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# Studies Towards the Total Synthesis of the Antibiotic Bu-2313 B and a Bu-2313 – Streptolydigin Hybrid

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

Presented by

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***"You have to believe in the long term plan you have but you need the short term goals to motivate and inspire you."***

- Roger Federer

*Per i miei genitori*

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# Curriculum Vitae

Claudio Bomio-Confaglia

Date of Birth: September 14th 1984

Place of Birth: Winterthur ZH, Switzerland

Hometown: Bellinzona TI, Switzerland

Nationality: Swiss

## Education

**PhD Thesis** at ETH Zürich in the group of Prof. Dr. K.-H. Altmann **01/2011 – 04/2016**

- "Studies Towards the Total Synthesis of the Antibiotic Bu-2313 B and a Bu-2313-Streptolydigin Hybrid"

**Bachelor and Master in Chemistry** at ETH Zürich **02/2008 - 09/2010**

- Focus on organic chemistry
- Master thesis in the group of Prof. Dr. K.-H. Altmann: "Synthesis of a key component of a peloruside A analog".
- Semester project in the group of Prof. Dr. P. Seeberger: "Towards the synthesis of a D-glucoronic acid building block from a side product of the L-iduronic acid synthesis".
- Semester project in the group of Prof. Dr. H.-J. Borschberg: "Towards the total synthesis of laurokamurene A".

**Bachelor in Chemistry** at FH Winterthur (ZHW/ZHAW) **09/2003 - 11/2006**

- Focus on organic chemistry and biological chemistry
- Bachelor thesis in the group of Prof. Dr. R. Marti: "Synthesis of folate-fluorescein conjugates".

**Apprenticeship as laboratory assistant** at ETH Zürich **08/2000 - 07/2003**

- Group of Prof. Dr. D. Seebach
- Mentor: A. K. Beck
- Focus on organic chemistry, synthesis of TADDOL derivatives

## Professional career

**R&D and teaching assistant** at ZHW Winterthur **12/2006 - 02/2008**

- Institute for organic chemistry, Group of Prof. Dr. R. Marti
- Synthesis of dye labeled peptides

## Publications

N. Scherr, P. Gersbach, J.-P. Dangy, C. Bomio, J. Li, K.-H. Altmann, G. Pluschke, *PLoS Negl. Trop. Dis.* **2013**, *7*, 2143.

## Teaching and Mentoring Experience

- Responsible for the supervision of two master students (16 weeks) and a project student (7 weeks) at ETH Zürich and four bachelor students (12 weeks) at ZHAW Winterthur.
- Teaching assistant at the Institute of Organic Chemistry at ZHAW Winterthur. Lecture: ”Organic Chemistry 1 and 2”. Supervision of exercise groups.
- Laboratory assistant at the Institute of Pharmaceutical Sciences at ETH Zürich. Course: “Pharmaceutical Biology” (Isolation and characterization of natural products). Supervision of four to six students.
- Laboratory assistant at the Institute of Inorganic Chemistry at ETH Zürich. Course: “Allgemeine Chemie Praktikum 1”. Supervision of 15 students.

# Table of Contents

# Abstract

Bu-2313 A/B (**I/II**) are highly potent, broad spectrum antibiotics which are produced by the oligosporic *actinomycete* strain No. E864-61 (Figure 1). Their isolation, structure and antibacterial activity were first described in 1979 by *Kawaguchi* and coworkers. They are members of the dienoyltetramic acid class of natural products that also includes the bacterial RNA polymerase inhibitor streptolydigin (**III**). In contrast to streptolydigin (**III**), the tetramic acid part in **I** and **II** is unsubstituted. Therefore, a hybrid structure **IV** between Bu-2313 (**I**/**II**) and streptolydigin (**III**) would be of great interest, in order to explore the general importance of the substitution of the tetramic acid moiety. So far only one total synthesis of streptolydigin (**III**) and none of Bu-2313 A/B (**I**/**II**) have been published.

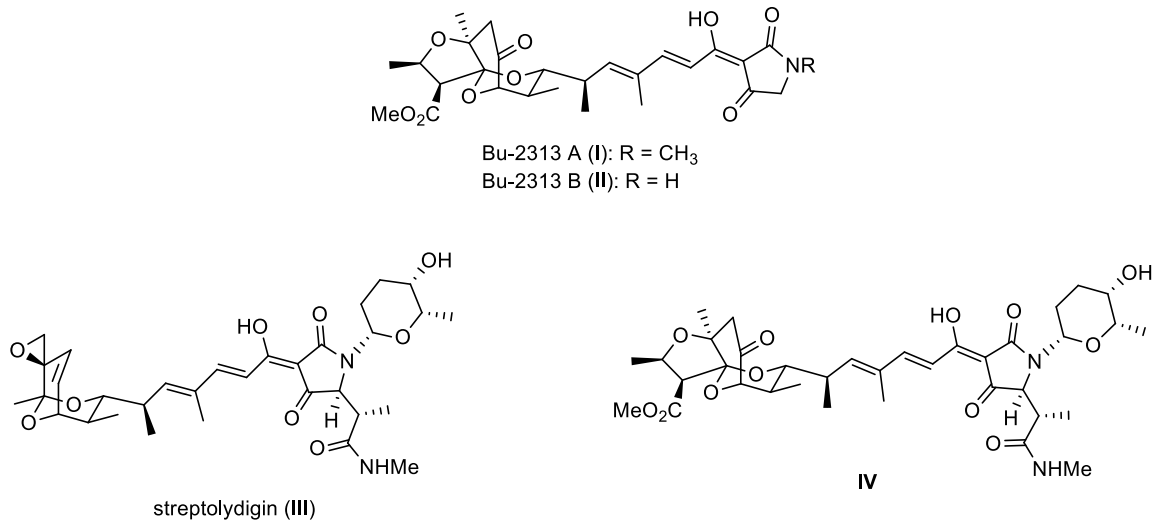



**Figure 1:** Structures of Bu-2313 A/B (**I/II**), streptolydigin (**III**) and the Bu-2313 – streptolydigin hybrid **IV**.

This PhD project was directed at the development of a stereoselective total synthesis of Bu-2313 B (**II**) and the Bu-2313 hybrid **IV**. Strategically, both target structures were to be assembled by HWE olefination between aldehyde **V** and the respective tetramic fragment **VI** or **VII** (Figure 2).

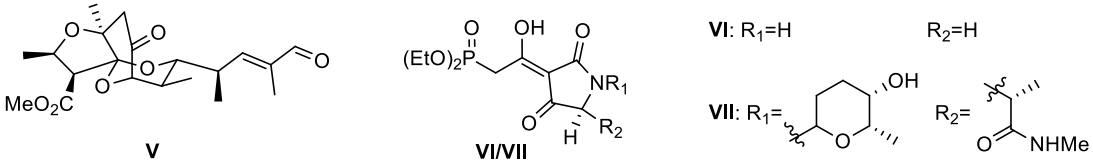
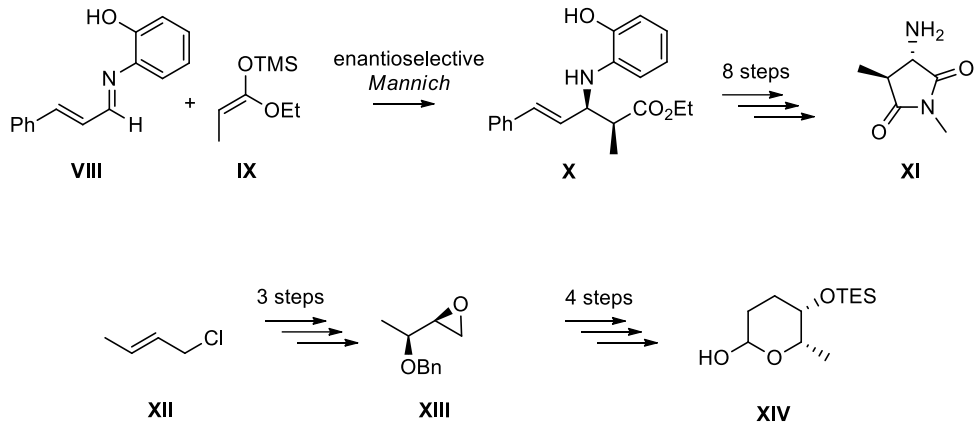



**Figure 2:** Assembly strategy of aldehyde **V** with the corresponding phosphonates **VI** and **VII**.

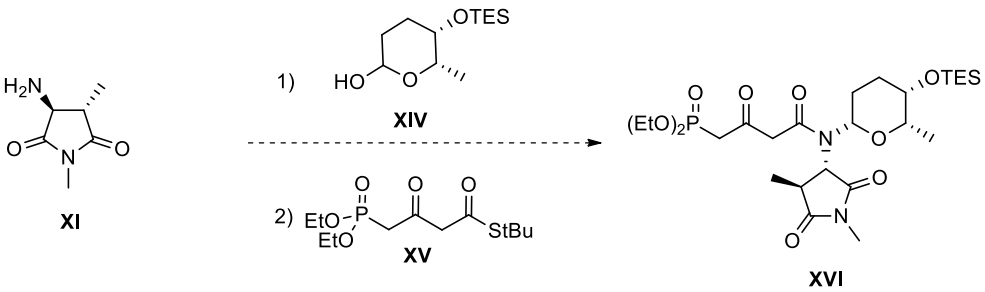
Initial steps towards these goals entailed the synthesis of succinimide **XI** and protected *L*-rhodinose **XIV** (Scheme 1). Starting from imine **VIII**, β-amino ester **X** was obtained by

enantioselective *Mannich* reaction using *Akiyama's* BINOL-derived catalyst. **X** was further converted to the succinimide fragment **XI** over 8 steps. The enantioselective synthesis of *L*-rhodinose **XIV** departed from commercially available (*E*)-crotylchloride (**XII**), using the *Sharpless* dihydroxylation protocol to install the desired stereocenters. **XIV** was obtained from **XII** in 7 steps and 24% overall yield.



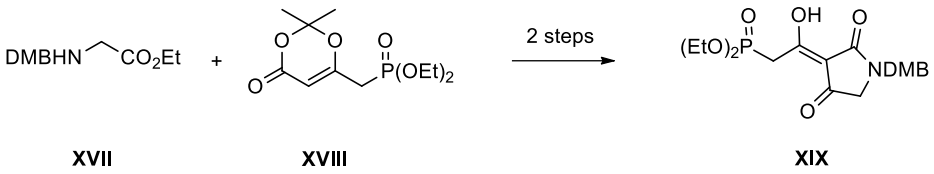

**Scheme 1:** Syntheses of succinimide fragment **XI** and *L*-rhodinose fragment **XIV**.

N-glycosylation of succinimide **XI** with rhodinose **XIV**, followed by Ag-promoted N-acylation with thioate **XV** was then to lead to phosphonate **XVI** as had been described by *Kozmin* and coworkers in the context of their synthesis of streptolydigin (**III**) (Scheme 2). According to this prior work, treatment of **XVI** with *t*BuOK induces a *Dieckmann*-type condensation to the phosphonate **VII** (*vide supra*), which would then be reacted *in situ* with aldehyde **V** to produce **IV**.




**Scheme 2:** Assembly of the succinimide **XI** and *L*-rhodinose **XIV** fragments.

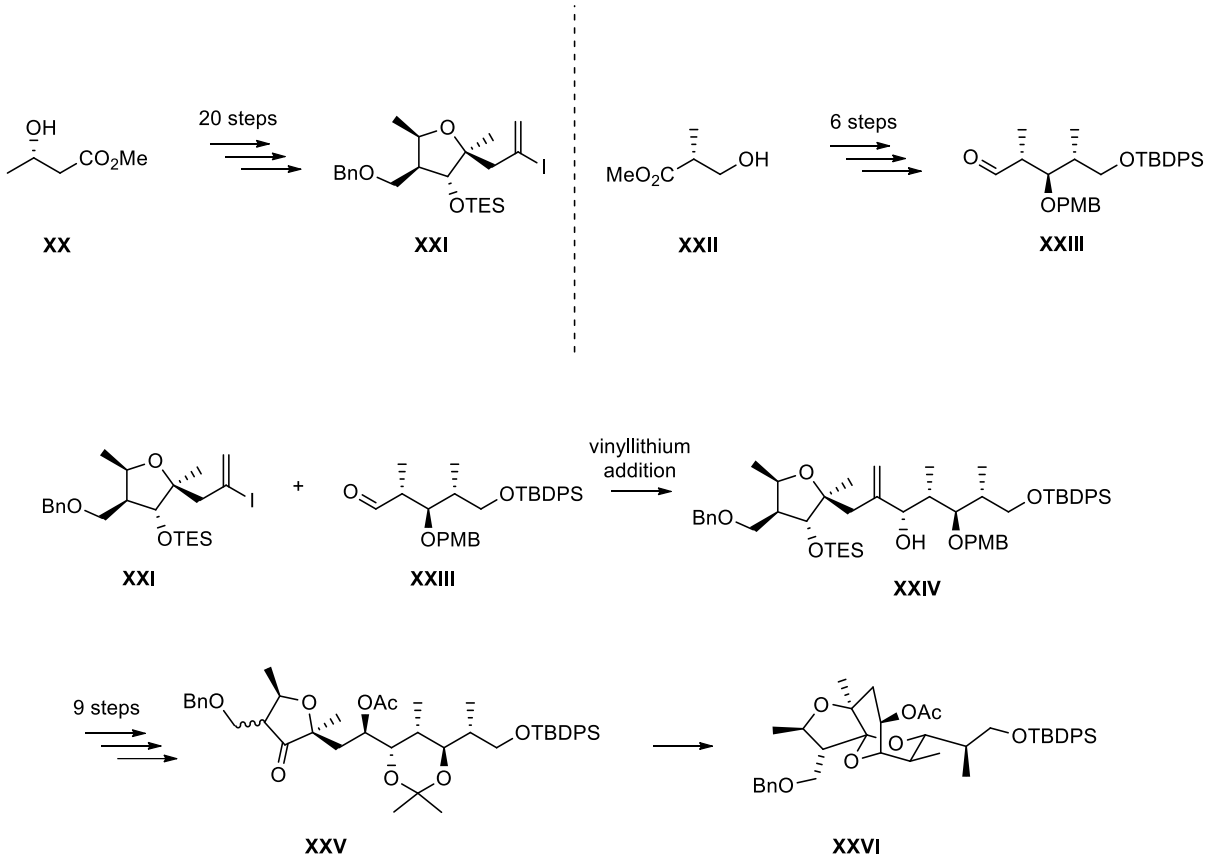
The synthesis of the Bu-2313 B tetramic acid fragment **XIX** was carried out as reported by *Boeckman* and coworkers by amide formation between glycine derivative **XVII** and dioxolenone **XVIII** followed by *Dieckmann* cyclization to give phosphonate **XIX** (Scheme 3).




**XVII** **XVIII** **XIX**

**Scheme 3:** Synthesis of tetramic acid fragment **XIX**. DMB = 2,4-Dimethoxybenzyl.

The by far most challenging aspect of the synthesis of **I** and **IV** is the construction of the carbon skeleton of their tricyclic core structure, which was assembled *via* addition of vinyl iodide **XXI** to aldehyde **XXIII** upon lithium-iodine exchange, to produce polyol **XXIV** (Scheme 4). Vinyl iodide **XXI** was synthesized in 20 steps starting from commercially available (*S*)-methyl-3-hydroxybutyrate (**XX**); aldehyde **XXIII** was elaborated from (*R*)-Roche ester (**XXII**) by making use of *Leighton's* crotylation methodology. **XXIV** was further transformed into ketone **XXV**, which served as a precursor for the intramolecular ketalization that was performed under acidic conditions to yield ketal **XXVI**.




**XX** **XXI** **XXII** **XXIII**

**XXI** **XXIII** **XXIV**

**XXV** **XXVI**

**Scheme 4:** Synthesis of ketal **XXVI** from vinyl iodide **XXI** and aldehyde **XXIII**.

Tricyclic ketal **XXVI** is the most advanced intermediate towards the synthesis of **I** and **IV** prepared in this thesis.

# Zusammenfassung

Bu-2313 A und B (**I/II**) sind stark wirksame Breitbandantibiotika aus der Naturstoffklasse der Dienoyltetramsäuren, die von dem *Actinomycetenstamm* Nr. E864-61 produziert werden (Abbildung 1). Die Isolierung dieser Naturstoffe sowie ihre Strukturaufklärung und biologischen Eigenschaften wurden erstmals im Jahre 1979 von *Kawaguchi et al.* beschrieben. Aufgrund ihrer strukturellen Ähnlichkeit mit Streptolydigin (**III**), einem anderen Naturstoff aus der Familie der Dienyltetramsäuren und Hemmer der bakteriellen RNA-Polymerase, kann vermutet werden, dass es sich auch bei Bu-2313 A/B (**I/II**) um RNA-Polymerasehemmer handelt. Im Unterschied zu Streptolydigin (**III**) ist jedoch die Tetramsäureeinheit im Falle von Bu-2313 A/B (**I/II**) sowohl am Stickstoff wie auch in der 5-Position unsubstituiert. Aus diesem Grund wäre es von Interesse ein Bu-2313 – Streptolydigin Hybrid **IV** herzustellen, um die Bedeutung der Substitution des Tetramsäureteils für die Hemmwirkung auf die bakterielle RNA-Polymerase untersuchen zu können.

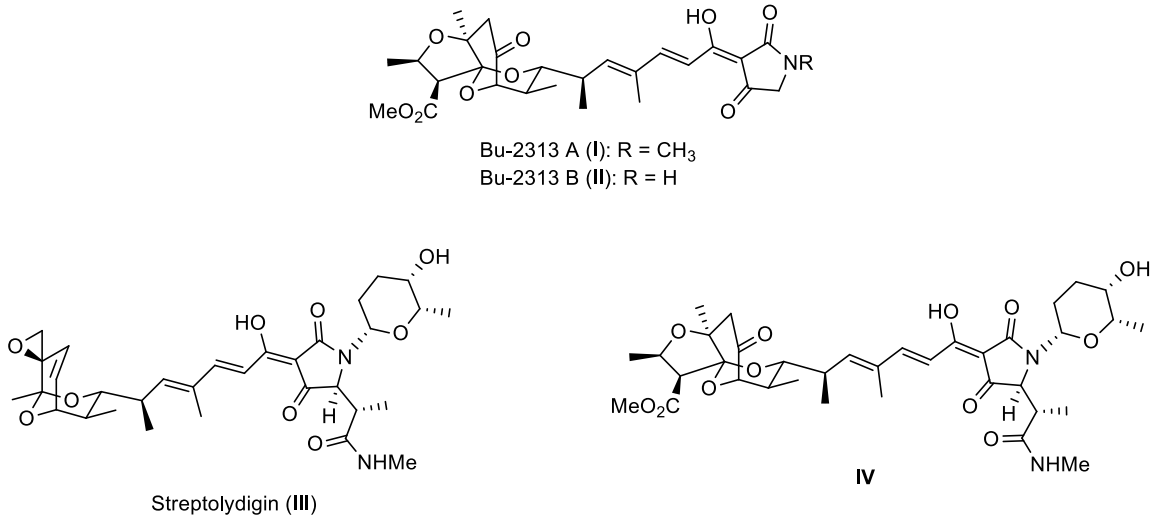



**Abbildung 1:** Strukturen von Bu-2313 A/B (**I/II**), Streptolydigin (**III**) und des Bu-2313 – Streptolydigin Hybrids **IV**.

Ziel dieser Doktorarbeit war die Entwicklung einer stereoselektiven Totalsynthese von Bu-2313 B (**II**) und des Bu-2313 – Streptolydigin Hybrids **IV** (Abbildung 2). Die sollte so geschehen, dass im letzten Schritt der Synthese das jeweilige Tetramsäurefragmente **VI** bzw. **VII** mittels einer *HWE*-Olefinierung mit dem Aldehyd **V** verknüpft würde.

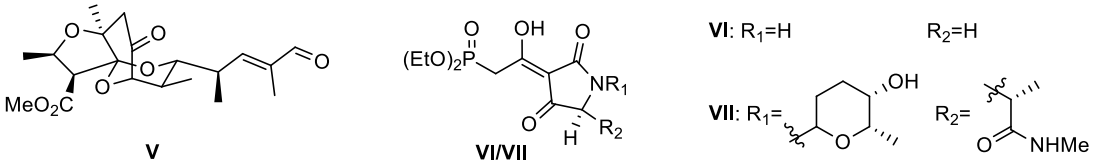



**Abbildung 2:** Verknüpfungsstrategie von Aldehyd **V** mit den Phosphonaten **VI** bzw. **VII**.

Die Tetramsäure **VII** wurde aus den Fragmenten **XI** und **XIV** aufgebaut. Die Synthese des Succinimids **XI** erfolgte über eine enantioselektive *Mannich*-Reaktion zwischen dem Imin **VIII** und dem Enolat **IX**, woran sich noch acht weitere Syntheseschritte anschlossen (Abbildung 3). Die Darstellung der *L*-Rhodinose **XIV** erfolgte ausgehend vom (*E*)-Crotylchlorid das über eine *Sharpless*-Dihydroxylierung in das Epoxid **XIII** überführt wurde. Letzteres wurde dann in vier weiteren Schritten in **XIV** überführt.

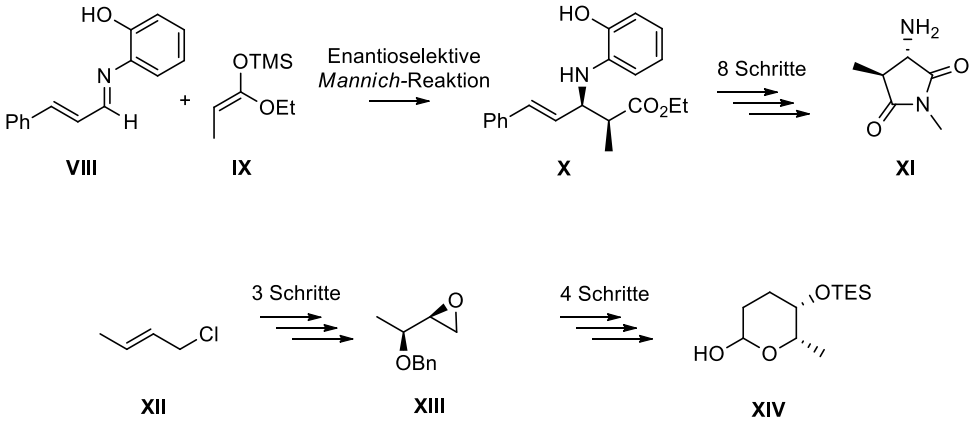



**Abbildung 3:** Synthese der Fragmente **XI** und **XIV**.

Analog zu der von *Kozmin et al.* im Rahmen der Totalsynthese des Streptolydigins (**III**) beschriebenen Vorgehensweise sollten sich die Verbindungen **XI**, **XIV** und **XV** zur Tetramsäure **XVI** verknüpfen lassen. Dabei würde das Succinimid **XI** mit der *L*-Rhodinose **XIV** glykosyliert und anschliessend mit dem Thioester **XV** acyliert (Abbildung 4). Das hierbei gebildete Phosphonat **XVI** würde dann durch Behandlung mit *t*BuOK über eine *Dieckmann*-Kondensation in das Phosphonat **VII** (vgl. Abbildung 2) umgelagert, das dann *in situ* mit dem Aldehyd **V** zu **IV** weiterreagieren könnte.

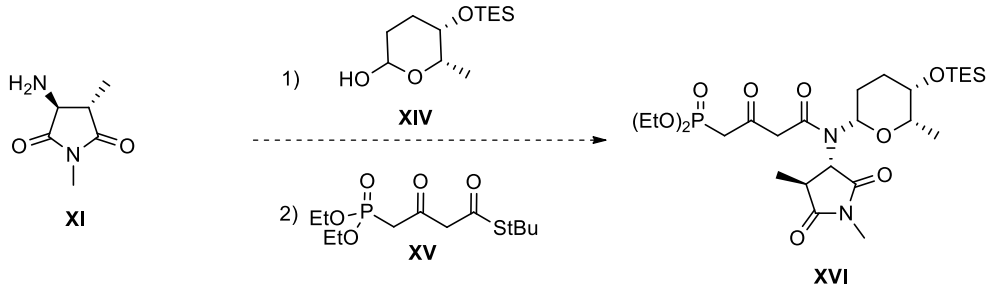



**Abbildung 4:** Verknüpfung von Succinimid **XI** und der *L*-Rhodinose **XIV**.

Das für die Synthese des Bu-2313 B (**II**) benötigte Tetramsäurefragment **XIX** wurde entsprechend einem von *Boeckman et al.* beschrieben Verfahren aus dem Glycinderivat **XVII** und dem Dioxolenon **XVIII** durch Amidbildung und anschliessende *Dieckmann*-Zyklisierung erhalten (Abbildung 5).

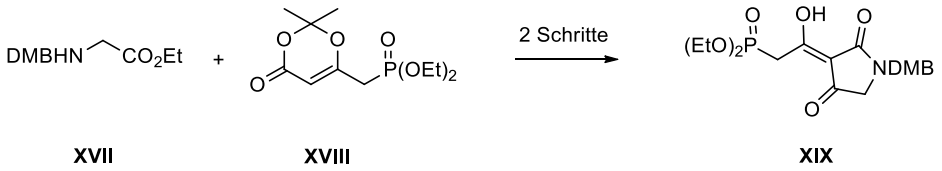



**Abbildung 5:** Tetramsäurefragment **XIX** Synthese. DMB = 2,4-Dimethoxybenzyl.

Die größte Herausforderung bei der Synthese des Bu-2313 B (**II**) bzw. des Bu-2313-Streptolydigin Hybrids **IV** bestand im Aufbau des Kohlenstoffgerüsts des trizyklischen Ketals, welcher über das Vinyliodid **XXI** und den Aldehyd **XXIII** bewerkstelligt wurde (Abbildung 6). Dabei wurde das Vinyliodid **XXI** in 20 Schritten ausgehend von (*S*)-Methyl-3-hydroxybutyrat (**XX**) hergestellt, der Aldehyd **XXIII** wurde ausgehend von (*R*)-Roche-Ester (**XXII**) in sechs Schritten erhalten.

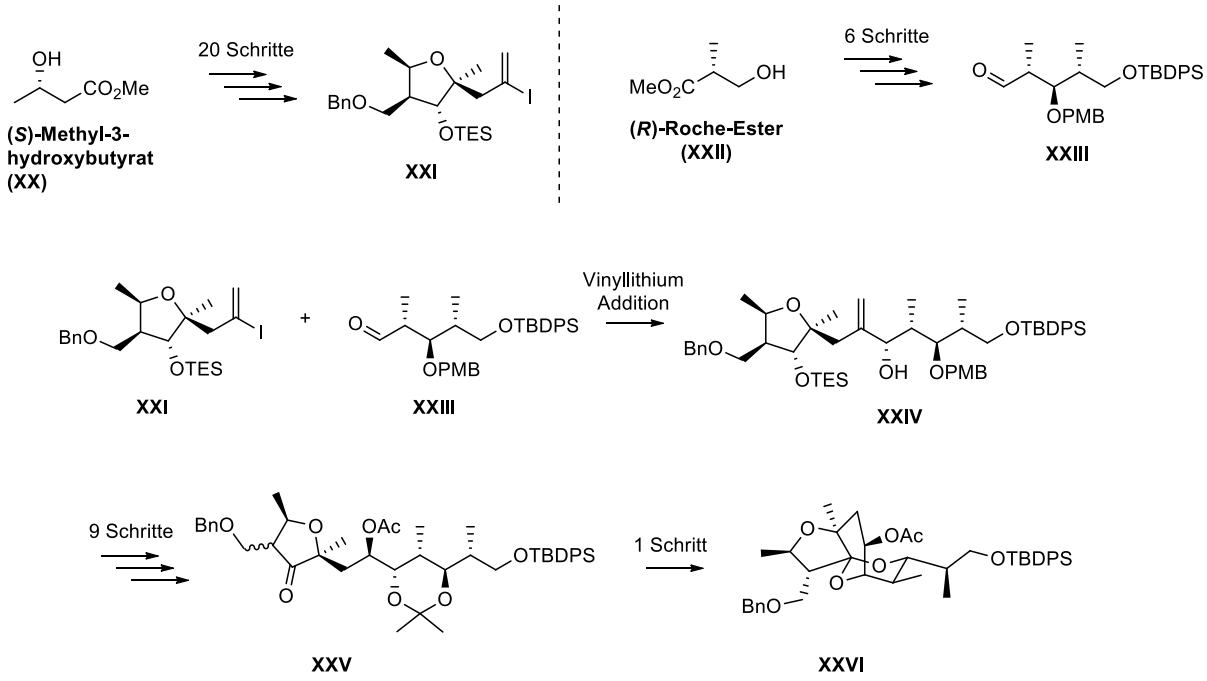



**Abbildung 6:** Synthese von Ketal **XXVI** ausgehend von Vinyliodid **XXI** und Aldehyd **XXIII**.

Die Addition von metalliertem **XXI** an **XXIII** lieferte dann den Allylalkohol **XXIV**, der in neun weiteren Syntheseschritten in das trizyklische Ketal **XXVI** überführt werden konnte. Ketal **XXVI** ist das am weitesten fortgeschrittene Zwischenprodukt bei der geplanten Synthese von **II** und **IV**, das im Rahmen dieser Doktorarbeit hergestellt wurde.

# List of Abbreviations, Acronyms and Symbols

***A***

| | |
|---|---|
| $[a]_D^T$ | specific rotation at temperature T at the sodium D line |
| Å | Ångstrom |
| Ac | acetyl |
| AD-mix | *Sharpless* asymmetric dihydroxylation mixture |
| aka | also known as |
| ALOX | aluminum oxide |
| aq. | aqueous |

***B***

| | |
|---|---|
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| 9-MeO-BBN | 9-methoxy-9- borabicyclo[3.3.1]nonane |
| BINOL | 1,1'-binaphthyl-2,2'-diol |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| BOMCl | benzyl chloromethyl ether |
| Bp. | boiling point |
| br | broadened (signal) |
| Bu | butyl |

***C***

| | |
|---|---|
| ca. | about, approximately |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| CBS | *Corey-Bakshi-Shibata* |
| Cbz | benzyloxycarbonyl |
| CoA | coenzyme A |
| Cp | cyclopentadiene |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| °C | degree centigrade |

***D***

| | |
|---|---|
| δ | NMR chemical shift in ppm |
| d | doublet |
| DB | dibenzo |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | N,N'-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| *de* | diastereomeric excess |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate |
| DIBALH | diisobutylaluminum hydride |
| DIPEA | N,N-diisopropylethylamine |
| DIPT | diisopropyl tartrate |
| $(DHQ)_2PHAL$ | hydroquinine 1,4-phthalazinediyl diether |
| $(DHQD)_2PHAL$ | hydroquinidine 1,4-phthalazinediyl diether |

| | |
|---|---|
| DMB | 2,4-dimethoxybenzyl |
| DMAP | 4-dimethylamino pyridine |
| DMF | N,N-dimethylformamide |
| DMP | Dess–Martin periodinane |
| DMSO | dimethyl sulfoxide |
| DMS | dimethylsulfide |
| DNA | deoxyribonucleic acid |
| *dr* | diastereomeric ratio |

***E***

| | |
|---|---|
| EDA | 1,2-ethylenediamine |
| EDC | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide |
| EDCI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| *ee* | enantiomeric excess |
| EI | electron ionization |
| EOE | ethoxyethyl |
| ESI | electrospray ionization |
| equiv | equivalent |
| Et | ethyl |

***F***

***G***

| | |
|---|---|
| g | gram |
| GC | gas chromatography |

***H***

| | |
|---|---|
| h | hour |
| HMPA | hexamethylphosphoramide |
| HPLC | high-performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| HWE | Horner-Wadsworth-Emmons |
| Hz | Hertz ($s^{-1}$) |

***I***

| | |
|---|---|
| *i* | *iso* |
| IBCF | isobutylchloroformate |
| ImH | imidazole |
| IR | infrared |

***J***

| | |
|---|---|
| *J* | coupling constant |

***K***

| | |
|---|---|
| k | kilo |
| KHMDS | potassium bis(trimethylsilyl)amide |

***L***

| | |
|---|---|
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |

| | |
|---|---|
| LiHMDS | lithium bis(trimethylsilyl)amide |

***M***

| | |
|---|---|
| m | multiplet |
| *m* | *meta* |
| M | molarity (moles per liter) |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| MDR | multidrug-resistant |
| Me | methyl |
| MEM | 2-methoxyethoxymethyl |
| mg | milligram |
| MHz | Megahertz |
| MIC | minimum inhibitory concentration |
| min | minute |
| ml | milliliter |
| mmol | millimole |
| μL | microliter |
| mol. | molecular |
| mol-% | mole percent |
| MOM | methoxymethyl |
| Mp. | melting point |
| MS | mass spectrometry |
| Ms | methanesulfonyl |
| *Mtb* | *Mycobacterium tuberculosis* |

***N***

| | |
|---|---|
| NAC | nucleotide addition cycle |
| NBS | N-bromosuccinimide |
| NIH | National Institutes of Health |
| NIS | N-iodosuccinimide |
| NMO | N-methylmorpholine N-oxide |
| n. d. | not determined |
| NOE | nuclear Overhauser effect |
| NMM | *N*-methylmorpholine |
| NMO | *N*-methylmorpholine oxide |
| NMR | nuclear magnetic resonance |
| NTP | nucleoside triphosphate |
| Nuc | nucleophile |

***O***

| | |
|---|---|
| *o* | *ortho* |

***P***

| | |
|---|---|
| *p* | *para* |
| PDC | pyridinium dichromate |
| PCC | pyridinium chlorochromate |
| PG | protecting group |
| Ph | phenyl |
| PhD | doctor of philosophy |
| pin | pinacol, 1,1,2,2-tetramethylethylene glycole |
| PivCl | pivaloyl chloride, trimethylacetyl chloride |

| | |
|---|---|
| Piv/Pv | pivaloyl |
| PMB | 4-methoxybenzyl |
| PMP | 4-methoxyphenyl |
| ppm | parts per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| PT | phenyltetrazole |
| Pr | propyl |
| pyr | pyridine |

***Q***

| | |
|---|---|
| q | quartet |
| quant | quantitative |

***R***

| | |
|---|---|
| RCM | ring-closing metathesis |
| $R_f$ | retention factor |
| RNA | ribonucleic acid |
| RNAP | ribonucleic acid polymerase |
| rsm | recovered starting material |
| $R_t$ | retention time |
| rsm | recovered starting material |
| rt | room temperature |

***S***

| | |
|---|---|
| s | second or singlet |
| SAR | structure-activity relationship |
| *sec* | *secondary* |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| $S_N$ | nucleophilic substitution |
| sm | starting material |

***T***

| | |
|---|---|
| t | triplet |
| *t* | *tert* |
| T | temperature |
| TAACF | Tuberculosis Acquisition and Coordination Facility |
| TAM | tirandamycin |
| TB | tuberculosis |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBAI | tetra-*n*-butylammonium iodide |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TCCA | trichloroisocyanuric acid |
| TEMPO | 2,2,6,6-tetramethylpiperidin-1-yloxy |
| TES | triethylsilyl |
| TfO | triflate = trifluoromethanesulfonate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilyl |

| | |
|---|---|
| Tol | tolyl |
| TPAP | tetra-*n*-propylammonium perruthenate |
| TsOH | *p*-toluenesulfonic acid |
| Tris | 2,4,6-tri-isopropylbenzenesulfonyl |
| trityl | triphenylmethyl |

***U***

| | |
|---|---|
| μ | micro |
| US | United States (of America) |
| UV | ultraviolet |

***V***

| | |
|---|---|
| VIS | visible |

***W***

**X**

# 1. Introduction

## 1.1. Bacterial RNA Polymerase

DNA-dependent bacterial ribonucleic acid polymerases (RNAPs) are responsible for the transcription of DNA into RNA and therefore are essential enzymes for cell survival in all living organisms, including archea, bacteria, and eukaryotes[1]. RNAPs were discovered in the early 1960s simultaneously by the laboratories of *Hurwitz,Weiss* and *Stevens*[2] and since then the structure and function of this complex molecular machine has been heavily investigated[3–5]. While the structure and mechanism of RNAPs from different life forms are fundamentally similar, differences do exist[6,7]. Thus, bacteria possess only one RNAP, whereas eukaryotes feature three different enzymes with distinct cellular functions: For example, the bacterial RNAP uses the σ-unit for promoter DNA recognition and the eukaryotic RNAP's make use of several transcription factors which are responsible for promoter DNA recognition upon binding to the RNAP and are by far more complex[8]. Importantly, also in the context of this PhD thesis, the differences between the bacterial and eukaryotic enzymes form the basis for the use of bacterial RNAP inhibitors for the treatment of bacterial infections, without affecting RNA synthesis in the host.

The structure of the bacterial RNAP consists of a catalytic core, which is composed of five subunits ($\alpha_2\beta\beta'\omega$), and an additional sigma (σ) unit (Figure 3). Overall, the structure of RNAP is highly conserved among bacteria, with the exception of the σ-unit, which can vary. While the catalytic core is mainly responsible for RNA synthesis, the σ-unit recognizes the promoter region of the DNA and directs it into the catalytic core of the enzyme. The shape of the RNAP is often referred to as resembling a crab-claw, with the β and β' units being the clamps or pincers of the claw. The catalytic center is located inside of the claw and includes two mobile elements, the bridge helix and the trigger loop, and a $Mg^{2+}$-ion, which is required for catalysis[5].

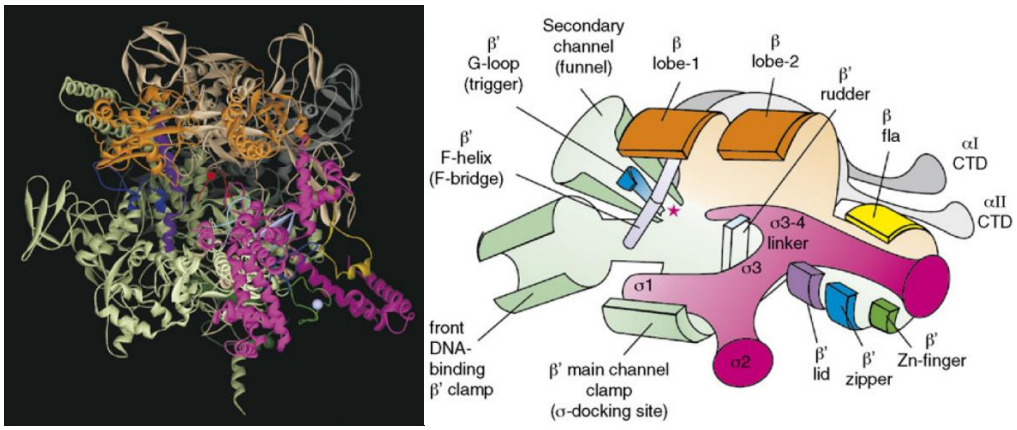



**Figure 3:** Left: High resolution structure (3.3 Å) of the *Thermus thermophiles* RNAP holoenzyme. Right: Simplified cartoon representation of the *Thermus thermophiles* RNAP holoenzyme using the same color code for the subunits as in the left hand picture. (αI, light grey; αII, grey; β, light brown; β', light green; ω, dark green; σ, magenta; β' bridge helix, purple; β' trigger loop, blue; active center, magenta star; $Mg^{2+}$-ion, red dot.)[5]

The catalytic cycle of the RNAP includes six steps (Figure 4): 1) Formation of the holoenzyme between the core and the σ-unit. 2) Identification of the '-10' and '-35' recognition sequences by the σ-unit and reversible binding of the promoter DNA, leading to the formation of what is referred to as the "closed complex". 3) In order to read the DNA, the RNAP isomerizes (unwraps) ~13 base pairs of the DNA into the catalytic core by opening the β'-clamp to form the transcription bubble, which is referred to as the "open complex". 4) Beginning of the RNA synthesis with the antisense DNA strand (green) as its template. Initially only short fragments of RNA are synthesized due to the RNAP still being bound to the promoter DNA. This stage is called "abortive initiation". 5) Elongation: After a few cycles of short RNA fragment synthesis, the connection between the RNAP core and the σ-unit gets disrupted due to a steric clash of the newly synthesized RNA with the σ-unit; the RNA can now be synthesized in its full length. 6) After RNA synthesis is complete, the DNA dissociates from the RNAP core, which is now able to reassemble with a σ-unit, thereby closing the catalytic cycle. This stage is called "termination".[5,9]

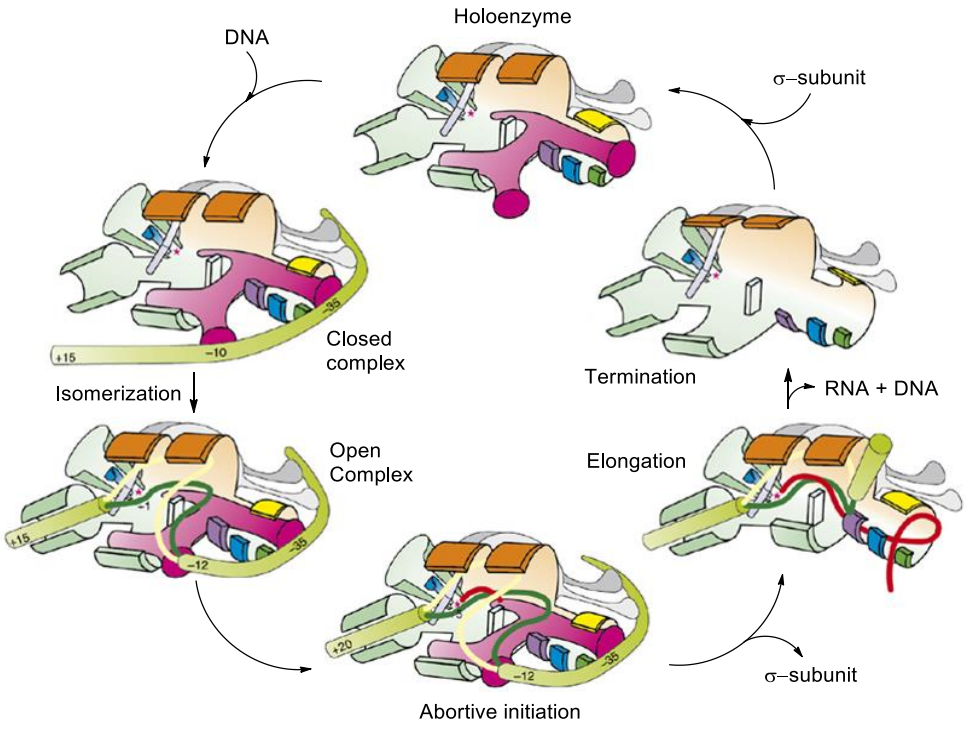



**Figure 4:** Cartoon of the RNAP catalytic cycle[5]. αI, light grey; αII, grey; β, light brown; β', light green; ω, dark green; σ, magenta; β' bridge helix, purple; β' trigger loop, blue; active center, magenta star; $Mg^{2+}$-ion, red dot; duplex DNA, green cylinders; nascent RNA, red strand; template DNA, dark green strand; non-template DNA, yellow strand.

During the stages "abortive initiation" and "elongation" the so called nucleotide addition cycle (NAC) is operative, where the nucleoside triphosphates (NTP's) are added to the nascent RNA chain in the RNAP active center[5] (Figure 5). This process is highly dependent on the two mobile elements of the active center, the "trigger-loop" and "bridge-helix". These two elements are responsible for the recognition, selection and placement of the NTP's, which enter the RNAP through the secondary channel. Furthermore, they perform the translocation of the nascent RNA strand after phosphodiester bond formation. This process involves conformational cycling of both the trigger-loop (folded and unfolded) and bridge-helix (bent and straight).

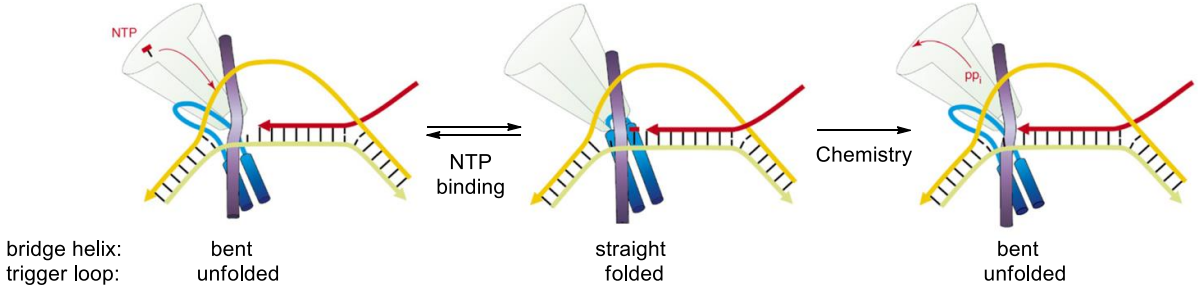



**Figure 5:** Cartoon of the nucleotide addition cycle (NAC)[5]. Bridge-helix, purple column; trigger loop, blue cylinders connected by a loop; DNA template strand, thick green; DNA non-template strand, orange; nascent RNA strand, red. The arrowheads are on the 3'-termini of the corresponding RNA or DNA strand.

## 1.1.1. Bacterial RNA Polymerase as a Target for Antibiotics

As indicated above, distinct structural and functional differences exist between RNAP's from bacteria and eukaryotes, which, in principle, make bacterial RNAP an attractive molecular target for drugs against bacterial infections. In spite of this, only few RNAP inhibitors are in clinical use today: The rifamycins (rifampicin, rifabutin, rifapentine), which are used since the 1960's as first line antibiotics against infections with *Mycobacterium tuberculosis* (Figure 6) and in 2011, tiacumycin B was introduced under the tradename *Dificid*® (generic name fidaxomicin) for the treatment of *Clostridium difficile*-associated diarrhea[9].

