2'} = 9.7 \text{ Hz, } 3J_{2',3} = 4.1 \text{ Hz, H-2'}), 4.12 \text{ (pentet, } 1\text{H, } 3J = 5.9 \text{ Hz, H-3), 7.32-7.38 \text{ (m, } 5\text{H, aromatic CH).}}
\]

\[
\begin{align*}
\text{13C-NMR (75 MHz, CDCl₃) } \delta \text{ (ppm): } 22.6 \text{ (C-2), 66.8 (C-3), 72.2 (C-5), 73.9 (C-4), 118.2 (C-1), 128.1, 128.4, 128.8, 137.4, \text{ (aromatic CH and Cq).}}
\end{align*}
\]

MS (APCI), m/z (%): 192.1 (92) \( [M^{+}+1] \), 193.1 (11), 181.2 (17), 149.1 (14), 91.0 (100).

\[\alpha^{20}_D: \text{ to be measured.}\]

HRMS, m/z: calcd. for C₁₁H₁₃NO₂Na 214.0844; found 214.0842.

\( (2\text{S})-1-[(4\text{-Methoxybenzyl)}\text{oxy}]-4-[(1,1,1\text{-trimethylsilyl})\text{methyl}]-4\text{-penten-2-ol} \)
Chapter 10. Experimental part

Method B: CuBr.SMe₂ was used. Purified by CC (φ 2.5 cm, 8 cm of SiO₂, 7 mL fractions; 5:1 = P.E.:EtAc) to give the titled compound as colourless oil (308.2 mg, 99%)

TLC (1:1 = P.E.:EtAc)

\[ R_f = 0.66 \]
\[ R_f = 0.45 \]

UV, KMnO₄, vanilline (deep blue), product

UV, KMnO₄, epoxide

\[^{1}H\text{-NMR (500 MHz, CDCl}_3\text{) } \delta (\text{ppm}): 0.03 (s, 9H, H-1), 1.53 (d, \text{ } 1H, ^2J_{3,3'} = 13.4 \text{ Hz, H-3}), 1.53 (d, \text{ } 1H, ^2J_{3',3} = 13.3 \text{ Hz, H-3'}), 2.13 \text{ and } 2.14 \text{ (brad s, 2H, H-5)}, 2.35 (d, \text{ } 1H, ^{3}J_{6,17} = 3.0 \text{ Hz, H-17}), 3.37 \text{ (dd, } 1H, ^{2}J_{7,7'} = 9.6 \text{ Hz, } ^{3}J_{7,6} = 4.4 \text{ Hz, H-7}), 3.50 \text{ (dd, } 1H, ^{2}J_{7',7} = 9.6 \text{ Hz, } ^{3}J_{7',6} = 3.3 \text{ Hz, H-7'}), 3.81 (s, 3H, H-15), 3.96 (m, 1H, H-6), 4.50 (s, 2H, H-9), 4.65 (s, 1H, H-16), 4.69 (t, 1H, J = 0.8 Hz, H-16'), 6.89 (d, 2H, ^{3}J_{12,11} = 8.5 \text{ Hz, H-12}), 7.27 (d, 1H, ^{3}J_{11,12} = 8.4 \text{ Hz, H-11}). \]

\[^{13}C\text{-NMR (125 MHz, CDCl}_3\text{) } \delta (\text{ppm}): 1.2 \text{ (C-1)}, 26.8 \text{ (C-3), 42.6 \text{ (C-5), 55.5 \text{ (C-15), 68.5 \text{ (C-6), 73.2 \text{ (C-9), 74.0 \text{ (C-7), 110.4 \text{ (C-16), 114.0 \text{ (C-12), 129.6 \text{ (C-11), 130.3 \text{ (C-10), 144.0 \text{ (C-4), 159.4 \text{ (C-13).}}}}}}}}}

MS (Cl\text{, CH}_4\text{, } m/Z (\%): 308.8 [M^+] (24), 259.5 (9), 208.9 (13), 157.7 (39), 137.1 (100), 120.8 (42), 88.5 (21), 83.0 (37), 73.2 (24).

\[^{[a]} ^{20}D: \text{ to be measured.}\]
Chapter 10. Experimental part

(2R)-1-[(4-methoxybenzyl)oxy]-4-penten-2-ol

Method B: CuBr.SMe$_2$ was used. Purified by CC ($\phi$ 2.5 cm, 8 cm of SiO$_2$, 7 mL fractions; 2:1 = P.E.:EtAc) to give the titled compound as colourless oil (221.3 mg, 99%)

TLC (1:1 = P.E.:EtAc)

$\alpha$$^\circ$20: $-2.34^\circ$ (c = 1.98, CHCl$_3$).

CAS number: [194342-84-2].
(2R)-1-(benzyloxy)-4-penten-2-ol

\[
\begin{align*}
\text{C}_{10}H_{12}O_2 & \quad \text{Mol. Wt.: 164.2} \\
\text{C}_{12}H_{16}O_2 & \quad \text{Mol. Wt.: 192.25}
\end{align*}
\]

\text{Method B: Starting from 23.0 mmol of epoxide. CuCN was used. Sufficiently pure product was obtained after the work-up (4.42g, quant.).}

\text{TLC (1:1 = P.E.:EtAc)}

\[
\begin{align*}
\text{Rf} & = 0.45 \\
\text{Rf} & = 0.66
\end{align*}
\]

\text{UV, KMnO}_4, \text{vanilline (deep blue), product}

\text{UV, KMnO}_4, \text{epoxide}

\text{1H-NMR (300 MHz, CDCl}_3\text{) } \delta (\text{ppm}): 2.28 (t, 2H, } J = 6.9 \text{ Hz, H-3), 2.55 (broad s, 1H, H-8), 3.9 (dd, 1H, }^{2}J_{5,5'} = 9.5 \text{ Hz, }^{3}J_{5,4} = 7.4 \text{ Hz, H-5), 3.53 (dd, 1H, }^{2}J_{5',5} = 9.5 \text{ Hz, }^{3}J_{5',4} = 3.5 \text{ Hz, H-5'\text{')), 3.88 (octet, 1H, }^{3}J = 3.5 \text{ Hz, H-4), 4.57 (d, 2H, H-7), 5.08-5.15 (m, 2H, H-1), 5.84 (m, 1H, H-2).}

\text{13C-NMR (75 MHz, CDCl}_3\text{) } \delta (\text{ppm}): 38.1 (C-3), 69.9 (C-4), 73.5 (C-7), 74.1 (C-5), 117.7 (C-1), 127.9, 127.9, 128.6, 129.6 and 138.1 (aromatic CH and C_q), 134.4 (C-2).