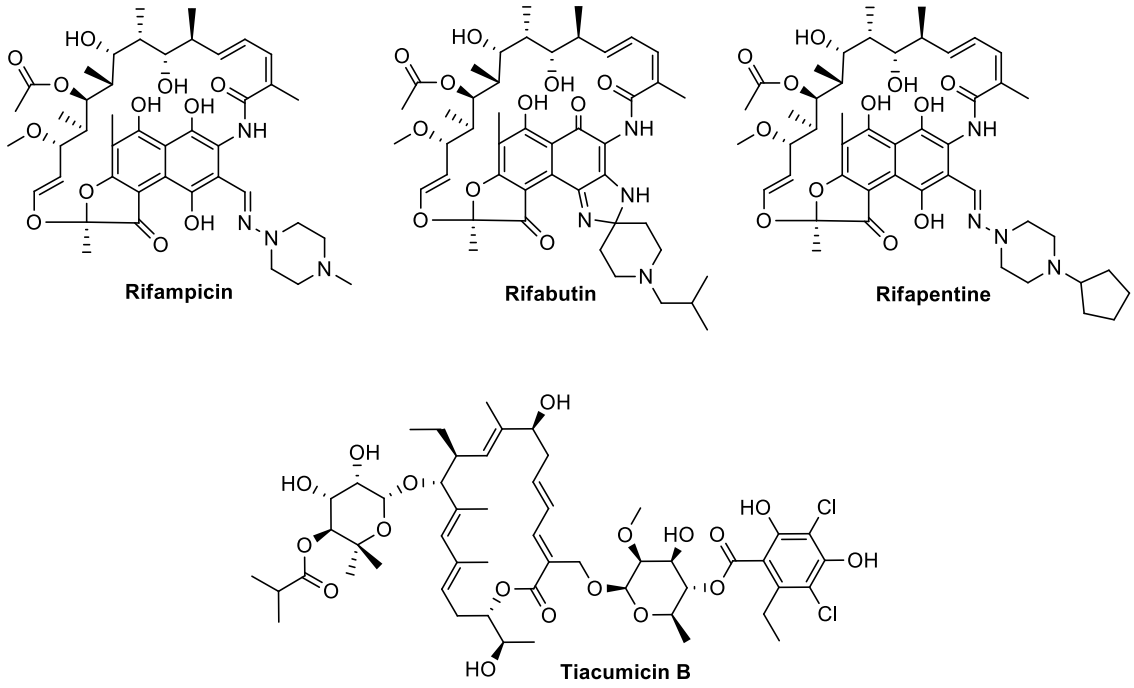



**Figure 6:** Clinically used RNA polymerase inhibitors.

In addition to the compounds mentioned above, which are in clinical use, several other natural and synthetic RNA polymerase inhibitors are known[1]. Depending on their binding site on the enzyme and their specific mode of action, these inhibitors can be divided into four different classes: 1) Inhibitors blocking nascent RNA extension. 2) Inhibitors which target the active center and directly compromise catalytic activity. 3) Inhibitors which block promoter complex formation. 4) Inhibitors which hinder the σ-core interactions[9]. In the following, a selection of well-studied inhibitors from the first three classes will be presented.

## 1.1.2. Inhibitors Blocking Nascent RNA Extension – Rifamycins

Rifamycin B was isolated in 1959 by *Sensi* and coworkers from the soil bacterium *Amycolatopsis mediterranei* and was found to have strong and broad range antibacterial activity (Figure 7). The conclusion was later corrected, as it was discovered that rifamycin B

is transformed into rifamycin S *in vivo*, which turned out to be the active species. From rifamycin S, rifamycin SV was developed and introduced into the market in 1963 for the treatment of infections with *Mycobacterium tuberculosis*. Further modification of the rifamycin scaffold led to the development of rifampicin, which has better therapeutic properties in terms of bioavailability and *in vivo* half-life than rifamycin SV. Since 1968 rifampicin is used as first line drug against tuberculosis[10–12].

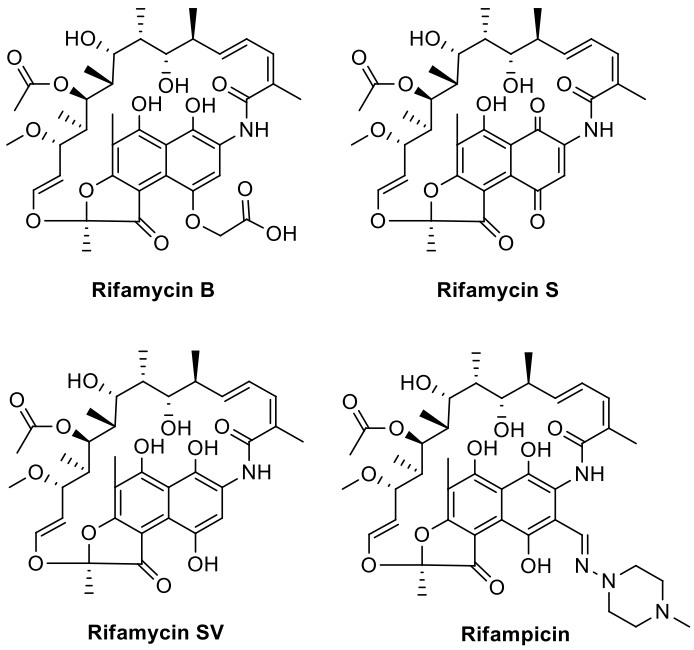



**Figure 7:** Structures of different rifamycins.

X-ray structure analysis of the RNAP core complexed with rifampicin showed that the binding site of rifampicin is located on the β-subunit of the enzyme in the RNA/DNA channel in about 12Å distance from the catalytic center ($Mg^{2+}$-ion) (Figure 8). For the mechanism of inhibition the "steric occlusion" model was proposed, where rifampicin sterically blocks the translocation of the nascent RNA strands after only 2-3 nucleosides[11,12]. Therefore, the catalytic cycle is interrupted at the stage of abortive initiation (Figure 4) and the RNAP continuously synthesizes RNA strands which have the length of 2-3 nucleosides. For RNAP in the elongation phase, rifampicin is not able to bind to the enzyme and hence no inhibition is observed at this stage of the catalytic cycle[11,12].

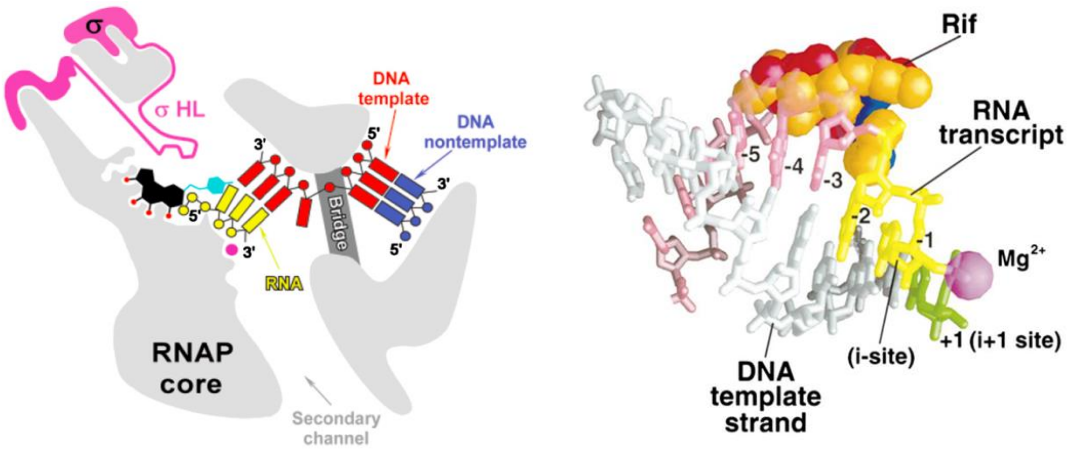



**Figure 8:** Left: Cartoon of the steric occlusion mechanism of rifampicin. Rifampicin, black rings and turquoise tail; $Mg^{2+}$-ion, magenta ball[11]. Right: Model of the RNAP active site. The model shows how rifampicin (orange = C atom, red = nitrogen atom and blue = oxygen atom) blocks the positions -3 to -5 of the RNA strand (pink). The positions of the RNA strand (-1 to -2) which can be occupied are shown in yellow. The incoming NTP at the +1 site is shown in green.[11,12]

### 1.1.3. Inhibitors Targeting the RNA Polymerase Active Center – Streptolydigin

Streptolydigin was isolated from the actinomycete *Streptomyces lydicus* by researchers at the *Upjohn* company in 1956 and it is a highly potent, broad spectrum antibiotic[13](Figure 9). Streptolydigin belongs to the dienoyl tetramic acid family of natural products (Chapter 1.2.1) and is known to inhibit bacterial RNAP during transcription initiation and elongation[14,15]. Using chemical mutagenesis, polymerase chain reaction and co-crystallization of the enzyme with streptolydigin, the binding site of streptolydigin was revealed to be located at the β and β' subunit of RNAP, adjacent to but not overlapping the active center. The streptolol part of streptolydigin thereby interacts with the part of the streptolydigin pocket which is located on the β-subunit and the bridge-helix, whereas the tetramic acid part is in contact with the trigger loop. A comparison of the X-ray structures of the unligated enzyme and the RNAP/streptolydigin complex reveals that both the bridge-helix and the trigger-loop adopt different conformations in the streptolydigin-bound state (Figure 9). The fact that the bridge-helix adopts a straight instead of a bent conformation suggests that streptolydigin inhibits the conformational cycling of the bridge-helix, which is an essential process in the nucleotide addition cycle (NAC)[15].

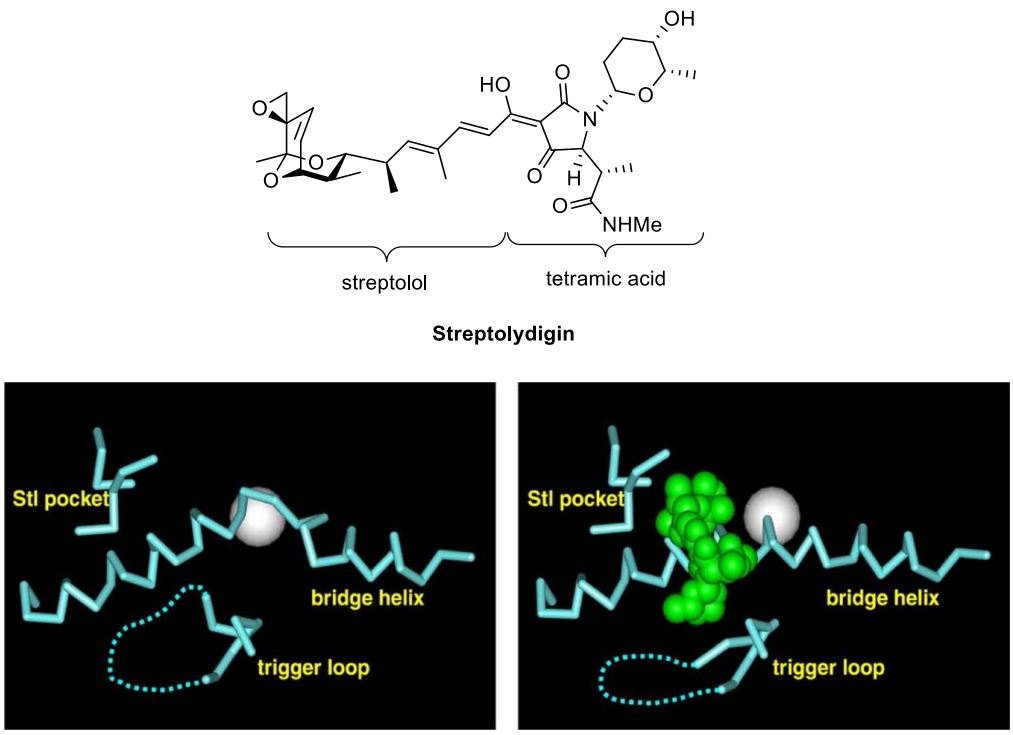



**Figure 9:** Top: Structure of streptolydigin. Bottom left: Structure of the RNAP active center conformation with a bent bridge-helix. Bottom right: Structure of the RNAP/streptolydigin active center conformation with a straight bridge-helix. Streptolydigin, green; $Mg^{2+}$-ion, white sphere.[15]

## 1.1.4. Inhibitors Blocking Promoter Complex Formation – Myxopyronin A

Myxopyronin A was isolated from the myxobacterium *Myxococcus fuluvs* by *Reichenbach* and coworkers in 1983 and it exhibits broad spectrum antibacterial activity[16] (Figure 10). Myxopyronin A inhibits the RNAP catalytic cycle between the stages of the closed and open complex formation and was found to be inactive during elongation. Biochemical, genetic and X-ray structural analysis of the RNAP/myxopyronin A complex revealed the switch-1 and switch-2 regions, which are located between the β and β'-subunits, as the binding site of myxopyronin A[17]. For the mechanism of action the "hinge jamming" model was proposed, where myxopyronin A inhibits the switch-2 (hinge) region and therefore the opening of the RNAP clamp which is needed to load the promoter DNA into the active cleft of the RNAP[17].

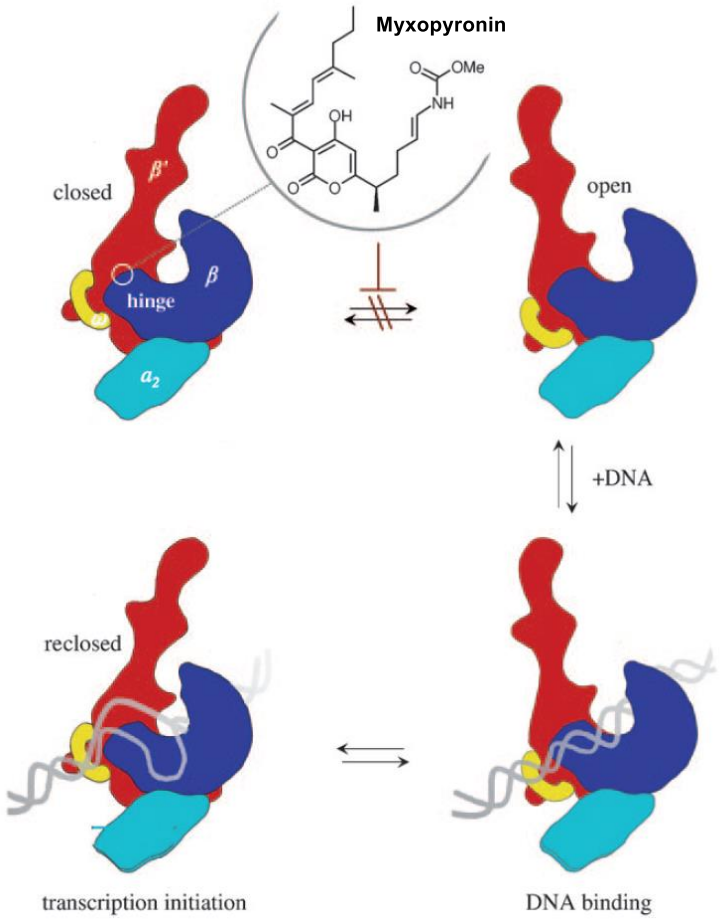



**Figure 10:** Cartoon of the mechanism of action of myxopyronin A. Myxopyronin A binds in the switch region between the β and β'-subunits and prevents the opening of the RNAP clamp, which is needed for the promoter DNA loading.[17]

## 1.1.5. Resistant Mutants and Cross Resistance

Pathogens developing resistance against antibiotic treatment are a severe issue and therefore extensive efforts have been (and are) undertaken to understand the origin of resistance and to develop antibiotics that act against resistant bacteria. In the case of rifampicin, resistance occurs via mutation in the β subunit of the RNA polymerase with an average mutation rate of $10^{-10}$ to $10^{-7}$ (mutation per bacterium per generation), depending on the organism and methodology that was used for the analysis[18–21]. As the RNA polymerase is highly conserved among bacteria also the mutation sites of rifampicin resistant mutants are (mutations occur on different amino acids but on the same site of the enzyme). For *Mycobacterium tuberculosis* two substitution sites at His (526/406) and Ser (531/411) are responsible for 36% and 41% of the rifampicin resistant strains, respectively[22].

Cross-resistance between two antibiotics is dependent on their binding sites and mechanisms of action. For example, the binding site of tiacumycin B is thought to overlap with that of myxopyronin (Chapter 1.1.4), but not with the one of rifampicin. Thus, neither myxopyronin nor tiacumicin B show cross-resistance with rifampicin[23,24]. The same applies

for streptolydigin, although their binding sites are very close; however, their mechanisms of action are distinctively different from each other and, therefore, no cross resistance is observed between rifampicin and streptolydigin[25,26]. Sorangicin A (Figure 11) on the other hand, binds to the rifampicin site and has the very same mechanism of action as rifampicin. As a consequence, sorangicin A is partially cross-resistant with rifampicin[22].

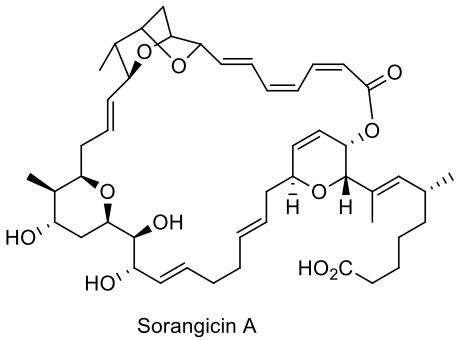



**Figure 11:** Structure of sorangicin A.

## 1.2. Tetramic Acids

The term "tetramic acid" for the 1,5-dihydro-4-hydroxy-2H-pyrrol-2-one (**I-1**) structure was introduced in 1909 by *Anschütz* and *Böcker*[27], who derived it from the corresponding oxygen analog, tetronic acid **I-2** (Figure 12). The first synthesis of tetramic acid **I-1** was accomplished in 1972 by *Mulholland*[28] and coworkers and it was found that the tetramic acid is a much weaker acid (p$K_a$ = 6.4) than its oxygen counterpart tetronic acid (p$K_a$ = 3.76[29]). As a consequence tetramic acid **I-1** mainly exists in the 2,4-diketo **I-1a** form instead of the enol form[28], which is in contrast to the situation for tetronic acid **I-2**. Tetramic acids show reactivity towards nucleophiles at the carbonyl function at C4, they can react with electrophiles upon metalation at C3 and they can be O4-acylated[30].

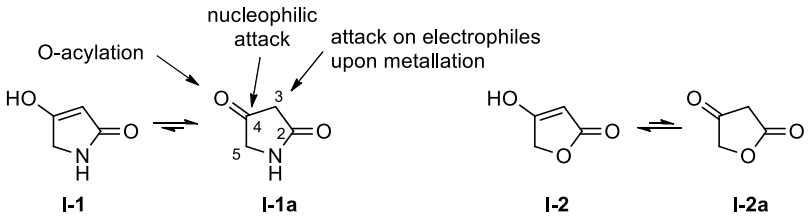



**Figure 12:** Tautomeric structures of tetramic acid **I-1/I-1a** and tetronic acid **I-2/I-2a**.[30]

The majority of the tetramic acid derivatives that are found in nature bear an acyl substituent at C3, which increases their acidity dramatically (p$K_a$ = 3.0-3.5)[31,32]. As a consequence, 3-acyltetramic acids always exist as mixtures of tautomers (Figure 13). The tautomers can be divided into two sets of internal tautomers, which undergo fast proton exchange (too fast on the NMR timescale) along the intramolecular hydrogen bond (**I-3a / I-3b** and **I-3c / I-3d**) and two pairs of external tautomers (**I-3a**, **I-3b / I-3c**, **I-3d**). The latter

undergo slow interconversion, due to the required rotation of the acyl group at C3[33]. Making use of $^{1}H$, $^{13}C$-NMR and X-ray structural analysis, *Steyn* and *Wessels*[34] determined the ratio of tautomers for 3-acyltetramic acids **I-4**, **I-5** and **I-6**. According to this analysis, the enolic forms **I-3b** and **I-3d** were the main tautomers with **I-3d** being the most abundant. The approximate ratio all tautomers of **I-3a** : **I-3b** : **I-3c** : **I-3d** was calculated as 5:15:0:80.

3-Acyltetramic acid are also excellent chelating agents for metal ions such as magnesium, iron or zinc and in some cases the biological activity is dependent on the metal which is complexed. It is assumed that complexed metal species are responsible for the cell penetration of tetramic acids[35].

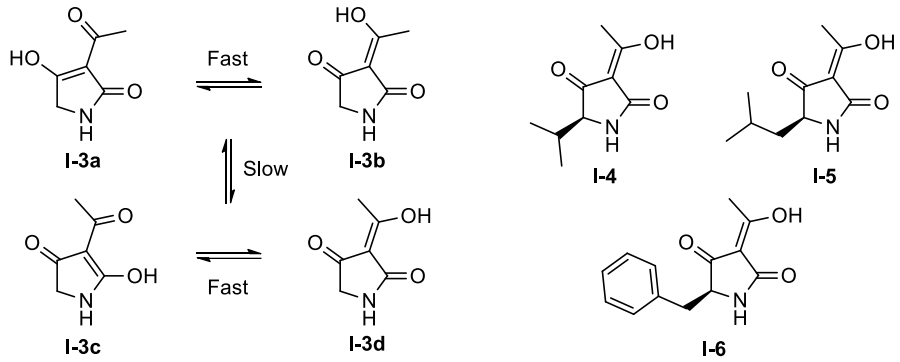



**Figure 13:** Left: Tautomeric forms of 3-acyltetramic acids. Right: Structures of 3-acyltetramic acids **I-4**, **I-5** and **I-6**.[34]

A large number of natural tetramic acids have been isolated from fungi, bacteria, cyanobacteria and marine sponges with biological activities including antimicrobial, antitumor, and antiviral effects[36,37]. The structural complexity of natural tetramic acid derivatives ranges from rather simple to very high. Thus, some representatives incorporate a large number of stereocenters, which makes the tetramic acid class very interesting not only in terms of biological activity but also as a target group for total synthesis (Figure 14)[36–38].

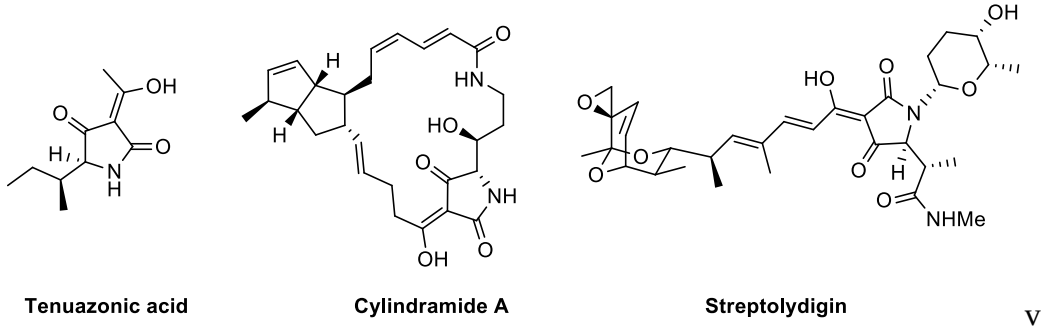



**Figure 14:** Structures of naturally occurring tetramic acids.

For example: In 2011, *Philipps* and co-workers published the discovery of kibdelomycin from an extract of *Kibdelosporangium* sp. (MA7385) (Figure 15)[39]. Kibdelomycin exhibits

strong antibacterial activity, especially against gram-positive strains and is described to be the first novel bacterial DNA gyrase inhibitor isolated from a natural source since the 1950s.

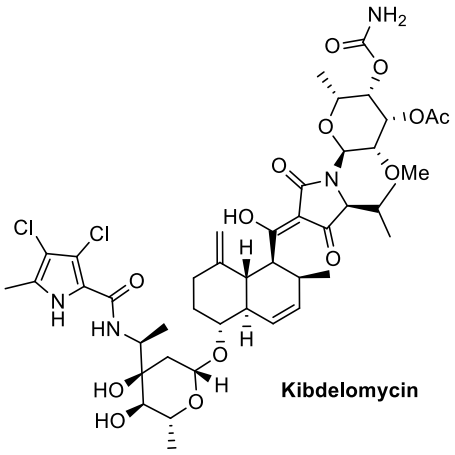



**Figure 15:** Structure of kibdelomycin.

## 1.2.1. Naturally Occurring Dienoyl Tetramic Acids

The family of the dienoyl tetramic acids includes tirandamycins A-H (TAM), tirandalydigin, streptolydigin, Bu-2313 A and B and nocamycin II, which all share a 3-dienoyl tetramic acid linked to a differently functionalized bicyclic ketal as common structural features. Differences in the structures of the dienoyl tetramic acids are mainly found in the bicyclic ketal moiety in terms of the level of functionalization and the degree of oxidation. Only streptolydigin differs from the other members of the class in the structure of the tetramic acid moiety, which is N-glycosylated and C5 substituted.

Streptolydigin (Figure 16) was the first member of the dienoyl tetramic acid family to be isolated (from *Streptomyces lydicus* in 1956, see section 1.1.3)[13]. In addition, several glycoside analogs of streptolydigin (LA to LD) were obtained from genetically engineered strains of *Streptomyces lydicus* in 2009[40] (Figure 16). The first correct proposal for the structure of streptolydigin was reported by *Rinehart* and coworkers in 1963 based on the analysis of several chemical degradation products by NMR, IR and UV spectroscopic techniques; however, the absolute configuration of the molecule could not be determined at that time[41–43]. The stereochemistry of the glycoside moiety was determined by *Stevens* and coworkers one year later by way of synthesis[44]. Finally, the absolute configuration of streptolydigin was determined by *Rinehart* in 1973 using X-ray crystallographic analysis[45]. The structural assignment by Rinehart has been confirmed through total synthesis of streptolydigin by *Kozmin* and coworkers in 2010[46].

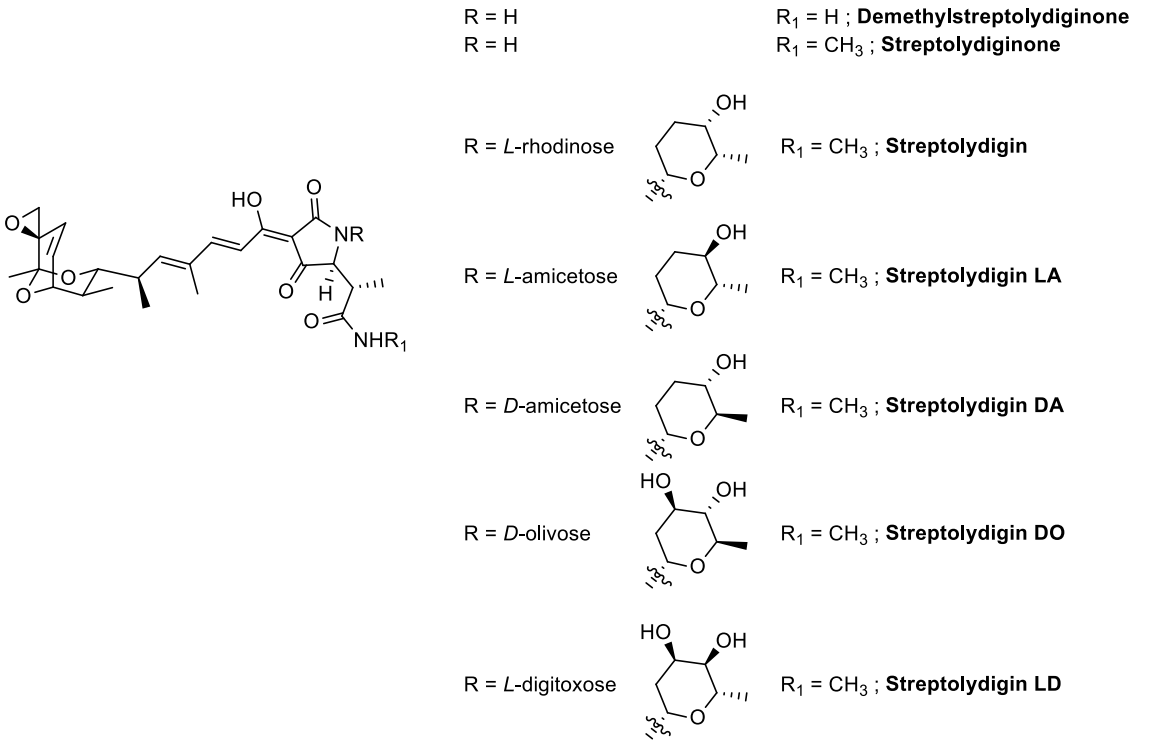



**Figure 16:** Structures of streptolydigin and variants isolated from genetically engineered strains of *Streptomyces lydicus*.[40]

Tirandamycins A and B were first isolated in the 1970s from *Streptomyces tirandis* and *S. flaveolus* by *Meyer*[47], *Scheer* and *Zähner*[48] (Figure 17). Almost 40 years later, in 2009, tirandamycin A and B were also isolated from the marine-derived *Streptomyces* sp. 307-9 along with its biosynthetic intermediates tirandamycins C and D by using a metabolite trapping method[49]. Furthermore, tirandamycins E-H from *Streptomyces* sp. 17944 were isolated in 2011 by *Yu* and coworkers during their search for a drug lead against *Brugia malayi*[50]. The assignment of the relative configuration of tirandamycin A was performed by *Rinehart* and coworkers in 1971 by means of NMR, IR and UV analysis which was followed by the assignment of its absolute configuration by means of X-ray crystallographic analysis in 1973 by the same group[45,51]. As part of this work they were also able to show that streptolydigin and tirandamycin A share the same absolute configuration, as they lead to a common degradation product[45]. The first total synthesis of tirandamycin A was published in 1985 by the group of *Schlessinger*[52] which confirmed the structural assignment.

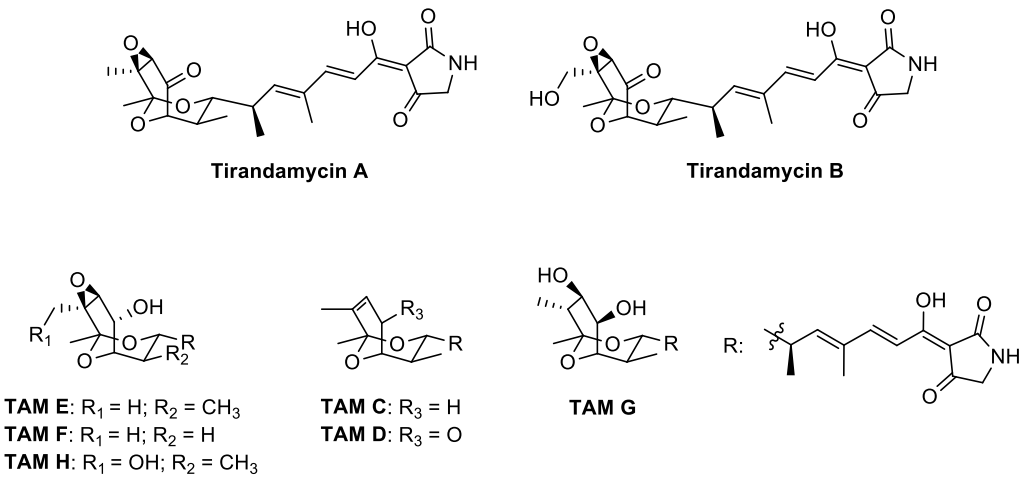



**Figure 17:** Structures of tirandamycin A and analogs thereof.

Tirandalydigin is a structural hybrid which consists of the tricyclic ketal part of streptolydigin and the tetramic acid part of tirandamycins (Figure 18). Tirandalydigin was isolated in1987 by researchers at *Abbott* Laboratories in Illinois (USA) from the *Streptomyces* sp. AB-1006A-9 and shows approximately a two-fold weaker bioactivity than its substituted counterpart streptolydigin and a similar bioactivity as tirandamycins A[53].

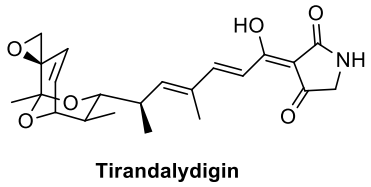



**Figure 18:** Structure of tirandalydigin.

In 1979 *Kawaguchi* and coworkers reported the isolation of Bu-2313 A and B from the unidentified oligosporic actinomycete strain No. E864-61[54] (Figure 19). Structural assignment using X-ray analysis showed that Bu-2313 A and B possesses a fused tetrahydrofuran ring on the bicyclic ketal moiety; Bu-2313 B shares the same tetramic acid unit as the tirandamycins, while Bu-2313 A bears an additional N-methyl group on the tetramic acid moiety[55]. Earlier in the same year a Russian group reported the isolation of two new dienoyl tetramic acids, which they named nocamycin I and II, but whose structures were assigned incorrectly. Subsequent comparative analysis of the available isolation and structural data revealed that the structures of nocamycin I and Bu-2313 B were identical, while the structure of nocamycin II differed from Bu-2313 B only in the oxidation state of the oxygen on the bicyclic ketal moiety[56,57].

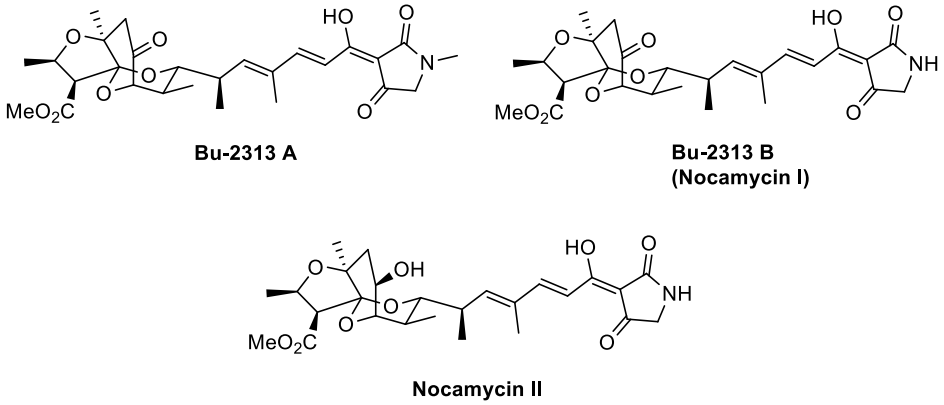
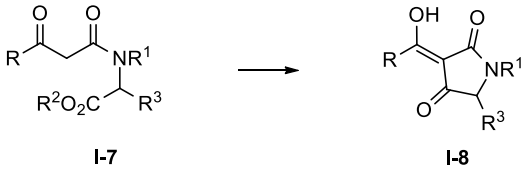



**Figure 19:** Structures of Bu-2313 A, Bu-2313 B and nocamycin II.

### 1.2.1.1. Biosynthesis

The biosynthesis of the dienoyl tetramic acids in the final steps involves the condensation of a polyketide precursor with an amino acid **I-7** followed by *Dieckmann* condensation to form the tetramic acid moiety **I-8** (Scheme 5). The tetramic acid part of streptolydigin incorporates a β-methylaspartic acid residue, while the tetramic acid moieties of the tirandamycins, tirandalydigin and Bu-2313 A/B are derived from glycine.




**Scheme 5:** Tetramic acid synthesis via *Dieckmann* condensation.

Of all dienoyl tetramic acids, the biosynthesis of streptolydigin has been investigated in most detail. Initial feeding studies with $^{14}C$- and $^{13}C$-labelled precursors, by *Rinehart* and coworkers in 1983 showed that the polyketide part of streptolydigin is derived from four acetate and four propionate units (Figure 20). The formation of the tetramic acid moiety involves the condensation of a polyketide precursor with β-methylaspartic acid and the rhodinose unit is derived from D-glucose. Lastly, the N-methyl group was shown to originate from methionine (Figure 20)[58]. In 2004 the origin of the $C_2$ units in the biosynthesis of streptolydigin was reinvestigated by the group of *Harrison*. According to this study all four acetate units of streptolydigin originate from malonyl-CoA. *Harrison* and coworkers also performed $^{18}O$-labelling studies to determine the origin of the oxygen atoms in streptolydigin, which led them to limit the formation of the bicyclic ketal unit to three putative pathways[59].

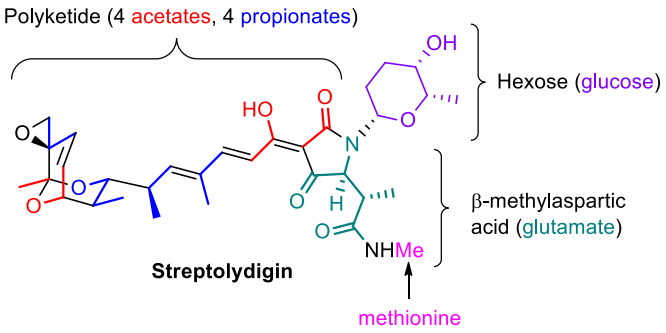



**Figure 20:** Units needed for the biosynthesis of streptolydigin.

Finally, in 2009 *Salas* and coworkers confirmed these findings by the elucidation of the streptolydigin biosynthesis gene cluster and established the complete biosynthetic pathway streptolydigin (Figure 21)[40].

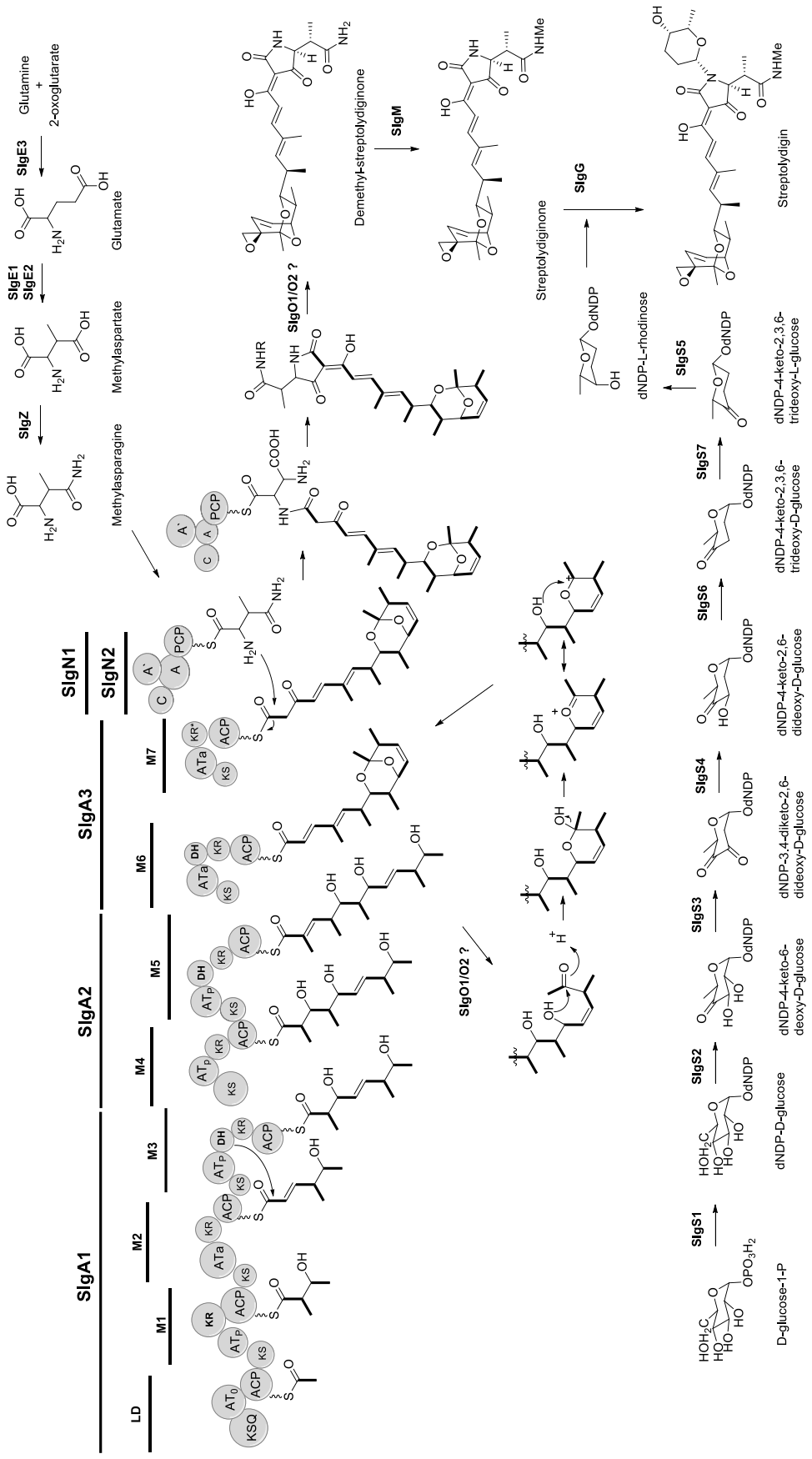



**Figure 21:** Pathway for streptolydigin biosynthesis proposed by *Salas et. al.*[40] LD: o loading module, M: module, KS: ketosynthase, AT: acyl transferase, a: malonyl-CoA specific, p: methylmalonyl-CoA specific, ACP: acyl carrier protein, DH: dehydratase, KR: ketoreductase, C: condensation, A: adenylation, PCP: peptidyl carrier protein.

### 1.2.1.2. Biological activity

All members of the dienoyl tetramic acid family show broad spectrum antibacterial activity, especially against gram-positive bacteria, with streptolydigin being the most potent compound (Table 1)[47,54,57,60]. Investigations on the mode of action showed that all dienoyl tetramic acids are inhibitors of the bacterial RNA polymerase during chain initiation and elongation. It is therefore assumed that the inhibition mechanism, which has been proposed for streptolydigin (see chapter 1.1.3), is identical for all members of the dienoyl tetramic acid family[9].

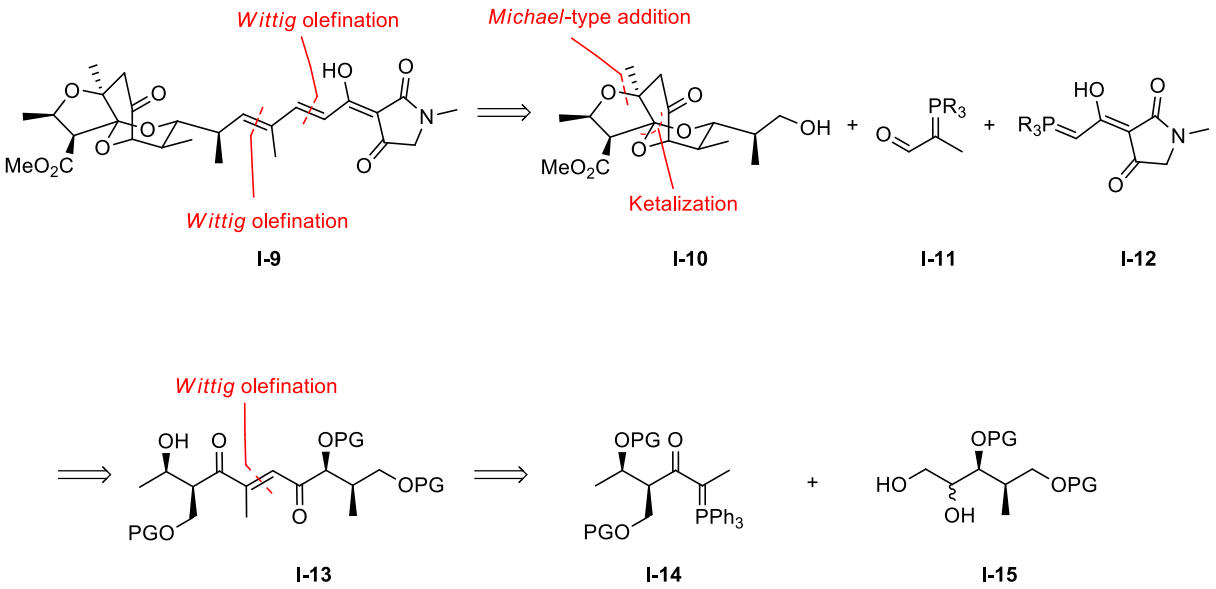
**Table 1:** Biological activity overview of the tetramic acids tirandalydigin, streptolydigin, tirandamycins A and Bu-2313 B. (*): Measurements were not performed under the same conditions.

| Entry | Test organism | MIC (mg/L) | | | |
|---|---|---|---|---|---|
| | | **Tirandalydigin** | **Streptolydigin** | **Tirandamycin A** | **Bu-2313 B** |
| **1** | B. fragilis (UC-2) | 0.5 | 1 | 1 | - |
| **2** | B. fragilis (A20926) | | | | 0.1 |
| **3** | B. melaninogenicus | 32 | 4 | 32 | - |
| **4** | B. vulgatus | 0.5 | 0.25 | 0.5 | - |
| **5** | Clostridium difficile | 32 | 8 | 16 | - |
| **6** | Bacillus subtilis | - | 6.2* | - | 1.6* |
| **7** | Clostridium acetobutylicum | - | 1.56* | - | 0.2* |
| **8** | Streptococcus viridans | - | 6.2* | - | 0.4* |

Due to its ability to inhibit RNA polymerase in a completely different manner compared to the rifamycin class of antibiotics and its reported activity against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* (MIC's of 1.6 mg/L and 6.25 mg/L, respectively), streptolydigin was considered to be a viable lead for new drugs against tuberculosis[9,15,54]. Unfortunately, in a more recent study performed by *Niederweis* and coworkers in 2013 MIC values of streptolydigin against *Mtb* were found to be substantially higher than originally reported (100 – 200 mg/L). *Niederweis* and co-workers suggest that the discrepancy between their own data and those previously reported by *Silver* and coworkers [60,61] are probably caused by the unreliable nature of the turbidometric measurements performed in the earlier experiments to assess growth inhibition[60]. Since the definition of a lead compound for anti-tuberculosis drug discovery by the NIH Tuberculosis Acquisition and Coordination Facility (TAACF) requires an MIC value of less than 10 mg/L, streptolydigin cannot be considered as viable anti-TB lead based on the data by *Niederweis*[61,62].

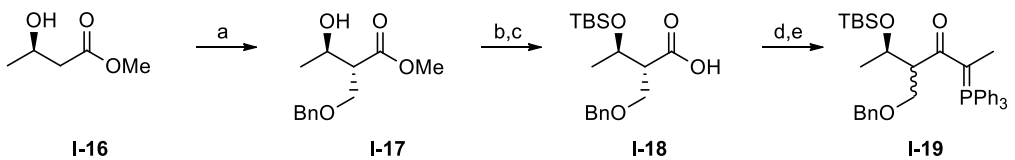
## 1.2.2. Synthetic studies on Bu-2313 A/B

So far only one synthesis attempt towards Bu-2313 A (**I-9**) has been reported, namely by *Ireland* and coworkers in 1986[63]. In their retrosynthesis they propose the assembly of the tetramic acid moiety **I-12** with the bicyclic ketal part **I-10** via *Wittig* chemistry (Scheme 6). The bicyclic ketal **I-10** was planned to be obtained via ketalization and the tetrahydrofuran ring was envisioned to be accessed via a *Michael*-type cyclization of **I-13**. For the synthesis of the enedione **I-13** a *Wittig* olefination between stabilized *Wittig* reagent **I-14** and α-keto aldehyde generated in situ from partly protected diol **I-15** was planned.



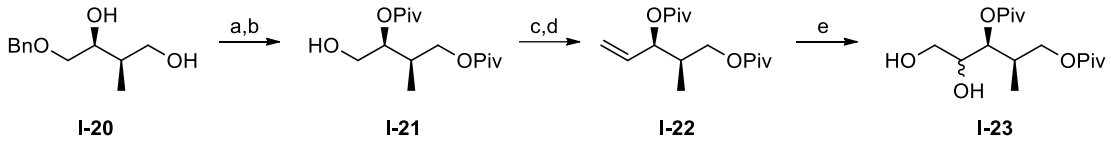

**Scheme 6:** Retrosynthetic analysis of Bu-2313A (**I-9**) by *Ireland* and coworkers.[63]

The synthesis of *Wittig* reagent **I-19** started with the alkylation of (*R*)-3-hydroxybutyrate (**I-16**) with benzyloxymethyl chloride (BOMCl) which afforded **I-17** in 42% yield and 9:1 *dr* (Scheme 7). TBS protection of alcohol **I-17** and subsequent hydrolysis of the methyl ester gave access to acid **I-18** in 63% yield over 2 steps. The hydrolysis of the methyl ester was accompanied by isomerization of the α-center and loss of the benzyloxy group by β-elimination, but both side products could be removed by means of flash chromatography. Formation of the acid chloride and treatment of the latter with ethyltriphenylphosphonium bromide ($EtP^+Ph_3Br^-$) gave phosphorane **I-19** in quantitative yield over two steps, but with isomerization of the stereocenter α to the ketone.




**Scheme 7:** a) LDA, BOMCl, THF, 42%; b) TBSCl, ImH, DMF, 86%; c) 1N LiOH, MeOH, 73%; d) $(COCl)_2$, DMF, benzene; e) $EtP^+Ph_3Br^-$, *n*-BuLi, benzene, 100% over 2 steps.

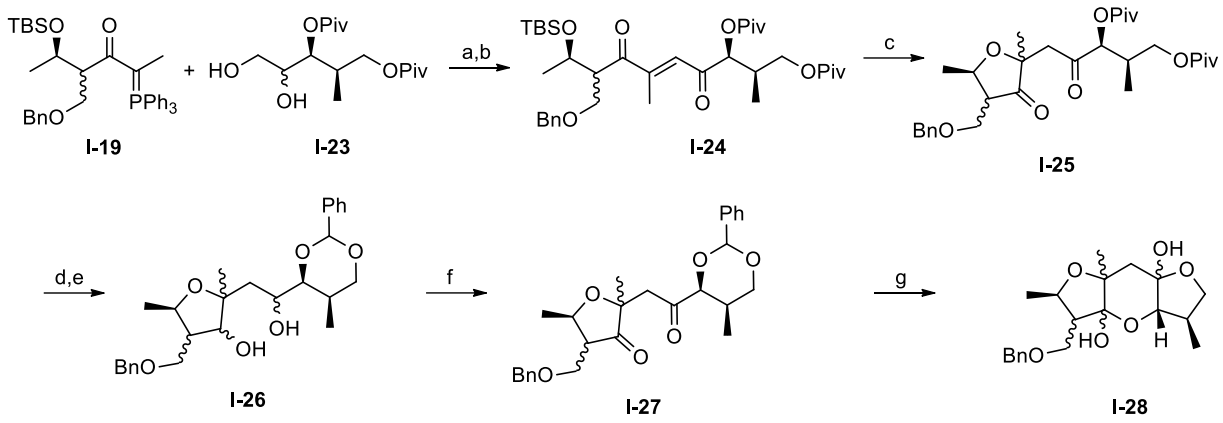
The synthesis of diol **I-23** started with the pivaloyl protection of known[64] diol **I-20** followed by benzyl group cleavage to give alcohol **I-21** in 87% yield over two steps (Scheme 8). Terminal alkene **I-22** was accessed by *Swern* oxidation of **I-21** and treatment of the intermediate aldehyde with *Tebbe's* reagent. Finally, dihydroxylation with osmium tetroxide furnished diol **I-23** in 90% yield.




**I-20** **I-21** **I-22** **I-23**

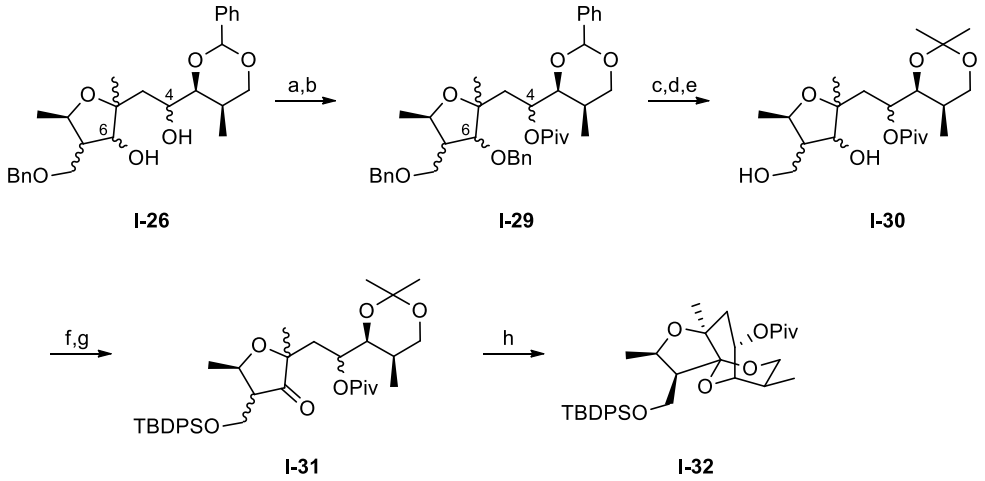
**Scheme 8:** a) PivCl, DMAP, pyridine, $CH_2Cl_2$, 97%; b) $H_2$, 10% Pd/C, EtOH, 90%; c) $(COCl)_2$, $Me_2SO$, $Et_3N$, $CH_2Cl_2$; d) Tebbe's reagent, pyridine, benzene, 47% over 2 steps; e) $OsO_4$, NMO, acetone, $H_2O$, 90%.

For the fragment assembly diol **I-23** was converted into the highly unstable α-keto aldehyde intermediate by means of *Swern* oxidation followed by treatment with phosphorane **I-19** to yield α,β-unsaturated ketone **I-24** in 42% yield (Scheme 9). Since *Wittig* reagent **I-19** was used as a diastereomeric mixture, enedione **I-24** was also obtained as a mixture of two isomers. Since the separation of these isomers was very tedious and as it was expected that the critical stereocenter would equilibrate to the thermodynamically most favored configuration upon formation of the tetrahydrofuran ring, *Ireland* and co-workers decided to continue the synthesis without isomer separation. Treatment of enedione **I-24** with lithium tetrafluoroborate ($LiBF_4$) and *p*-toluenesulfonic acid (TsOH) led to the formation of only two diastereoisomers of tetrahydrofuran **I-25**, thus suggesting a certain level of selectivity in the cyclization reaction. Simultaneous pivaloyl protecting group cleavage and ketone reduction using lithium aluminum hydride (LAH) followed by treatment of the resulting triol with benzaldehyde and TsOH then gave acetal **I-26** in 56% yield over two steps. *Swern* oxidation of **I-26** to the diketone **I-27** and acetal cleavage under acidic conditions led to the formation of the undesired tricyclic double hemiketal **I-28**, which unfortunately could not be dehydrated to the desired ketal.




**Scheme 9:** a) **I-23**, $(COCl)_2$, $Me_2O$, $Et_3N$, $CH_2Cl_2$; b) **I-19**, $CH_2Cl_2$, 42%; c) $LiBF_4$, TsOH; $CH_2Cl_2$, acetone, 81%; d) LAH, THF; e) PhCHO, TsOH, benzene, 56% over two steps; f) $(COCl)_2$, $Me_2O$, $Et_3N$, $CH_2Cl_2$, 81%; g) 10% HCl, THF, 72%.

In order to avoid the undesired attack of the primary hydroxy group on the exocyclic keto group, *Ireland* and co-workers decided to selectively protect the hydroxy group on C4 in **I-26** (Scheme 10). Unfortunately, benzyl protection experiments led to the (undesired) selective etherification of the C6 hydroxy group on the furan ring. Therefore, the remaining free hydroxy group was pivaloyl protected to yield the fully protected pentol **I-29** in 55% yield over two steps. Cleavage of the benzylidene acetal, acetonide installation and hydrogenolysis of the benzyl ethers gave access to diol **I-30**. TBDPS protection of the primary hydroxy group followed by *Swern* oxidation gave ketone **I-31** in 88% yield over two steps. Acidic cleavage of the acetonide and subsequent ketal cyclization allowed the isolation of the desired ketal **I-32** in 36% yield along with 55% of hemiketal products, which were not identified. NMR analysis of **I-32** showed that the product had the same configuration as the corresponding partial structure in the natural product, leading *Ireland* and co-workers to conclude that this configuration is the one that is most favored energetically is therefore formed exclusively.

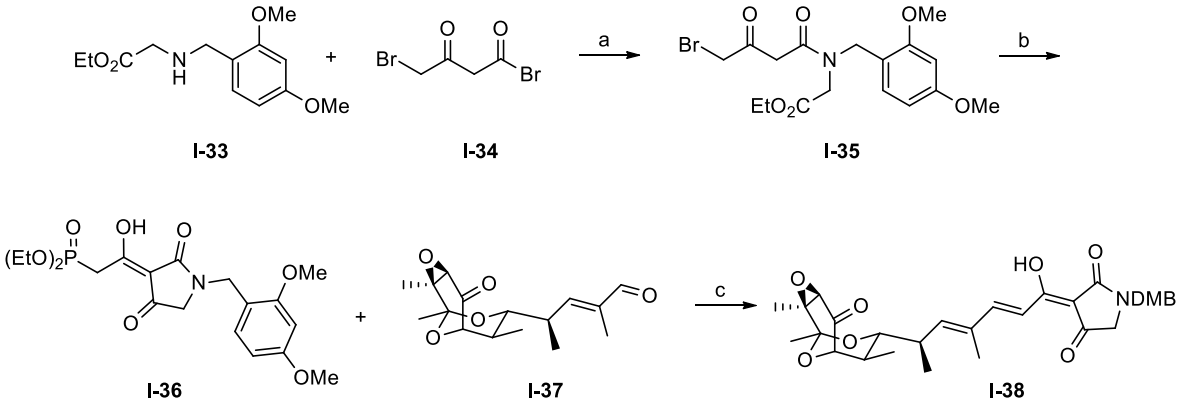



**Scheme 10:** a) BaO, $Ba(OH)_2$, BnBr, DMF, 74%, b) PivCl, DMAP, $CH_2Cl_2$, 75%; c) 10% HCl, THF; d) TsOH, 2,2-dimethoxypropane, acetone, 70% over two steps; e) $H_2$, 10% Pd/C, HOAc, EtOAc, 90%; f) TBDPSCl, DMAP, $CH_2Cl_2$, 91%; g) $(COCl)_2$, $Me_2O$, $Et_3N$, $CH_2Cl_2$, 97%; h) 10% HCl, THF, 36% + 55% hemiketals.

### 1.2.2.1. Synthetic Studies on the Tetramic Acid Part of Bu-2313 B

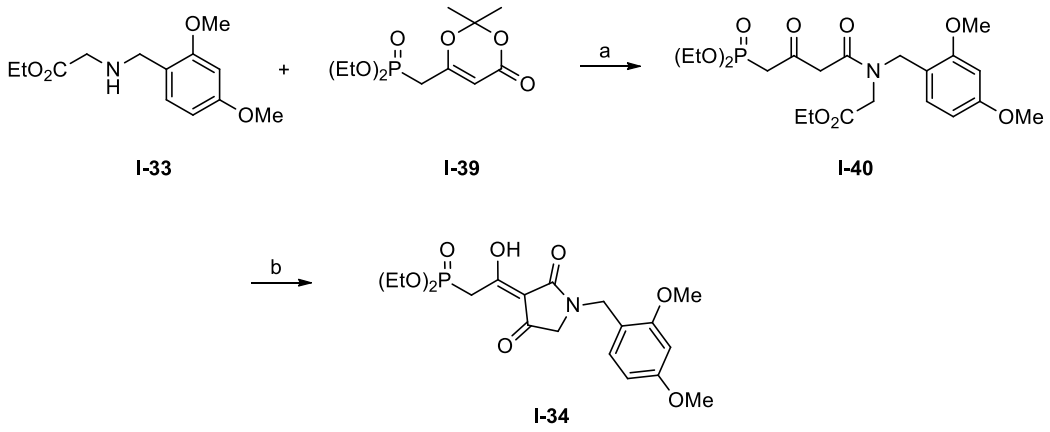
In the 1980's the groups of *Schlessinger*[52] and *Boeckman*[65] reported the total syntheses of tirandamycin A. By necessity, this also included the synthesis of the tetramic acid part of Bu-2313 B, which is identical for these two natural products.

The synthesis of *Schlessinger* and co-workers[52] started from *N*-dimethoxybenzyl protected glycine ethyl ester **I-33**, which upon acylation with γ-bromoacetoacetyl bromide (**I-34**) gave amide **I-35** (Scheme 11). Bromide displacement in **I-35** using potassium diethylphosphite ($(EtO)_2POK$) followed by *Dieckmann* condensation yielded phosphonate **I-36** in 82% yield which was coupled to the bicyclic ketal part of tirandamycin A **I-37** via *HWE* olefination upon dianion formation with *t*BuOK.




**Scheme 11:** a) $NEt_3$, $CH_2Cl_2$, 95%; b) $(EtO)_2POK$, THF, 82%; c) *t*BuOK, THF, 80%.

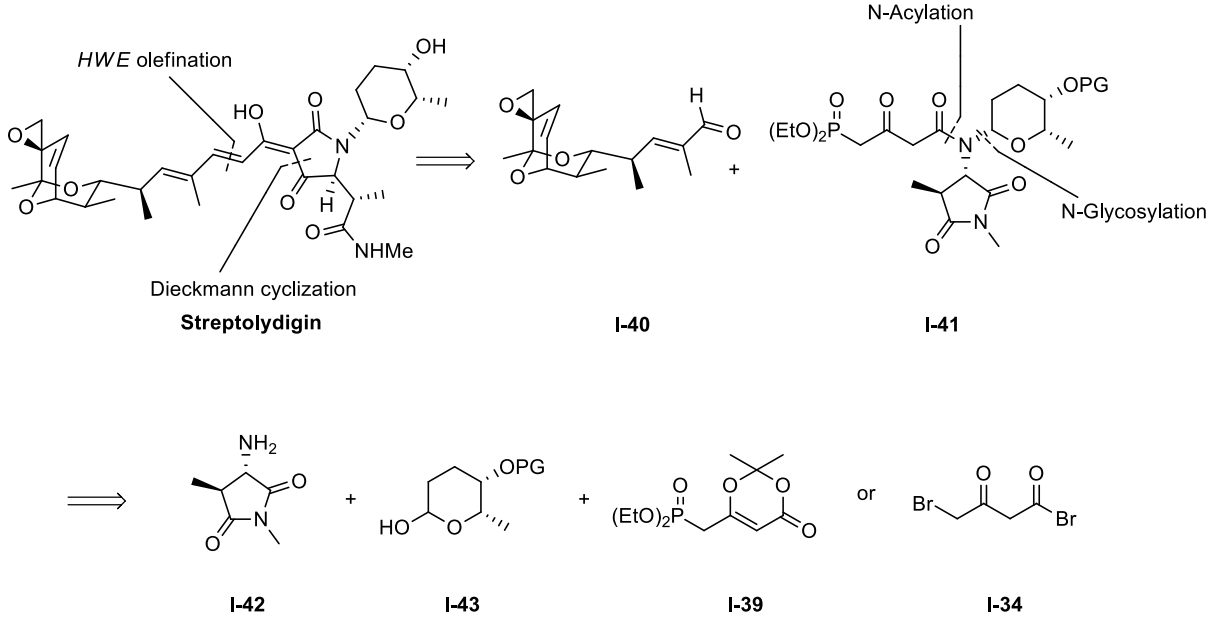
Very similar to the synthesis of *Schlessinger* and co-workers[52], the synthesis of *Boeckman* and coworkers[65] started with the condensation of **I-33** with dioxolenone **I-39** to give amide **I-40** (Scheme 12). *Dieckmann* cyclization upon treatment with *t*BuOK then furnished the tetramic acid phosphonate **I-34**.




**Scheme 12:** a) Xylene, reflux, 82%; b) KO*t*Bu, THF, 65%.

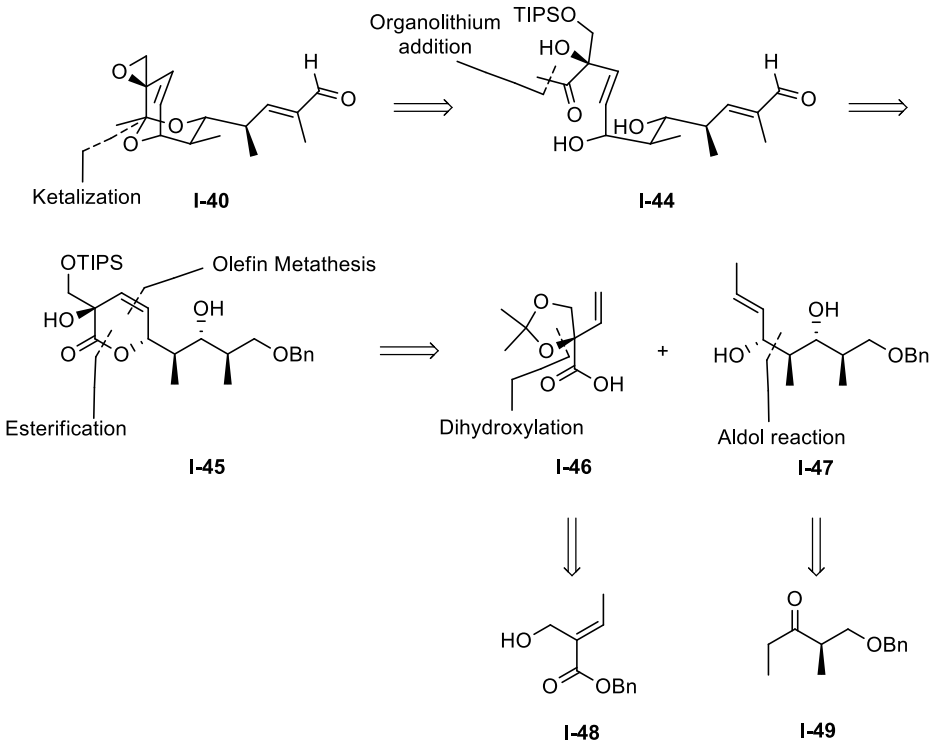
## 1.2.3. Synthetic Studies on Streptolydigin

The synthesis of the tetramic acid part of streptolydigin was first described in 1987, again by the groups of *Schlessinger*[66] and *Boeckman*[67]. Inspired by degradation experiments performed on streptolydigin[41,42], both groups proposed a strategy for the synthesis of streptolydigin to synthesize a phosphonate intermediate **I-41** which upon *Dieckmann* cyclization would react with streptolic aldehyde **I-40** by way of a *Horner-Wadsworth-Emmons* reaction (Scheme 13). Phosphonate **I-41** was envisioned to be obtained by *N*-glycosylation of amine **I-42** with a protected *L*-rhodinose derivative **I-43** followed by *N*-acylation using either dioxolenone **I-39** (*Boeckman*) or γ-bromoacetoacetyl bromide (**I-34**) (*Schlessinger*). In the case of acylation with γ-bromoacetoacetyl bromide (**I-34**) the phosphonate group had to be installed in an additional step as described in chapter 1.2.2.1. A very similar strategy was later implemented by *Kozmin* and coworkers in the first total synthesis of streptolydigin in 2010[46,68].




**Scheme 13:** Retrosynthetic analysis of streptolydigin by the groups of *Schlessinger*[66] and *Boeckman*[67].

The synthesis of streptolic aldehyde **I-40** was published by *Kozmin* and co-workers and entailed a late-stage epoxide formation with protected vicinal diol **I-44** upon ketalization. **I-44** was accessed by organolithium addition on ester **I-45**, which was obtained by chemoselective esterification of acid **I-46** with alcohol **I-47** followed by olefin metathesis to form the six membered ring. Synthesis of acid **I-48** started with *Sharpless* dihydroxylation of allylic alcohol **I-48** followed by elimination and diol **I-47** was accessed by *Aldol* reaction of **I-49** with crotonaldehyde.

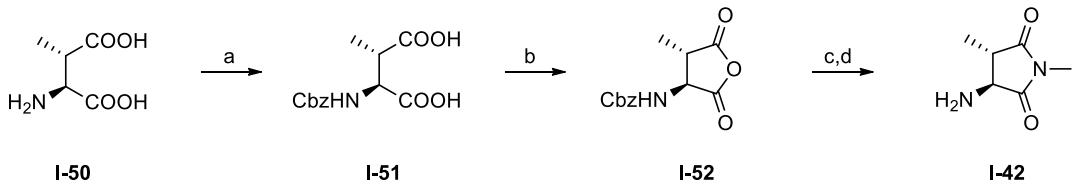



**Scheme 14:** Retrosynthesis of the streptolic aldehyde **I-40** synthesis published by *Kozmin* and co-workers[68].

### 1.2.3.1. Synthetic Studies on Succinimide Fragment I-42

Since 1978, four syntheses of the succinimide fragment **I-42** have been reported by the groups of *Rinehart*[69], *Schlessinger*[66], *Boeckman*[67] and *Kozmin*[46,68].

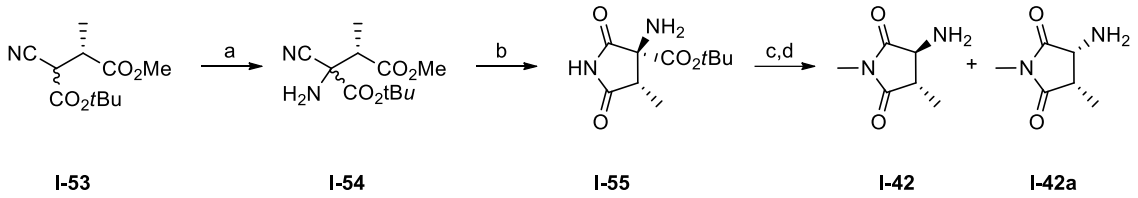
The synthesis of *Rinehart*[69] and coworkers commenced with the protection of DL-*threo*-β-methylaspartic acid (**I-50**) with CbzCl followed by succinic anhydride **I-52** formation with acetic anhydride (Scheme 15). Conversion of **I-52** into the succinimide by reaction with methylamine and subsequent cleavage of the Cbz group by hydrogenolysis then gave the desired succinimide fragment **I-42** (as a racemate).




**Scheme 15:** a) CbzCl, $NaHCO_3$, $H_2O$, 65%; b) $Ac_2O$, 95%; c) i) $MeNH_2$, $H_2O$ ii) $AcO_2$, 75%; d) $H_2$, Pd/C, MeOH, 90%.

The synthesis of *Schlessinger*[66] and coworkers started from succinate **I-53**, which was accessed by *Mitsunobu* coupling between *t*butyl cyanoacetate and methyl lactate (Scheme 16). Amination of **I-53** using *O*-(diphenylphosphinyl)hydroxylamine ($Ph_2P(O)ONH_2$) to form amine **I-54** followed by hydration of the nitrile led to the formation of succinimide **I-55**,

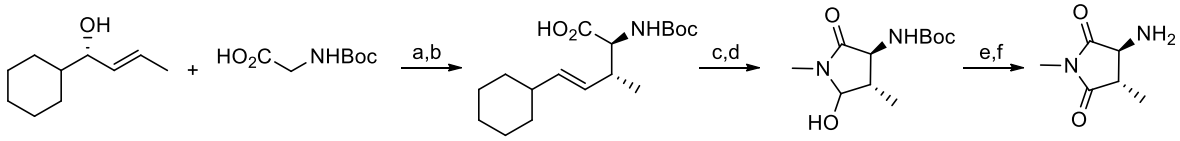
which was obtained as a pure isomer upon separation. *N*-methylation of **I-55** with diazomethane followed by *t*butyl ester cleavage with TFA and decarboxylation of the resulting acid under the reaction conditions led to a 2:1 mixture (**I-42** : **I-42a**) of the desired succinimide fragment **I-42**.




**I-53** **I-54** **I-55** **I-42** **I-42a**

**Scheme 16:** a) $Ph_2P(O)ONH_2$, MeOH/MeONa, 70%; b) $Bu_4NHSO_4$, $H_2O_2$/NaOH, 55%; c) $CH_2N_2$, 90%; d) TFA, 87%, *dr* = 2:1.

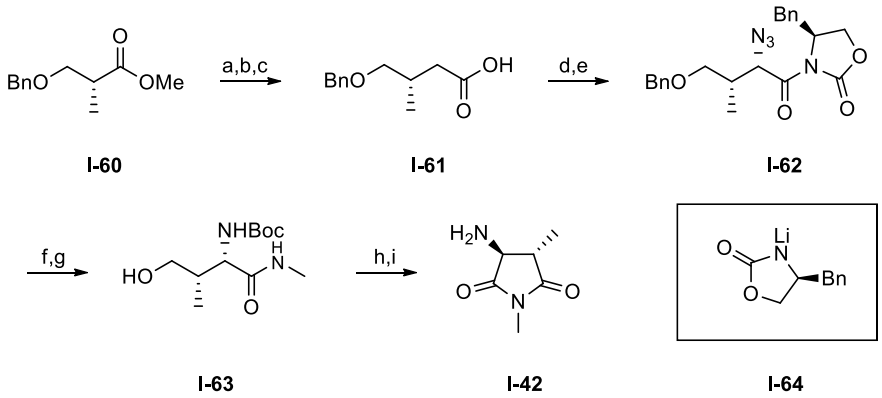
*Boeckman*[67] and coworkers started their synthesis with the esterification of chiral allylic alcohol **I-56** with Boc-protected glycine **I-57** followed by a TMS-enolate *Claisen* rearrangement to yield the α-amino acid **I-58** in 79% with a *dr* of 8:1 (Scheme 17). Conversion of **I-58** into the corresponding methyl amide via the mixed anhydride and subsequent ozonolysis with reductive workup led to the spontaneous cyclization of the intermediate aldehyde to hemiaminal **I-59**. Oxidation with pyridinium dichromate (PDC) and cleavage of the Boc group under acidic conditions finally gave the succinimide fragment **I-42**.




**I-56** **I-57** **I-58** **I-59** **I-42**

**Scheme 17:** a) DCC, DMAP, $Et_2O$; b) LDA, TMSCl, $Et_2O$, 79% over two steps; c) *i*BuOCOCl, $Et_3N$, benzene/$Et_2O$ (1:1) then $CH_3NH_2$; d) $O_3$, $Me_2S$, $CH_2Cl_2$, 71%; e) PDC, $CH_2Cl_2$; f) HCl (anhydrous), $Et_2O$, 60%.

The synthesis reported by *Kozmin*[46,68] and co-workers in the context of their total synthesis of streptolydigin started with the reduction of benzyl protected *R-Roche* ester **I-60** followed by a one carbon chain elongation via *Appel*-type and *Grignard* reaction to yield acid **I-61** in 77 % yield over 3 steps (Scheme 18). Conversion of **I-61** into an imide via addition of lithiated oxazolidinone **I-64** to the mixed anhydride and subsequent diastereoselective azide transfer using 2,4,6-tri-isopropylbenzenesulfonyl azide ($TrisN_3$) provided azide **I-62** in good yield. Displacement of the auxiliary with methylamine followed by concomitant benzyl group cleavage and azide reduction via hydrogenation led to the free amine which was in situ Boc protected to give amide **I-63** in 77% yield over 2 steps. The last steps of the synthesis included a TEMPO-mediated oxidative cyclization and Boc protecting group cleavage with TFA to give the succinimide fragment **I-42**.

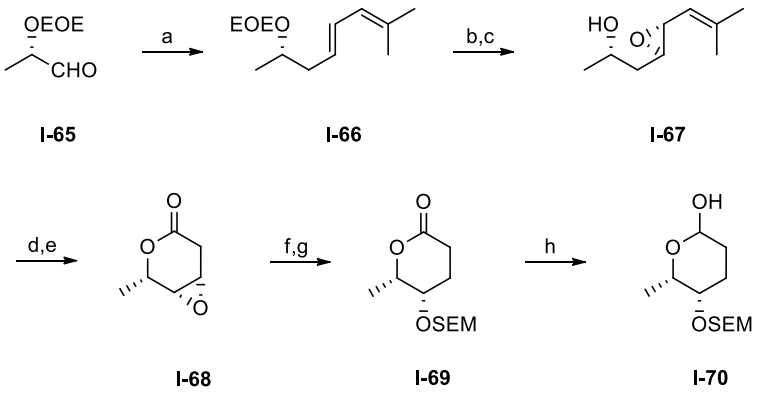



**Scheme 18:** a) $LiAlH_4$, THF; b) NBS, $PPh_3$, $CH_2Cl_2$; c) Mg, $(CH_2Br)_2$, $CO_2$, THF, 77% over three steps; d) PivCl, $Et_3N$, THF then **I-64**, 78%; e) KHMDS, $TrisN_3$, THF, 80%; f) $MeNH_2$, THF, 88%; g) $H_2$, Pd/C, $Boc_2O$, 88%; h) TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$, 80%; i) TFA, $CH_2Cl_2$, 100%.

### 1.2.3.2. Synthetic Studies on *L*-Rhodinose Fragment I-43

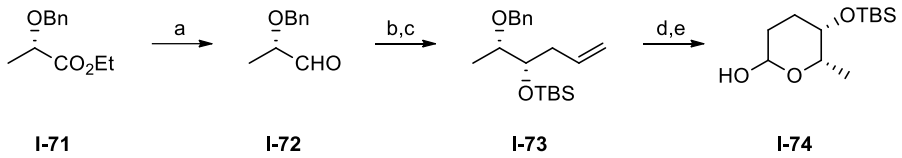
The synthesis of *L*-rhodinose has been described several times over the last 30 years[67,70–79], with most of the syntheses employing (*S*)-lactic acid as chiral starting material. In the following, a selection of the early syntheses of *L*-rhodinose, performed by the groups of *Boeckman*[67], *Schlessinger*[77] and *Takano*[75], will be presented.

The synthesis of *Boeckman*[67] and co-workers started with the conversion of (*S*)-lactic acid into aldehyde **I-65**, which was then further transformed into alkene **I-66** via *Wittig* olefination (Scheme 19). Removal of the ethoxyethyl protecting group under acidic conditions followed by a directed *Sharpless* epoxidation produced epoxide **I-67** as a single isomer. **I-67** was then converted into the aldehyde via ozonolysis, which spontaneously cyclized to the hemiacetal. Oxidation of the latter with PDC gave lactone **I-68**. Treatment of **I-68** with SEMCl and DIPEA led to epoxide opening and simultaneous SEM protection of the resulting hydroxy group. Subsequent reduction of the double bond by catalytic hydrogenation gave lactone **I-69**, which upon reduction with DIBALH gave the desired SEM-protected *L*-rhodinose **I-70**.




**Scheme 19:** a) $(CH_3)_2C{=}CHCH_2CH_2PPh_3^+Br^-$, KH, THF, 74%; b) MeOH, Dowex-50-W-X2 ($H^+$); c) *t*BuOOH, $Ti(OiPr)_4$, $CH_2Cl_2$; d) $O_3$, $MeOH/CH_2Cl_2$, $Me_2S$; e) PDC, $CH_2Cl_2$; 54% yield over 4 steps; f) SEMCl, DIPEA, $CH_2Cl_2$; $H_2$, Pd/C, EtOAc, 81% over two steps; h) DIBALH, $CH_2Cl_2$, 97%.

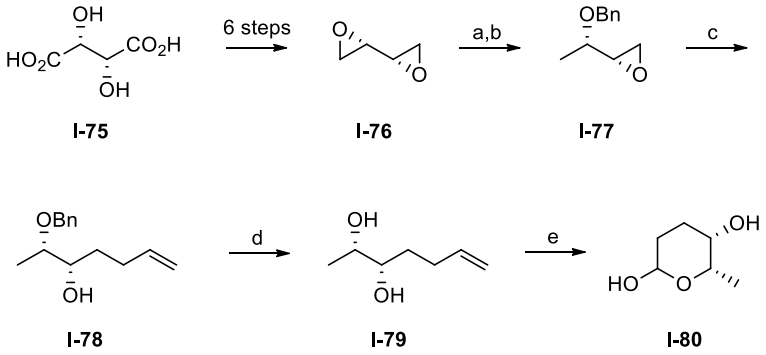
*Schlessinger*[77] and co-workers commenced their synthesis with the reduction of benzyl protected (*S*)-ethyl lactate **I-71** with DIBALH and immediate allylation of the resulting unstable aldehyde **I-72** with tributylallylstannane under chelation controlled conditions, to yield alkene **I-73** in 85% over two steps as single isomer (Scheme 20). Hydroboration of **I-73** followed by oxidation with PCC led to the formation of an aldehyde, which upon debenzylation with hydrogen and Pd/C spontaneously cyclized to the desired TBS-protected *L*-rhodinose **I-74**.




**I-71** **I-72** **I-73** **I-74**

**Scheme 20:** a) DIBALH, $CH_2Cl_2$; b) tributylallylstannane, MgBr•$Et_2O$, $CH_2Cl_2$, 85% over two steps; c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 98%; d) 9-BBN, $CH_2Cl_2$ then PCC, 61%; e) $H_2$, Pd/C, THF, 91%.

The synthesis of *Takano*[75] and coworkers started from $C_2$-symmetric diepoxide **I-76** which can be obtained from *L*-tartaric acid (**I-75**) over 6 steps (Scheme 21)[80]. Opening of diepoxide **I-76** with one equivalent of lithium triethyl borohydride followed by benzyl protection of the newly generated secondary hydroxy group yielded epoxide **I-77** in 45-60% over two steps. Subsequent cuprate-based epoxide opening with allylmagnesium chloride and copper iodide gave alcohol **I-78**. Benzyl cleavage under *Birch* conditions followed by ozonolysis yielded *L*-rhodinose (**I-80**) in 53% yield.




**I-75** **I-76** **I-77** **I-78** **I-79** **I-80**

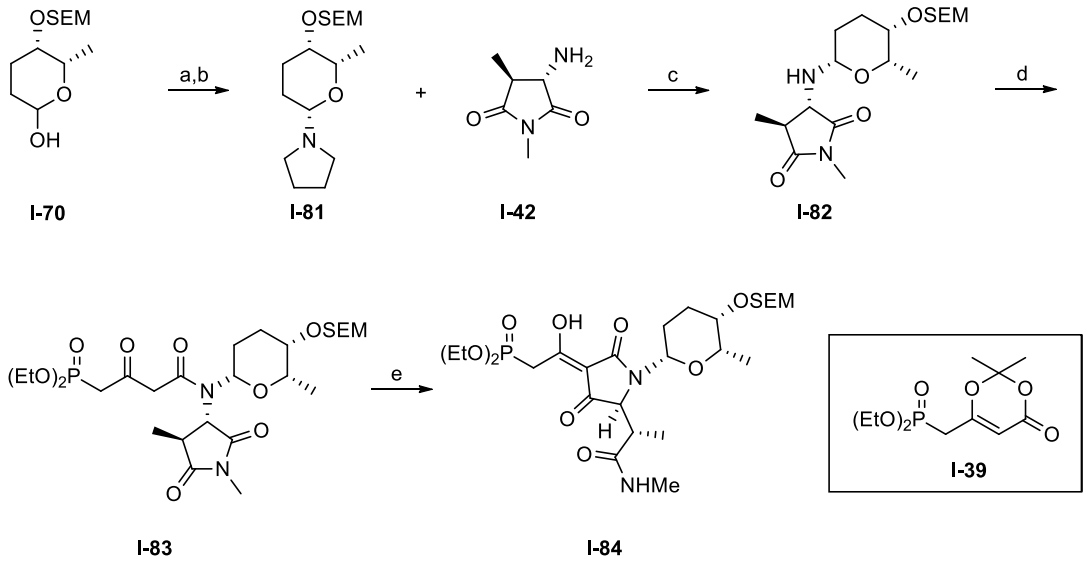
**Scheme 21:** a) $LiEt_3BH$, THF; b) NaH, BnBr, $Bu_4NI$, THF, 45-60% over two steps; c) Allylmagnesium chloride, CuI, THF; d) Li, $NH_3$, 73% over two steps; e) $O_3$, $Me_2S$, $CH_2Cl_2$, 53%.

### 1.2.3.3. Assembly of the Fragments

As mentioned above, the synthesis of the tetramic acid-containing streptolydigin fragment **I-41** has only been described by the groups of *Boeckman*, *Schlessinger* and *Kozmin*[68,81,82]. As all three syntheses are very similar, only those of *Boeckman* and *Kozmin* will be presented in the following.

The synthesis of *Boeckman* started with the conversion of *L*-rhodinose **I-70** into pyrrolidino-*L*-rhodinopyranoside **I-81** via the corresponding anomeric acetate. The

pyrrolidino moiety in aminal **I-81** could then be exchanged for amine **I-42** by treatment of **I-81** with camphor sulfonic acid (CSA) and **I-42** to yield the β-glycosyl amine **I-82** in almost quantitative yield. Treatment of **I-82** with dioxenone **I-39** in xylene at 135°C then gave β-keto amide **I-83**. *Dieckmann* condensation triggered by addition of KO*t*Bu finally yielded the desired phosphonate **I-84** in 74% yield.




**Scheme 22:** a) $Ac_2O$, DMAP, pyridine/$CH_2Cl_2$, 97%; b) pyrrolidine, $BF_3$•$Et_2O$, 90%; c) CSA, MeCN, 99%; d) **I-39**, xylene, 135°C, 53%; e) KO*t*Bu, THF, 74%.

While the group of *Boeckman* did not report any work on the HWE olefination with phosphonate **I-84**, the group of *Schlessinger* used their related phosphonate to synthesize the tirandamycin A – streptolydigin hybrid **I-85** (Figure 22)[82].

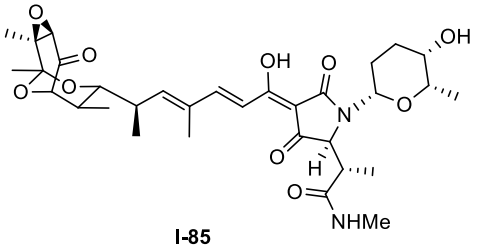
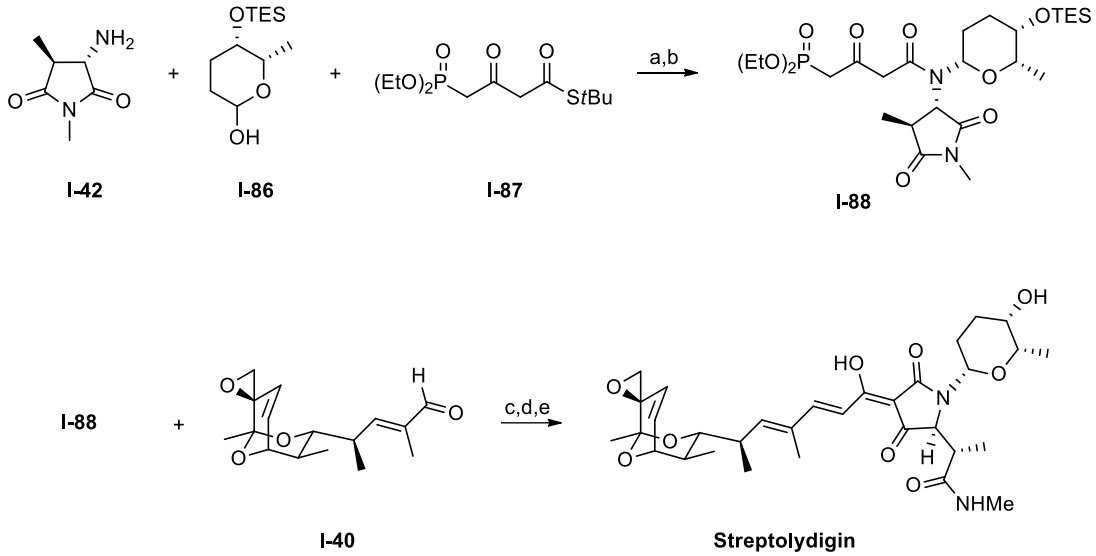



**Figure 22:** Structure of the tirandamycins-streptolydigin hybrid **I-85**.

The group of *Kozmin* performed the assembly of phosphonate **I-88** as part of their total synthesis of streptolydigin (Scheme 23). In their approach **I-42** was treated with TES-protected *L*-rhodinose **I-86** and followed by N-acylation of the glycosyl amine intermediate with thioester **I-87**. Treatment of phosphonate **I-88** with *t*BuOK triggered the desired *Dieckmann* condensation which was followed by the addition of aldehyde **I-40** and acidic work up that led to the formation of streptolydigin in 60% yield in a one pot procedure.

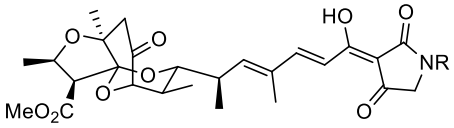



**Scheme 23:** a) **I-42**, **I-86** MeOH; b) **I-87**, $CF_3CO_2Ag$, THF, 60% over two steps; c) **I-88**, *t*BuOK, THF; d) **I-40**, THF; e) aqu. 1M HCl, THF, 60% over three steps.

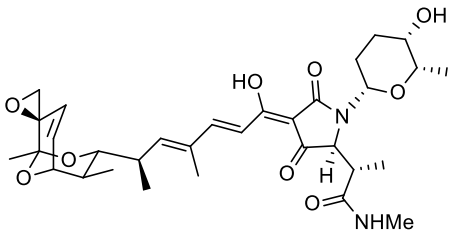
# 2. Aims and Scope

As outlined in the introduction, Bu-2313 A (**1**) and Bu-2313 B (**2**) are highly potent and broad spectrum antibiotics that are believed to be bacterial RNA-polymerase inhibitors. While this has not been demonstrated explicitly, the mode of action of Bu-2313 A/B (**1/2**) is assumed to be the same as for streptolydigin (**3**) and tirandamycin. As a consequence, like streptolydigin (**3**), Bu-2313 A/B (**1/ 2)** should also have minimal cross-resistance with the clinical RNA polymerase inhibitors rifamycin and tiacumicin B, which would make them valid lead candidates for the development of new agents against MDR pathogens.

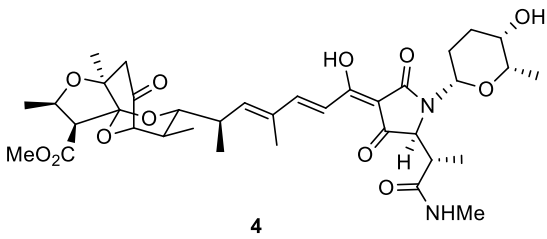
It was the goal of this Ph.D. project to establish the first total synthesis for Bu-2313 B (**2**), in order to enable mechanistic studies with the natural product and to provide a basis for the future synthesis of novel analogs and SAR investigations. In addition, a hybrid structure **4** between Bu-2313 (**1**/**2**) and streptolydigin (**3**) was to be prepared, in order to explore the general importance of the substitution of the tetramic acid moiety for RNA polymerase inhibition in streptolydigin-type structures.




Bu-2313 A (**1**): R = $CH_3$
Bu-2313 B (**2**): R = H



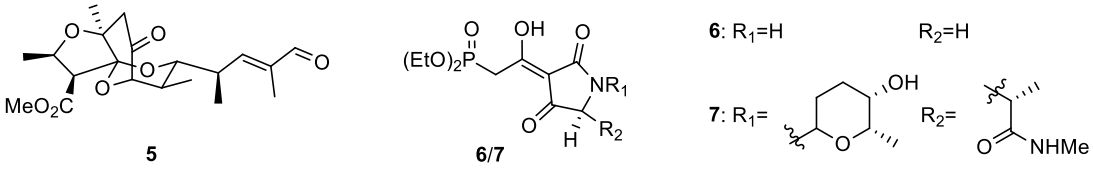

streptolydigin (**3**)




**4**

**Figure 23:** Structures of Bu-2313 A/B (**1/2**), streptolydigin (**3**) and the Bu-2313 – streptolydigin hybrid **4**.