\text{MS (APCI), } m/Z(%) : 193.0 [M^+1] (25), 181.1 (84), 157.1 (79), 129.1 (61), 105.0 (54), 91.0 (100).

\text{[\alpha]^{20}_D: -2.23^\circ (c = 2.65, CHCl}_3\text{).}

\text{CAS number: [194342-84-2]}. 
Chapter 10. Experimental part

(2R)-1-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-4-penten-2-ol

Method B: Starting from 10.0 mmol of epoxide. CuCN was used. Sufficiently pure product was obtained after the work-up (2.16 g, quant.).

TLC (10:1 = P.E.:EtAc)

UV, KMnO₄, vanilline (deep blue), product

UV, KMnO₄, epoxide

1H-NMR (300 MHz, CDCl₃) δ (ppm): 0.08 (s, 6H, H-6), 0.9 (s, 9H, H-8), 2.25 (tt, 2H, J = 6.2 Hz, J = 1.2 Hz, H-3), 2.41 (broad s, 1H, H-9), 3.3.47 (dd, 1H, 2J₅,₅' = 10.0 Hz, 3J₅,₄ = 7.1 Hz, H-5), 3.65 (dd, 1H, 2J₅',₅ = 10.0 Hz, 3J₅',₄ = 3.8 Hz, H-5'), 3.70 (m, partial overlap, 1H, H-4), 5.07-5.15 (m, 2H, H-1), 5.80 (m, 1H, H-2).

13C-NMR (75 MHz, CDCl₃) δ (ppm): -5.2 and -5.1 (C-6), 18.5 (C-7), 26.1 (C-8), 37.8 (C-3), 66.7 (C-4), 71.3 (C-5), 117.6 (C-1), 134.7 (C-2).

[α]D²⁰: -0.95° (c = 1.26, CHCl₃).

CAS number: [604775-01-1].
Chapter 10. Experimental part

(2R,3S) and (2R,3R)-1-[(4-Methoxybenzyl)oxy]-3-(phenylsulfonyl)butan-2-ol

Method C: Starting from 1.63 mmol of epoxide. Purified by CC (φ 3.5 cm, 11 cm of SiO₂, 20 mL fractions; 3:1 = P.E.:EtAc) to give 588 mg (99%) of thick colourless oil.

TLC (1:2 = P.E.:EtAc)

Mixture of C2 epimers (d.r. = 1.45:1).

$^1$H-NMR (250 MHz, CDCl₃) δ (ppm): 1.26 (d, 3H, $^3J_{1,2} = 8.6$ Hz, H-1), 1.11-1.61 (m, 2H, H-3), 2.01-2.18 (m, 1H, H-2), 2.56 and 2.70 (broad s, 1H, H-4 and H-4'), 3.24-3.29 (m, 3H, H-5 and H-4), 3.79 (s, 3H, H-11), 4.03 (broad s, 1H, H-12), 4.43 (s, 2H, H-6), 6.87 (d, 2H, $^3J_{8,9} = 8.7$ Hz, H-9), 7.21 (d, 2H, $^3J_{8,9} = 8.7$ Hz, H-8), 7.50-7.87 (m, 5H, aromatic CH).

$^{13}$C-NMR (125 MHz, CDCl₃) δ (ppm): 11.6 and 12.8 (C-1), 55.4 (C-11), 64.1 and 64.5 (C-2), 66.4 and 66.9 (C-4), 68.8 and 73.8 (C-3), 73.2 and 74.2 (C-5), 114.0 (C-9), 128.8-137.3 (aromatic CH and C₉), 159.4 (C-10).

MS (APCI), m/z (%): 365.2 [M⁺+1] (100), 255.2 (47), 241.2 (83), 121.1 (52).
Chapter 10. Experimental part

HRMS, \( m/z \): calcd. (C\(_{19}\)H\(_{24}\)O\(_5\)SNa) 387.1242; found 387.1239.

10.7.2 General procedure for epoxidation of olefins

Method A: \( m \)CPBA-mediated epoxidation

A solution of olefin (1.0 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (10 mL, 0.1 M) was cooled to 0°C and \( m \)CPBA (1.2 mmol, 70% \( m \)CPBA (contains 30% of H\(_2\)O and PhCOOH), 1.2 eq) was added in three portions. Solid dry NaHCO\(_3\) (4.0 mmol, 4 eq) was added and the resulting suspension was stirred at r.t. for 12h. Et\(_2\)O/H\(_2\)O = 2:1 (30 mL) was added and layers were separated. Aqueous layer was extracted with Et\(_2\)O (3x30 mL) and combined organic layers were washed with brine (10 mL), dried over MgSO\(_4\) and evaporated under reduced pressure.