Strategically, both target structures were to be assembled by HWE olefination between aldehyde **5** and the respective tetramic fragment **6** or **7**.




**Scheme 24:** Assembly strategy of aldehyde **5** with the corresponding phosphonates **6** and **7**.

More specific details of the retrosynthesis will be discussed in the following sections.

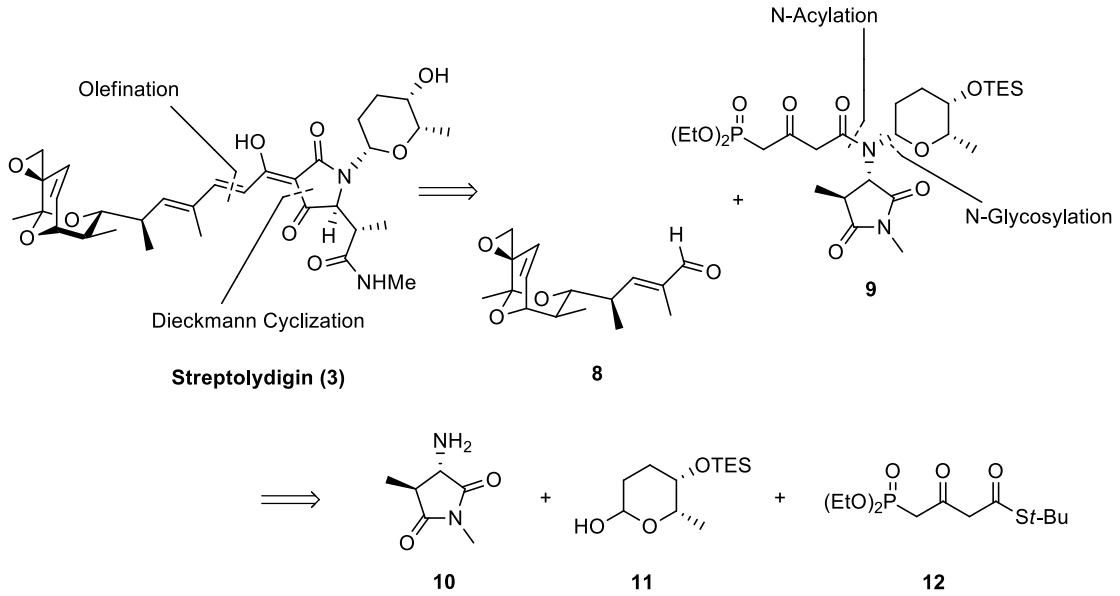
# 3. Results and Discussion

## 3.1. Tetramic Acid Part of Streptolydigin

### 3.1.1. Retrosynthesis

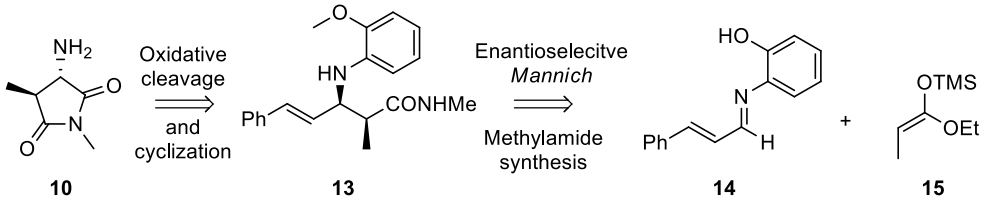
As alluded to in the introduction, the synthesis of phosphonate **9**, which incorporates the tetramic acid substructure of streptolydigin (**3**), has already been described in the literature by *Kozmin*[46] and co-workers as part of their work on the total synthesis of streptolydigin (**3**) in 2010. The synthesis was based on building blocks **10**, **11**, and **12** and followed the same overall approach that had been developed previously by *Schlessinger* et al.[82] and *Boeckman* et al.[81] in 1987 for the synthesis of alternatively protected variants of **9**. In all three cases, the *L*-rhodinose building block was ultimately derived from *S*-lactic acid as the source of chirality, while different routes were pursued for the synthesis of succinimide **10**.

Given its high level of convergency, the approach originally developed by *Schlessinger* et al. and *Boeckman* et al. for the synthesis of **9**-type structures was also to be followed in in this thesis (see Introduction). However, new stereoselective syntheses were to be developed for succinimide **10** as well as protected *L*-rhodinose **11**; in particular, fully enantioselective syntheses of **10** and **11** were targeted that would not rely on chiral pool compounds as starting materials.



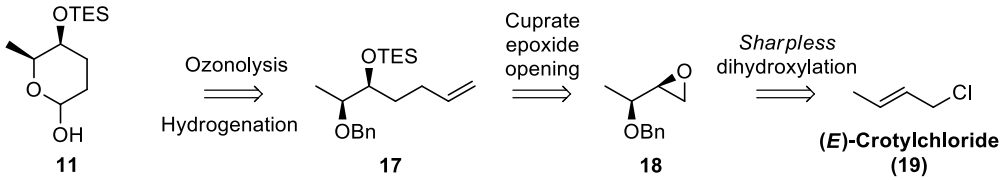

**Scheme 25:** Retrosynthetic analysis of streptolydigin **3**.

Thus, succinimide **10** was envisioned to be obtained from alkene **13** by oxidative cleavage of the double bond and oxidation of the ensuing cyclic hemiaminal (Scheme 26). The key step in the synthesis of olefin **13** was to be an enantioselective *Mannich* reaction between ketene acetal **15** and imine **14** according to *Akiyama*[83,84] and co-workers that should furnish the ethyl ester equivalent of **13**. The latter would then be converted into amide **13** by saponification and methyl amide formation. The enantioselective *Mannich* reaction uses a 2-hydroxyphenyl moiety as directing group, which is essential for the selectivity of the reaction. At the same time the 2-hydroxyphenyl group, or its 4-methoxy analog, could also serve as a protecting group during the subsequent steps of the synthesis.




**Scheme 26:** Retrosynthetic analysis of the succinimide fragment **10**.

The *L*-Rhodinose fragment **11** was planned to be obtained from alkene **17** by ozonolysis; upon cleavage of the benzyl protecting group by hydrogenation the resulting aldehyde would then spontaneously cyclize to give **11** (Scheme 27). The synthesis of alkene **17** was to be achieved by copper mediated epoxide opening of **18**, which in turn would be accessed by enantioselective *Sharpless*[85] dihydroxylation of (*E*)-crotylchloride (**19**).



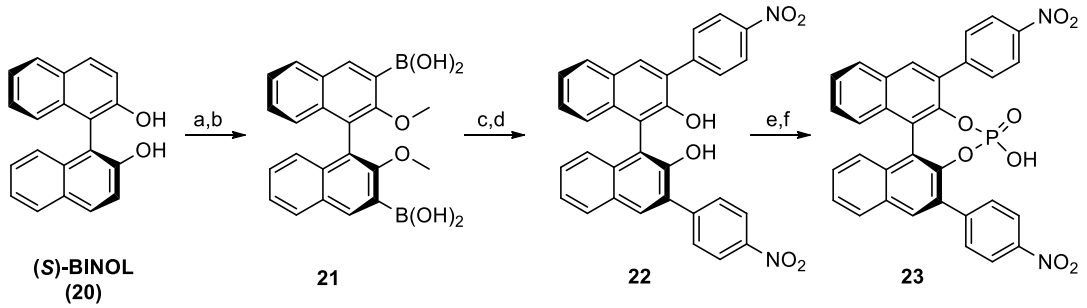

**Scheme 27:** Retrosynthetic analysis of the *L*-Rhodinose fragment **11**.

## 3.1.2. Synthesis of the Succinimide Fragment 10

### 3.1.2.1. Preparation of *Akiyama's* Catalyst 23

For the projected enantioselective *Mannich* reaction, the chiral Brønsted acid **23** was needed as organocatalyst and had to be synthesized according to the procedures reported by *Jørgensen*[86] and *Akiyama*[84] for the (*R*)-catalyst (Scheme 28). Starting from commercially available (*S*)-BINOL (**20**), the hydroxy groups were methylated using potassium carbonate and iodomethane. Double lithiation with *n*BuLi in the presence of TMEDA and reaction of the lithiated intermediate with $B(OEt)_3$ at -78°C gave a bis-boronate ester that hydrolyzed under acidic conditions to furnish the corresponding bis-boronic acid **21** in 66% yield. *Suzuki*[87] coupling of **21** with 1-bromo-4-nitrobenzene in the presence of $Ba(OH)_2$ and catalytic amounts of $Pd(PPh_3)_4$ followed by demethylation with $BBr_3$ gave diol **22** in 87%

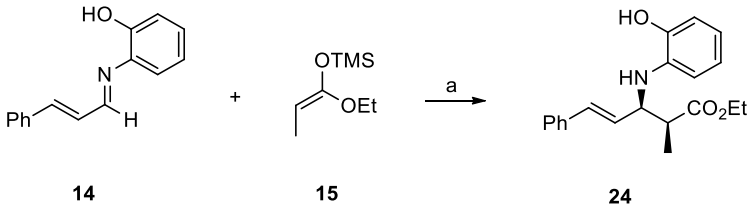
yield over two steps. Treatment of **22** with $POCl_3$ followed by acid hydrolysis with 6M HCl yielded the desired chiral phosphodiester **23** in 77% yield.




**Scheme 28:** a) $K_2CO_3$, MeI, acetone, reflux, 94%; b) *n*BuLi, TMEDA, $Et_2O$, rt, then $B(OEt)_3$, -78°C to rt, then 1M HCl, 0°C to rt, 66%; c) $Ba(OH)_2 \bullet 8H_2O$, $Pd(PPh_3)_4$, 1-Bromo-4-Nitrobenzene, dioxane/$H_2O$ (3:1), reflux; d) $BBr_3$, $CH_2Cl_2$, 0°C, 87% over two steps; e) $POCl_3$, pyridine, rt; f) 6M HCl, 0°C then reflux, 77%.

### 3.1.2.2. Enantioselective *Mannich* reaction

Having the chiral catalyst **23** in hand, the enantioselective *Mannich* reaction was carried out with the known aldimine **14** and ketene acetal **15** according to *Akiyama* and co-workers, yielding the *Mannich* product **24** in 78% yield and with an *ee* of 90% and a *dr* of 92:8 (Scheme 29).




**Scheme 29: 14**, **23** then **15**, toluene, -78°C, 78%, 90% *ee*, 92:8 *dr*.

As already mentioned, the 2-hydroxyphenyl group on the aldimine **14** is essential for the selectivity of the *Mannich* reaction. Density functional theory calculations performed by *Akiyama* and co-workers[84] led to the conclusion that the reaction proceeds through the 9-membered, zwitterionic transition state (**TS**), which includes two hydrogen bonds between the free oxygen atoms of the phosphodiester group and the protonated nitrogen of the aldimine and the phenolic hydroxy group, respectively (Figure 24). The geometry of the 9-membered transition state and π-stacking between the 2-hydroxyphenyl group and the *p*-nitroaryl group of **23** fix the spatial position of the aldimine **14** in such a way as to favor the *re*-face attack by the TMS-enolate **15**.

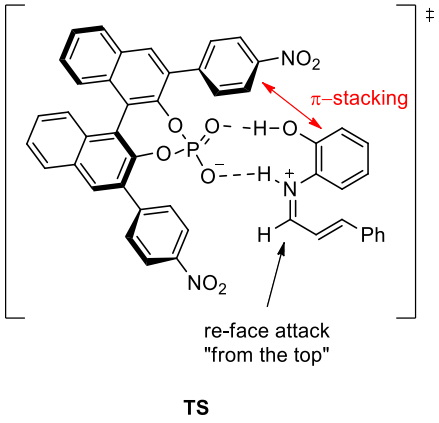
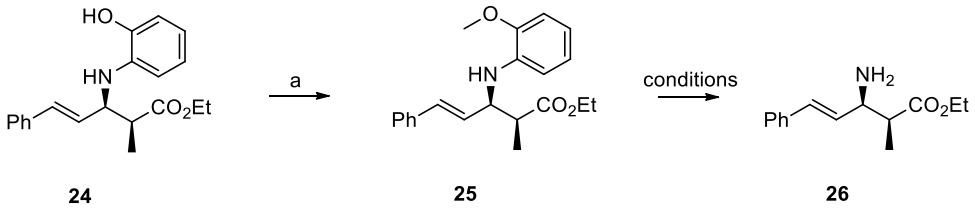



**Figure 24:** Transition state proposed by *Akiyama* and coworkers for the enantioselective *Mannich* reaction.

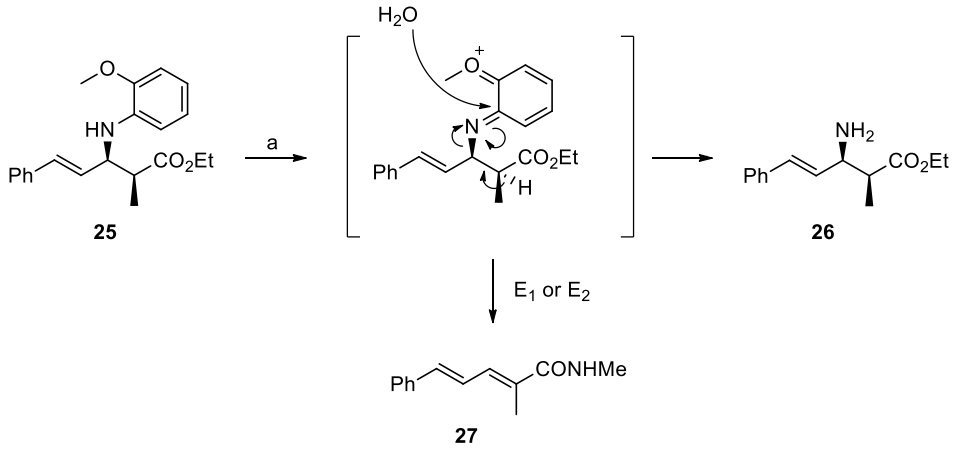
## 3.1.3. 1st Generation Synthetic Strategy Towards Succinimide Fragment 10

As mentioned above, it was envisioned to retain the 2-hydroxyphenyl directing group as a protecting group for the amine throughout the remainder of the synthesis after the *Mannich* reaction (Scheme 30). However, in order to ascertain the validity of this strategy, the feasibility of cleaving the 2-hydroxyphenyl from an amino group was investigated first, as low yields have been reported in literature for such deprotections[84]. Following literature procedures[84], the phenolic hydroxy group in **24** was methylated with iodomethane and potassium carbonate. However, contrary to what has been reported by *Akiyama*[84], treatment of the resulting methyl ether with cerium ammonium nitrate (CAN) only led to decomposition and none of the amine **26**. Fortunately, a method reported by *Verkade* and coworkers[88] for the cleavage of *p*-methoxyphenyl groups from amines, which involves the use of periodic acid in combination with sulfuric acid, could be successfully applied to **25** and allowed the successful conversion into the free primary amine **26** in 41% yield. This yield, although not truly satisfactory, was comparable to deprotection yields that have been reported for other *Mannich* products[84].




**Scheme 30:** a) MeI, $K_2CO_3$, acetone, rt, 92%; Conditions: 1) CAN, MeCN/$H_2O$ (1:1) or MeOH, 0°C, 0%; 2) $H_5IO_6$, $H_2SO_4$, MeCN/$H_2O$ (1:1), rt, 41%.

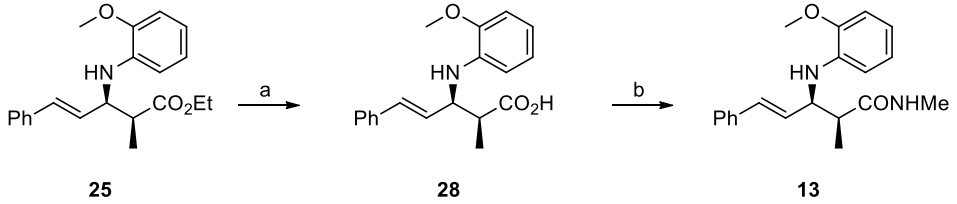
The main issue with the removal of the 2-methoxyphenyl group was a competing elimination, leading to the conjugated dienoic ester **27** (Scheme 31). Since the deprotection is performed under acidic conditions, an $E_1$ mechanism via a highly stabilized cinnamyl cation is assumed to be the likely pathway for the formation of **27**.




**Scheme 31:** a) $H_5IO_6$, $H_2SO_4$, MeCN/$H_2O$ (1:1), rt, 41%.

In order to overcome the elimination problem, the possibility of oxidizing the alkene to the corresponding diol prior to removal of the 2-methoxyphenyl group was considered. However, it was decided to postpone the investigation of such additional deprotection studies until after installing the methyl amide functionality.

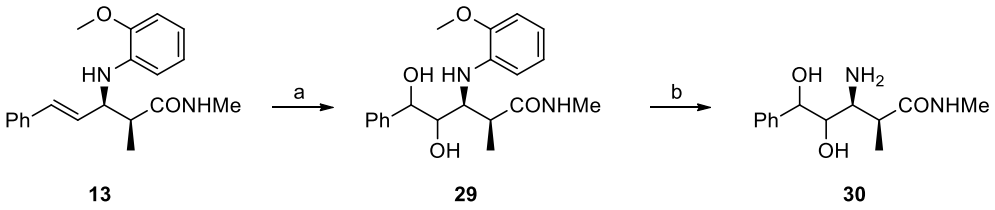
Ethyl ester **25** was saponified using LiOH, which gave acid **28** in 97% yield without any traces of isomerization at the α-position (Scheme 32). Transformation to the amide **13** was achieved by conversion of the acid **28** to the mixed anhydride with isobutylchloroformate (IBCF) and *N*-methylmorpholine (NMM) followed by addition of methyl amine. The amide **13** was obtained in 93% yield and again without any signs of α-isomerization.




**Scheme 32:** a) LiOH, THF/MeOH/$H_2O$ (1:2:1), 0°C to rt, 97%; b) NMM, IBCF, THF, -20°C to rt then aqu. Methylamine, rt, 93%.

In the following, the dihydroxylation of alkene **13** was performed under *Upjohn*[89] conditions at 45°C, which produced the desired diol **29** in 63% yield (Scheme 33). As the use of periodic acid was believed to result in diol cleavage, the removal of the 2-methoxyphenyl group from **29** was attempted with trichloroisocyanuric acid (TCCA) as an oxidant: this reagent had also been reported by *Verkade*[88] to cleave *p*-methoxyphenyl amines efficiently. Applying this alternative method resulted in a clean cleavage of the 2-methoxyphenyl group according to MS and TLC analysis. Unfortunately, due to the high polarity of the product **30**, it was nearly impossible to get the compound into the organic phase during workup, which resulted in very low yields. Direct isolation from the aqueous phase failed to provide the product in pure form, since the side products formed in the oxidation could not be removed.

At this point it was decided to investigate the selective diol cleavage first, in order to avoid a product with very high polarity.

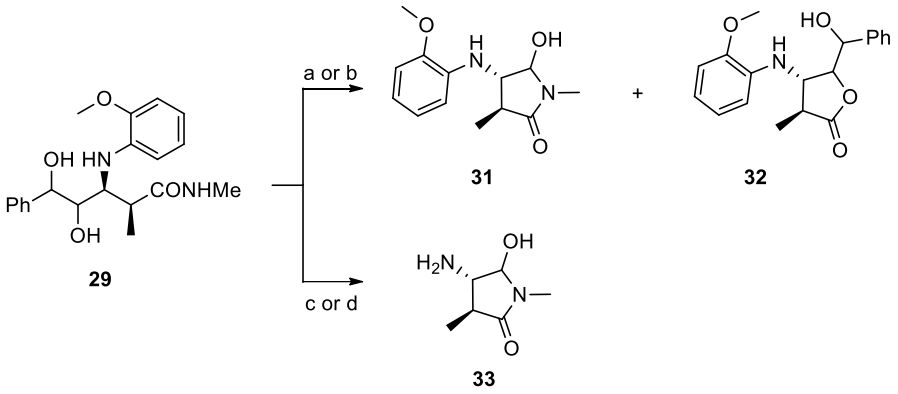



**13** **29** **30**

**Scheme 33:** a) $OsO_4$, NMO, acetone/$H_2O$ (10:1), 45°C, 82%; b) TCCA, $H_2SO_4$, MeCN/$H_2O$ (1:1), rt, 2-10%.

In order to prevent uncontrolled loss of the 2-methoxyphenyl group (and ensuing undesired side reactions), the diol cleavage was performed under slightly basic conditions using $NaIO_4$ or $Pb(OAc)_4$ as oxidant (Scheme 34). With both reagents the 5-membered lactam **31** was isolated in about 20% yield; unfortunately the major product of the reaction was lactone **32**, which was obtained in ~40% yield.

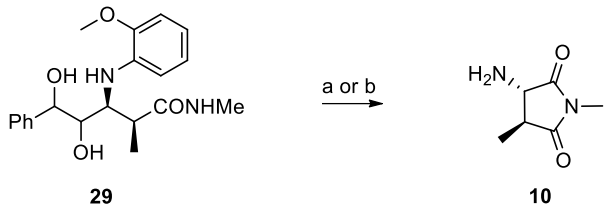
As expected, when the diol cleavage was performed under acidic conditions the 2-methoxyphenyl group was also cleaved, but while the resulting amine **33** was observed by MS, this compound could never be isolated.




**29** **31** **32** **33**

**Scheme 34:** a) $NaIO_4$, 2,6-lutidine , acetone/$H_2O$ (10:1), rt, 22% **31** + 43% **32**; b) $Pb(OAc)_4$, 2,6-lutidine, acetone/$H_2O$ (10:1), rt, 23% **31** + 37% **32**¸c) $NaIO_4$, $H_2SO_4$ , acetone/$H_2O$ (10:1), rt, **33** observed in MS but not isolable; d) $Pb(OAc)_4$, $H_2SO_4$ , acetone/$H_2O$ (10:1), rt, **33** observed in MS but not isolable.

Realizing that selective diol cleavage was very difficult to achieve, the desired succinimide **10** was tried to be accessed by simultaneous diol cleavage and 2-methoxyphenyl group removal, followed by *Jones* oxidation in the same pot (Scheme 35). However, treatment of diol **29** with periodic acid in MeCN/$H_2O$/$H_2SO_4$ followed by addition of *Jones*[90] reagent yielded the desired succinimide fragment **10** in 10% only. When a stepwise procedure was tried, i. e. first deprotection of the 2-methoxyphenyl group with TCCA, followed by diol cleavage and *Jones* oxidation, the succinimide fragment **10** was also isolated in about 10% yield.

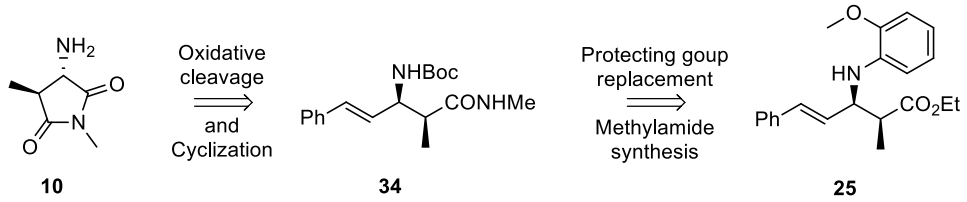



**Scheme 35:** a) $H_5IO_6$, MeCN/$H_2O$/ 0.5 M $H_2SO_4$ (4:3:1), rt then $CrO_3$, $H_2SO_4$, rt, 10%; b) TCCA, $H_2SO_4$, MeCN/$H_2O$ (1:1), rt then $H_5IO_6$, rt then $CrO_3$, $H_2SO_4$, 10%.

In conclusion, the desired succinimide **10** was accessible via the strategy outlined in Scheme 26, but only in low yield. The data collected during the implementation of this strategy strongly suggested that any possible improvement in yield would require a switch of the amine protecting group, since nearly all problems were caused by the 2-methoxyphenyl group.

## 3.1.4. 2nd Generation Synthetic Strategy of Succinimide Fragment 10

In light of the conclusion presented at the end of the previous section, it was envisioned to replace the 2-methoxyphenyl group by a Boc-protecting group before the oxidative cleavage of the double bond, such as to avoid difficulties related to the presence of the 2-methoxyphenyl group during this step (Scheme 36).




**Scheme 36:** Retrosynthetic analysis of the 2nd generation strategy.

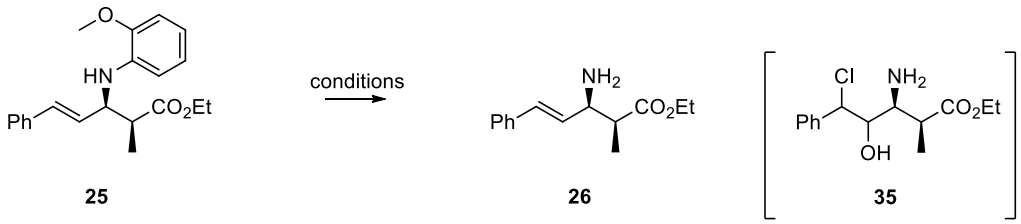
### 3.1.4.1. 2-Methoxyphenyl Group Cleavage Screening

The earliest possible opportunity to cleave the 2-methoxyphenyl group was immediately after the *Mannich* reaction and methylation of the Mannich product **24**. Therefore, a screening of cleavage conditions for the 2-methoxyphenyl group was performed on ethyl ester **25** (Scheme 37, Table 2). The first conditions screened were those reported by *Verkade*[88] and co-workers, using periodic acid as an oxidant (entries 1-5), as already described in the previous section. These experiments showed that the yield was strongly dependent on the concentration of the substrate **25** and less so on the number of equivalents of periodic acid used or the temperature of the reaction.

If TCCA was used as oxidant instead of periodic acid under the otherwise same conditions, the desired amine **26** was not observed, instead, the formation of a compound with the mass of chlorohydroxylated product **35** was observed in the MS (entry 6). Likewise, other oxidants such as *N*-iodosuccinimide (NIS) or *Dess-Martin* periodinane (DMP) gave none of the desired product **26**, but gave rise to unknown decomposition products instead.

Finally, a procedure reported for 2-methoxyphenyl group cleavage from amines by *Hoveyda*[91] and coworkers was examined that makes use of diacetoxyiodobenzene ($PhI(OAc)_2$) as an oxidant followed by acidic work-up with HCl. Similar to the experiments with periodic acid, better yields were obtained when the reaction was run at lower substrate concentrations (entries 9+10). If the solvent was changed from MeOH to a mixture of MeOH/$CH_2Cl_2$ (8:5) an improvement in yield of 10% was observed. An explanation for this could be that the elimination (E1) side reaction is less favored in the less protic solvent mixture containing $CH_2Cl_2$. Exchange of HCl with AcOH in the workup led to a diminished yield.

In conclusion, a viable method had now been identified for the removal of the 2-methoxyphenyl group from ethyl ester **25**.



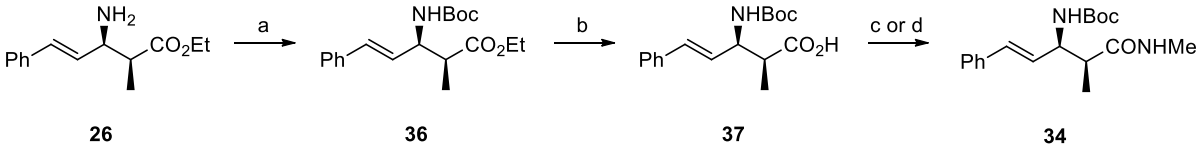

**Scheme 37:** Screening of cleavage conditions for the 2-methoxyphenyl group.

**Table 2:** Conditions screened for 2-methoxyphenyl group cleavage.

| Entry | Oxidant | Eq. | Acid | Solvent | Workup | Concentration [M] | T [°C] | t | Yield [%] |
|---|---|---|---|---|---|---|---|---|---|
| **1** | $H_5IO_6$ | 0.3 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.050 | rt | 5d | 18 |
| **2** | $H_5IO_6$ | 1.0 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.050 | rt | 5d | 18 |
| **3** | $H_5IO_6$ | 4 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.050 | rt | 5d | 11 |
| **4** | $H_5IO_6$ | 4 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.015 | rt | 5d | 41 |
| **5** | $H_5IO_6$ | 1 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.050 | 60 | 2.5h | 25 |
| **6** | TCCA | 0.5 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.030 | rt | 3h | "**35**" |
| **7** | NIS | 4 | $H_2SO_4$ | MeCN/$H_2O$ (1:1) | - | 0.040 | rt | 2h | 0 |
| **8** | DMP | 1.2 | - | $CH_2Cl_2$ | HCl | 0.015 | rt | 2h | 0 |
| **9** | $PhI(OAc)_2$ | 4 | - | MeOH | HCl | 0.050 | rt | 18h | 24 |
| **10** | $PhI(OAc)_2$ | 4 | - | MeOH | HCl | 0.013 | rt | 18h | 48 |
| **11** | $PhI(OAc)_2$ | 4 | - | MeOH/ $CH_2Cl_2$ (8:5) | HCl | 0.050 | rt | 18h | 39 |
| **12** | $PhI(OAc)_2$ | 4 | - | MeOH/ $CH_2Cl_2$ (8:5) | HCl | 0.013 | rt | 18h | 58 |
| **13** | $PhI(OAc)_2$ | 4 | - | MeOH/ $CH_2Cl_2$ (8:5) | AcOH | 0.013 | rt | 18h | 42 |

### 3.1.4.2. Applying the new Protecting Group Strategy

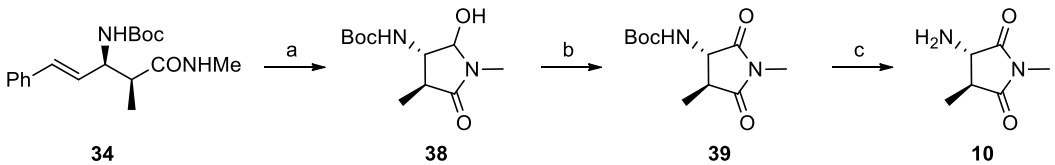
The free amine **26** was Boc protected using Boc-anhydride in a biphasic solvent system consisting of ethyl acetate and aqu. saturated $NaHCO_3$ (Scheme 38). Ethyl ester **36** was then saponified using the same conditions as described in Chapter 3.1.3, thus providing the Boc-protected β-amino acid **37** in quantitative yield. Transformation of **37** into the methyl amide **34** by the mixed anhydride method that had been employed successfully in the synthesis of amide **13**, unfortunately, led to isomerization of the α-stereocenter. Therefore, the amide coupling conditions were changed and activation of **37** was performed with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) in combination with catalytic amounts of DMAP. This method is known to minimize isomerization during amide coupling reactions[92] and we were delighted to obtain the methyl amide **34** in excellent yield (97%, crude) and without detectable isomerization. Since isomerization of the methylamide **34** was observed during purification over silica gel, the synthesis was continued using the crude material.




**26** **36** **37** **34**

**Scheme 38:** a) $Boc_2O$, $NaHCO_3$ (aq.), EtOAc, rt, 72%; b) LiOH, THF/MeOH/$H_2O$ (1:2:1), 0°C to rt, 100%; c) NMM, IBCF, THF, -20°C to rt then aqu. $NH_2Me$, rt, 69%, *dr* = 2.4:1; d) EDC•HCl, DMAP, $CH_2Cl_2$, rt then $NH_2Me$, rt, 97% crude.

The oxidation of alkene **34** was initially planned to be carried out by ozonolysis as reported by *Boeckman*[65] and coworkers for their similar substrate (see introduction, chapter 1.2.3.1) (Scheme 39). However, the double bond of alkene **34** proved to be less reactive towards ozone than for *Boeckman's* intermediate which led to decomposition of the cleavage product **38** before complete consumption of the starting material. Therefore, **34** was dihydroxylated using a catalytic amount of $OsO_4$ with $NaIO_4$ as the stoichiometric oxidant. These conditions also led to oxidative cleavage of the diol intermediate and furnished lactam **38** in 75% yield. The latter was oxidized to the succinimide **39** using pyridinium dichromate (PDC). Final Boc cleavage with trifluoroacetic acid (TFA) gave the desired succinimide **10** in 73% yield.[1]



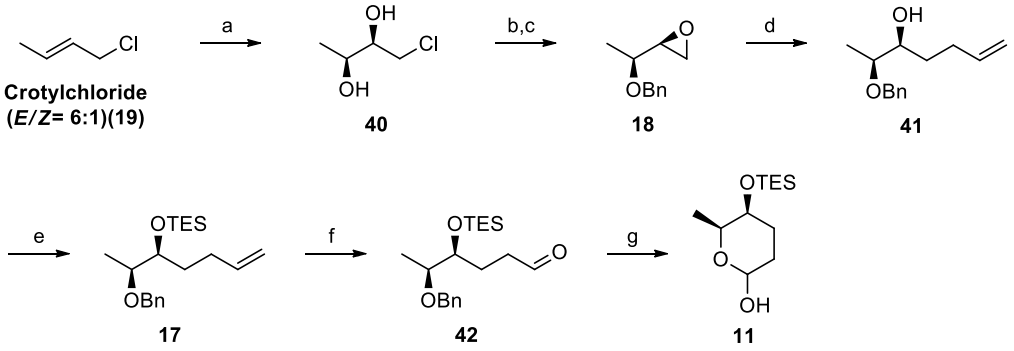

**34** **38** **39** **10**

**Scheme 39:** a) $OsO_4$, $NaIO_4$, 2,6-lutidine, acetone/$H_2O$ (10:1), rt, 75%; b) PDC, $CH_2Cl_2$, rt, 92%, c) TFA, $CH_2Cl_2$, rt, 73%.

[1] The 2nd generation strategy was carried out by Barbara Stoessel in the course of her Master thesis.

## 3.1.5. Synthesis of Protected *L*-Rhodinose 11

The synthesis of the protected L-rhodinose started with the dihydroxylation of a commercially available 6:1 *E/Z* mixture of crotyl chloride (**19**), under *Sharpless*[85,93] conditions (Scheme 40). The resulting diol **40** was then treated with sodium hydride, to induce epoxide formation, followed by addition of benzyl bromide to provide protected epoxide **18** in 60% yield. At this stage the diastereoisomers resulting from the *E/Z* mixture of crotylchloride (**19**) were separated and GC analysis was performed in order to determine the *ee* obtained in the *Sharpless* dihydroxylation, which was found to be 80%. This number is in good agreement with the value reported by *Rychnovsky*[93], but lower than the value reported by *Sharpless*[85]. The epoxide **18** was then opened with an *in situ* generated allylcuprate to give the alcohol **41** in 84% yield. Consecutive TES protection and ozonolysis of the resulting alkene **17** then gave aldehyde **42** in excellent yields (93% and 90%, respectively). The final removal of the benzyl group by means of hydrogenation over Pd/C, which had already been reported by *Kozmin*[68] and coworkers for the same substrate, proved to be more challenging as expected. It was eventually found that this was due to simultaneous TES cleavage, caused by the *in situ* generation of HCl arising from $PdCl_2$ impurities in the Pd/C catalyst[94]. Efforts to neutralize the reaction mixture by the addition of bases or buffer (entries 4,5,8,10,12 and 14) were unsuccessful, however according to *Hirota*[94] and co-workers the acidity of the Pd/C catalysts varies with the supplier (Table 3). Therefore Pd/C catalysts from different suppliers were tested (entries 1-5,7 and 8 Acros; 9-14 Aldrich), but, unfortunately, no significant differences were observed. In order to determine if TES deprotection in fact only occurred after addition of hydrogen, an experiment without hydrogen was performed and indeed no TES cleavage was observed (entry 11). Finally, by using Pd(OH)/C as a catalyst (entries 6, 15, 16) in an aprotic solvent (entry 16), TES cleavage was at least partially suppressed and the desired *L*-Rhodinose building block **11** was obtained in 68% yield.




**Scheme 40:** a) AD-mix-α, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH/$H_2O$ (1:1), 0°C, 82%, *ee* = 80%; b) NaH, THF, 0°C; c) BnBr, THF, 0°C, 60% over two steps + separation of diastereoisomers; d) allylMgBr, CuI, THF, -40°C, 84%; e) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 93%; f) $O_3$, $CH_2Cl_2$, -78°C then $PPh_3$, -78°C to rt, 91%; g) $H_2$ (5 bar), $Pd(OH)_2$/C, EtOAc, rt, 68%.

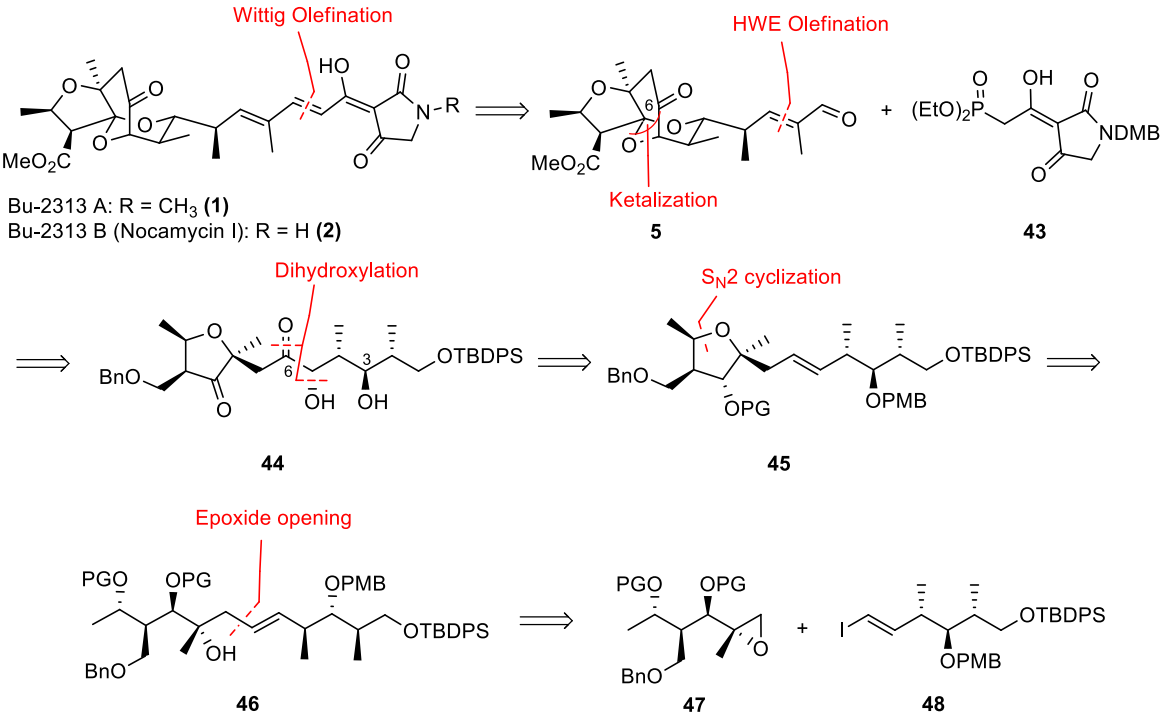
**Table 3:** Screening of hydrogenations conditions for benzyl group cleavage.

| Entry | Reagent | Solvent | Hydrogen Pressure | Conc. [M] | % Pd/C (w/w) | t [h] | Results |
|---|---|---|---|---|---|---|---|
| **1** | Pd/C (Acros) | THF | Balloon | 0.08 | 50 % | 3 | 37 % |
| **2** | Pd/C (Acros) | THF | Balloon | 0.1 | 50 % | 12 | decomposition |
| **3** | Pd/C (Acros) | MeOH | Balloon | 0.1 | 9 % | 2 | Selective TES deprotection |
| **4** | Pd/C (Acros) | MeOH+ 1eq. $NaHCO_3$ | Balloon to 5 bar | 0.1 | 9 % | 12 | No conversion |
| **5** | Pd/C (Acros) | MeOH+ 1eq. $NaHCO_3$ | 8 bar | 0.1 | 40 % | 12 | No conversion |
| **6** | $Pd(OH)_2/C$ | MeOH | 5 bar | 0.1 | 20 % | 0.25 | Selective TES deprotection |
| **7** | Pd/C (Acros) | THF | 5 bar | 0.1 | 50 % | 0.5 | 59 % + TES cleavage + double deprotection |
| **8** | Pd/C (Acros) | THF+ 1eq. $NaHCO_3$ | 5 bar | 0.1 | 50 % | 0.5 | 59 % + TES cleavage + double deprotection |
| **9** | Pd/C (Aldrich) | THF | 5 bar | 0.1 | 50 % | 0.5 | Full TES cleavage + double deprotection |
| **10** | Pd/C (Aldrich) | THF+ 1eq. pyrridine | 5 bar | 0.1 | 50 % | 1.5 | Double deprotection |
| **11** | Pd/C (Aldrich) | THF | No hydrogen | 0.1 | 50 % | 12 | No conversion |
| **12** | Pd/C (Aldrich) | MeOH + Acetate Buffer | Balloon | 0.05 | 50 % | 2 | Double deprotection TES deprotected first |
| **13** | Pd/C (Aldrich) | THF | Balloon | 0.01 | 10 % | 12 | No full conversion, double deprotection |
| **14** | Pd/C (Aldrich) | EtOH + Acetate Buffer | Balloon | 0.05 | 50 % | 7 | Bn + double deprotection but no selective TES deprotection |
| **15** | $Pd(OH)_2/C$ | THF | Balloon | 0.05 | 25 % | 7 | Mainly Bn cleavage but also clear spots of TES and double deprotected products |
| **16** | $Pd(OH)_2/C$ | EtOAc | Balloon | 0.05 | 25 % | 7 | Selective Bn cleavage and only traces of double deprotection |

# 3.2. Bu-2313 B (Nocamycin I)

## 3.2.1. Retrosynthesis

As described for the synthesis of the related natural products tirandamycins A-C[52,65,95–97], we opted to connect the tetramic acid moiety of Bu-2313 B (**2**) with its tricyclic core by an olefination reaction between literature known[52,65] phosphonate **43** and aldehyde **5** (Scheme 41). The enal moiety in **5** was to be established by a two-carbon extension through *HWE* olefination, while the tricyclic core structure was to be constructed by intramolecular ketal formation. *Ireland* and coworkers[63] had shown that cyclization to the desired ketal cannot be performed in the presence of a keto group at C6, due to preferential 5-membered ring hemiketal formation with the hydroxy group at C3. Therefore, it was planned to perform the cyclization with the C6 keto group masked as a thioketal or as a protected hydroxy group instead of a carbonyl at C6. α-Hydroxy ketone **44** was planned to be accessed by dihydroxylation of alkene **45** and discrimination of the newly formed OH groups via 1,3-PMP acetal formation. The tetrahydrofuran ring in **45** was to be formed via $S_N2$ displacement after assembly of the full carbon skeleton by an epoxide opening reaction between **47** and vinyl iodide **48**.

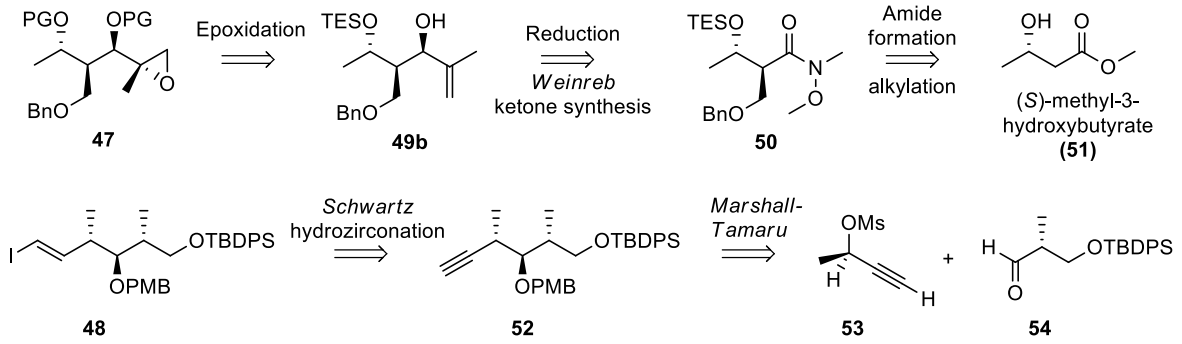



**Scheme 41:** Retrosynthetic analysis of Bu-2313 B (Nocamycin I) (**2**).

Epoxide fragment **47** was envisioned to be built up by diastereoselective epoxidation[98] of allylic alcohol **49b** which would be accessed by *Weinreb*[99] ketone synthesis and diastereoselective reduction (Scheme 42). Amide **50** was planned to be obtained via *Fràter-*

*Seebach*[100,101] alkylation of (*S*)-methyl-3-hydroxybutyrate (**51**) followed by hydroxy group protection and *Weinreb* amide formation.

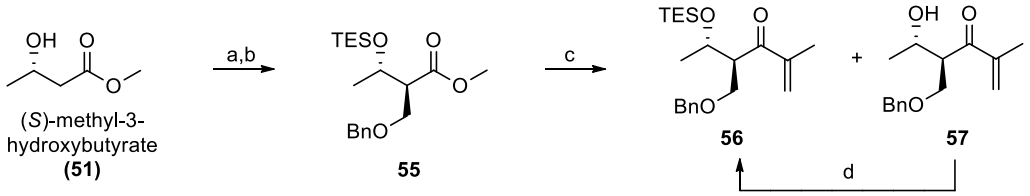
Vinyl iodide **48**, on the other hand was planned to be synthesized via *Schwartz* hydrozirconation[102] of alkyne **52** followed by trapping of the alkenylzirconium intermediate with iodine (Scheme 42). Finally, alkyne **52** was to be obtained via *Marshall-Tamaru*[103,104] propargylation between alkyne **53** and aldehyde **54**, which would allow to build up the stereotriad in a 1,2-*anti* (methyl-hydroxyl) and 1,3-*syn* (methyl-methyl) fashion.




**Scheme 42:** Retrosynthetic analysis of epoxide fragment **47** and vinyl iodide fragment **48**.

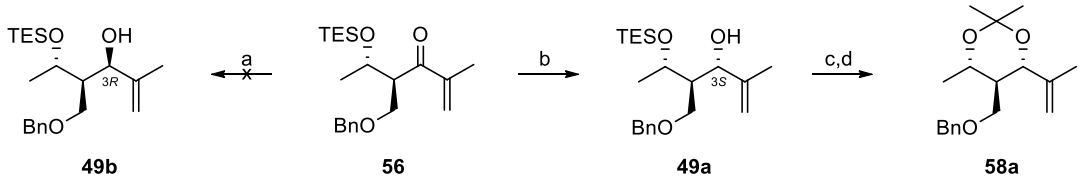
## 3.2.2. Synthesis of epoxide 47

The synthesis of epoxide **47** commenced with the *Fràter-Seebach*[100,101] alkylation of (*S*)-methyl-3-hydroxybutyrate (**51**) with BOMCl as reported by *Ireland*[63] and *Ham*[105] (Scheme 43). *Ireland et al.* stated that the alkylation proceeded in 42% yield (76% brsm) and with 9:1 *dr* by just using LDA and BOMCl. *Ham et al.*, on the other hand reported that by the addition of HMPA to the reaction, the yield increased to 70% and the *dr* to 25:1. Unfortunately, in our hands only the *dr* reported by *Ham et al.* could be reproduced. The reaction yielded the alkylation product in 39% yield, which is in the yield-range reported by *Ireland* and coworkers; in addition, 36% of the starting material was recovered. The free hydroxy group was then TES protected to give ester **55** in 94% yield, which was converted into the α,β-unsaturated ketone **56** by *Weinreb* ketone synthesis. Unfortunately, significant quantities of the TES deprotected product **57** were also formed upon conversion of **55** into **56**. However, this material could be readily reprotected by reaction with TESCl to furnish **56** in a total yield of 94% from **55**.




**Scheme 43:** a) LDA, BOMCl, HMPA, THF, -78 °C, 39% (75% brsm), *dr* > 20:1; b) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 92%; c) 2-propenyl-MgBr, Me(OMe)NH•HCl, THF, -5 °C to rt, 70% (20% **56**; 50% **57**); d) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 94%.

Since the selectivity of the projected epoxidation was to be substrate-controlled[98], the stereocenter at the allylic position (C3) in **49** had to be installed with the correct (in this case 3*R*, **49b**) stereochemistry (Scheme 44). In order to do so, it was initially planned to selectively reduce ketone **56** via *CBS*-reduction[106], but, unfortunately, all conditions investigated failed to give the desired product. When catecholborane was used as the reducing agent, no conversion was observed, even at higher temperatures. With $BH_3$, conversion was very slow and the starting material decomposed over time. In contrast, the use of DIBALH led to allylic alcohol **49a** in 54% yield with an excellent *dr* of 16:1, but with the wrong (3*S*) configuration at the allylic position. The configuration of the newly formed stereocenter at C3 in **49a** was determined by comparison of the characteristic $^{13}$C-NMR signals in the corresponding acetonide **58a** with the reference values that have been established by *Rychnovsky* and co-workers[107,108] for the acetonides of syn- and anti- 1,3-diols (Figure 25).




**Scheme 44:** a) (*S*)-CBS cat., $BH_3$•THF / $BH_3$•DMS or catecholborane, toluene, -78°C to rt, 0%; b) DIBALH, $CH_2Cl_2$, -78 °C, 54%, *dr* = 16:1; c) AcOH / THF / $H_2O$ (3:1:1), rt, 82%; d) CSA, 2,2-dimethoxypropane, rt, 87%.

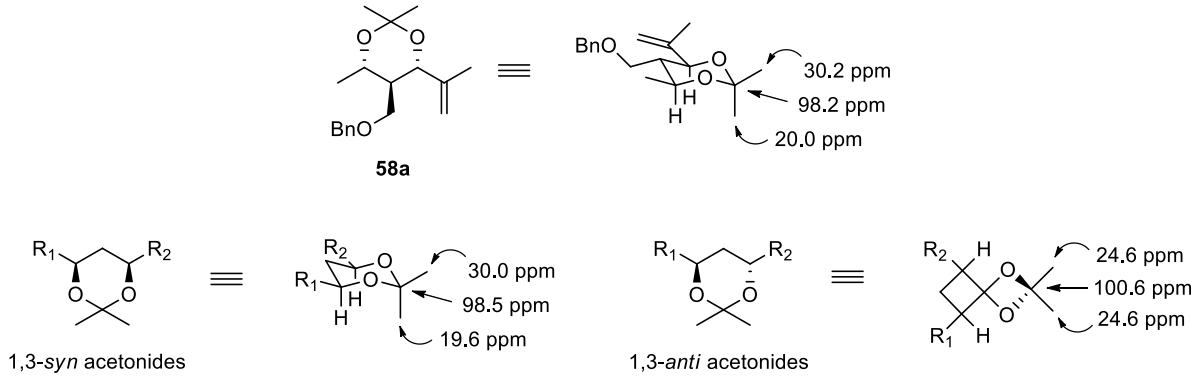
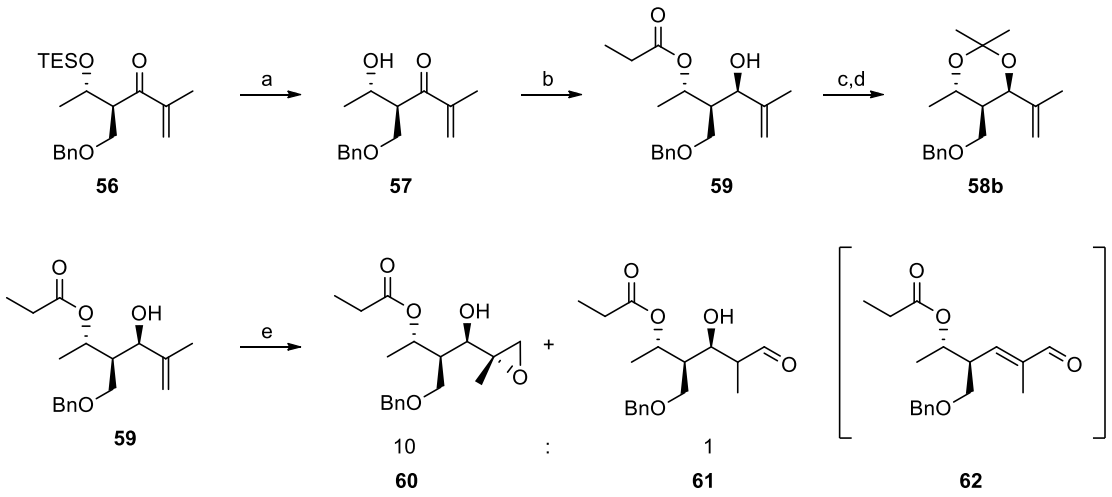


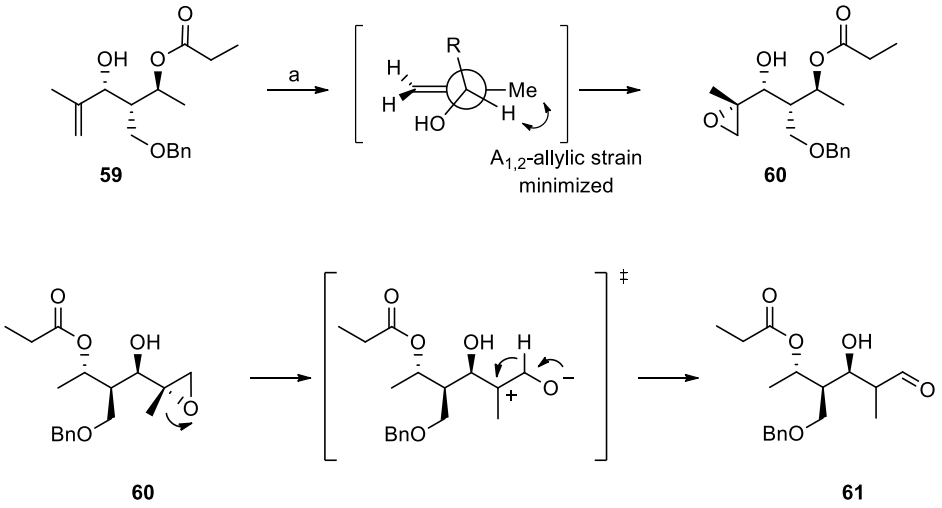

**Figure 25:** $^{13}$C chemical shifts for **58a** and those reported by *Rychnovsky* and coworkers for acetonides of 1,3-*syn* and 1,3-*anti* diols[107,108].

At this point it was decided to switch strategy and to investigate the use of an *Evans-Tishchenko*[109] reduction. To this end, the TES group was removed from **56** with AcOH to obtain keto alcohol **57**. Treatment of **57** with propionaldehyde and samarium(II)-iodide furnished the desired allylic alcohol **59** in 95% yield and with a *dr* >25:1 (Scheme 45). The absolute configuration of **59** was again ascertained by the *Rychnovsky*[107,108] method at the level of acetonide **58b**. The directed epoxidation of allylic alcohol **59** with $VO(acac)_2$ then led to one isomer only, which according to model considerations (minimization of allylic $A_{1,2}$-strain, directing effect of the hydroxy group) and based on literature precedent[98], was

expected to be the desired **60** (Scheme 46, top). Unfortunately the formation of aldehyde side product **61** was also observed, which arises from carbocation formation through epoxide opening followed by a 1,2-hydride shift (Scheme 6, bottom).




**Scheme 45:** a) AcOH / THF / $H_2O$ (3:1:1), rt, 80%; b) $SmI_2$, propionaldehyde, THF, -15°C, 95%, *dr* >25:1; c) DIBALH, $CH_2Cl_2$, -78°C, 96%; d) CSA, 2,2-dimethoxypropane, rt, 91%; e) *t*BuOOH, $VO(acac)_2$, $CH_2Cl_2$, 0°C to rt, 63% (mixture), *dr* >25:1.




**Scheme 46:** Top: Proposed model of directed vanadium-catalyzed epoxidation. a) *t*BuOOH, $VO(acac)_2$. Bottom: Proposed mechanism for the formation of aldehyde **61**.

Depending on the reaction and workup conditions, the ratio of isolated epoxide **60** to aldehyde **61** varied from 10:1 to aldehyde **61** only (Table 4). The data show that the $VO(acac)_2$ had to be added to the reaction mixture portion-wise, in order to minimize aldehyde and other side product formation. The best work up conditions turned out to be reductive and basic (entries 6, 7). If a slightly acidic workup was performed, the undesired aldehyde **61** was isolated almost exclusively (entry 5). When the reaction mixture was filtered over ALOX (entry 4), the elimination product **62** (Scheme 5, bottom) was observed.

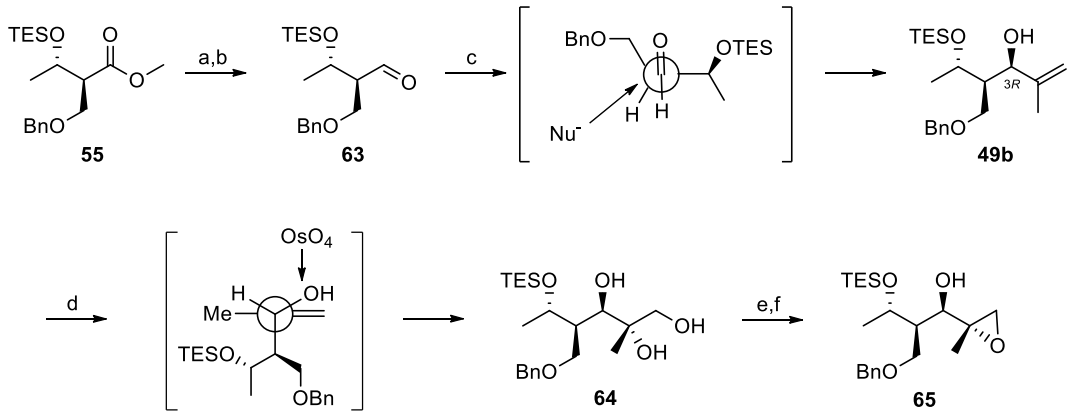
**Table 4:** Screening of reaction and workup conditions for the epoxidation of **59**.

| Entry | $VO(acac)_2$ equiv. | Workup | Yield (mixture) [%] | Ratio (Epoxide/Aldehyde) |
|---|---|---|---|---|
| 1 | 0.01<br>+0.02 | $Na_2S_2SO_3$ | 54 | 1.5 / 1 |
| **2** | 0.01<br>+0.02 | $NaHCO_3$ | 53 | 5.5 / 1 |
| **3** | 0.1 | - | - | ~ 1 / 1<br>+ decomposition |
| **4** | 2 x 0.01<br>1 x 0.005 | ALOX<br>filtration | 80 | elimination<br>Product **62** |
| **5** | 2 x 0.01<br>1 x 0.005 | Silica<br>filtration | quant.<br>(crude) | Aldehyde **61**<br>only |
| **6** | 2 x 0.01 | $Na_2SO_3$ | 68 | 5.4 / 1 |
| **7** | 3 x 0.01 | $Na_2SO_3$ | 63 | 10 / 1 |

In light of the lack of robustness of the direct epoxidation approach, we then investigated whether the desired epoxide **47** might also be obtained by substrate controlled dihydroxylation[110] followed by an $S_N2$ displacement. In addition, and inspired by the outcome of the DIBALH reduction of ketone **57**, which had provided the *Felkin-Anh*[111–115] product **49a** almost exclusively (Scheme 4), an alternative approach towards the allylic alcohol **49b** was also investigated that involved, vinyl *Grignard* addition to aldehyde **63** (Scheme 47).

Aldehyde **63** was obtained by reduction of ester **55** to the primary alcohol using DIBALH and subsequent oxidation of the latter with DMP. Unfortunately, aldehyde **63** could not be obtained directly from **55**, as even the use of just 1.0 equiv. of DIBALH led to partial overreduction. The *Grignard* addition of 2-propenylmagnesium bromide to aldehyde **63** yielded the desired allylic alcohol **49b** in 89 % yield and with 4:1 *dr* in favor of the 3*R*-isomer, i. e. is the expected *Felkin-Anh* product. Fortunately, the isomers were separable on silica gel, allowing for **49b** to be isolated as a single isomer in 69% yield. Substrate controlled dihydroxylation under *Upjohn* conditions[89], using osmium tetroxide with NMO as stoichiometric oxidant, gave the desired diol **64** in good yield (81%) and with excellent selectivity (15:1 *dr*), which is in good agreement with the findings of *Evans* and coworkers on similar systems[116]. The selectivity can be rationalized with the *Stork/Houk* model[117,118], such that $A_{1,2}$-allylic strain is minimized and the attack of the electrophile occurs from the side of the free hydroxyl group.

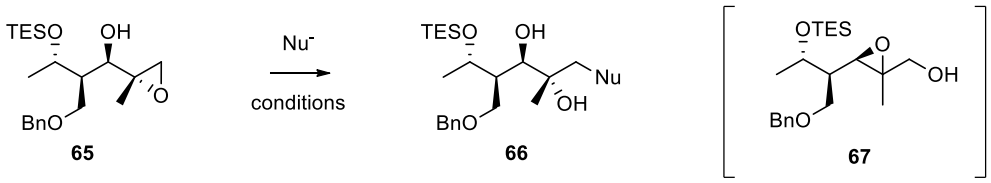
The following activation of the primary alcohol with mesyl chloride and treatment of the resulting mesylate with base yielded the desired epoxide **65** in 73% yield over two steps and, importantly, without any traces of side product **61**. The stereochemistry of **65** was identical with the one obtained via direct epoxidation, which was also performed with **49b** using the same conditions as for **59**.




**Scheme 47:** a) DIBALH, $CH_2Cl_2$, -78°C, 85%; b) DMP, $NaHCO_3$, $CH_2Cl_2$, rt, 91%; c) 2-propenylMgBr, THF, 0 °C, 89%, *dr* = 4:1, 69% single isomer; d) $OsO_4$, NMO, THF/acetone/$H_2O$, rt, 81%, *dr* = 15:1; e) $Et_3N$, MsCl, $CH_2Cl_2$ -40 °C; f) $K_2CO_3$, MeOH, rt, 73% (over two steps).

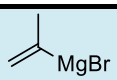
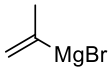
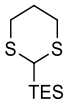
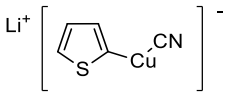
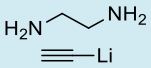
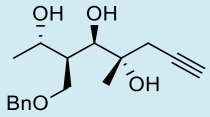
### 3.2.2.1. Epoxide Opening Trials

With the epoxide **65** in hand, the opening of the oxirane ring with different nucleophiles was investigated (Table 5, Scheme 48). As it turned out this transformation was much more difficult than expected. The first epoxide opening experiments were performed with a lower order organocuprate,[119,120] obtained from 2-propenylmagnesium bromide and catalytic amounts of CuI. When the reaction was performed at 0 °C, only the halohydrin product **(66**, Nu = Br or I) was obtained (entry 1), while no conversion was observed at lower temperature. Likewise, the use of dithianes[121] as nucleophiles (entries 3+4) gave no conversion to the desired product. Applying higher order organocuprate chemistry by using stoichiometric amounts of either CuCN or thienylcyanocuprate[122,123] together with 1-TMS-vinyl bromide also failed to produce any product (entries 5+6). Only with a large excess of *n*BuLi in the presence of CuCN, conversion to **66** was observed (entry 7). The use of *Lewis* acid, as expected, led to extensive formation of the isomeric epoxide **67**, due to intramolecular epoxide opening (entry 8). The last experiments were performed with the lithium acetylide/EDA complex (entry 9) which had been reported to work on a similar substrate[124]. Unfortunately, also these conditions did not lead to the desired product, rather, the free triol **68** was isolated in 10% yield.

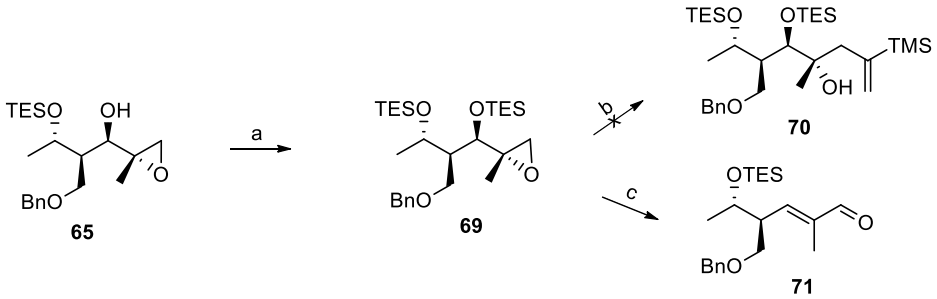



**Scheme 48:** Epoxide opening trials.

**Table 5:** Epoxide opening trials.

| Entry | Nucleophile | Base | Additive | Conditions | Result |
|---|---|---|---|---|---|
| **1** |  | - | CuI (cat.) | THF, 0 °C | Halohydrin product, Nu = Br or I |
| **2** |  | - | CuI (cat.) | THF, -40 °C to rt | No conversion |
| **3** |  | *n*BuLi | - | THF, -78 °C to rt | No conversion |
| **4** |  | *t*BuLi | - | $Et_2O$, -78 °C to -45 °C | No conversion |
| **5** |  | *t*BuLi | CuCN (0.5 equiv) | $Et_2O$, -78 °C to 0 °C | No conversion |
| **6** |  | *t*BuLi |  | $Et_2O$, -78 °C to 0 °C | No conversion |
| **7** | *n*BuLi (20 equiv) | - | CuCN | THF, -78 °C to 0 °C | ~1:1 mixture of starting material and product |
| **8** |  | *n*BuLi | $BF_3$•$Et_2O$ | THF, -78 °C | Side product **67** formation |
| **9** |  | - | - | DMSO, rt | 10 % of  **68** |

At this point it was decided to perform some last epoxide opening experiments with the fully protected epoxide **69,** in order to exclude problems which could have been caused by the presence of the free hydroxy group (Scheme 49). However, even with this substrate no conversion was observed upon attempted organocuprate addition as it had been the case with the free alcohol **65**. When *Lewis* acid was used (conditions c) to enhance the reactivity of the epoxide, a 1,2 hydride shift followed by elimination of the TES protected hydroxy group took place to form **71**.

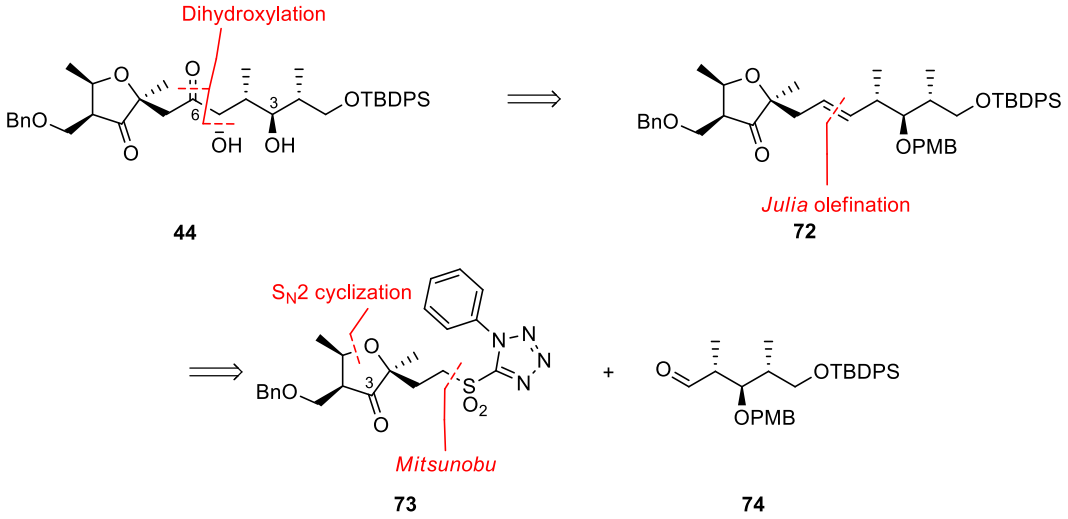


**Scheme 49:** a) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 78%; b) 1-(trimethylsilyl)vinylMgBr, CuCN, THF, -78 °C to -30 °C, 0%; c) ethynyltrimethylsilane, *n*BuLi, $BF_3$•$Et_2O$, THF, -78 °C, 50%.

In conclusion, no appropriate method was found to open the epoxide ring in either **65** or **69** in satisfactory yields. Therefore, the strategy towards Bu-2313 B (**2**) as outlined in Scheme 41 was abandoned and a new retrosynthesis was elaborated.

### 3.2.3. Revised Retrosynthesis of Bu-2313 B (Nocamycin I) – *Julia* Olefination Strategy

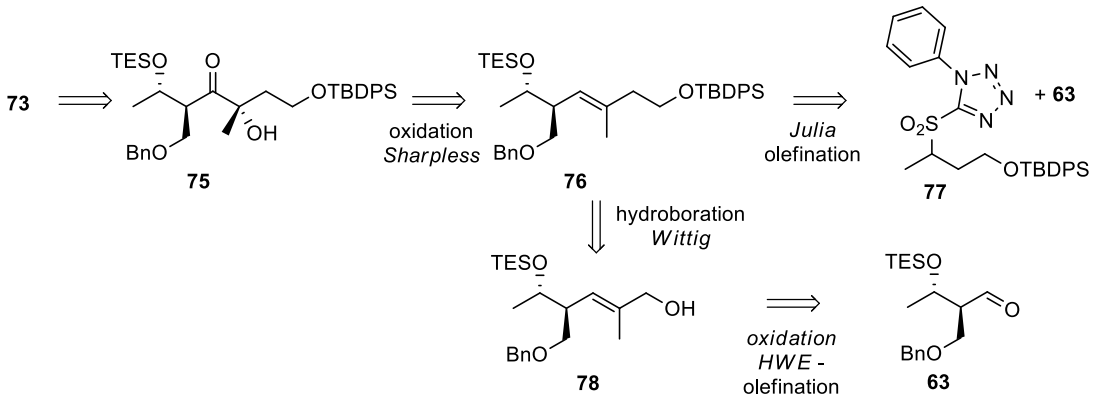
According to the revised retrosynthesis for Bu-2313 B (**2**) the advanced intermediate **72** was to be assembled by *Julia* olefination of sulfone **73** and the known aldehyde **74** (Scheme 50). The resulting olefin would then be elaborated into Bu-2313 B (**2**) via **44**, at which stage this second generation approach converges with the original strategy depicted in Scheme 41, Section 3.2.1. Being cognizant of the fact that the *Julia* olefination would most likely not be feasible with **73** directly, due to the similar pKa values of ketones (~26) and sulfones (~25)[125,126], we expected that the C3 keto group would have to be masked as a suitably protected hydroxy group during this transformation. *Julia* sulfone **73** was planned to be synthesized via *Mitsunobu*[127] reaction and the construction of the tetrahydrofuran ring would be performed before sulfone formation and before fragment assembly by means of an intramolecular $S_N2$ reaction.




**Scheme 50:** Retrosynthetic analysis of **44** via *Julia* olefination.

**73** was to be derived from ketone **75**, which in turn was envisioned to be obtained by *Sharpless* dihydroxylation of alkene **76**, followed by oxidation of the secondary hydroxy group. The trisubstituted alkene **76** was to be accessed either via *Julia* olefination between aldehyde **63,** which was already in hand (Scheme 51) and *Julia* sulfone **77** or by means of a *Wittig* or *HWE* reaction with ylide **79** or phosphonate **82**, respectively (Scheme 52). In the case of the *Wittig* and *HWE*-type olefinations, elaboration of the resulting coupling products into **76** would require reduction to alcohol **78**, followed by oxidation, *Wittig* olefination, and hydroboration of the terminal double bond. The *Julia* olefination route, in principle, would

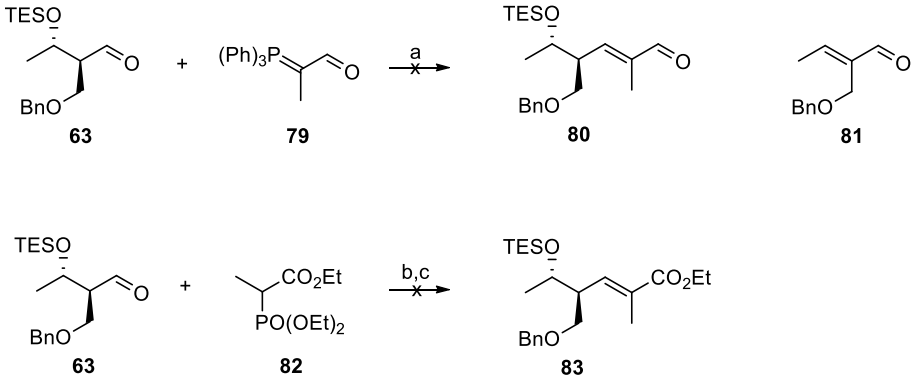
give fast access to the desired alkene **76**, but it is known, that *Julia* olefinations involving α-disubstituted sulfones are generally characterized by low *E*/*Z*-selectivity[128]. The *HWE* or Wittig approaches, on the other hand were expected, to give good *E*/*Z*-selectivity, but via a longer reaction sequence.




**Scheme 51:** Retrosynthetic analysis of **73**.

## 3.2.4. Synthesis of Sulfone 73

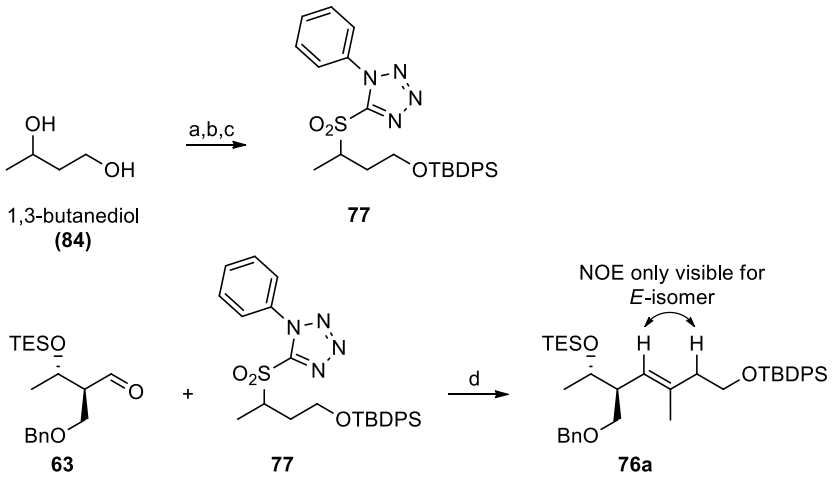
The synthesis of olefin **76** via the *HWE* or Wittig-approach was investigated first. When aldehyde **63** was refluxed together with ylide **79** in benzene, only elimination product **81** was isolated (Scheme 52). Applying standard *HWE* conditions[129] with phosphonate **82** in combination with LiHMDS led to decomposition of the starting material. Decomposition prevailed even under very mild conditions like LiCl / DBU[130] and only traces of the desired product **83** were observed.




**Scheme 52:** a) Benzene, reflux, 0%; b) **82**, LiHMDS, then **63**, THF, -78 °C to rt, 0% or LiCl, DBU, then **82** and **63**, MeCN, rt, 0%.

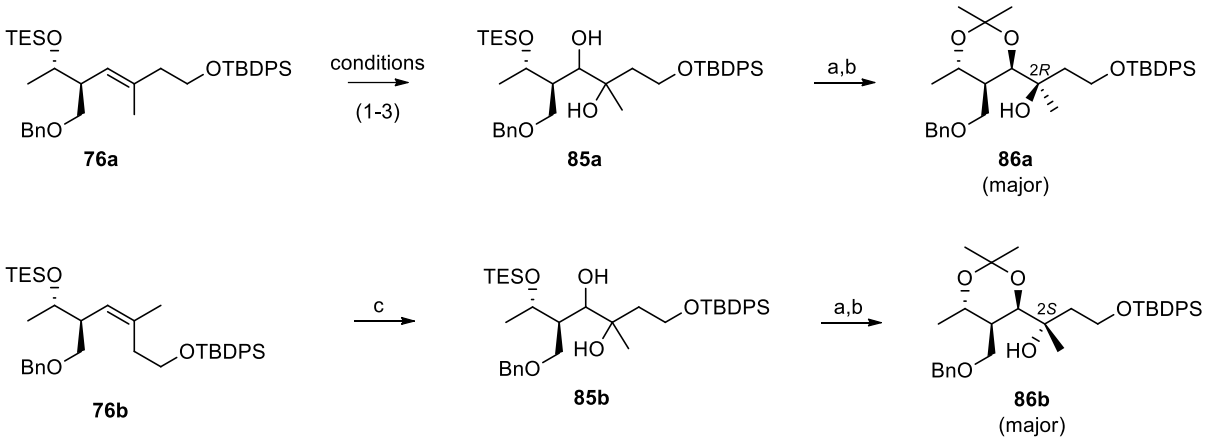
The implementation of the *Julia* olefination required access to sulfone **77**, which was synthesized in 3 steps from 1,3-butanediol (**84**) (Scheme 53). The reaction between aldehyde **63** and sulfone **77** under standard *Julia* conditions with LiHMDS in THF at -78°C[128] gave the desired alkene **76** as a 1.3:1 mixture of E/Z isomers. Fortunately, the isomers were separable on silica gel and the desired *E* isomer **76a** was finally obtained in 26% yield. The

configurational assignment of the two isomers was based on NOE NMR analysis (Scheme 53).



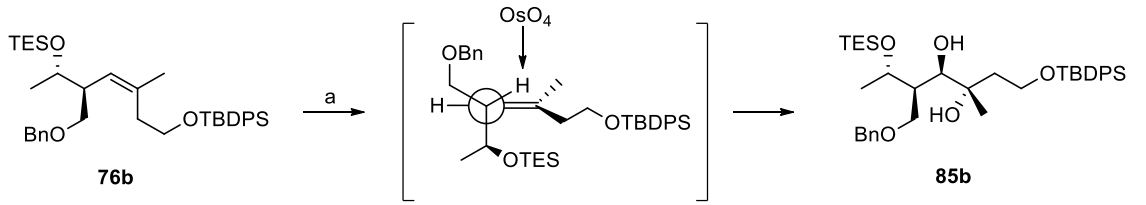

**Scheme 53:** a) TBDPSCl, ImH, THF, rt, 85%; b) 1-phenyl-1H-tetrazole-5-thiol, $PPh_3$, then DEAD, THF, 0°C to rt, 81 %; c) *m*CPBA, $CH_2Cl_2$, rt, 78%; d) **77**, LiHMDS, then **63**, THF, -78°C, 64%, *E*/*Z* = 1.3:1, 25% *E*-isomer, 21% *Z*-isomer, 12% *E*/*Z* mixture.

When the pure *E* isomer **76a** was submitted to *Sharpless* dihydroxylation conditions (AD-mix, methansulfoneamide, $NaHCO_3$ in *t*BuOH/$H_2O$[131])(Scheme 54), no conversion was observed. In a next step it was therefore investigated, if carrying out the reaction under *Upjohn* conditions[89], i. e. in the absence of a chiral catalyst, would provide any level of substrate-controlled selectivity. Even under *Upjohn* conditions the reaction mixture had to be heated to 45°C for two days, in order to reach full conversion. In the end, the desired diol **85** was obtained in 57% yield and with a *dr* of 4.5:1 with the mixture of isomers being inseparable at this point. In order to determine the configuration of the newly formed stereocenters, the TES group was removed and the resulting free triol was converted into acetonide **86**. Analysis of the $^{13}$C-NMR spectrum of **86** according to *Rychnovsky*[107,108] showed that the major isomer **86a** exhibited a 1,3-*anti* configuration, i. e. the dihydroxylation had delivered the undesired product with an (2*R*)-configuration at the tertiary stereocenter as the major isomer. In order to access the required product **86b** with a C2 (*S*)-configuration, the *Upjohn* dihydroxylation was also performed with the (*Z*)-alkene **76b**. Submission of **76b** to Upjohn dihydroxylation conditions gave the diol product in 75% yield and with 7:1 *dr*. Conversion of the mixture into the corresponding mixture of acetonides and subsequent spectroscopic analysis revealed that the major product in this case was the desired 2*R* isomer **86b** with a 1,3-anti configuration. Mechanistically, this implies that the attack of the electrophile on the double bond of **76b** in the dihydroxylation step had occurred from the same side as with the (*E*)-isomer **76a**.



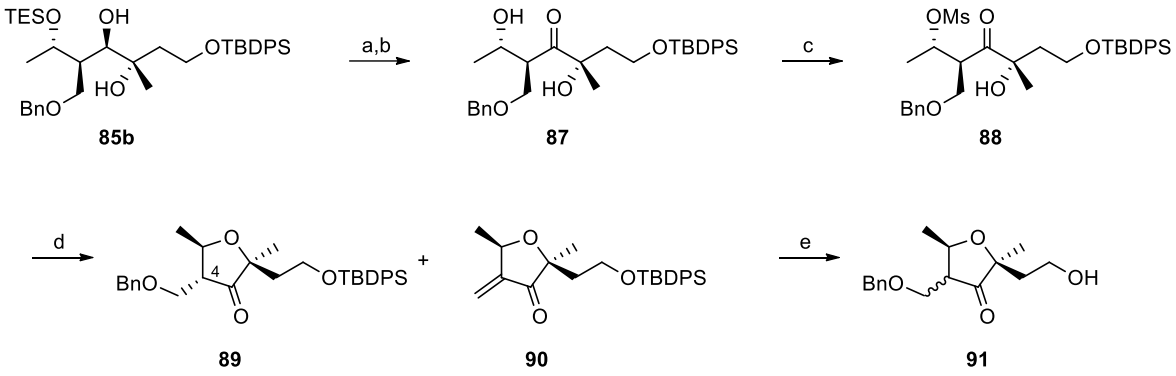

**Scheme 54:** Conditions: 1) AD-mix-α, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH, $H_2O$, 0°C to rt, 0%; 2) AD-mix-β, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH, $H_2O$, 0°C to rt, 0%; 3) $OsO_4$, NMO, 2,6-lutidine, acetone/$H_2O$ (10:1), 45°C, 57%, *dr* = 4.5:1; a) PPTS, MeOH/THF (2:1), rt, 94%, b) CSA, 2,2-dimethoxypropane, rt, 98%, products **86a** and **86b** were still present as isomeric mixtures; c) $OsO_4$, NMO, 2,6-lutidine, acetone/$H_2O$ (10:1), 45°C, 75%, *dr* = 7:1.

Upon optimization of the reaction and purification conditions, we were able to obtain diol **85b** as pure isomer in 73% yield. The selectivity of the dihydroxylation can be explained by a model where $A_{1,3}$ allylic strain is minimized and the TES protected hydroxy group as the largest substituent occupies the least hindered position. The attack of $OsO_4$ occurs from the least hindered face (Scheme 55).



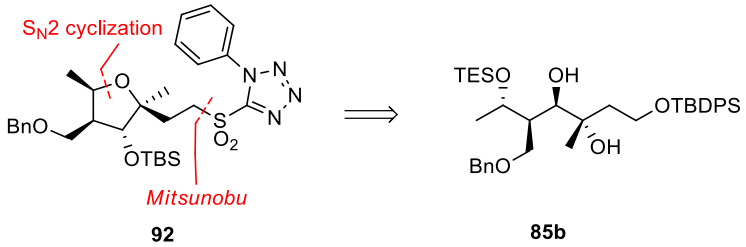

**Scheme 55:** a) NMO, 2,6-lutidine, acetone/$H_2O$ (10:1), 45°C, 73%, single isomer. Proposed model for the dihydroxylation.

In the following, diol **85b** was oxidized to the corresponding hydroxy ketone by means of *Swern* oxidation, which was followed by TES cleavage, to give β-hydroxy ketone **87** in good yields (77%, 88%) (Scheme 56). Subsequent mesylation of **87** led to mesylate **88** which was submitted to the cyclization conditions reported by *Wu* and *Sun*[132]. This led to the isolation of a mixture containing the product **89** and the elimination product **90**, which were separable only by HPLC. NOE-NMR analysis showed that the stereocenter at C4 (α to the ketone) had epimerized under the cyclization conditions. After TBDPS removal on pure C4-isomer **89** with pyridine-buffered HF, the primary alcohol **91** was isolated as a 1:1 mixture of diastereoisomers. It has to be noted that the experiments depicted in Scheme 56 were performed starting with a diastereomeric mixture of **85b** (7:1) and so are the corresponding products. For the ease of understanding only the major isomer is shown.




**Scheme 56:** a) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, -78°C, 77%; b) AcOH/THF/$H_2O$ (3:1:1), rt, 88%; c) MsCl, $NEt_3$, $CH_2Cl_2$, -40°C, crude; d) 2,6-lutidine, 120°C, 31% **89**, single isomer + 15% **90**; e) HF•pyridine, THF, 0°C, 66%, 1:1 mixture of isomers.

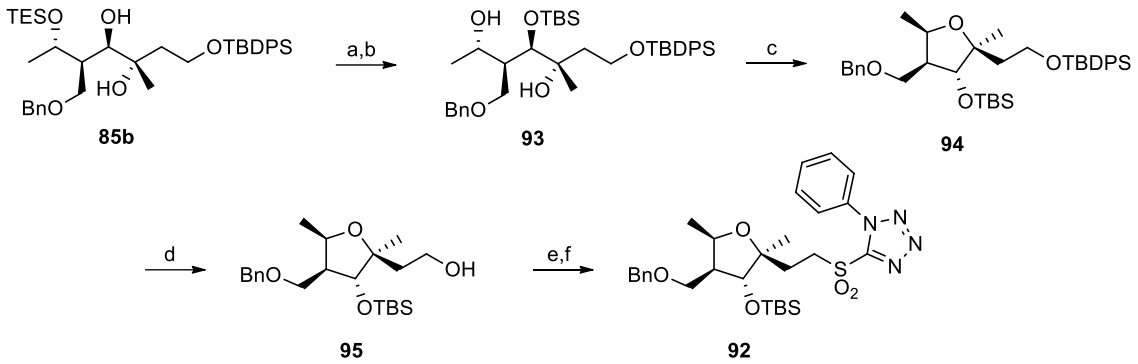
At this point it became clear that the synthesis of the sulfone **73** had to be approached differently. In order to avoid the isomerization and elimination problem, the cyclization was planned to be performed with a protected hydroxy group instead of a keto group as in **87**. In addition, deprotection and oxidation of this hydroxy group was to be performed only after the *Julia* olefination, in order to avoid isomerization during the fragment synthesis. As a consequence of these considerations, sulfone **92** emerged as a new building block for fragment synthesis (Scheme 57).




**Scheme 57:** Revised retrosynthetic analysis of the *Julia* sulfone fragment **92**.

## 3.2.5. Synthesis of Sulfone 92

In order to access *Julia* sulfone **92**, diol **85b** was TBS-protected followed by selective cleavage of the TES ether with PPTS, to give a new diol **93** in excellent overall yield (79% from **85b**) (Scheme 58). Mesylation of the secondary hydroxy group in **93** led to spontaneous cyclization to tetrahydrofuran **94**, which was isolated in 78% yield, without any hints at the formation of an elimination product. The following selective TBDPS cleavage was carried out with HF buffered in pyridine, to give the desired primary alcohol **95** in a moderate yield of 66%. Finally, **95** was converted into the phenyltetrazolyl sulfone (PT-sulfone) **92** by reaction with 1-phenyl-1H-tetrazole-5-thiol under standard *Mitsunobu*[133] conditions and subsequent oxidation with *m*CPBA.




**Scheme 58:** a) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, -78°C, 90%; b) PPTS, MeOH/THF (2:1), rt, 88%; c) $NEt_3$, MsCl, $CH_2Cl_2$, -40°C to rt, 78%; d) HF•pyridine, THF, rt, 66%; e) 1-phenyl-1H-tetrazole-5-thiol, $PPh_3$, then DEAD, THF, 0°C, 88%; f) *m*CPBA, $CH_2Cl_2$, rt, 96%.

Having shown that it was in principle possible to access the desired furan **92** from Z-olefin **85b**, the route needed to be optimized. In particular, an alternative method needed to be identified that would provide selective access to **76b** in order to be able to produce larger amounts of the fragment (see next Chapter).

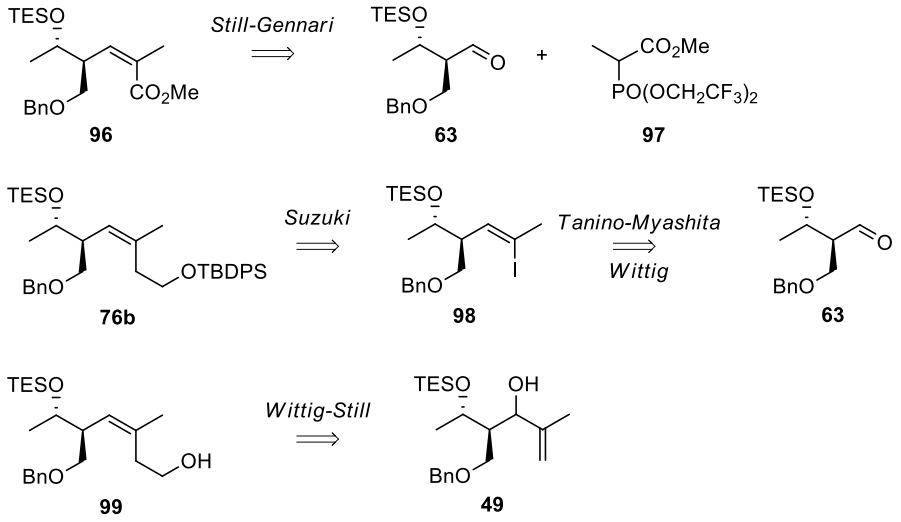
## 3.2.6. Approaches Towards the Selective Synthesis of Z alkene 76b

At the outset of our efforts towards a selective synthesis of alkene **76b**, the following possible approaches were considered and examined experimentally (Scheme 59):

The first approach entailed a modified *HWE* reaction of aldehyde **63** with the *Still-Gennari*[134] reagent, which is known to yield trisubstituted alkenes with good *Z*-selectivity. Given the previous unsuccessful trials with the standard *HWE* reagent **82** (Chapter 3.2.4), not much success was to be expected from this approach.

The second approach would made use of the *Tanino-Myashita*[135] protocol to synthesize the (*Z*)-vinyliodide **98** selectively, which would be followed by a $sp^3$-$sp^2$ *Suzuki* coupling to access the desired alkene **76b**.

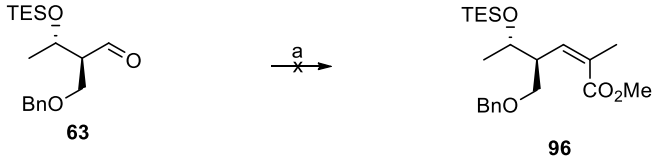
The third approach would deliver alkene **99** by a *Z*-selective *Wittig-Still* [2,3] rearrangement[136] starting from already synthesized allylic alcohol **49**.