\((R)-(+)\)-Goniothalamine oxide

Starting from 0.1 mmol of olefin. Purified, acid and water free, \( m \)CPBA (4.0 eq) and dry NaHCO\(_3\) (10 eq) were used. Purified by column chromatography (\( \phi \) 1.5 cm, 10 cm of SiO\(_2\), 6 mL fractions; P.E.:EtAc = 3:1) yielding 21.2 mg (98%) of colourless crystals.
Chapter 10. Experimental part

TLC (1:1 = P.E.:EtAc)

\[ \begin{array}{c}
R_f = 0.38 \\
R_f = 0.31 \\
\end{array} \]

UV, KMnO₄, olefin

\[ \begin{array}{c}
\text{UV, KMnO₄, alcohol} \\
\end{array} \]

\[ \text{O} \]

\[ \begin{array}{c}
\text{Ph} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{5} \\
\text{6} \\
\text{7} \\
\end{array} \]

\[ \begin{array}{c}
\text{1H-NMR} \\
\text{Synthetic (300 MHz)} & \text{Natural (60 MHz)}^{454} \\
\text{Natural (60 MHz)}^{454} \\
\end{array} \]

\[ \begin{array}{c|c|c}
\text{H-4} & 2.61 (m, 2H) & 2.55 (m, 2H) \\
\text{H-6} & 3.29 (dd, 1H, J₆,₅ = 5.6 Hz, J₆,₇ = 2.0 Hz) & 3.25 (dd, 1H, J = 5.4 Hz and 1.8 Hz) \\
\text{H-7} & 3.91 (d, 1H, J₇,₆ = 1.8 Hz) & 3.86 (d, 1H, J = 1.8 Hz) \\
\text{H-5} & 4.45 (dt, 1H, J₅,₄ = 9.4 Hz, J₅,₄' and ₆ = 5.6 Hz) & 4.48 (dt, 1H, J = 7.4 Hz and 5.4 Hz) \\
\text{H-2} & 6.09 (dt, 1H, J₂,₃ = 9.7 Hz, J₂,₄ = 2.0 Hz, J₂,₄ = 5.6 Hz) & 6.03 (dt, 1H, J = 9.5 Hz and 1.6 Hz) \\
\text{H-3} & 6.97 (m, 1H) & 6.92 (dt, 1H, J = 9.5 Hz and 4.7 Hz) \\
\text{Aromatic CH} & 7.34-7.40 (m, 5H) & 7.30 (m, 5H) \\
\end{array} \]

\[ \begin{array}{c|c|c}
\text{C-4} & 26.2 & 25.8 \\
\text{C-6} & 57.5 & 57.2 \\
\text{C-7} & 61.7 & 61.4 \\
\text{C-5} & 77.4 & 77.0 \\
\text{C-2} & 121.8 & 121.6 \\
\end{array} \]

\[ \text{13C-NMR} \]

\[ \text{Synthetic (75 MHz)} \]

\[ \text{Natural (20 MHz)}^{454} \]

Chapter 10. Experimental part

<table>
<thead>
<tr>
<th>Aromatic CH and Cq</th>
<th>125.9-135.9</th>
<th>125.8-135.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3</td>
<td>144.5</td>
<td>144.2</td>
</tr>
<tr>
<td>C-1</td>
<td>163.0</td>
<td>162.7</td>
</tr>
</tbody>
</table>

M.p. = 91-92°C; lit.\(^4\text{54}\) 90-94°C.

IR (KBr) \(\nu\)(cm\(^{-1}\)): 3053 (m), 3024 (m), 2923 (m), 1721 (s, C=O), 1601 (m), 1243 (m), 1032 (m), 804 (m).

MS (APCI), \(m/z\) (%): 217.0 (100) [M\(^{+}\)H], 199.0 (46), 171.1 (83), 143.1 (45), 139.0 (32), 105.0 (31), 91.0 (31).

HRMS, \(m/z\): calcd. for C\(_{13}\)H\(_{12}\)O\(_{3}\) [M+Na\(^{+}\)] 239.0684; found 239.0682.

\([\alpha]\text{\scriptsize{20}}} = +101.4^\circ \ (c \ 0.88, \ CHCl_3); \ \text{lit.\(^4\text{54}\)} \ [\alpha]\text{\scriptsize{25}}} = +100.7^\circ \ (c \ 0.70, \ CHCl_3).

CAS number: [110011-51-3]

10.8 Reformatsky-type reactions

10.8.1 Blaise reaction

![Blaise reaction diagram]

To a suspension of Zn (3.0 mmol, 3.0 eq) and nitrile (1.0 mmol, 1.0 eq) in THF (10 mL, 0.1M), MeSO\(_3\)H (0.01 mmol, 1 mol%) was added and resulting mixture was refluxed for 10 min. Then, bromoester (1.8 mmol, 1.8 eq) in THF (2 mL) was added to the refluxing reaction mixture via syringe pump over a period of 69 min. The resulting dark brown suspension was refluxed for additional 1 h and cooled to 0°C. 2.0 M aqueous solution of HCl (3 mL or until solution became clear) was carefully added and the resulting mixture was stirred at r.t. for next 30 min. EtAc (60 mL) was added and the
whole mixture was washed with saturated aqueous solution of NaHCO₃ (20 mL), brine, dried over MgSO₄ and evaporated under reduced pressure.

Methyl (5R)-6-(benzyloxy)-5-hydroxy-3-oxohexanoate

\[
\begin{align*}
\text{C}_{11}
& \quad \text{H}_{14}
\quad \text{N}_{2}
\quad \text{O}_{2}
\quad \text{MeO}
\quad \text{OBn}
\quad \text{OH}
\quad \text{NC}
\quad \text{OBn}
\quad \text{OH}
\quad \text{MeO}
\quad \text{OBn}
\end{align*}
\]

Mol. Wt.: 191.23

Mol. Wt.: 266.29

Purification by CC (ϕ 3.5cm, 9 cm of SiO₂, 10 mL fractions; P.E.:EtAc = 4:1→1:1) yielded 186 mg (70%) of colourless oil.

TLC (1:1 = P.E.:EtAc)

Presented as a mixture of keto-enol forms (keto:enol = 91:9).

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3032, 2951, 1741, 1638.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ (ppm): 2.76 (broad s, 1H, H-4), 2.78 (d, 1H, \(^3J_{4',5} = 3.5\) Hz, H-4’), 2.82 (broad s, partial overlap, 1H, H-9), 3.45 (dd, 1H, \(^3J_{6,6'} = 10.2\) Hz, \(^3J_{6,5} = 6.4\) Hz, H-6), 3.51 (dd, partial overlap, 1H, \(^3J_{6',6} = 10.2\) Hz, \(^3J_{6',5} = 4.4\) Hz, H-6’), 3.52 (s, 2H, H-7), 4.30 (pentet, 1H, \(^3J = 5.0\) Hz, H-5), 3.74 (s, 3H, H-8), 4.56 (s, 2H, H-7), 7.28-7.39 (m, 5H, aromatic CH).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) δ (ppm): 46.5 (C-4), 49.9 (C-2), 52.6 (C-8), 66.9 (C-6), 73.3 (C-5), 73.7 (C-7), 128.0, 128.3, 128.7, 138.0 (aromatic CH and Cq), 167.6 (C-1), 202.5 (C-3).
Chapter 10. Experimental part

MS (APCI), m/z (%): 266.8 (9) [M⁺+1], 248.1 (7), 171.1 (12), 141.0 (19), 91.0 (100), 81.0 (14).

[α]₂₀ D: to be measured.

CAS number: [221082-58-2]

Methyl (5R)-6-(benzyloxy)-5-hydroxy-2-methyl-3-oxohexanoate

Starting from 2.5 mmol of nitrile. Purification by CC (ϕ 4.5cm, 8 cm of SiO₂, 20 mL fractions; P.E.:EtAc = 4:1→1:1) yielded 547 mg (78%) of slightly yellow oil.

TLC (1:1 = P.E.:EtAc)

Two diastereoisomers + keto-enol forms.

IR (NaCl, neat) ν(cm⁻¹): 3032, 2951, 1743, 1635.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 1.34 (d, 3H, ³J₉₂ = 7.0 Hz, H-9), 1.35 (d, 3H, ³J₉₂ = 7.4 Hz, H-9'), 2.76-2.88 (m, 2H, H-4), 3.40-3.62 (m, 3H, H-6 and H-2), 3.75 (s, 3H, H-8), 3.78 (s, 3H, H-8'), 4.30 (broad s, 1H, H-5), 4.56 (s, 2H, H-7), 4.59 (s, 2H, H-7'), 7.29-7.39 (m, 5H, aromatic CH).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 12.8 and 12.9 (C-9), 44.9 and 45.0 (C-4), 52.8 (C-8), 53.4 and 53.5 (C-2), 66.9 and 67.0 (C-6), 73.2 and 73.3
(C-5), 73.6 (C-7), 127.7-138.0 (aromatic CH and Cq), 166.1 and 166.4 (C-1), 205.7 (C-3).

MS (APCI), m/z (%): 283.1 (100) [M+2], 257.1 (74), 227.0 (93), 211.0 (60), 157.1 (84), 91.0 (34).

HRMS, m/z: calcd. for C_{15}H_{20}O_{5}Na 280.1311; found 280.1319.

10.8.2 Intramolecular Reformatsky-type cyclization

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \quad \text{O} \quad \text{R}^2 \\
\text{Br} & \quad \text{O} \quad \text{O} \\
\text{R}_1 & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

A solution of bromoester (1.0 mmol, 1.0 eq) in THF (10 mL, 1.0 M) was cooled to 0°C and Zn (2.0 mmol, 2.0 eq), followed by I$_2$ (3 mg), was added in one portion. The resulting mixture was refluxed for 3h and then allowed to cool to r.t. EtAc (30 mL) was added and the resulting slurry was filtered over a pad of Celite. Filter-cake was washed with EtAc (2x20 mL) and collected filtrates were dried over Na$_2$SO$_4$ and evaporated.

**Ethyl 3-(propionyloxy)butanoate**

\[
\begin{align*}
\text{Br} & \quad \text{O} \quad \text{O} \\
\text{C}_9\text{H}_{16}\text{O}_4 & \quad \text{Mol. Wt.: 188,22} \\
\end{align*}
\]

Starting from 0.187 mmol of bromoester. Yielded 35 mg (99%) of ester as colourless oil.
Chapter 10. Experimental part

TLC (2:1 = P.E.:EtAc)

\[
\begin{array}{c}
\text{UV, KMnO}_4, \text{bromoester} \\
\text{UV, KMnO}_4, \text{ester} \\
\end{array}
\]

IR (NaCl, neat) \(\nu (\text{cm}^{-1})\): 2985, 2951, 1733.

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.10 (t, 3H, \(^3\)J\(_{9,8}\) = 7.5 Hz, H-9), 1.24 (t, 3H, \(^3\)J\(_{7,6}\) = 7.2 Hz, H-7), 1.29 (d, 3H, \(^3\)J\(_{4,3}\) = 6.4 Hz, H-4), 2.28 (q, 2H, \(^3\)J\(_{6,7}\) = 7.5 Hz, H-6), 1.48 (dd, 1H, \(^3\)J\(_{2,2'}\) = 15.5 Hz, \(^3\)J\(_{2,3}\) = 6.0 Hz, H-2), 2.63 (dd, 1H, \(^3\)J\(_{2',2}\) = 15.5 Hz, \(^3\)J\(_{2',3}\) = 7.5 Hz, H-2'), 4.12 (q, 2H, \(^3\)J\(_{8,9}\) = 7.1 Hz, H-8), 5.28 (sexet, 1H, \(^3\)J = 7.1 Hz, H-3).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): 9.3 (C-7), 14.4 (C-9), 20.1 (C-4), 28.0 (C-6), 41.2 (C-2), 60.8 (C-8), 67.4 (C-3), 170.5 (C-1), 173.9 (C-9).

MS (APCI), \(m/z\) (%): 188.9 (100) [M\(^++1\)], 142.9 (43), 114.9 (96), 68.9 (55).

CAS number: [253865-54-2].