**Scheme 59:** Possible approaches towards the (*Z*)-selective synthesis of alkene **76b**.

### 3.2.6.1. The *Still-Gennari* Approach

Unfortunately, but not unexpectedly, the *Still-Gennari* variant of the *HWE* reaction did not yield the desired alkene **96** and this approach was quickly abandoned (Scheme 60).



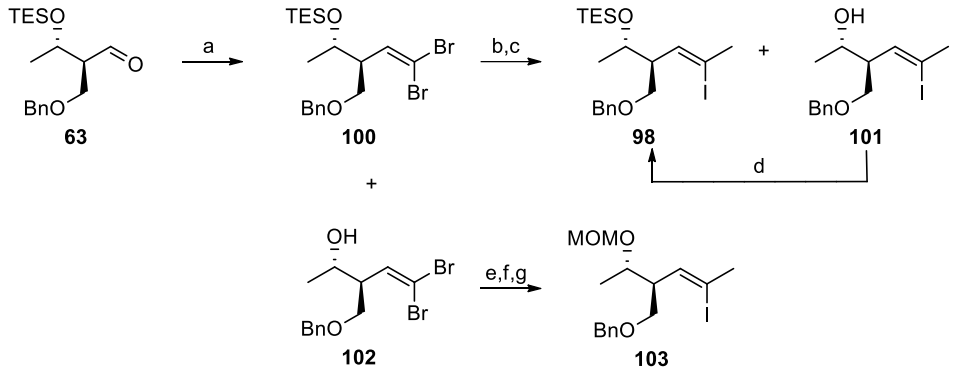

**Scheme 60: 97**, KHMDS, 18-crown-6, then **63**, THF, -78°C, 0%.

### 3.2.6.2. The *Tanino-Myashita* Approach

In order to perform the (*Z*)-selective *Tanino-Myashita*[135] vinyl iodide synthesis, the aldehyde **63** had to be converted to the dibromoalkene **100** by using *Wittig* chemistry (Scheme 61). Unfortunately, during workup partial TES deprotection occurred which gave the desired dibromoalkene **100** in only 55% yield accompanied by 38% of the deprotected product **102**. When the *Tanino-Myashita* conditions (generation of dimethyl cuprate using methyl lithium and copper iodide, followed by treatment with iodine) were applied to dibromoalkene **100**, the vinyl iodide **98** was isolated in 31% yield as a 1:2.6 mixture of *E*/*Z* isomers, along with 32% of the TES-deprotected product **101** as a 1:6.6 mixture of *E*/*Z* isomers; the latter was easily reprotected to the desired product **98**.

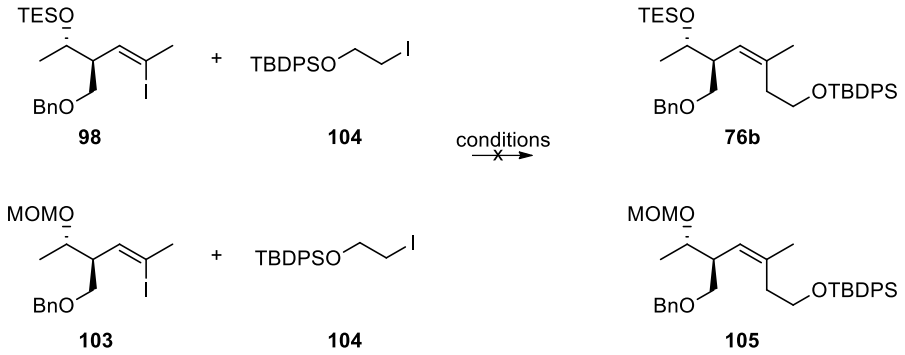
According to literature,[137] cross coupling reactions often show low to no conversion when a silyl protected hydroxy group is present in the β-position of the alkene. Since this is the case in **98**, the side product **102** was protected as a MOM ether, which was then submitted to the *Tanino-Myashita* conditions. Unfortunately the cuprate formation was incomplete with the MOM-protected substrate and, therefore, a mixture of inseparable products was obtained,

containing the desired product **103** (*E*/*Z* = 1:8), starting material and a doubly methylated side product in a ratio of 2.3:1.2:1 (**103**:SM:double methylated product).




**Scheme 61:** a) $CBr_4$, $PPh_3$, 2,6-lutidine, $CH_2Cl_2$, -78°C, 55% **100** and 35% **102**; b) MeLi, CuI, then **100**, $CH_2Cl_2$, -78°C; c) $I_2$, $CH_2Cl_2$, -78°C, 31% **98** *E*/*Z* = 1:2.6 and 32% **101** *E*/*Z* = 1:6.6 over two steps; e) MOMCl, DIPEA/$CH_2Cl_2$ (1:1), rt, 96%; f) MeLi, CuI, then **102**, $CH_2Cl_2$, -78°C; g) $I_2$, $CH_2Cl_2$, -78°C, ~40% *E*/*Z* = 1:8 over two steps.

For the conversion of the vinyl iodides **98** / **103** into the desired trisubstituted alkenes **76** / **105** the *Suzuki*[138] and the *Kumada*[139] cross couplings with iodide **104** were investigated (Scheme 62). Although vinyl iodide **103** was not available in pure form, it was nevertheless used for a test reaction. Unfortunately, every single condition investigated failed to give even a trace of the desired product for either substrate, therefore this strategy was abandoned.




**Scheme 62:** Conditions: 1) **104**, *t*BuLi, 9-MeO-BBN, $Et_2O$, -78°C, then **98** / **103**, $Pd(dppf)Cl_2$, $AsPH_3$, $CsCO_3$, THF, rt, 0%; 2) **104**, Mg, $Et_2O$, reflux, then **98** / **103**, $Pd(PPh_3)_4$, LiCl, $Et_2O$, rt, 0%.

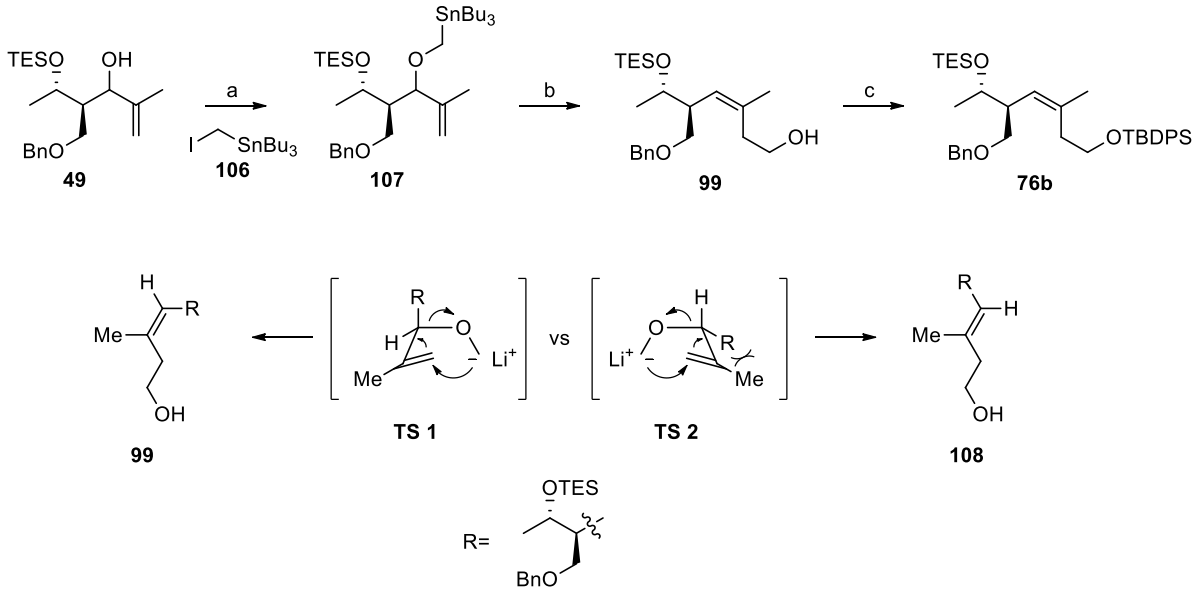
### 3.2.6.3. The *Wittig-Still* Approach

The final approach investigated towards the selective synthesis of trisubstituted *Z*-alkene **76b** was the [2,3]-sigmatropic-*Wittig* rearrangement of a stannylmethyl ether, as described by *Still*[136] (Scheme 63). To this end, the allylic alcohol **49** had to be alkylated with iodide **106**, which gave the rearrangement precursor **107** in excellent 93% yield. In initial experiments, the yield of the alkylation was very low, but when dibenzo-18-crown-6 was added as a complexing agent for potassium cations[140], the reaction proceeded smoothly. The following lithium-tin exchange is mostly performed without isolation of intermediate **107**[136]. In our

case, this procedure led to better yields, but much lower *E*/*Z*-ratios (Table 6). After some optimization work for the reaction with isolated **107** (Table 6), the desired rearrangement could be triggered by lithium-tin exchange with *n*BuLi, to give homoallylic alcohol **99** in 64% yield and with an *E*/*Z* ratio of 1:19. What turned out to be highly critical parameter for the success of this transformation were (1) the temperature at which the reaction was conducted and (2) the rate at which the *n*BuLi was added to the reaction. If the reaction temperature was too low (i. e. ≤ -78 ˚C, entries 4 and 8) the yield decreased massively; if *n*BuLi was added too slowly (entries 7 and 8), the *E/Z*-selectivity dropped. The optimal conditions identified entailed the relatively rapid addition of *n*BuLi at – 78 ˚C and the subsequent transfer of the reaction vessel (i. e. after *n*BuLi addition was complete) to a -20°C cooling bath.

The high *Z*-selectivity of the reaction arises from transition state **TS 1**, with the R substituent in a pseudoaxial position, being strongly preferred over the alternative transition state **TS 2**. The preference implies that the steric interaction between the R substituent with the methylene is much less than the interaction of the R substituent with the vinyl methyl.

Unfortunately, the reaction stopped at a certain point and could not be pushed towards completion; therefore, two iterations were needed in order to obtain 64% yield. While the Z/E isomers were not separable after the rearrangement, subsequent TBDPS protection of the primary hydroxy group gave TBDPS ether **76b** in 82% yield as single isomer after flash chromatography (see also Chapter 3.2.4).



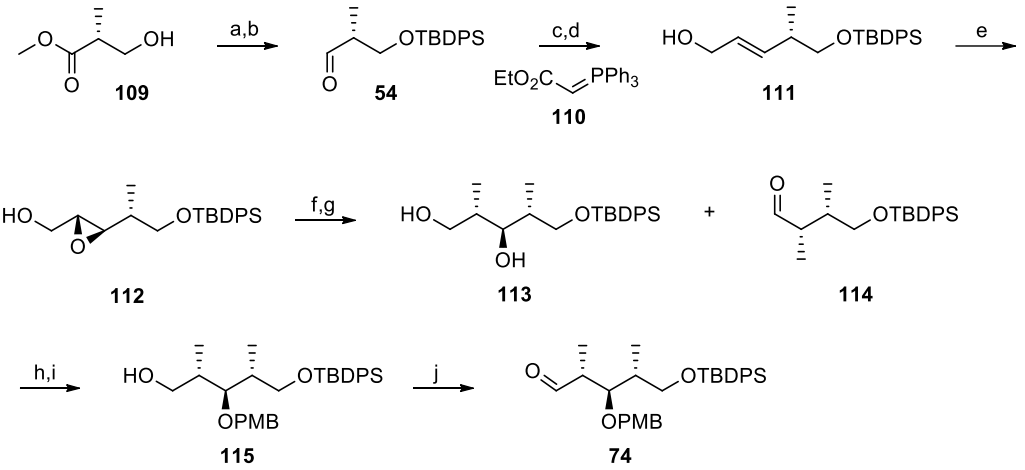

**Scheme 63:** a) KH, **106**, dibenzo-18-crown-6 (DB-18-C-6), THF, 0°C to rt, 93%; b) *n*BuLi, THF, -78°C to -20°C, 63% *E*/*Z* = 1:19, two iterations; c) TBDPSCl, ImH, $CH_2Cl_2$, rt, 82% single isomer. **TS 1/2**: Proposed transition states of the [2,3]-sigmatropic rearrangement by *Still* and *Mitra*[136].

**Table 6:** Optimization work performed on the [2,3]-*Wittig-Still* rearrangement.

| Entry | Start (49/107) | *n*BuLi [equiv.] | Temp. [°C] | Time [h] | Yield | *E/Z* |
|---|---|---|---|---|---|---|
| **1** | **49** (KH only) | 1.50 | -78 | 1.0 | 38% | 1:4 |
| **2** | **49** (KH only) | 1.50 + 1.00 | -78 | 1.0 + 2.0 | 47% | 1:4 |
| **3** | **107** | 4 • 1.10 | -78 | 4 • 0.5 | 36% | 1:4 |
| **4** | **107** | 2.00 | -100 | 0.2 | 13% (82% RSM) | 1:10 |
| **5** | **49** (KH + DB-18-C-6) | 1.50 (fast addition) | -78 | 2.0 | 51% | 1:13 |
| **6** | **49** (KH + DB-18-C-6) | 1.50 | -78 | 2.5 | 64% (two iterations) | 1:7 |
| **7** | **49** (KH + DB-18-C-6) | 1.50 (very slow addition) | -78 | 2.5 | 54% | 1:5 |
| **8** | **49** (KH + DB-18-C-6) | 1.50 (down the cold flask wall) | -78 | 2 | 20% | 1:5 |
| **9** | **107** | 1.20 (fast addition) | -78 to rt | 3 | 24% | 1:17 |
| **10** | **107** | 1.02 (fast addition) | -78 to -20 | 1 | 41% | 1:14 |
| **11** | **107** | 1.02 (fast addition) | -78 to -20 | 2 | 64% (two iterations) | 1:19 |

## 3.2.7. Synthesis of Aldehyde 74

The aldehyde building block **74** was synthesized according to *Kishi et al.*[141] and *Kocienski et al.*[142] (Scheme 64). Starting from *R*-Roche ester **109** the primary hydroxy group was TBDPS protected and the ester moiety was reduced to give aldehyde **54**. *Wittig* reaction with phosphorane **110** followed by DIBALH reduction then gave allylic alcohol **111** in excellent yield (77% over three steps) and with complete *E*-selectivity. *Sharpless* epoxidation[143] of **111** furnished epoxide **112** in 92% yield of as a single isomer. Subsequent epoxide ring opening with *in situ* generated lithiumdimethylcuprate resulted in a mixture of two inseparable diols: The desired 1,3-diol **113** and its 1,2-diol regioisomer. In order to separate these regioisomers, the crude mixture was treated with $NaIO_4$, to transform the 1,2-diol into the corresponding aldehyde **114**, which allowed for the isolation of **113** in 68% yield. Diol **113** was then converted into the corresponding PMP acetal, which was selectively reduced to primary alcohol **115** using DIBALH. Finally, alcohol **115** was oxidized to aldehyde **74**, thus completing the synthesis of aldehyde **74** in 38% yield over 9 steps from *R*-Roche ester (**109**).




**Scheme 64:** a) TBDPSCl, ImH, $CH_2Cl_2$, rt, 95%; b) DIBALH, $CH_2Cl_2$, -78°C, 97% (crude); c) **110**, THF, reflux, 84%, *E*-only; d) DIBALH, $CH_2Cl_2$, -78°C, 96%; e) (-)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, $CH_2Cl_2$, -20°C, 92%, single isomer; f) MeLi, CuI, then **113**, $Et_2O$, -45°C, crude then g) $NaIO_4$, $MeCN/H_2O$, rt, 68% of **113**; h) $PMP(OMe)_2$, CSA, $CH_2Cl_2$, rt, then i) DIBALH, $CH_2Cl_2$, -78°C to rt, 94% over 2 steps; j) DMP, pyridine, rt, 86%.

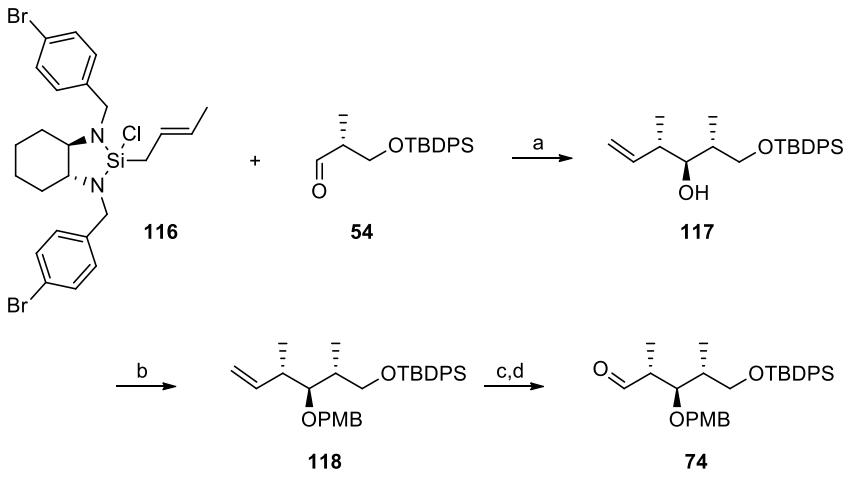
## 3.2.8. Alternative Synthesis of Aldehyde 74 via *Leighton* crotylation

Although the synthesis described in the previous chapter allowed us to easily access large quantities of aldehyde **74**, we opted to develop a new and faster route to access aldehyde **74** by using modern methods. An alternative synthesis of aldehyde **74** was established by making use of the *Leighton*[144] crotylation protocol for silyl protected *Roche*-ester derived aldehydes, such as **54**. In contrast to other crotylation methods (for example the ones developed by *Roush, Brown*)[145,146], the use of the *Leighton's* crotylsilane **116** provides for an exceptionally high level of reagent control, which allows to override the diastereofacial bias of the chiral aldehyde.

Performing the *Leighton* crotylation on aldehyde **54**, using freshly prepared (*R,R)*-crotylsilane **116**[147], gave the homoallylic alcohol **117** in 59% yield and a 14:1 *dr* (Scheme 65). Compared to the literature values for the crotylation of similar aldehydes[144] (81% yield and 97:3 *dr*), these results, for reasons that are not understood and were not explored, were significantly worse.

PMB protection of the secondary hydroxy group of **117** followed by dihydroxylation and oxidative cleavage of the resulting diol, gave the desired aldehyde **74** in 29% yield over 6 steps. Although this route is 3 steps shorter than the one described in Chapter 3.2.7, the total yield of 9% is lower. In addition, this route is also somewhat hampered by the fact that the isomers originating from the crotylation reaction, could only partially be separated either after the reaction itself or at any subsequent step (i. e. **74** obtained by this route was a ~14:1

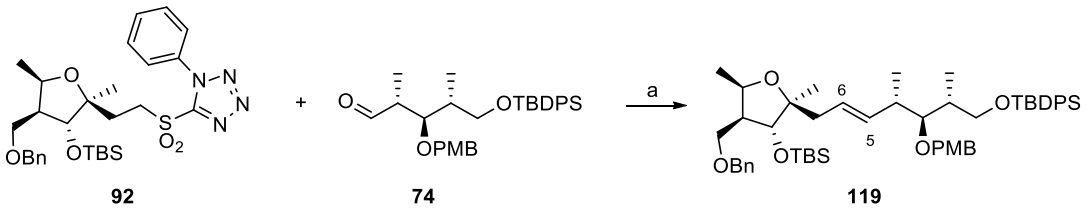
mixture). In order to make this route a preferred alternative, optimization work has to be carried out especially on the crotylation and on the PMB protection step.[2]




**Scheme 65:** a) $Sc(OTf)_3$, $CH_2Cl_2$, 0°C then HCl (1.00 M), $CH_2Cl_2$, 0°C, 59%, *dr* = 14:1; b) NaH, 15-crown-5, THF, 0°C then PMBBr, 0°C to rt, 64%; c) $OsO_4$, NMO, 2,6-lutidine, THF/acetone/$H_2O$ (5:5:1), rt, 87%; $NaIO_4$, THF/$H_2O$ (10:1), rt, 96%.

## 3.2.9. Fragment Assembly via *Julia* Olefination

The assembly of sulfone **92** and aldehyde **74** via *Julia* olefination, using KHMDS as a base, yielded the desired alkene **119** in 55% yield and with complete *E*-selectivity (Scheme 66). The configuration of the double bond in **119** was established by analysis of the NMR coupling constants of the olefinic protons (Figure 26).




**Scheme 66:** a) **74**, KHMDS, then **74**, -78°C, 55%, *E*-isomer only.

For **119** a C5-C6 coupling constant of 15.5 Hz was extracted from the respective homodecoupled $^1$H-NMR spectra, in which the couplings between the protons at C4 and C5 and between those at C7 and C6 were suppressed by irradiation at ca. 2.45 ppm or 2.13 ppm, respectively.

[2] The alternative aldehyde strategy was carried out by Peter Müller in the course of his Master thesis.

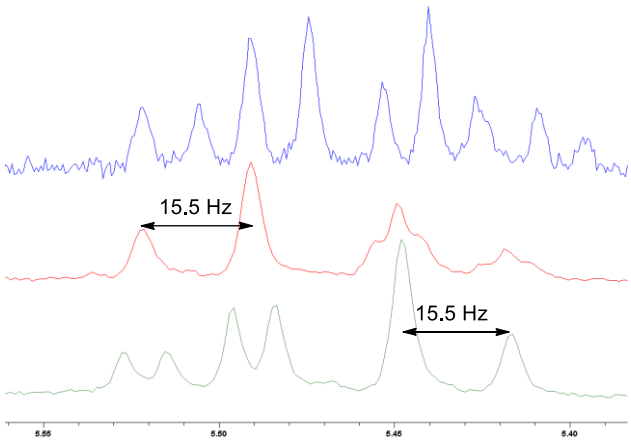
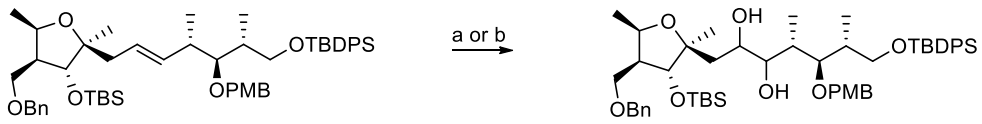



**Figure 26:** Top (blue): Excerpt from the 500 MHz $^1$H-NMR spectrum of **119** in $CDCl_3$ from 5.39 to 5.56 ppm. Middle (red): Homodecoupled spectrum from 5.39 to 5.56 ppm with irradiation at 2.45 ppm. Bottom (green): Homodecoupled spectrum from 5.39 to 5.56 ppm with irradiation at 2.13 ppm. From both homodecoupled spectra a C5-C6 coupling constant of 15.5 Hz can be extracted.

With the *E*-alkene **119** in hand, the first dihydroxylation experiments were performed (Scheme 67). Dihydroxylation under *Upjohn*[89] conditions yielded the diol **120** in 57% yield and with a *dr* of 1:2.5. The dihydroxylation had to be performed at 45°C in order to reach conversion, a clear indication that the system is sterically demanding. Dihydroxylation under *Sharpless* conditions (using both AD mixes) led to no conversion, probably due to sterically hindered nature of the system.



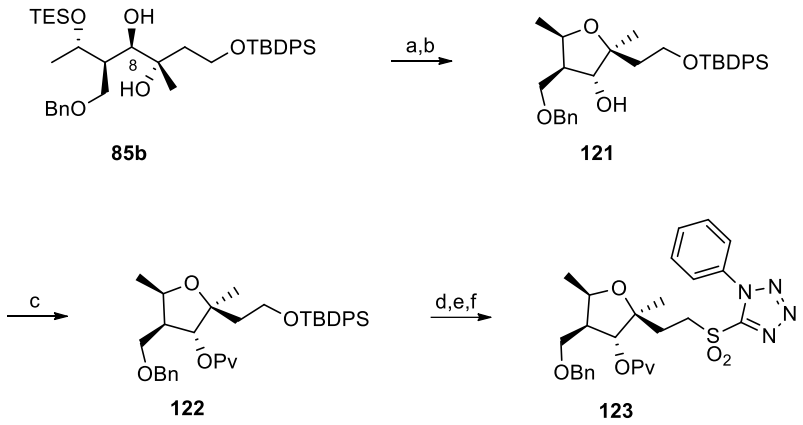

**119** **120**

**Scheme 67:** a) $OsO_4$, NMO, 2,6-lutidine, acetone/$H_2O$ (10:1), 45°C, 57%, *dr* = 1:2.5; b) AD-mix (α,β), $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH, $H_2O$, 0°C to rt to 80°C, 0%.

Since it was believed that one of the main issues in the dihydroxylation of **119** was steric hindrance caused by the TBS-ether moiety on the tetrahydrofuran ring, it was envisioned that the dihydroxylation might proceed more efficiently with the corresponding free alcohol. Since the selective removal of a TBS group from a secondary hydroxy group in the presence of a primary TBDPS-ether is known to be difficult[148], it was decided to replace the TBS group on the *Julia* sulfone fragment **92** with a pivaloyl protecting group, which is orthogonal to the TBDPS group.

## 3.2.10. Synthesis of *Julia* Sulfone 123

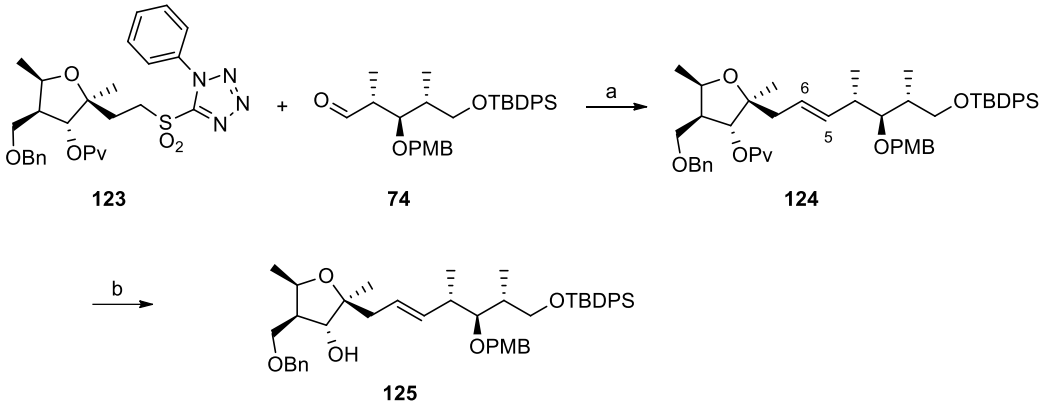
In contrast to the synthesis of **92**, the diol **85b** was not directly pivaloyl protected, due to very slow conversion (Scheme 68). Instead, it was found that the cyclization to tetrahydrofuran **121** could also be performed with the free hydroxy group at C8. Thus, after removal of the TES group with PPTS, the cyclization could be performed according to the previously developed protocol without any changes (see Chapter 3.2.5). Interestingly the reactivity of the secondary hydroxy group was significantly enhanced after cyclization, thus providing the desired pivaloate **122** in excellent yield (91%). The subsequent TPDPS deprotection proceeded smoothly, to furnish the free alcohol in 90% yield. The synthesis of the PT-sulfone **123** via *Mitsunobu*[133] reaction and *m*CPBA oxidation was performed in the same way as in previous cases and worked in good yields.




**Scheme 68:** a) PPTS, MeOH/THF (2:1), rt, 82%; b) $NEt_3$, MsCl, $CH_2Cl_2$, -40°C, 88%; c) PivCl, DMAP, pyridine, $CH_2Cl_2$, rt, 91%; d) HF•pyridine, THF, rt, 90%; e) 1-phenyl-1H-tetrazole-5-thiol, $PPh_3$, then DEAD, THF, 0°C, 84%; f) *m*CPBA, $CH_2Cl_2$, rt, 80%.

## 3.2.11. 2nd Fragment Assembly via *Julia* olefination

With the new *Julia* sulfone **123** in hand, the *Julia* olefination with aldehyde **74** was performed under essentially the same conditions that had been employed for the reaction with sulfone **92**, yielding alkene **124** as an inseparable mixture in 60% with a *E/Z*-selectivity of 11:1 (Scheme 69). Again the selectivity was verified by analysis of the NMR coupling constants between the olefinic protons at C5 and C6 (Figure 27), which was found to be 15.5 Hz. Pivaloyl deprotection using DIBALH finally furnished alcohol **125**.




**Scheme 69:** a) **123**, KHMDS, then **74**, THF, -78°C, 60%, *E/Z* = 11:1; b) DIBALH, $CH_2Cl_2$, -78°C, 77%.

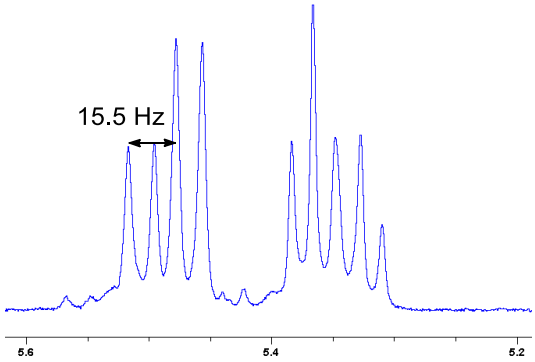
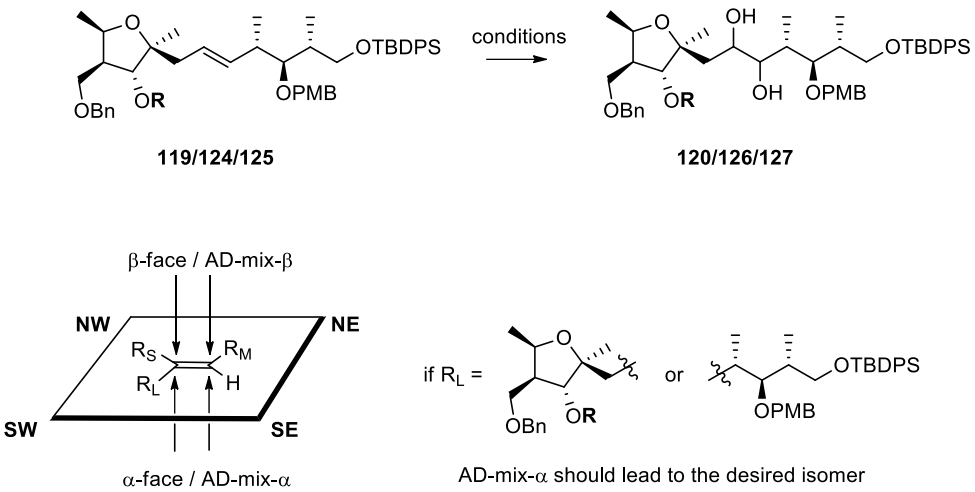



**Figure 27:** Cutout from the 400 MHz $^1$H-NMR spectrum of **124** in $CDCl_3$ from 5.6 to 5.2 ppm. From the signals a C5-C6 coupling constant of 15.5 Hz can be extracted.

Dihydroxylation experiments with $OsO_4$ clearly showed that the double bond of alkene **125** is more accessible than in **119** (dihydroxylation could be carried out at 0°C to rt instead of 45 °C) and that one side is now clearly preferred for electrophilic attack (dr~1:5, isomers not separated). Unfortunately, still no conversion could be observed by applying Sharpless conditions. Therefore, the Sharpless dihydroxylation was performed under modified conditions using $OsO_4$, NMO and the corresponding ligand $(DHQ)_2PHAL$ (α) or $(DHQD)_2PHAL$ (β). These conditions are also known as "super AD-mix"[149]. The experiments showed that the ligands have only little influence on the selectivity meaning that the selectivity is mostly controlled by the substrate itself and therefore only one isomer of **126** (and also protected versions of it) can be obtained in excess. An alarming fact was that for the AD-mix reactions the higher selectivity was obtained with the β-ligand. According to the empirical model of *Sharpless* (mnemonic device)[150] it was the α-ligand that should have led to the desired diol **126** (Scheme 70).

In Table 7 all the dihydroxylation experiments are summarized, including those performed on **119**.



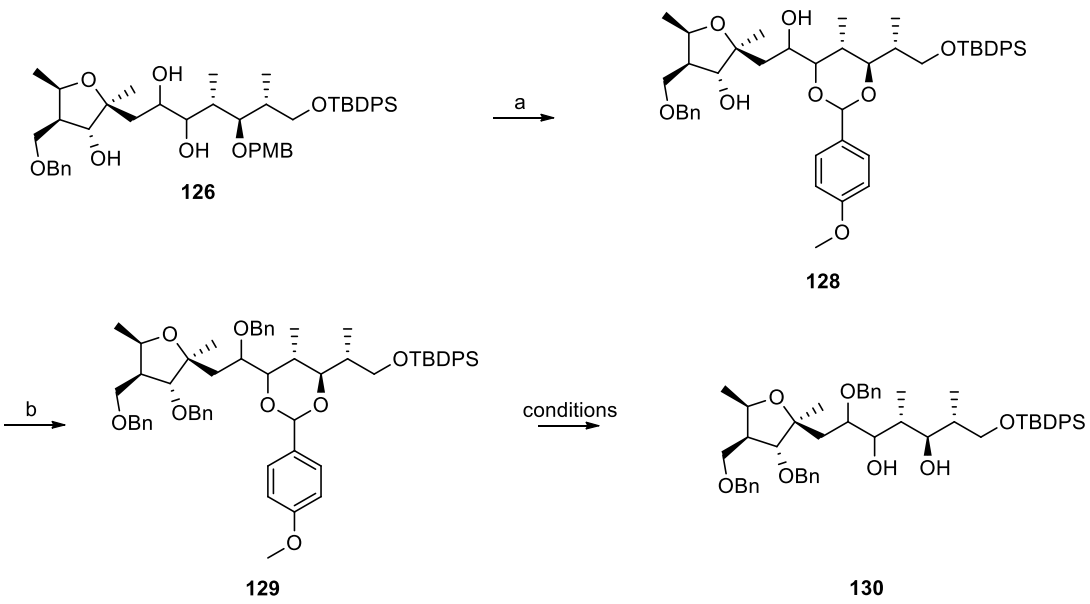

**Scheme 70:** Overview on dihydroxylation experiments.

**Table 7:** Dihydroxylation experiments on alkenes **119**, **124** and **125**.

| Entry | Substrate | Reagents | Temp. | yield | *dr* |
|---|---|---|---|---|---|
| **1** | **R** = TBS (**120**) | $OsO_4$, NMO, 2,6-lutidine | 0°C to rt | 0% | - |
| **2** | **R** = TBS (**120**) | $OsO_4$, NMO, 2,6-lutidine | 45°C | 57% | 1:2.5 |
| **3** | **R** = TBS (**120**) | AD-mix (α,β), $CH_3SO_2NH_2$ | 0°C to rt to 80°C | 0% | - |
| **4** | **R** = H (**125**) | $OsO_4$, NMO, 2,6-lutidine | 0°C to rt | 70% | 1:5.5 |
| **5** | **R** = H (**125**) | AD-mix (α,β), $CH_3SO_2NH_2$ | 0°C to rt to 80°C | 0% | - |
| **6** | **R** = H (**125**) | $OsO_4$, NMO, $(DHQ)_2PHAL$ (α) | 0°C | 89% | 1:4 |
| **7** | **R** = H (**125**) | $OsO_4$, NMO, $(DHQD)_2PHAL$ (β) | 0°C | 80% | 1:5.4 |
| **8** | **R** = Pv (**124**) | $OsO_4$, NMO, $(DHQ)_2PHAL$ (α) | 0°C | 65% | 1:2.7 |
| **9** | **R** = Pv (**124**) | $OsO_4$, NMO, $(DHQD)_2PHAL$ (β) | 0°C | 71% | 1:3.2 |

In order to determine which dihydroxylation product was formed preferentially, it was planned to prepare the 1,3-acetonide of diol **130**, which could then be analyzed according to the *Rychnovsky*[107] method (Scheme 71). To this end, **126** was first converted into PMP acetal **128** using DDQ in the absence of water. The remaining free hydroxy groups of **128** were then benzyl-protected by reaction with benzyl bromide in the presence of sodium hydride, to furnish the fully protected intermediate **129**. Unfortunately, the envisioned and required selective cleavage of the PMP-acetal in **129** could not be realized under any of the conditions

investigated (Table 8). Therefore, another analysis had to be found for the configurational assignment of the dihydroxylation product **126**.




**Scheme 71:** a) DDQ, $CH_2Cl_2$, 0°C, 60%; b) BnBr, NaH, THF, 0°C to rt, 81%.

**Table 8:** Tested conditions for PMP acetal cleavage.

| Entry | Acid | Equiv. | Solvent | Temp. | outcome |
|---|---|---|---|---|---|
| **1** | AcOOH | - | THF/$H_2O$/AcOOH (4.5:4.5:1) | rt | No conversion |
| **2** | HCl | - | 10% HCl in THF | rt | No conversion |
| **3** | PPTS | 1.0 | 2-propanol/MeCN (1:1) | 65°C | decomposition |
| **4** | PPTS | 0.2 | MeOH | 65°C | decomposition |
| **5** | PPTS | 2.0 | MeOH/THF (4:1) | rt | No converison |
| **6** | PPTS | 2.0 | MeOH/THF (4:1) | 50°C | Slow decomposition |
| **7** | CSA | 1.0 | MeOH | rt | PMP and TBDPS cleavage |

By searching through the literature it was discovered that the NMR chemical shift of the proton signal on the PMP-acetal carbon (1) for similar structures[151–154] is always in a similar range, but varies depending on the configuration of the diol (1,3-*syn* vs 1,3-*anti*) (Figure 28). For 1,3-*syn* PMP-acetals, the signal for the acetal proton was usually found in the 5.3-5.5 ppm range, while the signal was located between 5.7-6.2 ppm for 1,3-*anti* PMP-acetal. In addition, the 6-membered ring of the PMP-acetal can also be analyzed by means of NOE NMR

analysis. While in the 1,3-*syn* acetal two NOE signals between the protons on C1, C2 and C3 are visible, only one NOE signal between the protons on C1 and C3 is visible in the 1,3-*anti* acetal.

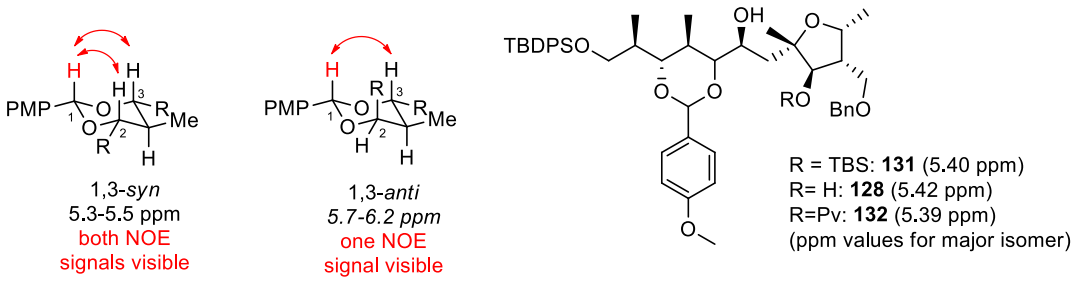
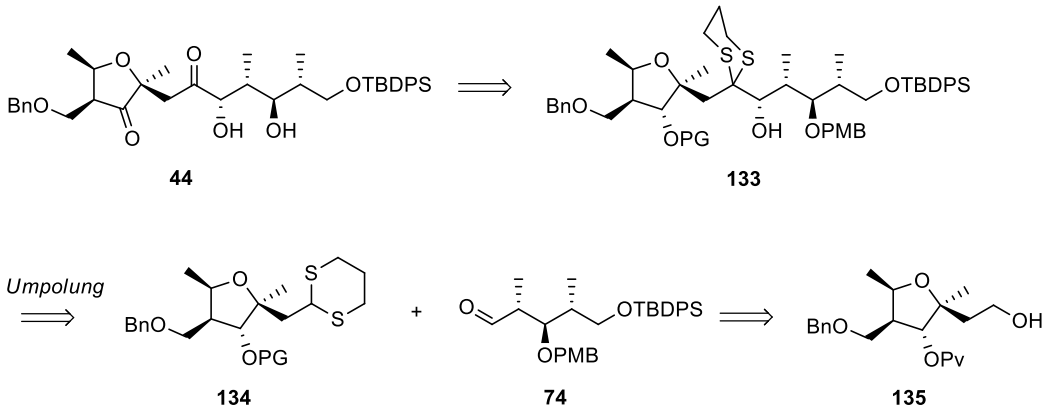



**Figure 28:** Configurational analysis of PMP-acetals **131**, **128** and **132**.

To our disappointment, the NMR signal of the acetal proton of the major isomer had a shift between 5.3-5.5 ppm for all of the synthesized PMP acetals (**128**, **132** and **131**), which strongly suggested that these products were all 1,3-*syn* configured. This assignment is also in line with the results of the NOE analysis. Thus, the dihydroxylation reactions had always delivered to the undesired 1,3-*syn* isomer preferentially. Globally, these findings led to the conclusion that any strategy towards Bu-2313 B (**2**) that would have to rely on the stereoselective dihydroxylation of olefins such as **119/156/159** would not be viable and, therefore, had to be abandoned.

### 3.2.12. 2nd Revised Retrosynthesis of Bu-2313 (Nocamycin I) – The Umpolung Approach

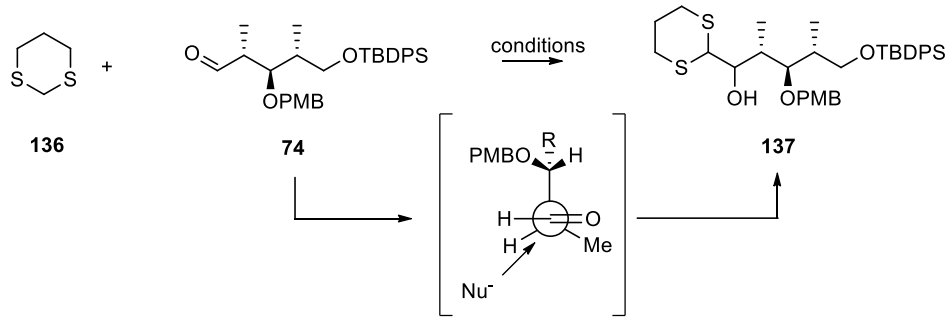
In this retrosynthesis we envisioned to assemble dithiane **133**, as a direct precursor of ketone **44**, from two main fragments **134** and **74** by means of an Umpolung reaction[155] (Scheme 72). While the synthesis of aldehyde **74** had already been established as part of the Julia-based strategy (see Chapter 3.2.7 and 3.2.8), dithiane fragment **134** was envisioned to be accessible from tetrahydrofuran **135** (see Chapter 3.2.10). Since dithianes are usually deprotonated with *n*BuLi, the pivaloyl protecting group was incompatible with this new approach and was thus planned to be replaced right after the dithiane moiety had been installed.




**Scheme 72:** Retrosynthetic analysis of **44** via Umpolung.

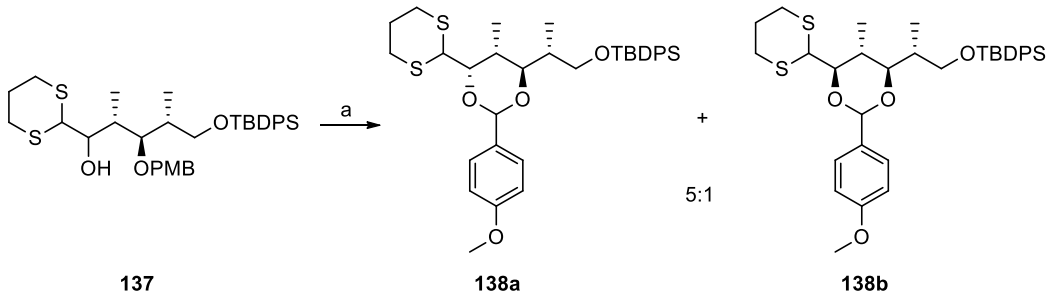
## 3.2.13. Test Reactions on Aldehyde 74

Before committing to the synthesis of dithiane **134**, a number of test reactions were performed on aldehyde **74**, in order to get an idea on the feasibility of the *Umpolung* (Scheme 73). In these reactions, dithiane **136** was first treated with *n*BuLi and then aldehyde **74** was added. When *n*BuLi was employed in THF without co-solvent, no conversion to the desired product **137** was observed. Fortunately, when HMPA was added as co-solvent, the desired product **137** was obtained in 75% yield and with 5:1 *dr*. The use of *t*BuLi instead of *n*BuLi had little influence on the yield and none on the diastereoselectivity.




**Scheme 73:** conditions: 1) **136**, *n*BuLi, then **74**, THF, -78°C, 0%; 2) **136**, *n*BuLi, HMPA, then **74**, THF, -78°C, 75%, *dr* = 5:1; 3) **136**, *t*BuLi, HMPA, then **74**, THF, -78°C, 61%, *dr* = 5:1.