10.9 Allylation of nitriles

A solution of nitrile (1.0 mmol, 1.0 eq) and allylsilane (1.1 mmol, d = 0.719 g.mL\(^{-1}\), 1.1 eq) in CH\(_2\)Cl\(_2\) (1 mL, 1.0 M) was cooled to 0°C and BCl\(_3\) (1.2 mmol, 1.0 M solution in heptane, 1.2 eq) was added slowly. The resulting yellowish suspension was allowed to stir at r.t. for 21h. The reaction progress was followed by IR spectroscopy. The resulting suspension was cooled to 0°C and saturated aqueous solution of NaHCO\(_3\) (10 mL) was
carefully added. Layers were separated and aqueous layer was extracted with CH$_2$Cl$_2$ (3x10 mL). Combined organic layers were washed with brine, dried over MgSO$_4$ and evaporated under reduced pressure. The residue was then purified by distillation due to its instability on silica gel (thermodynamically more stable olefin isomer is formed).

**Methyl 3-oxo-5-hexenoate**

Starting from 20.2 mmol of cyanoacetate. Purified by distillation (b.p. = 60°C at 2.9x10$^{-1}$ mbar) to give 2.07g (72%) of colourless oil. IMPORTANT: the temperature of the oil bath has to be kept under 70°C (65°C is optimal) to avoid the double bond migration).

**IR** (NaCl, neat) $\nu$ (cm$^{-1}$): 2857, 2852, 1753, 1718, 1668, 1618, 1560, 1438.

**1H-NMR** (250 MHz, CDCl$_3$) $\delta$ (ppm): 3.30 (broad d, 2H, $J = 7.1$ Hz, H-3), 3.48 (s, 2H, H-5), 3.73 (s, 3H, H-7), 5.14-5.25 (m, 2H, H-1), 5.88 (m, 1H, H-2).

**13C-NMR** (62.5 MHz, CDCl$_3$) $\delta$ (ppm): 47.9 (C-3), 48.6 (C-5), 53.7 (C-7), 120 (C-1), 129.7 (C-2), 163.6 (C-6), 201.1 (C-4).

**MS** (CI, CH$_4$/N$_2$O), $m/z$ (%): 142.8 (100) [M$^+$+1], 142.0 (42), 114.0 (28), 100.0 (18).

CAS number: [100636-39-3].
Chapter 10. Experimental part

**Methyl 2-methyl-3-oxo-5-hexenoate**

![Chemical structure](image)

Starting from 10.5 mmol of cyanoacetate. Purified by distillation (b.p. = 60°C at 2.8x10⁻¹ mbar) to give 1.23g (75%) of colourless oil. IMPORTANT: the temperature of the oil bath has to be kept under 70°C (65°C is optimal) to avoid the double bond migration).

IR (NaCl, neat) \(\nu^\text{r}(\text{cm}^{-1})\): 2859, 2851, 1753, 1717, 1668, 1617, 1560, 1431.

\(^1\)H-NMR (250 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.68 (d, 3H, \(^3\)J\(_{5,2}\) = 7.3 Hz, H-8), 3.31 (broad d, 2H, \(^2\)J = 7.1 Hz, H-3), 3.69 (q, 1H, \(^3\)J\(_{2,5}\) = 7.3 Hz, H-5), 3.75 (s, 3H, H-7), 5.13-5.26 (m, 2H, H-1), 5.87 (m, 1H, H-2).

\(^1\)C-NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) (ppm): 14.7 (C-8), 48.0 (C-3), 51.9 (C-5), 53.8 (C-7), 119.4 (C-1), 130.2 (C-2), 163.8 (C-6), 201.3 (C-4).

MS (Cl, CH\(_3\)/N\(_2\)O), \(m/z\) (%): 156.3 (42) [M⁺], 155.0 (100), 83.9 (27).

**10.10 Allylsilane synthesis**

(2-Bromoallyl)(trichlorosilane)

![Chemical structure](image)

---

To a solution of CuCl (264 mg, 2.66 mmol, 0.05 eq) and TEA (7.43 mL, 53.3 mmol, 1.0 eq) in dry Et₂O (27 mL, 2.0 M), a mixture of allyl bromide (5.0 mL, 53.3 mmol, 1.0 eq) and HSiCl₃ (5.9 mL, 58.6 mmol, 1.1 eq) was added dropwise over 40 min. The resulting white suspension was stirred at r.t. for 4.5 h and filtered over Celite®. Filter cake was washed with Et₂O (3x50 mL) and combined filtrates were evaporated under reduced pressure furnishing 13.4 g (99%) of the desired product as a slightly yellow oil. The product was used in the next step without further purification.

\[
\begin{align*}
\text{Br} & \quad \text{SiCl}_3 \\
\text{MeMgBr} & \quad \text{THF, -78°C to r.t.}
\end{align*}
\]

\[\text{C}_3\text{H}_4\text{BrCl}_3\text{Si} \quad \text{C}_6\text{H}_{13}\text{BrSi} \]

Mol. Wt.: 254.41
Mol. Wt.: 193.16

A solution of trichlorosilane (13.5 g, 53.3 mmol, 1.0 eq) in dry THF (107 mL, 0.5 M) was cooled to -78°C and MeMgBr (62.2 mL, 186.6 mmol, 3.5 eq) was added over 45 min. Resulting mixture was stirred at -78°C for additional 30 min and then was allowed to warm to r.t. overnight. The resulting suspension was cooled to 0°C and saturated aqueous solution of NH₄Cl (50 mL) was carefully added. Layers were separated and the aqueous
Chapter 10. Experimental part

phase was extracted with Et₂O (3x150 mL). Combined organic layers were washed with brine (50 mL), dried over MgSO₄ and evaporated under reduced pressure from the cold (0°C) bath (product is volatile) yielding 9.73 g (93%) of the desired product as a slightly green oil. Further distillation (20 mm Hg, 85°C on Buchi) did not afford the desired product in better purity.

\[
\begin{align*}
\text{SiMe}_3 & \quad \text{Br} \\
3 & \quad 2 & \quad 1 \\
\text{Br} & \quad \text{SiMe}_3^n
\end{align*}
\]

**1H-NMR** (500 MHz, CDCl₃) δ(ppm): 0.12 (s, 9H, H-4), 2.11 (d, 1H, J = 0.9 Hz, H-3), 5.23 (d, 1H, \(^2\)J₃,₃' = 1.4 Hz, H-3), 5.32 (d, 1H, \(^2\)J₃',₃ = 0.6 Hz, H-3').

**13C-NMR** (125 MHz, CDCl₃) δ(ppm): -1.3 (C-4), 33.6 (C-1), 114.1 (C-3), 131.4 (C-2).

**MS (APCI)**, m/z (%): 194.9 [M⁺] (13), 192.0 (12), 180.8 (72), 163.0 (41), 149.1 (49), 106.9 (33), 104.9 (44), 90.9 (33), 72.9 (100).

CAS number: [81790-10-5]

**2-Allyltrimethylsilane magnesium bromide (solution in THF)**

A suspension of Mg (138.4 mg, 5.69 mmol, 1.1 eq) in dry THF (10.4 mL, 0.5 M) was cooled to 0°C and bromoallylsilane (1.0 g, 5.18 mmol, 1.0 eq) was added. The resulting mixture was refluxed for 4 h. The resulting suspension was cooled to 0°C and remaining magnesium was allowed to sedimentate. After 30 min, slightly yellow-green solution was transferred via cannula to flame dried Schlenk under argon atmosphere. The NMR titration showed the concentration of the Grignard reagent to be 0.413 M.
The concentration of the obtained Grignard reagent was established by the following way:

\[
\text{MeO} \quad \text{CHO} \quad \text{MeO} \quad \text{OH} \\
\text{C}_8\text{H}_8\text{O}_2 \quad \text{C}_{14}\text{H}_{22}\text{O}_2\text{Si} \\
\text{Mol. Wt.: 136,15} \quad \text{Mol. Wt.: 250,41}
\]

A solution of \( p \)-methoxybenzaldehyde (100 mg, 0.73 mmol, 1.0 eq) in THF (2.0 mL, 0.36 M) was cooled to 0°C and Grignard reagent (734 μL, 0.37 mmol, 0.5 eq, ~0.5 M sol. in THF) was added. After 1 h at r.t., saturated aqueous solution of NH\(_4\)Cl (2 mL) was added and layers were separated. Aqueous layer was extracted with Et\(_2\)O (2x5 mL). Pooled organic layers were dried over MgSO\(_4\) and evaporated under reduced pressure. The concentration of the Grignard reagent was established by comparison of the methoxy-signals of the starting material and adduct.

**10.11 Cyclopropanation of vinyl boronates**

\[
\begin{array}{c}
\text{R'\O} \quad \text{B} \quad \text{OR}^1 \\
\text{R^2} \quad \text{EtN}_2 \\
\text{Pd(OAc)}_2 \\
\text{Et}_2\text{O, 0°C}
\end{array} \rightarrow \begin{array}{c}
\text{R'\O} \quad \text{B} \quad \text{OR}^1 \\
\text{R^2} \quad \text{EtN}_2 \\
\text{Pd(OAc)}_2 \\
\text{Et}_2\text{O, 0°C}
\end{array}
\]

To a suspension of \( N \)-ethylnitrourea (12.0 mmol) in Et\(_2\)O (7 mL, 0.7 M) in brown sample tube, 50% aqueous solution of KOH (2 mL) was added dropwise within 1 min at 0°C and the resulting mixture was stirred at 0°C for 15 min. The organic layer was transferred to a suspension of vinyl boronate (1.0 mmol, and Pd(OAc)$_2$ (0.2 mmol, 20 mol%) in Et\(_2\)O (10 mL, 0.1M) within 5 min. The resulting mixture was stirred at 0°C for next 30 min. Evaporation of the solvent yielded brown oil which was further purified by column chromatography on silica gel.

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Chapter 10. Experimental part

tert-Butyl[(1R,2S,3S) and (1R,2S,3R)-2-(4R,5R)-4,5-di[ methoxy (diphenyl)methyl]-1,3,2-dioxaborolan-2-yl-3-methylcyclopropyl) methoxy]dimethylsilane

Starting from 0.32 mmol of olefin. Purified by CC (φ1.0 cm, 13 cm of SiO₂, 4 mL fractions; 10:1 = P.E.:Et₂O) to give 214 mg (85%) of white foam.

Obtained as a mixture of two diastereoisomers at the C2 position (d.r. = 64:36). * for the minor stereoisomer.

IR (NaCl, neat) ν₁(cm⁻¹): 3060, 3027, 1386, 1075.

¹H-NMR (300 MHz, CDCl₃) δ (ppm): -0.97 (dd, 1H, ³J₁,₂ = 5.1 Hz, ³J₁,₃ = 5.2 Hz, H-1), 0.74 (m, 1H, H-3), 1.05 (s, 10H, H-2 and H-7), 1.08 (broad s, 3H, H-5), 3.01 (s, 6H, H-9), 3.52 (dd, 1H, ³J₄,₄' = 11.0 Hz, ³J₄,₃ = 8.4 Hz, H-4), 3.82 (dd, 1H, ³J₄',₄ = 11.0 Hz, ³J₄',₃ = 5.7 Hz, H-₄'), 5.27 (s, 2H, H-8), 7.21-7.71 (m, 30H, aromatic CH).