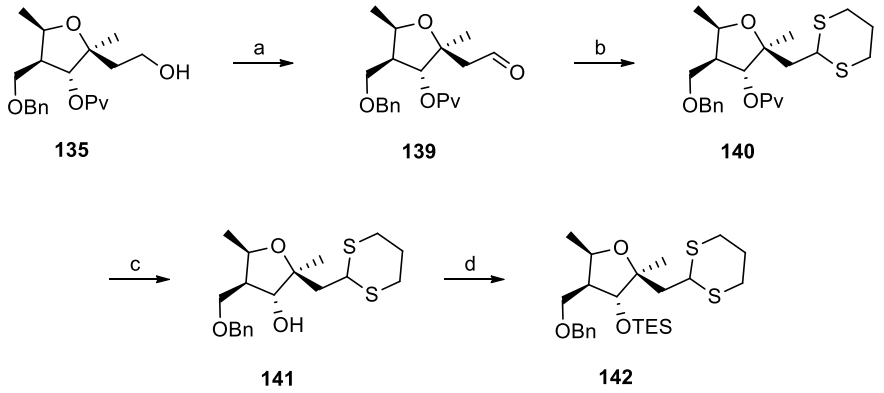
According to the *Felkin-Anh* model with reinforcing stereocenters[156] the product **137** with the hydroxyl group in 1,2-*syn* (hydroxy-methyl) and 1,3-*anti* (hydroxy-hydroxy) configuration should be formed preferentially (Scheme 74). In order to verify this prediction, **137** was converted into the PMP acetals **138a** and **138b**, which was analyzed according to the principles discussed in Chapter 3.2.11. Based on both the chemical shift analysis of the acetal proton (5.80 ppm) and NOE experiments, the **138a** isomer with a 1,3-*anti* configuration was the major product. These findings were very encouraging and, therefore, the synthesis of dithiane fragment **134** was embarked on, in order to study the *Umpolung* with this complex and relevant dithiane **134**.




**Scheme 74:** a) DDQ, 4Å mol. sieves, $CH_2Cl_2$, 0°C, 70%. Chemical shift of the PMP-acetal proton of the major isomer = 5.80 ppm.

## 3.2.14. Synthesis of Dithiane 134

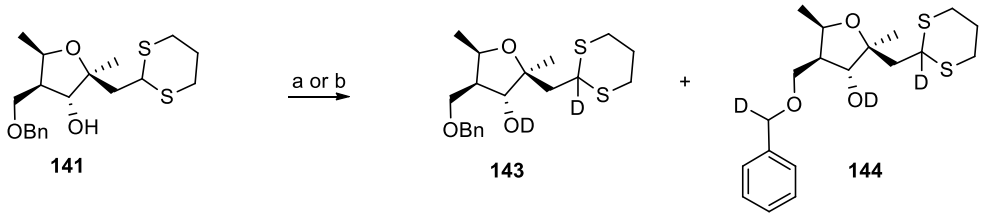
The synthesis of the dithiane fragment **134** started from the alcohol **135** (Scheme 75), which was oxidized to the aldehyde **139** using DMP. Reaction of **139** with 1,3-propanedithiol gave the desired dithiane **140** in good yield (78%). The pivaloyl group was then reductively removed with DIBALH and the free hydroxyl group was reprotected as a TES-ether, which should have been more feasible for *n*BuLi chemistry.




**Scheme 75:** a) DMP, pyridine, $CH_2Cl_2$, rt, 91%; b) 1,3-propanedithiol, $BF_3$•$Et_2O$, $CH_2Cl_2$, -78°C, 78%; c) DIBALH, $CH_2Cl_2$, -78°C, 70%; d) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 95%.

### 3.2.14.1. Preliminary Studies on the Deprotonation of Dithiane 141

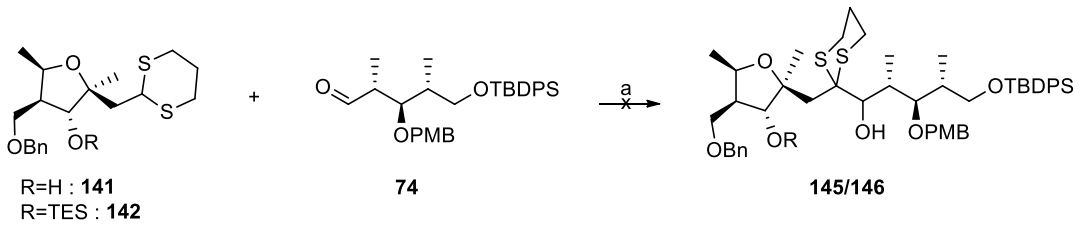
To determine if the dithiane **141** can be deprotonated and which base would be most suited for this purpose, a deuterium incorporation experiment was performed (Scheme 76). Thus, dithiane **141** was treated once with *n*BuLi at -78°C in THF/HMPA, once with *t*BuLi at -78°C in THF/HMPA and then quenched with MeOD. The results of these experiments indicated that only the dithiane proton was removed with *n*BuLi together with the hydroxy proton. In contrast, when *t*BuLi was used as a base, deprotonation occurred also partially at the benzylic position. As an obvious conclusion from this pilot study, it was clear that *n*BuLi was to be used for the *Umpolung* experiments and not *t*BuLi.




**Scheme 76:** a) *n*BuLi, HMPA, MeOD quench, THF, -78°C, 47% deuterium incorporation (**143**); b) *t*BuLi, HMPA, MeOD quench, THF, -78°C, 30% deuterium incorporation (**143**) and 14% deuterium incorporation (**144**).

## 3.2.15. Fragment assembly via *Umpolung*

The *Umpolung* was performed with both the dithiane **142** and the corresponding free alcohol **141** (Scheme 77). Unfortunately, applying the same conditions as in the model studies with aldehyde **74** and 1,3-dithiane (Chapter 3.2.13), no conversion to the desired products **145/146** was observed.



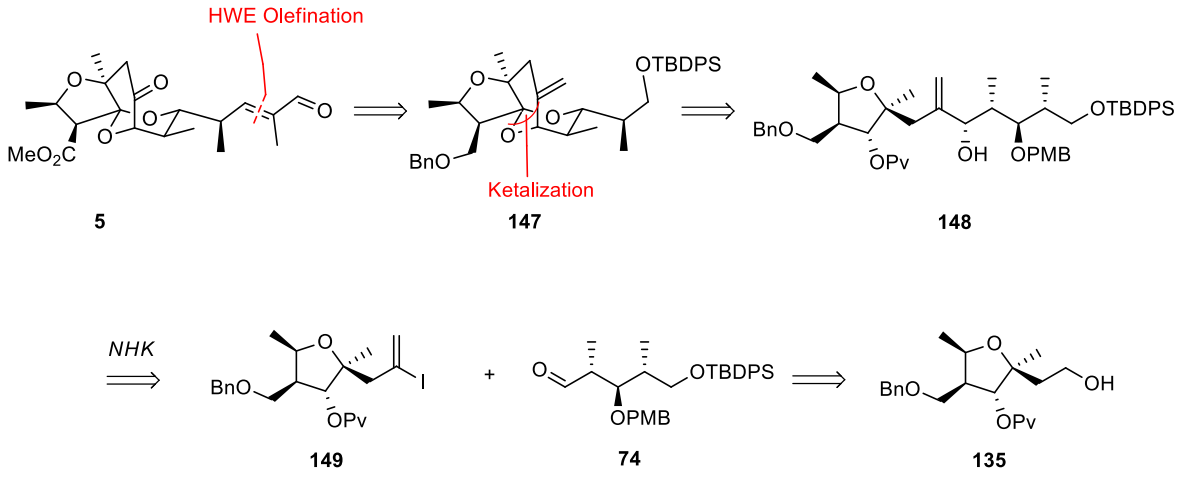

**Scheme 77:** a) **141** or **142**, *n*BuLi, HMPA, then **74**, THF, -78°C, 0% in both cases.

A possible reason for the unsuccessful coupling could be the deprotonation of aldehyde **74** in α-position by the lithiated dithianes **141/142** and the associated quench of the nucleophile. This hypothesis was investigated by reisolation of aldehyde **74** after the reaction. If aldehyde **74** had been deprotonated, this would have led to isomerization of the α-stereocenter. However, no such isomerization of the reisolated aldehyde **74** was observed; since no other issues, except steric or electronical problems, could be identified that could have been addressed by specific measures, and no obvious solutions exist to solve the problem of the lack in reactivity of the dithianes **141/142**, the Umpolung approach was also aborted.

## 3.2.16. 3rd Revised Retrosynthesis of Bu-2313 B (Nocamycin I) – Vinylmetal Addition Approach

Similarly to the *Umpolung* strategy, our newly revised strategy towards Bu-2313 B (**2**) was to rely on a vinylmetal addition to aldehyde **74** by means of a *Nozaki-Hiyama-Kishi* (*NHK*) reaction with vinyl iodide **149** (Scheme 78). The *NHK* reaction was chosen, because it can be conducted under very mild conditions and due to its high functional group tolerance.

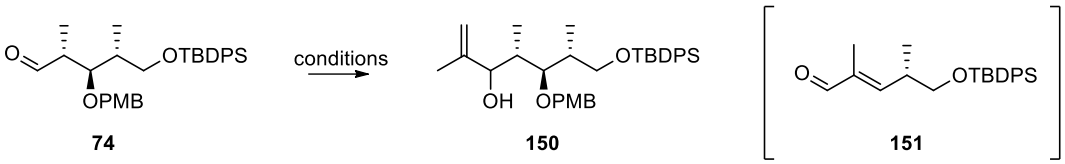
The vinyl iodide fragment **149** was again envisioned to be accessed from alcohol **135** by conversion into a terminal alkyne and subsequent iodination of the triple bond.




**Scheme 78:** Retrosynthetic analysis of Bu-2313 B via vinylmetal addition.

## 3.2.17. *NHK* Model Reactions with Aldehyde 74

Prior to embarking on the synthesis of vinyl iodide fragment **149**, a number of *NHK* test reactions were performed with aldehyde **74**, in order to assess how the substrate behaves with respect to conversion and selectivity (Scheme 79, Table 9). The first experiments were conducted with 2-bromopropene in DMSO at rt and at 50 °C. In both experiments an inseparable mixture of the desired product **150**, starting material **74** and elimination product **151** was isolated. A thorough literature search then revealed[157] that in order to avoid α,β-elimination, the reaction should be performed in DMSO and in the absence of oxygen. Therefore, the above reaction was repeated in degassed DMSO and only the desired product **150** was observed under these conditions (entry 3). When other solvents like THF or THF/DMF/4-*t*BuPy (for better solvation of the chromium species) were used, elimination prevailed (entry 4) or was observed exclusively (entry 5).

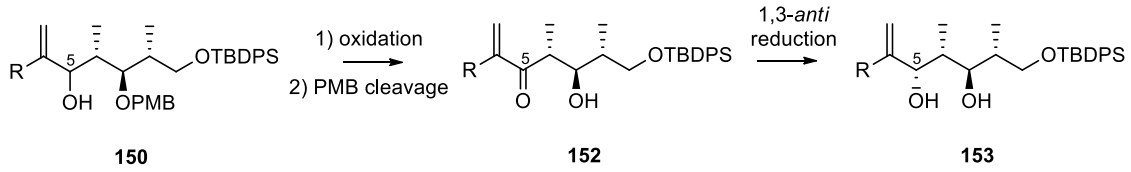



**Scheme 79:** *NHK* reaction screening.

**Table 9:** Screening of the optimal conditions for the *NHK* reaction.

| Entry | Metal | Nucleophile | Solvent | Temp. | *dr* | products |
|---|---|---|---|---|---|---|
| **1** | $CrCl_2$, $NiCl_2$ | 2-bromopropene | DMSO | rt | ~1:1 | **150** + **151** + **74** |
| **2** | $CrCl_2$, $NiCl_2$ | 2-bromopropene | DMSO | 50°C | ~1:1 | **150** + **151** + **74** |
| **3** | $CrCl_2$, $NiCl_2$ | 2-bromopropene | DMSO (degassed) | rt | ~1:1 | **150** only |
| **4** | $CrCl_2$, $NiCl_2$ | 2-bromopropene | THF | rt | ~1:1 | **150** + **151** |
| **5** | $CrCl_2$, $NiCl_2$ | 2-bromopropene | THF/DMF/4-*t*BuPy | rt | ~1:1 | **151 only** |

Although the reaction shows virtually no selectivity, it was nevertheless decided to attempt the synthesis of vinyl iodide **149** and to investigate its use in a NHK coupling, since the stereocenter at C5, in principle, could also be installed by means of 1,3-*anti* reduction (Scheme 80).




**150** **152** **153**

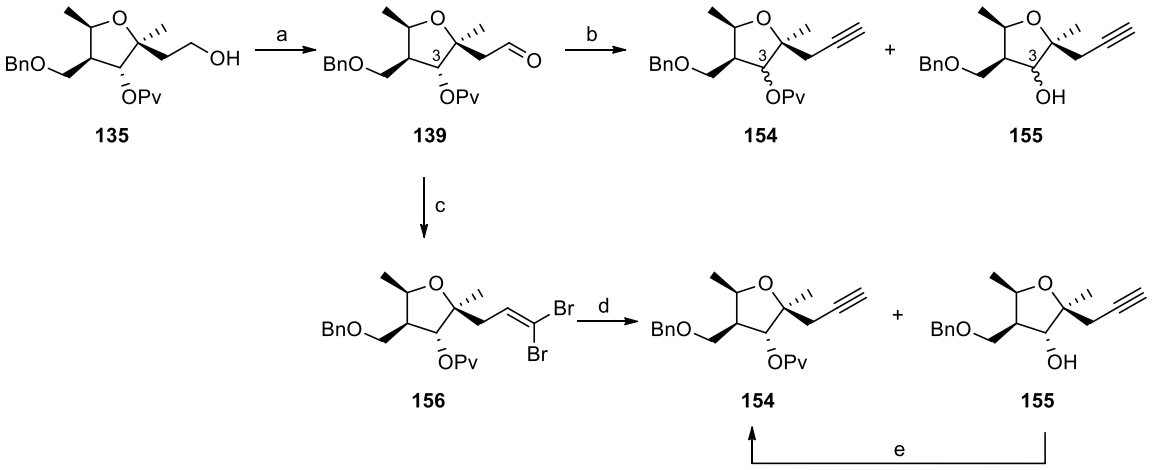
**Scheme 80:** Possible approach to the desired 1,3-*anti* diol **153** via β-hydroxyketone **152** reduction.

## 3.2.18. Synthesis of Vinyl Iodide 149

The synthesis of vinyl iodide **149** started with the oxidation of alcohol **135** to aldehyde **139** using DMP which was planned to be followed by a *Seyferth-Gilbert*[158,159] homologation using the *Bestmann-Ohira*[160] reagent (Dimethyl(1-diazo-2-oxopropyl)phosphonate)) (Scheme 81). Unfortunately, the homologation gave the desired alkyne **154** in 41% yield only, accompanied by 13% of the pivaloyl deprotected product **155**. Strangely, both products were isolated as isomeric mixtures and it was assumed that the isomerization occurred at C3, but this was not further investigated.

As an alternative the application of the *Corey-Fuchs*[161] protocol was investigated for the conversion of aldehyde **139** into alkyne **154**. Dibromoolefination to **156** worked without problems and treatment of the latter with *n*BuLi gave the desired alkyne **154** in 42% yield, again accompanied by 42% of the pivaloyl deprotected product **155**; however no signs of isomerization were observed under these conditions. Both **154** and **155** were then used to investigate their conversion into the internal vinyl iodide. For completeness, the pivaloyl

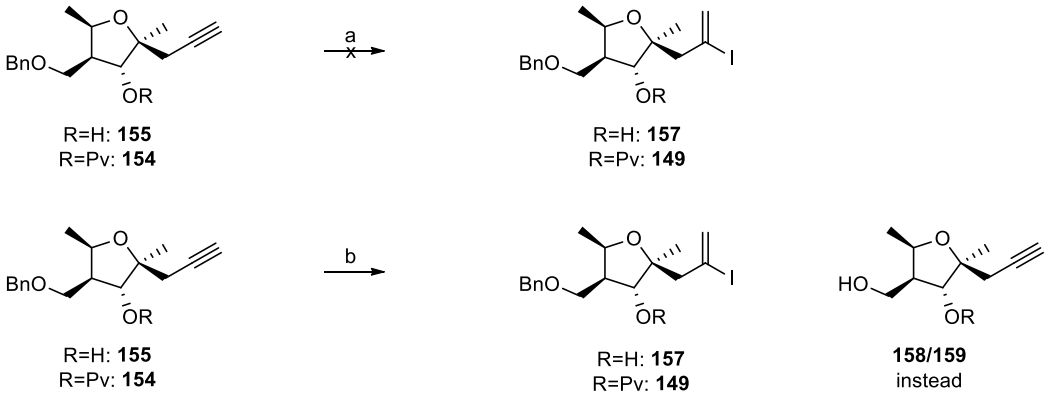
protecting group could also be reinstalled to give the desired alkyne **154** by reaction of **155** with pivaloyl chloride.




**Scheme 81:** a) DMP, pyridine, $CH_2Cl_2$, rt, 96%; b) Dimethyl(1-diazo-2-oxopropyl)phosphonate, $K_2CO_3$, MeOH, rt, 31% **154** and 13% **155**, both products isomerized; c) $CBr_4$ $PPh_3$, $CH_2Cl_2$, -78°C, 96%; d) *n*BuLi, THF, -78°C, 42% **154** and 42% **155**; e) PivCl, pyridine, DMAP, $CH_2Cl_2$, rt, 95%.

The conversion of alkynes **154** and **155** into the corresponding internal (α) vinyl iodides **157** and **149** was initially planned to be performed via haloboration with β-I-9-BBN[162], but, unfortunately, when this method was applied to alkynes **154** and **155**, only decomposition to unknown products was observed (Scheme 82).

*Ogawa*[163] has described a method for the conversion of terminal alkynes into internal vinyl iodides, which uses an iodine-hydrophosphine binary system for selective hydroiodination. Unfortunately, only partial deprotection of the benzyl group **158**/**159** was observed when applying this method to **154**/**155**.

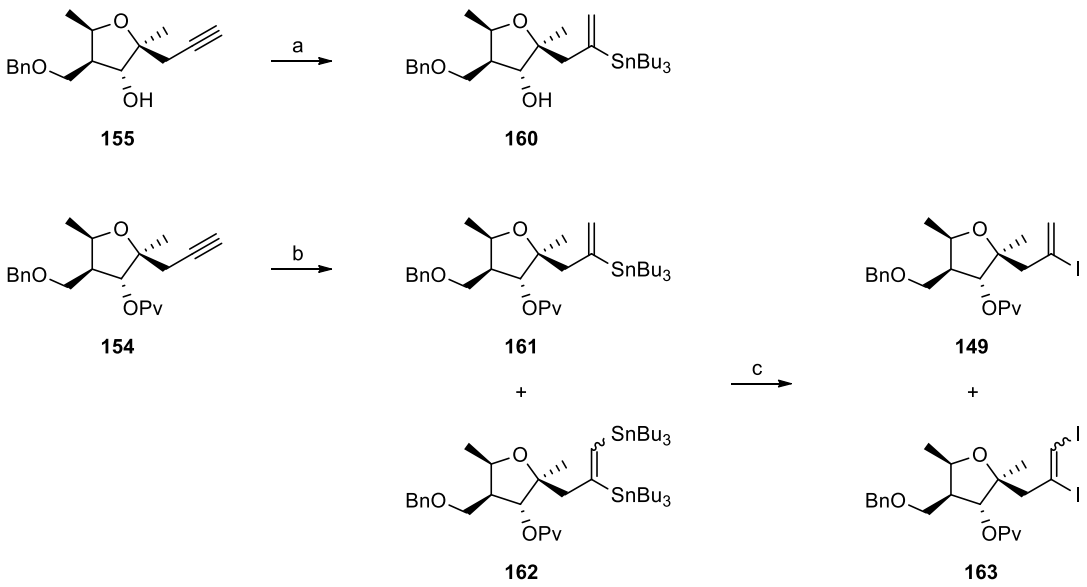



**Scheme 82:** a) β-I-9BBN, AcOH, $CH_2Cl_2$, 0°C, 0%; b) $Ph_2P(O)H$, $I_2$, $CHCl_3$, 0°C to rt, 15% of **158**/**159**.

Since direct iodination methods failed in our hands, the vinyl iodides **157**/**149** were tried to be accessed from alkynes **154**/**155** in a two-step process.

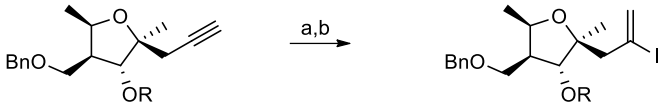
According to work of *Oehlschlager*[164] stannylalumination of terminal alkynes with *in situ* generated $Bu_3SnAlEt_2$ leads to internal (α) vinylstannanes, which can then be converted into the corresponding internal vinyl iodides. When applying these stannylalumination conditions to alkyne **155**, the desired vinylstannane **160** was isolated in only 19% yield and 44% of the starting material was recovered. In light of the poor conversion, probably due to the presence of free hydroxy group, the subsequent iodination was not investigated (Scheme 83).

When the stannylalumination conditions were applied on alkyne **154**, the conversion was much better, but the reaction produced an inseparable 1:1 mixture of the desired vinylstannane **161** and the doubly stannylated product **162** (Scheme 83). This outcome could perhaps be related to the generation of the very sensitive stannylalumination reagent ($Bu_3SnAlEt_2$). When the mixture of stannanes was reacted with NIS, the desired vinyl iodide **149** was isolated along with the doubly iodinated product **163,** as an inseparable mixture, which arises from the stannyl intermediate **162**. Although the desired product was partially obtained with this method, other methods which are less sensitive were investigated.




**Scheme 83:** a) $Bu_3SnAlEt_2$, CuCN, THF, -30°C, 19% (44% RSM); b) $Bu_3SnAlEt_2$, CuCN, THF, -30°C, 1:1 mixture containing **161** and **162**. c) NIS, $CH_2Cl_2$, rt, 2:1 mixture containing **149** and **163**.

In parallel with the stannylalumination work, a hydrosilylation-based approach reported by *Trost*[165] and coworkers, using a cationic ruthenium complex, followed by iododesilylation, was investigated. Fortunately, this protocol allowed the formation of both vinyl iodides **157**/**149** in around 70% yield over two steps (Scheme 84). It is worth mentioning that the hydrosilylation was fast and clean, while the iododesilylation from the vinylsilane intermediate to the vinyl iodide was sluggish and substantially more iodine had to be used than reported in literature[166]. Therefore, this approach would clearly have required improvement, should it have been used for the synthesis of larger amounts of the vinyl iodides **157/149**.

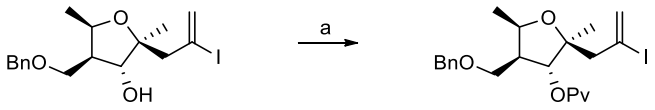



R=H: **155**
R=Pv: **154**

R=H: **157**
R=Pv: **149**

**Scheme 84:** a) $Et_3SiH$, $[CpRu(NCCH_3)_3]PF_6$, $CH_2Cl_2$, 0°C ; b) $I_2$, 2,6-lutidine, $CH_2Cl_2$, rt, 72% (**157**) or 70% (**149**) over two steps.

Vinyl iodide **155**, bearing a free hydroxy group on the tetrahydrofuran ring, could readily be converted into pivaloate **149** under standard conditions (Scheme 85).



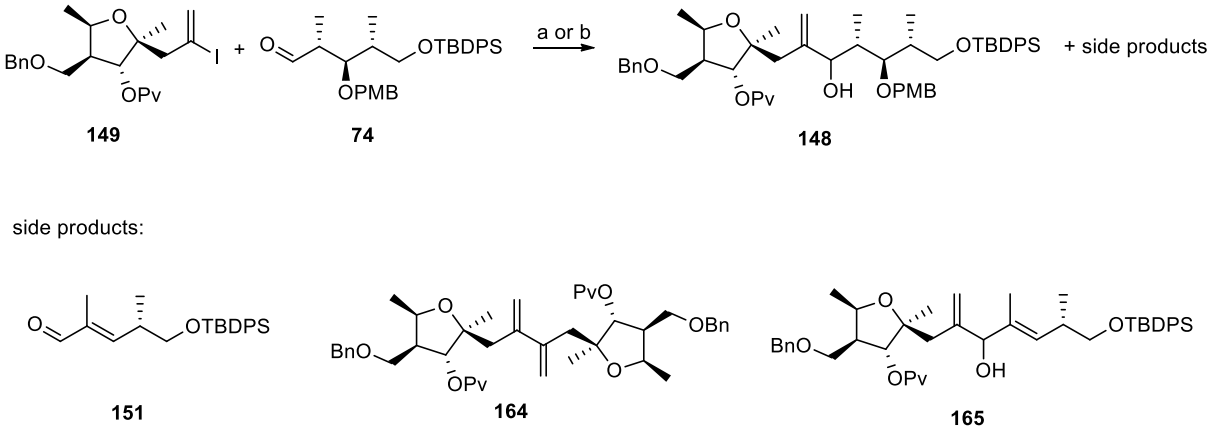

**157** **149**

**Scheme 85:** a) PivCl, pyridine, DMAP, $CH_2Cl_2$, rt, 86%.

## 3.2.19. Fragment Assembly via *NHK* Reaction

Applying the optimized *NHK* coupling conditions elaborated in Chapter 3.2.17 to aldehyde **74** and vinyliodide **149**, the desired coupling product **148** was obtained in 54% yield after 5 d reaction time with a *dr* of 1:1.5 (Scheme 86). Unfortunately, the undesired elimination product **151** was also formed in very small amounts, although the reaction was performed in degassed DMSO. In order to shorten the reaction time, the reaction was performed at 50°C, but, unfortunately, these conditions led to a significantly reduced yield of 31%. This was due to an increase in the amount of elimination product **151** and the additional formation of the homocoupling product **164** and the addition product **165**, derived from vinyl iodide **149** and the elimination product **151**.

The *NHK* results were only partially reproducible on larger scale. Performing the reaction on larger scale resulted in lower yields and prolonged reaction times were needed to reach full conversion. For example, on a 5 mg scale (vinyl iodide **149**), complete conversion was observed after 5 d; in a 40 mg scale, it took 14 d to observe full conversion. Additionally, larger amounts of elimination product **151** were observed.

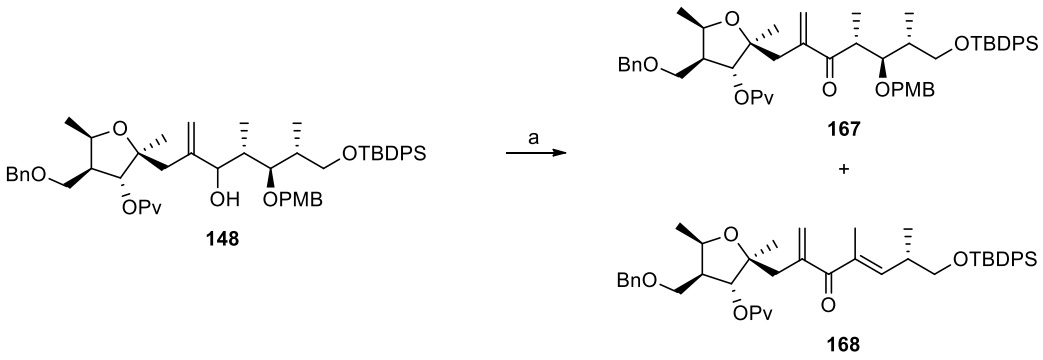



**Scheme 86:** a) $CrCl_2$; $NiCl_2$, DMSO (degassed), rt, 54 %, *dr* = 1:1.5; b) $CrCl_2$, $NiCl_2$, DMSO (degassed), 50°C, 31%.

## 3.2.20. Towards the Construction of the Tricyclic Ketal

With the assembled fragments in hand, the synthetic steps towards the cyclization precursor **173** were examined. Since the *NHK* reaction showed very poor selectivity, the desired stereoinformation had to be installed by means of a 1,3-*anti* reduction, as outlined in Chapter 3.2.17.

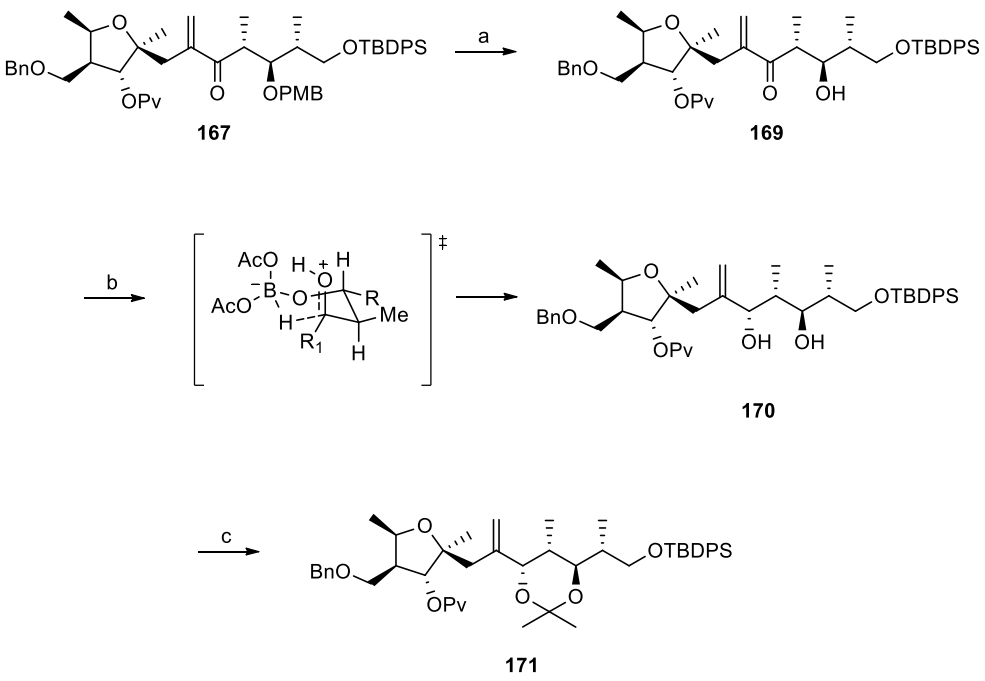
Oxidation of the allylic alcohol **148** with DMP gave the desired enone **167** in 66% yield as an inseparable 10:1 mixture with the elimination product **168** (Scheme 87). In order to prevent elimination of the PMB protected hydroxy group, the oxidation was also performed under *Ley*[167] and *Swern*[168] conditions. Oxidation under *Ley* conditions, however, even led to enhanced elimination. When *Swern* conditions were applied the ketone **167** was isolated in 64% yield, which was comparable with the yields obtained by oxidation with DMP. Although the formation of the elimination product **168** could not be completely suppressed with the *Swern* protocol, it was favored over the DMP conditions in terms of reactivity and reproducibility.




**Scheme 87:** a) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, -78°C, 64%.

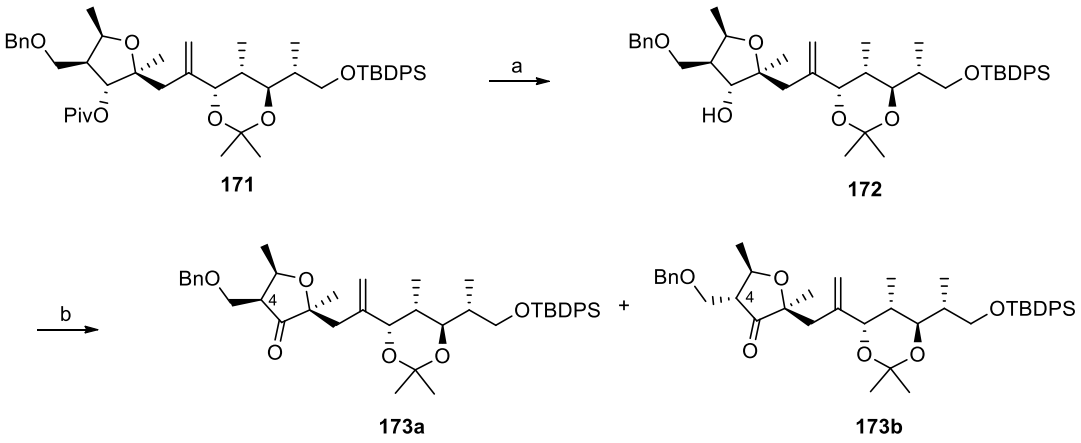
The following cleavage of the PMB group under standard conditions with DDQ in wet $CH_2Cl_2$ gave the desired β-hydroxyketone **169** in 78% yield (Scheme 88). *Evans*[169] 1,3-*anti* reduction of the β-hydroxyketone **169** using the *Gribble*[170] reagent (tetramethylammonium triacetoxyborohydride) gave the desired diol **170** in 75% yield and with excellent diastereoselectivity (*dr* > 25:1).

It is assumed that an acetoxy ligand of the *Gribble* reagent is exchanged with the free hydroxy group which then induces the reduction via intramolecular hydride attack in a chair-like transition state (Scheme 88). Dimethylmethylacetal protection of the diol **170** with 2,2-dimethoxypropane gave the desired acetal **171** in 92% yield. At this stage the 1,3-*anti* diol configuration of **171** was confirmed by making use of the *Rychnovsky*[107] acetonide method.




**Scheme 88:** a) DDQ, $CH_2Cl_2$ with 10% $H_2O$, 78%; b) $Me_4NBH(OAc)_3$, MeCN/AcOH (2:1), -20°C to rt, 75%, single isomer; c) CSA, 2,2-dimethoxypropane, rt, 92%.

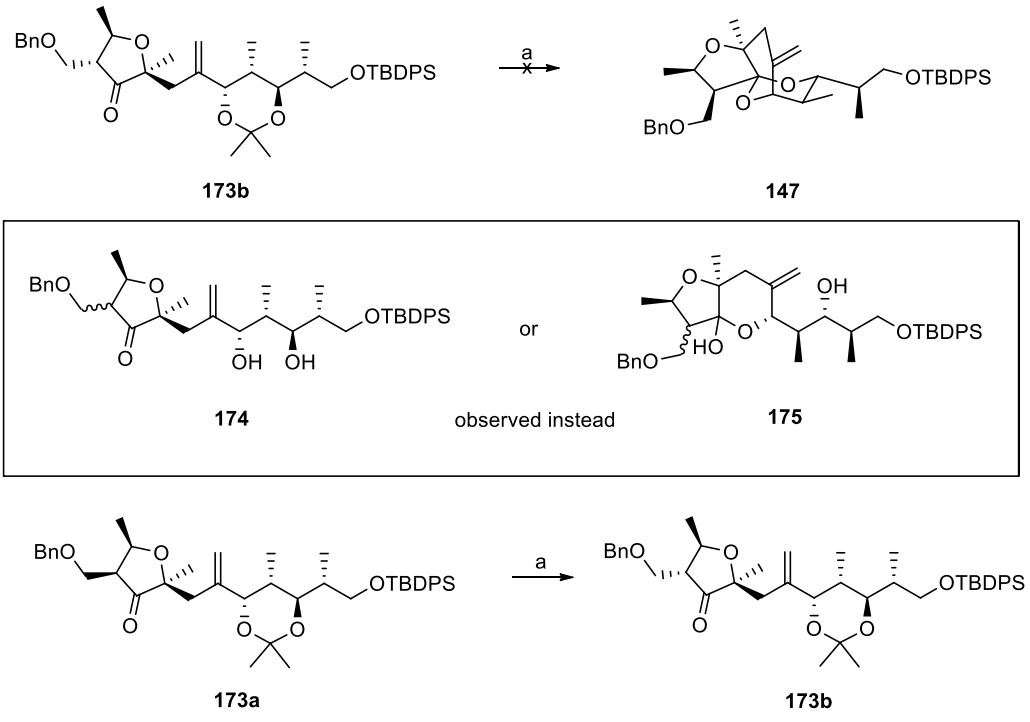
Cleavage of the pivaloyl protecting group with DIBALH gave the desired alcohol **172** in good yield (70%) (Scheme 89). For the following oxidation to the ketone **173** DMP was used first, which turned out to react very slowly and gave the desired ketone **173** in only 43% yield. When the oxidation was performed under *Swern* conditions instead, the desired product was obtained in excellent 96% yield as a mixture of diastereoisomers (**173a/173b**) at C4 (*dr* = 1:1.5), which was expected based on previous experience (see Chapter 3.2.4). Interestingly, these isomers had significantly different $R_f$ values and were easily separated by means of flash chromatography.




**Scheme 89:** a) DIBALH, $CH_2Cl_2$, -78°C, 70%; b) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, -78°C, 96%.

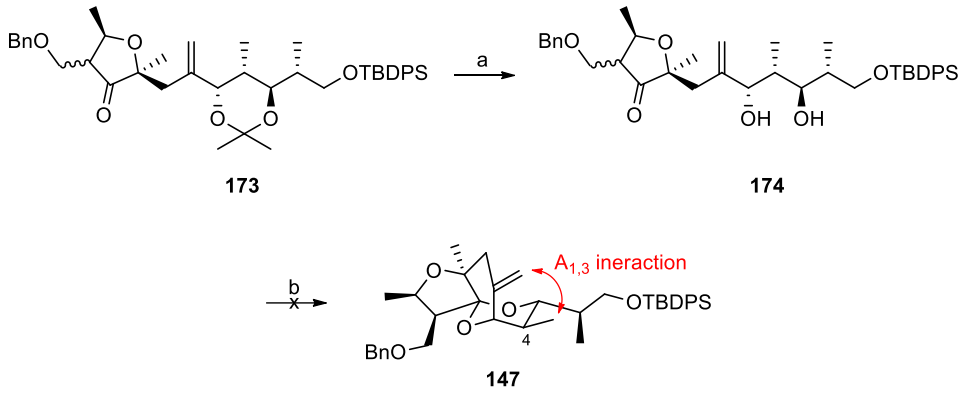
The cyclization to form ketal **147** was first attempted with the presumed (*R*)-isomer **173b** using 10% HCl in THF, which are the conditions that have been reported by *Ireland*[63] and coworkers in their attempted synthesis of Bu-2313 (see Section 1.2.2). It was expected that during the cyclization the desired isomer **147** would be formed naturally (Scheme 90). Unfortunately, this was not the case and the reaction stopped at an intermediate stage which had the same mass as the diol **174** and the hemiketal **175**. If the reaction was stirred for too long under these conditions, TBDPS deprotection at the primary hydroxy group occurred.

When the presumed (*S*)-isomer **173a** was submitted to the same conditions immediate isomerization to the (*R*)-isomer of **173b** was observed on TLC and again the reaction stopped at an intermediate stage.




**Scheme 90:** a) 10% HCl/THF, rt, 0%.

The cyclization attempt was repeated with a mixture of (*R*,*S*)-isomers **173a/173b** and PPTS in $CH_2Cl_2$/MeOH, in order to prevent TBDPS deprotection. After a much longer reaction time, the same intermediate as in the previous cyclization attempts was observed (Scheme 91). After isolation and full NMR analysis it was clear that the intermediate product was the diol **174** and not the hemiketal **175**. In order to push the diol intermediate **174** to the cyclic product **147**, it was treated with CSA in toluene in the presence of molecular sieves at 100 °C. But even under these harsh and water absorbing conditions, no cyclization to the desired product **147** was observed.



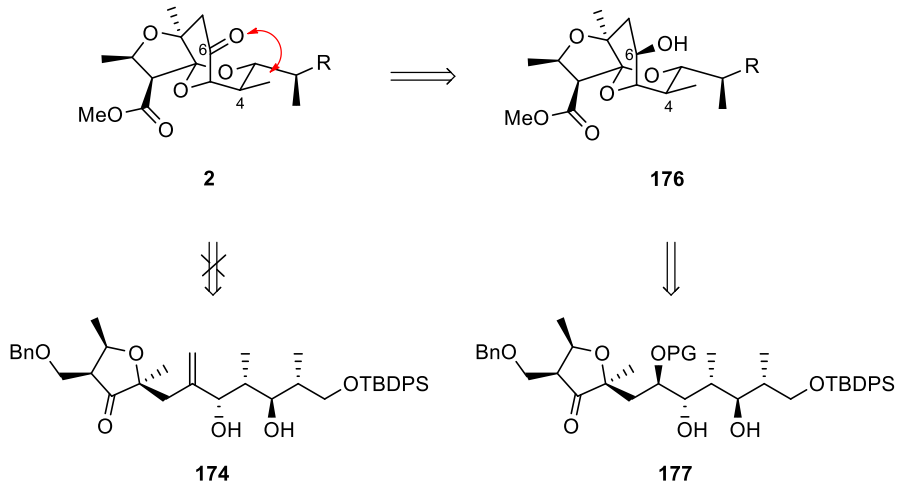

**Scheme 91:** a) PPTS, $CH_2Cl_2$/MeOH (1:1), rt, 54%; b) CSA, 4Å mol. sieves, toluene, 100 °C, 0%.

In light of these results, a closer look was taken at the cyclization reaction by means of a 3D model and a thorough literature research. Based on the analyses, the following possible explanations emerged for the lack of cyclization:

- The cyclization to the hemiketal can occur, but the second ring cannot be closed, due to unfavorable $A_{1,3}$ interactions between the exomethylene group and the methyl group at C4 of **147**. The equilibrium between the hemiketal **175** and the diol **174** lies thereby heavily on the side of the diol.

- The cyclization to the hemiketal cannot occur due to the ring strain of the newly formed six membered ring, which is further aggravated by the exomethylene group.

Out of these two possible explanations, the first seemed more likely, since 6-membered acetals bearing exomethylene groups similar to the one that must be formed from **174** are known in literature[171]. In addition, the first also seems more likely as a derivative of the natural product Bu-2313 B (nocamycin I) (**2**) is known, bearing a hydroxy group at C6 instead of a keto group named nocamycin II (**176**) (Scheme 92). This also seems to imply that the keto functionality in Bu-2313 B (**2**) is formed by means of a late stage oxidation step during the biosynthesis.




**Scheme 92:** Analysis of the ketal cyclization.

Taking a closer look at the 3D model of Nocamycin II (**176**) it can clearly be seen, that the hydroxyl group at C6 is not in the same plane as the methyl group at C4 and, which minimizes the unfavorable steric interaction (Scheme 92 and Figure 29).

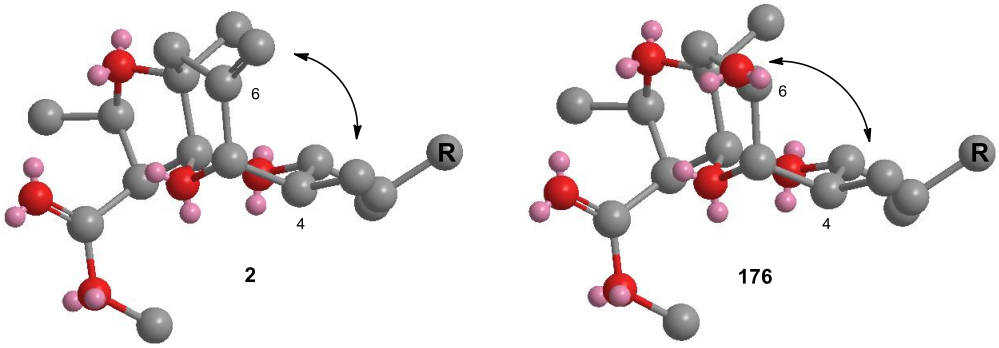
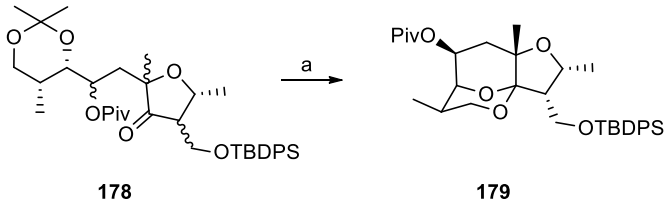



**Figure 29:** 3D models of Bu-2313 B (**2**) and Nocamycin II (**176**).

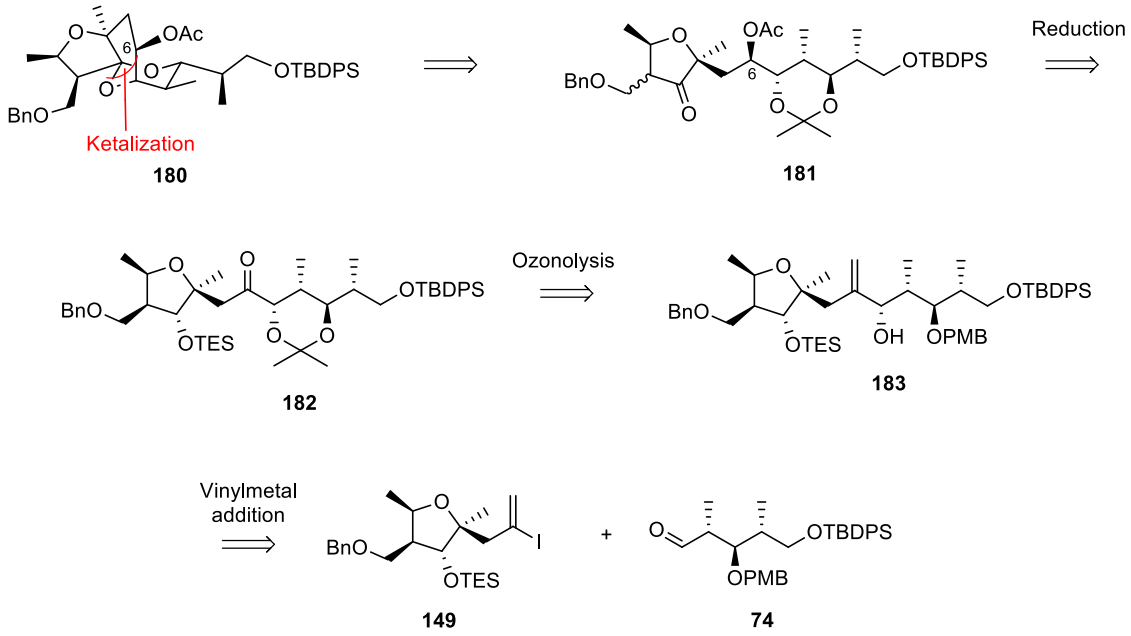
Also knowing that *Ireland* and coworkers[63] (Scheme 93) were able to perform the cyclization in their attempted synthesis of Bu-2313 with **178**, it became obvious, that the cyclization would have to be performed with a protected hydroxyl group at C6 instead of a methylene group.