Minor diastereoisomer: ¹H-NMR (300 MHz, CDCl₃) δ (ppm): -1.02 (dd, 1H, ³J₁,₂ = 9.3 Hz, ³J₁,₃ = 5.2 Hz, H-1'), 0.51 (m, 1H, H-3'), 1.05 (s, 10H, H-2' and H-7), 1.08 (broad s, 3H, H-5), 3.01 (s, 6H, H-9), 3.52 (dd, 1H, ³J₄,₄' = 11.0 Hz, ³J₄,₃ = 8.4 Hz, H-4), 3.82 (dd, 1H, ³J₄',₄ = 11.0 Hz, ³J₄',₃ = 5.7 Hz, H-₄'), 5.27 (s, 2H, H-8), 7.21-7.71 (m, 30H, aromatic CH).
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\[^{13}\text{C}-\text{NMR (75 MHz, CDCl}_3\) \delta (ppm): -3.4 (C-1), 13.8 (C-2), 16.9 (C-5), 19.3 (C-6), 20.0 (C-3), 26.9 (C-7), 51.7 (C-9), 64.3 (C-4), 77.7 (C-10), 83.2 (C-8), 122.9, 127.0, 127.2, 127.3, 127.5, 128.2, 128.6, 128.9, 129.2, 129.5, 130.1, 130.4, 132.3, 132.8, 133.8, 134.2, 134.4, 135.3, 141.0, 141.2 (aromatic CH and C\text{q}).\]

MS (APCI), \(m/z\) (%): no molecular peak, characteristic peak: 197.0 (100) \([(\text{Ph}_2\text{COMe})^+\]).

El. anal.: calcd. C, 77.85, H, 7.05; found C, 77.91, H, 7.09;

\textit{tert}-Butyl[(1R,2S,3S) and (1R,2S,3R)-2-(4R,5R)-4,5-di[methoxy(diphenyl)methyl]-1,3,2-dioxaborolan-2-yl-3-methylcyclopropyl]methoxy]dimethylsilane

Starting from 0.12 mmol of olefin. Purified by CC (\(\phi 1.0\) cm, 10 cm of SiO\(_2\), 4 mL fractions; 10:1 = P.E.:Et\(_2\)O) to give 69 mg (87\%) of white foam.

Obtained as a mixture of two diastereoisomers at the C2 position (\(d.r. = 71:29\)). \* for the minor stereoisomer.

IR (NaCl, neat) \(\nu (\text{cm}^{-1})\): 3060, 3026, 1385, 1077.

\[^{1}\text{H}-\text{NMR (300 MHz, CDCl}_3\) \delta (ppm): -0.94 (dd, 1H, \(^3J_{1,2} = 5.3\) Hz, \(^3J_{1,3} = 5.2\) Hz, H-1), -0.01 and 0.00 (s, 3H, H-6), 0.73 (m, 1H, H-3), 0.88 (s,
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10H, H-2 and H-7), 1.06 (broad s, 3H, H-5), 3.02 (s, 6H, H-9), 3.46 (dd, 1H, \(3J_{4',4} = 11.0 \text{ Hz}, 3J_{4,3} = 8.1 \text{ Hz}, H-4\)), 3.79 (dd, 1H, \(3J_{4',4} = 11.0 \text{ Hz},\) \(3J_{4',3} = 5.6 \text{ Hz}, H-4'\)), 5.26 (s, 2H, H-8), 7.23-7.36 (m, 20H, aromatic CH).

**Minor diastereoisomer:** \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm): -0.98 (dd, 1H, \(3J_{1,2} = 9.2 \text{ Hz}, 3J_{1,3} = 5.1 \text{ Hz}, H-1^*\)), -0.01 and 0.00 (s, 3H, H-6), 0.49 (m, 1H, H-3*), 0.88 (s, 10H, H-2* and H-7), 1.06 (broad s, 3H, H-5), 3.02 (s, 6H, H-9), 3.46 (dd, 1H, \(3J_{4',4} = 11.0 \text{ Hz}, 3J_{4',3} = 5.6 \text{ Hz}, H-4'\)), 3.79 (dd, 1H, \(3J_{4',4} = 11.0 \text{ Hz}, 3J_{4',3} = 5.6 \text{ Hz}, H-4'\)), 5.26 (s, 2H, H-8), 7.23-7.36 (m, 20H, aromatic CH).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm): -5.1 and -5.0 (C-6), -2.2 (C-1), 14.1 (C-2), 16.8 (C-5), 18.4 (C-7), 20.3 (C-3), 26.0 (C-8), 51.8 (C-10), 63.2 (C-4), 77.8 (C-11), 83.1 (C-9), 122.9 127.0, 127.2, 127.3, 128.2, 129.2, 129.5, 133.8, 135.3, 141.0, 141.2 (aromatic CH and C\(_q\)).

MS (APCI), \(m/z\) (%): no molecular peak, characteristic peak: 197.2 (100) \([(\text{Ph}_2\text{COMe})^+]\).

El. anal. (C\(_{41}\)H\(_{51}\)BO\(_5\)Si): calcd. C, 74.30, H, 7.76; found C, 74.35, H, 7.73.

\(((1R,2S,3S) \text{ And } (1R,2S,3R)-2-(4R,5R)-4,5-di[methoxy(diphenyl)methyl] -1,3,2-dioxaborolan-2-yl-3-methylcyclopropyl)methoxy\text{(trimethyl)silane}

Starting from 0.24 mmol of olefin. Purified by CC (ϕ 1.0 cm, 9 cm of SiO\(_2\), 5 mL fractions; 10:1 = P.E.:Et\(_2\)O) to give 125 mg (84%) of white foam.
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Obtained as a mixture of two diastereoisomers at the C2 position (d.r. = 82:78). * for the minor stereoisomer.

IR (NaCl, neat) ν\(^{-1}\)(cm\(^{-1}\)): 3061, 3026, 1385, 1077.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ (ppm): -0.93 (dd, 1H, \(^3\)J\(_{1,2}\) = 5.2 Hz, \(^3\)J\(_{1,3}\) = 5.2 Hz, H-1), 0.03 (s, 9H, H-6), 0.76 (m, 1H, H-3), 0.97 (m, 1H, H-2), 1.08 (broad s, 3H, H-5), 3.01 (s, 6H, H-9), 3.39 (dd, 1H, \(^3\)J\(_{4,4'}\) = 10.5 Hz, \(^3\)J\(_{4,3}\) = 8.0 Hz, H-4), 3.61 (dd, 1H, \(^3\)J\(_{4',4}\) = 10.5 Hz, \(^3\)J\(_{4',3}\) = 5.2 Hz, H-4'), 5.27 (s, 2H, H-8), 7.22-7.37 (m, 20H, aromatic CH).

Minor diastereoisomer: \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ (ppm): -0.96 (dd, 1H, \(^3\)J\(_{1,2}\) = 9.1 Hz, \(^3\)J\(_{1,3}\) = 5.2 Hz, H-1*), 0.03 (s, 9H, H-6), 0.50 (m, 1H, H-3*), 0.93 (m, 1H, H-2*), 1.08 (broad s, 3H, H-5), 3.01 (s, 6H, H-9), 3.39 (dd, 1H, \(^3\)J\(_{4,4'}\) = 10.5 Hz, \(^3\)J\(_{4,3}\) = 8.0 Hz, H-4), 3.61 (dd, 1H, \(^3\)J\(_{4',4}\) = 10.5 Hz, \(^3\)J\(_{4',3}\) = 5.2 Hz, H-4*), 5.27 (s, 2H, H-8), 7.22-7.37 (m, 20H, aromatic CH).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)) δ (ppm): -1.7 (C-1), 0.3 (C-6), 14.4 (C-2), 16.9 (C-5), 20.5 (C-3), 51.8 (C-8), 63.1 (C-4), 77.8 (C-9), 83.1 (C-7), 127.1, 127.3, 127.4, 128.3, 129.7, 141.2, 141.4 (aromatic CH and Cq).
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\((1R,2S,3S)-2-(4R,5R)-4,5\text{-dimethoxy(diphenyl)methyl}-1,3,2\text{-dioxaborolan-2-yl-3-methylcyclopropyl)methanol}\)

\[
\begin{align*}
\text{P} &\text{O} \\
\ce{Ph2(MeO)C\cdotsB\cdotsC3H3BO3} \\
\text{P} &\text{O} \\
\ce{Ph2(MeO)C} \\
\text{Mol. Wt.: 520.42} \\
\text{P} &\text{O} \\
\ce{Ph2(MeO)C\cdotsB\cdotsC35H37BO5} \\
\text{P} &\text{O} \\
\ce{Ph2(MeO)C} \\
\text{Mol. Wt.: 548.48}
\end{align*}
\]

Starting from 0.15 mmol of olefin. Purified by CC (ϕ1.0 cm, 9 cm of SiO\(_2\), 5 mL fractions; 10:1 = P.E.:Et\(_2\)O) to give 70.9 mg (86%) of white foam.

Obtained as a mixture of two diastereoisomers at the C2 position (\textit{d.r.} = 91:9).

IR (NaCl, neat) \(\nu_{\text{cm}}^{-1} (\text{cm}^{-1})\): 3406, 3061, 3026, 1385, 1077.

\(^1\text{H-NMR (300 MHz, CDCl}_3\) \(\delta\) (ppm): -0.89 (dd, 1H, \(^3J_{1,2} = 5.5\) Hz, \(^3J_{1,3} = 5.5\) Hz, H-1), 0.75 (m, 1H, H-3), 0.97 (m, 1H, H-2), 1.09 (broad s, 3H, H-5), 3.01 (s, 6H, H-9), 3.33 (dd, 1H, \(^3J_{4,4'} = 10.3\) Hz, \(^3J_{4,3} = 7.8\) Hz, H-4), 3.52 (dd, 1H, \(^3J_{4',4} = 10.3\) Hz, \(^3J_{4',3} = 4.9\) Hz, H-4'), 5.27 (s, 2H, H-8), 7.21-7.37 (m, 20H, aromatic CH).

\(^13\text{C-NMR (75 MHz, CDCl}_3\) \(\delta\) (ppm): -1.5 (C-1), 14.5 (C-2), 16.8 (C-5), 20.6 (C-3), 51.8 (C-8), 63.1 (C-4), 77.8 (C-9), 83.1 (C-7), 127.1, 127.3, 127.4, 128.2, 129.7, 141.3, 141.5 (aromatic CH and C_q).

El. anal. (C\(_{35}\)H\(_{37}\)BO\(_5\)): calcd. for C, 76.64, H, 6.80; found C, 76.67, H, 7.75.
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\((4R,5R)-4,5\text{-Di[methoxy(diphenyl)methyl]-2-[(1R,2S,3S)-2-methyl-3-vinylcyclopropyl]-1,3,2-dioxaborolane}\)

Starting from 0.15 mmol of olefin. Purified by CC (\(\phi 1.0\) cm, 9 cm of SiO\(_2\), 5 mL fractions; 10:1 = P.E.:Et\(_2\)O) to give 70.9 mg (86\%) of white foam.

\(\text{IR (NaCl, neat) } \nu^{-1}(\text{cm}^{-1}): 3406, 3061, 3026, 1385, 1077.\)

\(^1\text{H-NMR (250 MHz, CDCl}\(_3\)) \delta (ppm): -0.74 (dd, 1H, \(^3\)J\(_{1,2}\) = 5.4 Hz, \(^3\)J\(_{1,3}\) = 5.4 Hz, H-1), 0.81 (m, 1H, H-3), 1.02 (m, 1H, H-2), 1.10 (broad s, 3H, H-6), 2.99 (s, 6H, H-9), 5.11-5.34 (m, 2H, H-5), 5.34 (s, 2H, H-8), 6.13-6.28 (m, 1H, H-4), 7.24-7.37 (m, 20H, aromatic CH).

\(^{13}\text{C-NMR (75 MHz, CDCl}\(_3\)) \delta (ppm): -1.5 (C-1), 14.5 (C-2), 16.8 (C-5), 20.6 (C-3), 51.8 (C-9), 77.8 (C-7), 83.1 (C-8), 113.4 (C-5), 127.1, 127.4, 127.4, 128.3, 129.6, 141.2, 141.5 (aromatic CH and C\(_\alpha\)), 143.5 (C-4).

El. anal. (C\(_{36}\)H\(_{37}\)BO\(_4\)): calcd. for C, 79.41, H, 6.85; found C, 79.48, H, 6.79.

\([\alpha]_{20}^D: -47.2^\circ (c = 1.0, \text{CHCl}_3).\)
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