**Scheme 93:** a) 10% HCl, THF, 36% **179** + 55% hemi-ketals.

## 3.2.21. Fourth Revised Retrosynthesis of Bu-2313 B (Nocamycin I) and Nocamycin II – Cyclization with Protected Hydroxyl Group

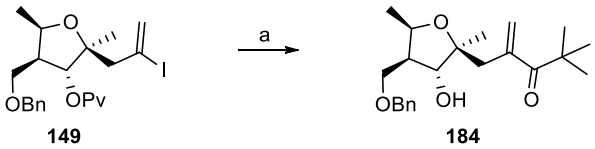
Based on the conclusions derived in Chapter 3.2.20, the new cyclization strategy called for the installation of an appropriately configured protected hydroxy group at C6 of the nocamycin scaffold, leading to synthon **181** as pro-precursor for the cyclization reaction. The configuration at C6 was required to be R, corresponding to the configuration of this center in nocamycin II (*vide supra*) (Scheme 94). In order to install the required stereoinformation at C6, a chelation controlled reduction of ketone **182** with $LiEt_3BH$ (aka "super hydride") was planned and the ketone **182** was envisioned to be obtained by ozonolysis of alkene **183**. For the fragment assembly, an alternative to the slow and unselective *NHK* reaction was searched for and the addition of lithiated vinyl iodide **149** to aldehyde **74** was to be investigated in this context. In particular, after having observed the promising selectivity in the 1,3-dithiane addition experiments to aldehyde **74** (Chapter 3.2.13), it was hoped that this would allow to circumvent the detour of the additional oxidation and 1,3-*anti* reduction steps.




**Scheme 94:** Revised retrosynthetic analysis of Bu-2313 B (Nocamycin I) (**2**) including the new cyclization strategy from a precursor bearing a protected hydroxy group at C6 instead of a methylene group.

## 3.2.22. Synthesis of Vinyl Iodide Fragment 149

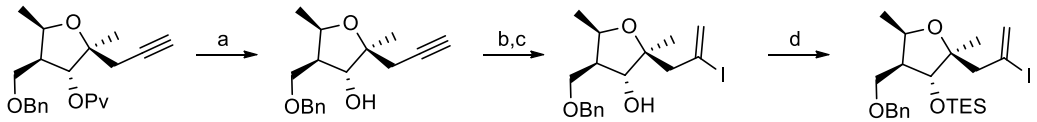
For the lithium-iodine exchange, the pivaloyl protecting group had to be replaced, since in this case this group is not suited for *n*BuLi-metalation chemistry due to side product (**184**) formation. Therefore, a synthesis for a slightly modified variant of vinyl iodide **149** (i. e. **185**) was established.




**149** **184**

**Scheme 95:** a) *n*BuLi, THF, -78°C.

Treatment of pivaloate ester **154** with *n*BuLi gave the alcohol **155** in excellent yield, which also shows that it would be possible to obtain alcohol **155** as the only product during the *Corey-Fuchs* reaction by adding additional *n*BuLi to the reaction (see Chapter 3.2.18) (Scheme 96). Hydrosilylation of **155** under *Trost*[165] conditions at this point followed a different iododesilylation protocol that involved the use silver carbonate and *N*-iodo succinimide in hexafluoroisopropanol[172] and that yielded the desired vinyl iodide **157** in excellent 80% yield in a fast and clean transformation. This more recent protocol is clearly superior over the previously used method (see Chapter 3.2.18).

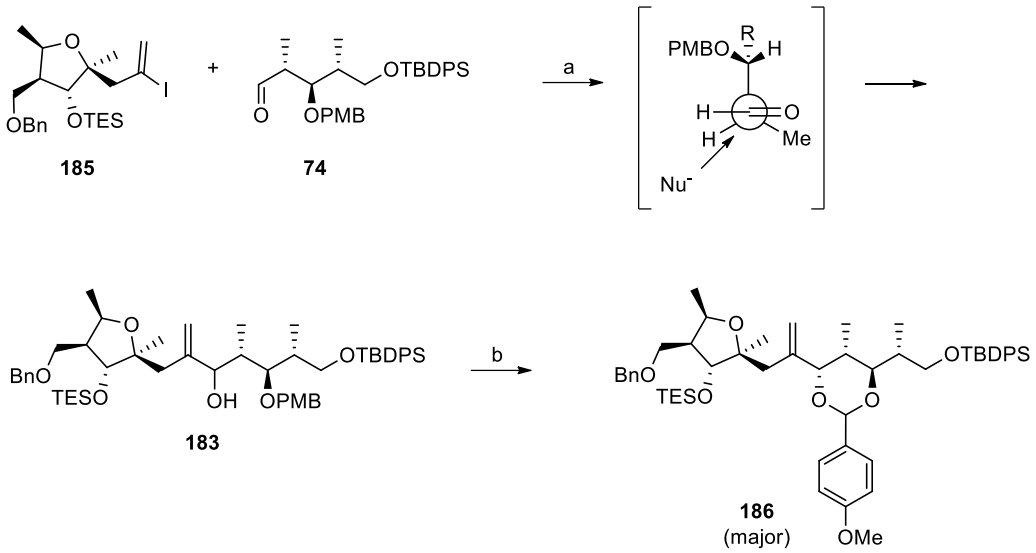



**154** **155** **157** **185**

**Scheme 96:** a) *n*BuLi, THF, -78°C, 99%; b) $Et_3SiH$, $[CpRu(NCCH_3)_3]PF_6$, $CH_2Cl_2$, 0°C; c) $Ag_2CO_3$, NIS, $(CF_3)_2CHOH$, 0°C, 80% over two steps; d) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 97%.

## 3.2.23. Fragment Assembly via Vinyllithium Addition

Already the first attempt of the vinyllithium addition to aldehyde **74** using vinyl iodide **185** and *n*BuLi showed promising results (Scheme 97). The yield of the reaction was 48 % and the ratio of the isolated (inseparable) isomers of allylic alcohol **183** was about 4:1; unfortunately, the product was slightly contaminated with an inseparable side product. According to the *Felkin-Anh* model, which has already discussed in Chapter 3.2.13, the desired product, with the free and the PMB-protected hydroxy groups in a 1,3-*anti* configuration, should again be formed preferentially. In order to assess the configuration of the major isomer the mixture of allylic alcohols **183** was transformed into the mixture of the corresponding PMP-acetals **186** by treatment with DDQ in 45 % yield. Pleasingly, the NMR data showed that the major isomer had the desired acetal with 1,3-*anti* configuration.



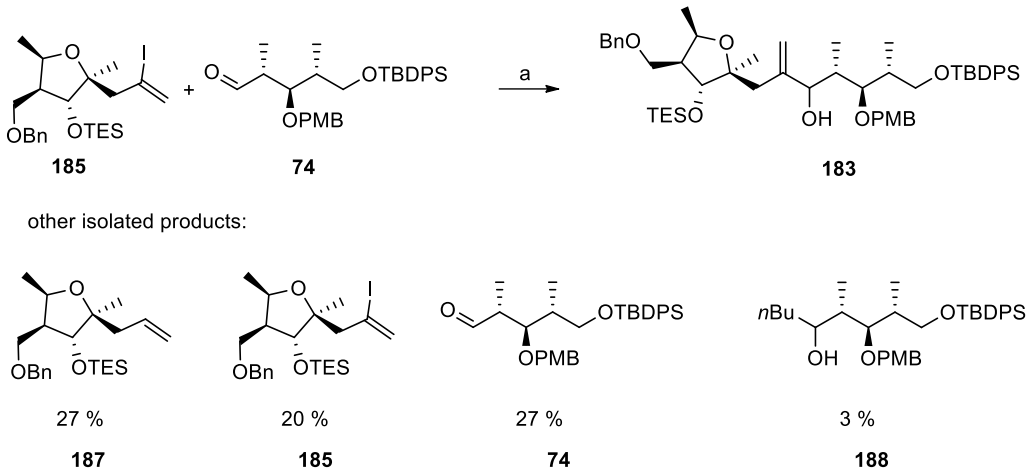

**Scheme 97:** a) *n*BuLi, $Et_2O$, -78°C, then **74**, 48% (slightly impure), *dr* = 4:1; b) DDQ, 4Å mol. sieves, $CH_2Cl_2$, 0°C, 45%.

After confirmation of the configuration of the major product, the vinyllithium addition to the aldehyde **74** was analyzed further. The characterization of all the products isolated from the reaction (**183, 185**, **74**, **188** and **187** (Scheme 98) led to the following conclusions:

- The addition product **183** was only partially separable from the *n*BuLi addition product **188**.

- The re-isolation of the aldehyde **74** and the isolation of alkene **187** indicated that full conversion was not reached even for the part of the vinyl iodide that was transformed to the vinyllithium species. Furthermore, the aldehyde **74** was isolated as pure isomer, which excludes the possible α-deprotonation by the vinyllithium intermediate.

- The re-isolation of vinyliodide **185** and the isolation of *n*BuLi addition product **188** showed that the lithium-iodine exchange was incomplete at the time of addition of aldehyde **74**.




**Scheme 98:** a) *n*BuLi, $Et_2O$, -78°C, then **74**, 45% + 3.5% **188**, *dr* = 4:1.

To address the problem of incomplete lithium-iodine exchange, *n*BuLi was added to vinyl iodide **185** under different conditions and the reaction was monitored by TLC (Table 10). When the amount of added *n*BuLi was doubled to 2 equiv., still no full lithium-iodine exchange was observed. Performing the metalation at higher temperatures then -78 °C led to slow decomposition and the same behavior was observed when the reaction was stirred for a longer period at -78°C.

**Table 10:** Metalation experiments on **185**.

| Entry | *n*BuLi | Temp. [°C] | Time [min] | Comments |
|---|---|---|---|---|
| 1 | 1.05 equiv. | -78 | 30 | Incomplete exchange |
| 2 | 2.00 equiv. | -78 | 30 | Incomplete exchange |
| 3 | 1.05 equiv. | -35 | 30 | Partial decomposition |
| 4 | 1.05 equiv. | -78 | 60 | Traces of decomposed material |

The reasons for incomplete lithium-iodine exchange, after this limited screening, remain unclear. The results could hint at a stability problem with the vinyl iodide **185** during metalation. For a better understanding of the metalation reaction, more experiments would have to be carried out, including, for example, the use of *s*BuLi or *t*BuLi instead of *n*BuLi or other solvents, such as a mixture of $Et_2O$ and pentane or $Et_2O$ in combination with HMPA.

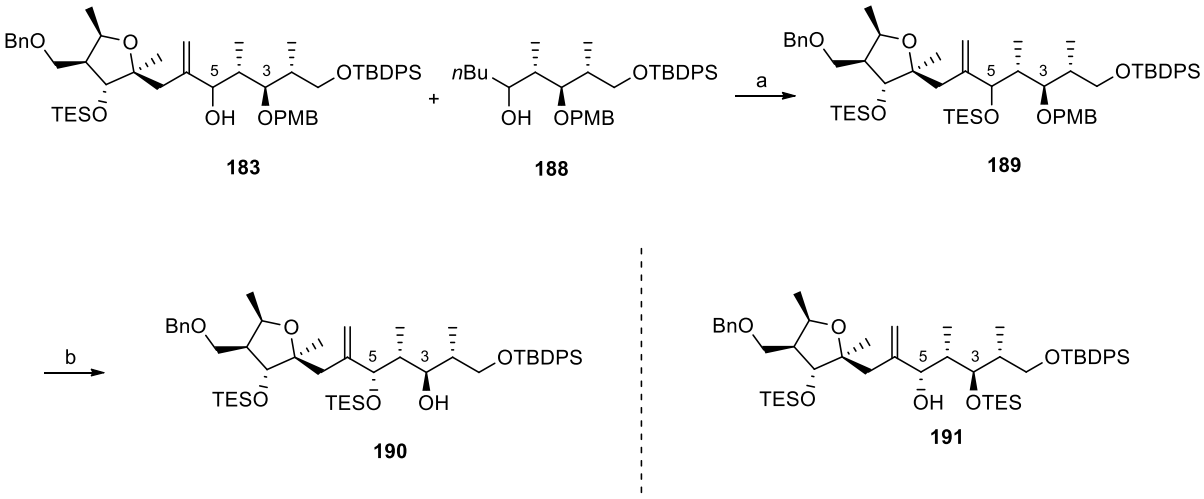
To address the problem of incomplete conversion, three additional addition experiments were performed. In the first experiment, the reaction time was extended from 1 h to 3 h, without significant changes in conversion and yield. In the second experiment, the solvent was changed from ether to THF. Unfortunately, the conversion and yield of the reaction was slightly lower and the *dr* of the reaction dropped from 4:1 to 2:1. In the third experiment, a 2.8 fold excess of vinyl iodide **185** was used in order to reach higher conversion with respect to the aldehyde **74**, but, unfortunately, also in this case no significant changes were observed.

At this point no further optimization work was performed.

## 3.2.24. Installation of the New Stereocenter and Synthesis of the Cyclization Precursor 181

The new strategy was only poorly compatible with the originally envisioned PMP-acetal formation, due to the competitive oxidation of the allylic hydroxy group with DDQ and in light of the difficulties encountered when trying to cleave the PMP-acetal in previously synthesized structures (Chapter 3.2.11). As a consequence it was now planned to install a less stable 1,3-dimethylmethylacetal that could be cleaved more readily, in order to reveal the cyclization precursor.

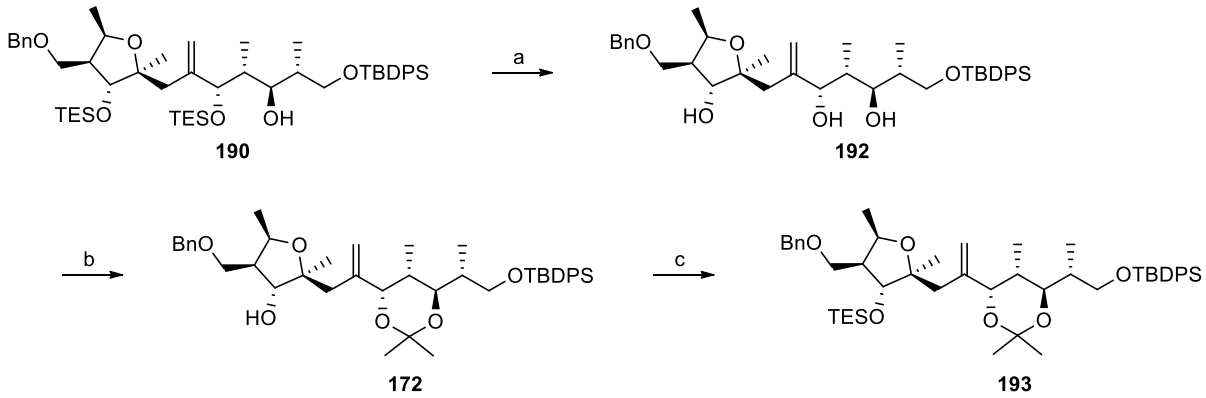
Based on these considerations the allylic hydroxy group in **183** was TES-protected, which allowed the complete separation of the side product **188** as its silyl ether (Scheme 99). The following PMB cleavage with DDQ and pH 7 buffer yielded the alcohol **190** in 86% yield; in addition, we were delighted to find out that the C5 isomers arising from the vinyllithium addition step were separable at this stage. It has to be pointed out that when the PMB cleavage was performed without pH 7 buffer, an almost complete migration of the TES group to the hydroxy group at C3 was observed, resulting in the isolation of **191** in 68% yield as an inseparable mixture of isomers.




**Scheme 99:** a) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 90%; DDQ, pH 7 buffer, $CH_2Cl_2$, 0°C, 86% (66% desired isomer and 20% undesired isomer).

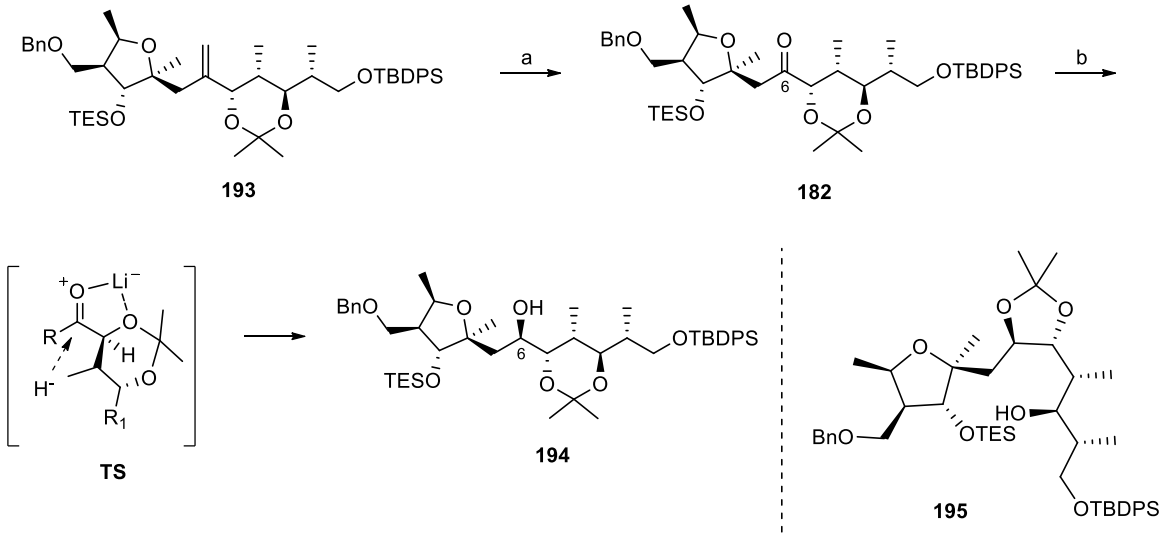
The two TES protecting groups were then both cleaved using PPTS and the resulting free triol was converted into acetonide **172** using CSA and 2,2-dimethoxypropane (Scheme 100). In addition to the previous analysis, the *Rychnovsky* NMR data analysis confirmed that the acetonide **172** had the 1,3-*anti* configuration as was required for elaboration into the natural product. TES protection of the hydroxy group on the tetrahydrofuran ring under standard conditions gave the silyl ether **193** in 93 % yield. It should be noted here that compounds **190** and **172** showed only limited stability. Thus, alcohol **190** underwent TES group migration if stored at room temperature, especially if traces of acid / *Lewis* acid were present. Under the

same conditions, unknown degradation products were formed from alcohol **172**. No stability issues were found for the free triol **192** or the fully protected intermediate **193**.



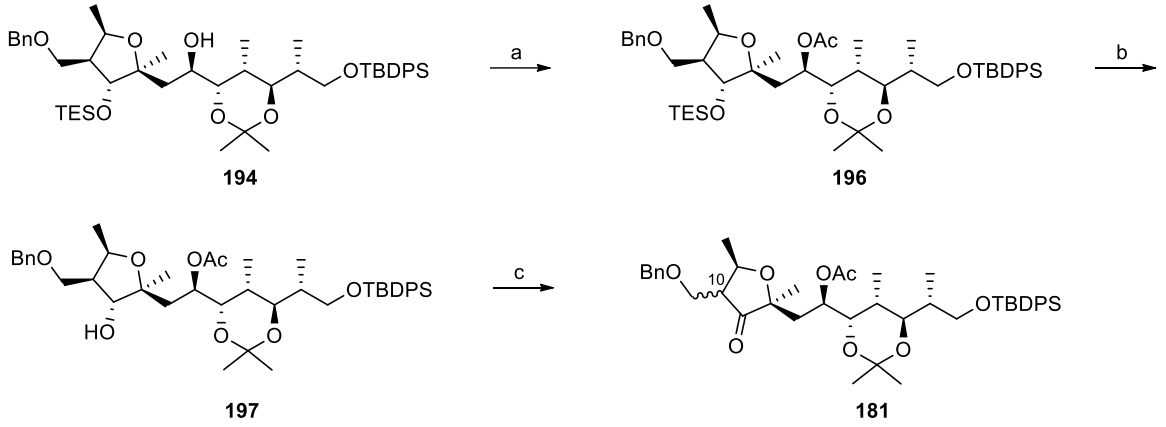

**Scheme 100:** PPTS, MeOH/THF (2:1), rt, 96%; b) CSA, 2,2-dimethoxypropane, rt, 96%; c) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 93%.

Ozonolysis of alkene **193** followed by reductive workup with triphenylphosphine, furnished ketone **182** in high yield (94%) (Scheme 101). Likewise, reduction of the keto group in **182** with $LiEt_3BH$ (super hydride)[173,174] yielded alcohol **194** in an excellent yield of 95% and with a *dr* > 25:1. The configuration of the new stereocenter was not determined, but according to literature[173,174] the desired isomer **194** should have been formed selectively. This can be explained by the *Cram*-chelate[113,173] transition state **TS** which has the lithium ion chelated between the oxygen atoms to form a 5-membered ring and the hydride attacking from the sterically less hindered face (in this case from the back of the paper plane). It was observed that a careful removal of the boron species was necessary during workup of the reduction in order to avoid side product formation by means of acetal **195**. As in previous cases, the alcohol **194** was prone to protecting group migration if traces of acid / *Lewis* acid were present. For future reactions the possibility to quench with $H_2O_2$[175], to remove all boron species, should be considered.




**Scheme 101:** a) $O_3$, $CH_2Cl_2$, -78°C, then $PPh_3$, -78°C to rt, 94%; b) $LiEt_3BH$, $CH_2Cl_2$, -78°C, 95%. **TS**: Proposed *Cram*-chelate transition state of the reduction. The attack occurs from the less hindered face, in this case from behind the paper plane.

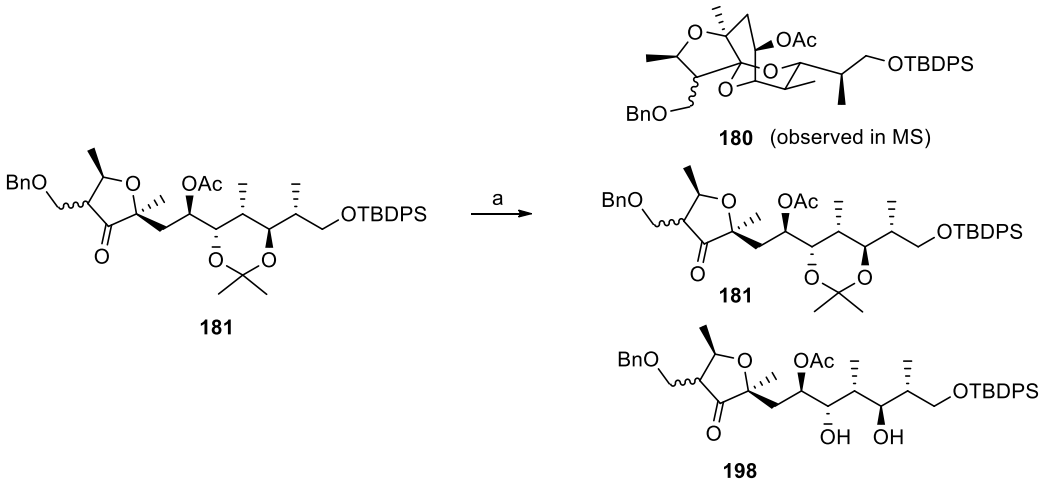
The alcohol **194** was then acetylated and the TES protecting group on **196** was cleaved with PPTS. Unfortunately, partial cleavage of the acetonide could not be prevented during TES removal (Scheme 102). *Swern* oxidation of the alcohol **197** gave the desired ketone **181** in 90% yield as a 1:1.6 diastereomeric mixture at C10. Again, like in previous cases, intermediates bearing a free hydroxyl group (**194** and **197**) had some stability issues and were therefore converted to the fully protected or oxidized species as quickly as possible.




**Scheme 102:** a) $Ac_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, 0°C to rt, 94%; b) PPTS, MeOH/THF (2:1), rt, 70%; c) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, -78°C, 90%,.

## 3.2.25. Applying the New Cyclization Strategy

With ketone **181** in hand, the first cyclization experiments were performed by treatment with 10 % HCl (aqu.) in THF. Under these conditions, according to TLC-MS formation of the diol **198** (assumed) and the desired product **180** was observed already after 10 min (Scheme 103). Unfortunately, the reaction did not seem to proceed further towards the desired product **180** and after 1.5 h of stirring, traces of the TBDPS deprotected product were observed. Therefore the reaction was quenched at that point; unfortunately, based on mass spectrometry, in the crude product mixture obtained after work-up only diol **198** (assumed) and starting material **181**, without any traces of the desired cyclized product **180** were observed.




**Scheme 103:** a) 10% HCl/THF, rt, mixture of products.

The crude mixture was then treated with PPTS in MeOH together with $(EtO)_3CH$ as dehydrating agent[171] (Scheme 104). To our satisfaction, the desired product **180** was now isolated in 90 % yield as a 1:1 mixture of isomers on C10. Strangely, when the isomers were tried to be separated by means of a second chromatography, 72 % of the desired product **180** was isolated, but this time the ratio of the isomers was about 1:6 and the rest of the material was lost.


**Scheme 104:** PPTS, MeOH/$(EtO)_3CH$ (10:1), rt, 90% (after first purification), *dr* = 1:1, 72% (after second purification, *dr* = 6:1.

After NOE NMR analysis it was possible to identify the major isomer as the product (10*R*)-isomer **180a** with the undesired stereochemistry at C10 (Figure 30). This was concluded from the NOE signal between the hydrogen on C10 and the methyl group at C11 (marked in blue), which was present in the major isomer **180a**, but was not detectable for the minor (10*S*)-isomer **180b**. This result was unexpected, since *Ireland* and coworkers[63] reported the isolation of the desired isomer upon cyclization (see section 1.2.2.1), although not with the same system. Overall, however, the stereochemistry at C10 is of no major concern for **180**, since the configuration can still change upon oxidation of the side chain to the methyl ester. Much more importantly at this point, it was shown that the tricyclic core structure of **180** had the same configuration as found in the natural product, which ultimately confirmed that the reduction of ketone **182** with "super hydride" delivered the desired isomer on C6 of alcohol **194**. This was concluded from the NOE signals between the hydrogens on C3 and C6 and the methyl group at C8 (marked in red) which were on the same face of the molecule.

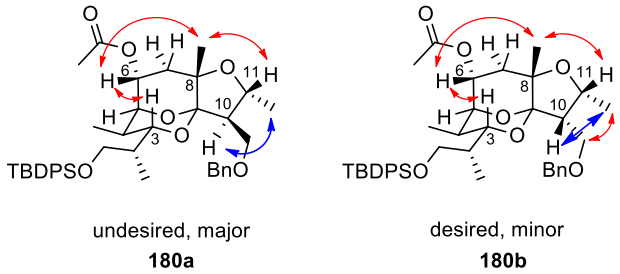
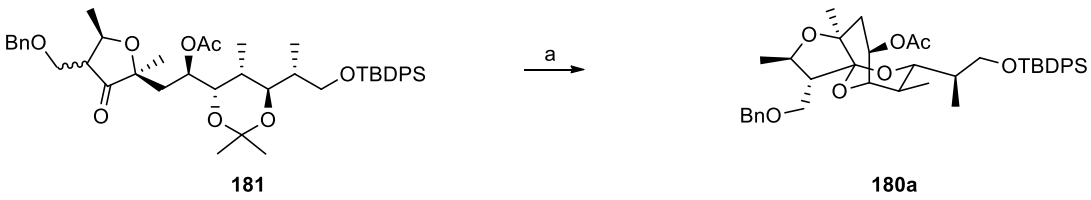



**Figure 30:** NOE NMR interpretation of **180**.

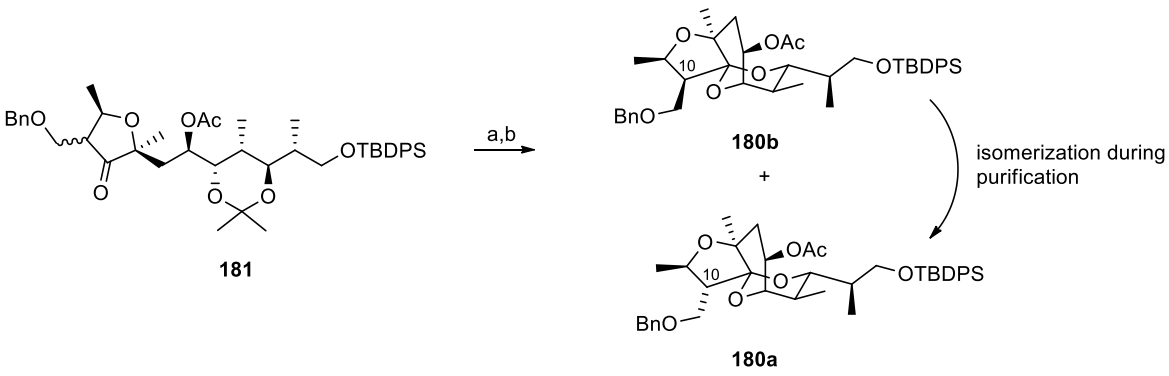
In order to probe the scope of the cyclization reaction, it was also investigated if cyclization could be induced by treatment of **181** with PPTS in MeOH/$(EtO)_3CH$ at room temperature. This proved indeed to be possible and the desired product was obtained in 59 % yield (*dr* = 4:1, (**180a** : **180b**), but the reaction proceeded very slowly and full conversion was not achieved even after a very long reaction period. Therefore, the reaction was quenched although starting material **181** and intermediate products **198** were still visible.




**Scheme 105:** PPTS, MeOH/$(EtO)_3CH$ (10:1), rt, 59%, *dr* = 4:1.

In a final attempt (in the context of this PhD thesis), the first method by using HCl in THF followed by treatment with PPTS in MeOH / $(EtO)_3CH$ was used again. After the first part the reaction showed identical behavior as in the first trial, but unfortunately after treatment with PPTS at room temperature the reaction could not be pushed towards full

conversion. Only after heating to 60 °C for 5 h, full conversion was observed. The product **180a** was isolated in 42 % (pure isomer) and 32 % (1: 1.9 mixture (**180a** : **180b**) yield. Again, after second purification the ratio in the mixture changed and additional 15 % of isomerically pure **180a** material was obtained and 12 % of a 1.8:1 (**180a** : **180b**) mixture. It seemed like the desired (10*S*)-isomer **180b** is not very stable and can isomerize partially to the undesired (10*R*)-isomer **180a**.




**Scheme 106:** a) 10% HCl/THF, rt; b) PPTS, MeOH/$(EtO)_3CH$ (10:1), 60°C, 74%, 42% pure isomer, 32%, 1:1.9 mixture.

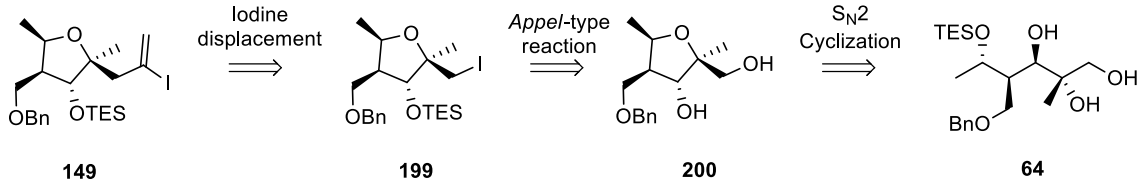
At this stage the experimental work for this PhD thesis was stopped. For future directions on the completion of the total synthesis of Bu-2313 B (nocamycin I/**2**) see chapter 4 "Conclusions and Outlook".

## 3.2.26. Other Strategies towards the Synthesis of Bu-2313 B (Nocamycin I)

### 3.2.26.1. Iodine Displacement Strategy towards Vinyl Iodide Fragment 185

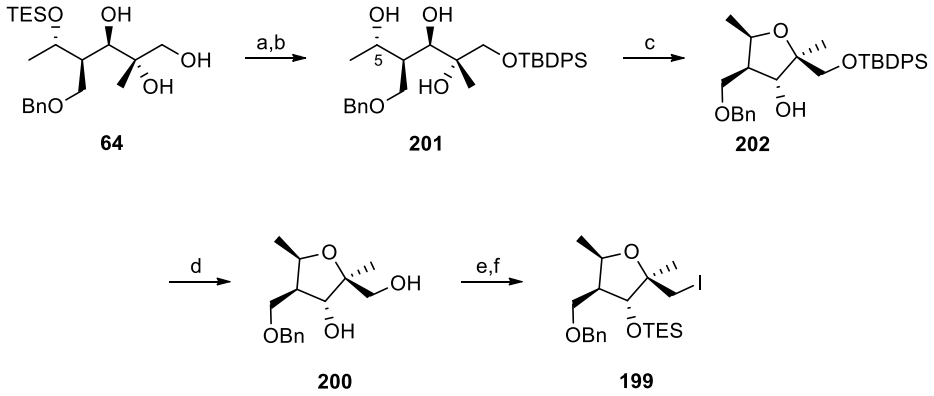
Inspired by the epoxide opening strategy (Chapter 3.2.1) we embarked on an alternative synthesis of vinyl iodide fragment **149** that would involve iodide displacement with **199** (Scheme 62). Notwithstanding the difficulties that had been encountered with the epoxide opening strategy and also being cognizant of the fact that an $S_N2$ displacement on the sterically demanding iodide **199** by a vinylmetal species would not be trivial, such an approach appeared to be sufficiently attractive to deserve exploration.

A displacement reaction of iodide **199** with either a vinyl or alkynyl nucleophile was planned to give either direct access to vinyl iodide **149** or to one of its precursor. Iodide **199** was to be obtained by an *Appel*-type[176] reaction with primary alcohol **200**, which was planned to be accessed by $S_N2$ cyclization of triol **64**, for which a synthesis had already been established (see Chapter 3.2.2).




**Scheme 107:** Retrosynthetic analysis of the iodine displacement approach.

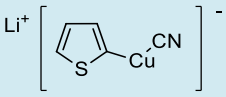
Free triol **64**, was converted into TBDPS-ether **201** by reaction with TBDPSCl followed by TES removal with PPTS in quantitative yield. Free triol **201** was then cyclized to tetrahydrofuran **202** via $S_N2$ displacement of the mesylated secondary hydroxy group at C5 by the tertiary hydroxyl group in 82% yield. Removal of the TBDPS group using HF buffered in pyridine followed by iodide formation under *Appel*-type[176] conditions and subsequent TES protection of the free secondary hydroxy group gave the desired iodide **199** in 70 % yield over three steps.




**Scheme 108:** a) TBDPSCl, ImH, DMAP, $CH_2Cl_2$, rt, quant.; b) PPTS, MeOH/THF (2:1), rt, quant.; c) MsCl, $NEt_3$, $CH_2Cl_2$, -40°C then MeOH, rt, 82%; d) HF•pyr, THF, 0°C, 99%; e), $I_2$, $PPh_3$, ImH, THF, reflux, 99%; f) TESCl, ImH, DMAP, $CH_2Cl_2$, rt, 72%.

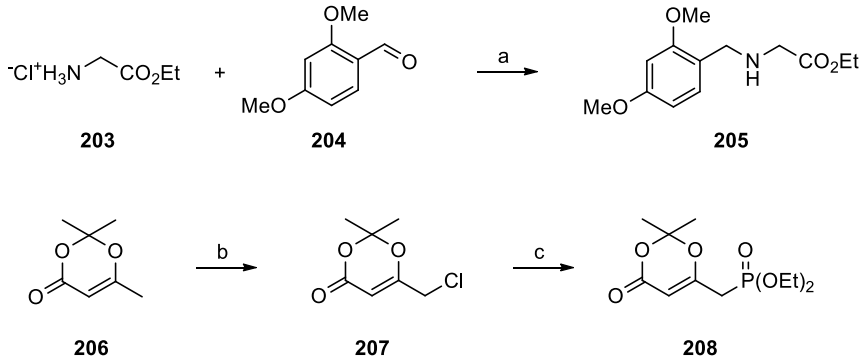
A number of carbon nucleophiles were evaluated for their ability of affect iodide displacement from **199** and the results of these experiments are summarized in Table 11. Unfortunately, no iodide displacement was achieved for any of the conditions investigated, which probably (at least in part) reflects the steric crowding around the iodine-bearing carbon. At this stage, the iodine displacement strategy was aborted.

**Table 11:** Iodine displacement attempts

| Entry | Nucleophile | Activation | Additive | Conditions | Result |
|---|---|---|---|---|---|
| **1** |  | *n*BuLi | HMPA | THF, -78 °C to rt | No conversion |
| **2** |  | *t*BuLi | HMPA | $Et_2O$, -78 °C to 0 °C | No conversion |
| **3** |  | *t*BuLi |  | $Et_2O$, -78 °C to 0 °C | No conversion |
| **4** |  | Mg | CuI | THF, -78 °C to 0 °C | No conversion |
| **5** |  | Zn/Cu | $Pd(PPh_3)_4$ | Toluene, DMA 110°C | No conversion |

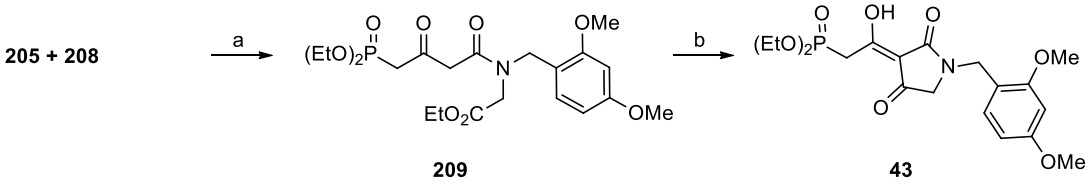
## 3.2.27. Tetramic Acid Building Block 43

Phosphonate **43**, which incorporates the tetramic acid substructure of Bu-2113 B (**2**), was synthesized according to the procedure reported by *Boeckman*[67] and coworkers (Scheme 109). Dimethoxybenzyl (DMB) protected glycine ethyl ester (**205**) was prepared from glycine ethyl ester **203** and 2,4-dimethoxybenzaldehyde (**204**) by reductive amination in 89 % yield. Dioxolenone phosphonate **208** was obtained by chlorination of acetylketene equivalent **206** followed by a $S_N2$ displacement of chloride anion with diethylphosphite.




**Scheme 109:** a) $NaB(OAc)_3H$, $CH_2Cl_2$, rt, 89%; b) LDA, **206**, THF, -78°C then hexachloroethane, -52°C to -20°C, 50%; c) diethylphosphite, *t*BuOK, DMF, 0°C then **207**, DMF, 0°C, 56%.

Treatment of dioxolenone phosphonate **208** with **205** in xylene at 150°C furnished β-keto-amide **209**, which upon treatment with potassium *tert*-butoxide provided the tetramic acid fragment **43** via *Dieckmann* condensation (Scheme 110).[3]



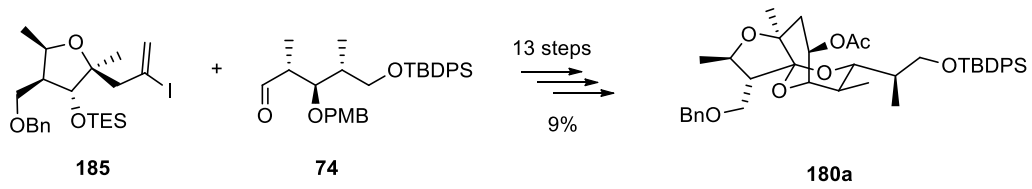

**Scheme 110:** a) **205**, **208**, xylene, 150°C, 93%; b) *t*BuOK, THF, rt, 79%.

[3] Carried out by Peter Müller in the course of a seven week undergraduate project.

# 4. Conclusions and Outlook

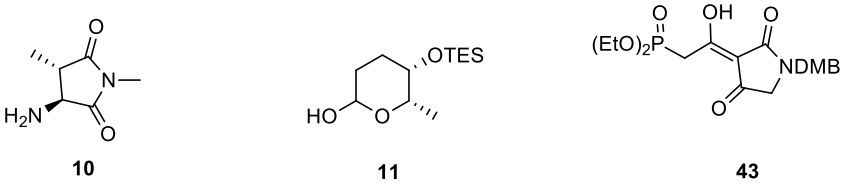
The synthetic studies performed in this PhD thesis provide robust access to the tricyclic ketal **180a**, which represents a highly advanced intermediate for the total synthesis of the complex natural dieonyltetramic acids Bu-2313 B (Nocamycin I) and Nocamycin II. Key intermediates en route to **180a** were vinyl iodide **149** and aldehyde **74** which were connected by means of iodine-lithium exchange in **185** and subsequent addition of the ensuing vinyllithium species to **74**.

Vinyl iodide **185** was elaborated from commercially available (*S*)-methyl-3-hydroxybutyrate (**51**) in 20 linear steps and 4.5% overall yield. Two independent routes to aldehyde **74** were developed that both departed from (*R*)-*Roche* ester (**109**) and yielded **74** in 12 steps and 38% yield and 6 steps and 29% yield, respectively.




**Scheme 111:** Synthesis summary of **180a**.

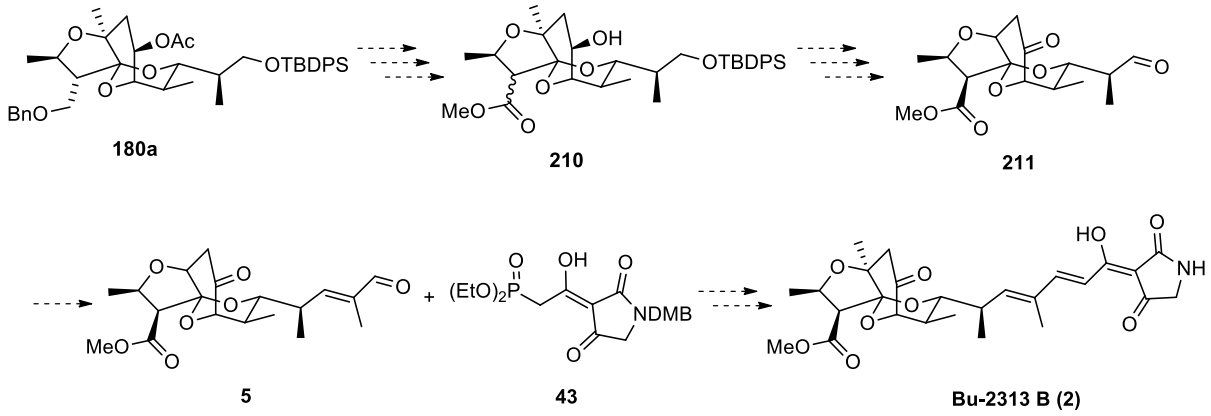
In addition, stereoselective syntheses were elaborated for succinimide **10** and protected *L*-rhodinose **11**, while phosphonate **43** was obtained according to literature procedures. These compounds represent enabling building blocks for the synthesis of Bu-2313 B (**2**) and the Bu-2313-streptolydigin hybrid (**4**).




**Scheme 112:** Overview of synthesized fragments.

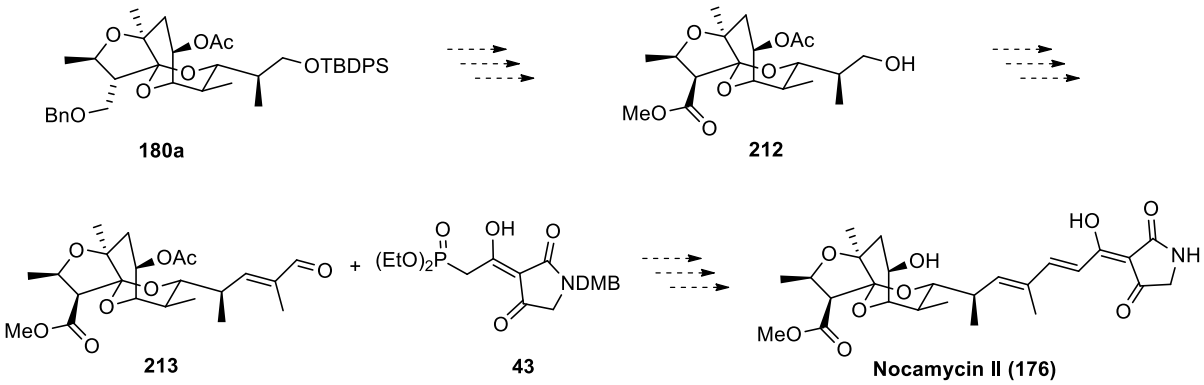
For time reasons the steps that would lead from **180a** to the natural products Bu-2313 B (Nocamycin I / **2**) or Nocamycin II (**176**) or the targeted Bu-2313-streptolidigin hybrid (**4**) could not be investigated. As outlined in Scheme 41 (Section 3.2.1), this would first require the elaboration of **180** into aldehyde **5** and the individual steps that would be involved in this process are depicted in Scheme 113. Thus, benzyl ether cleavage on **180** via catalytic hydrogenation should yield the primary alcohol, which would be oxidized to the

corresponding carboxylic acid by means of *Swern* and *Pinnick*[177,178] oxidations. Synthesis of methyl ester **210** is envisioned to be accomplished with (trimethylsilyl)diazomethane followed by cleavage of the acetate moiety with methanol and potassium carbonate. It is believed that the stereocenter in α-position of the methyl ester should epimerize at this stage, thus leading to the configuration which is present in the natural product Bu-2313 B (**2**), although epimerization may also occur earlier. Deprotection of **210** followed by oxidation and two-carbon extension would then provide the requisite aldehyde **5**. To access the natural product Bu-2313 B (Nocamycin I / **2**) the fragment assembly of **5** with phosphonate **43** should be first investigated under the conditions established by *Roush* and co-workers[179]. Finally, removal of the dimethoxybenzyl (DMB) group, for example with TFA should provide the desired natural product Bu-2313 B (Nocamycin I / **2**).




**Scheme 113:** Projected synthesis of Bu-2313 B (**2**) from tricyclic ketal **180**.

**180a** could also serve as a precursor for the natural product nocamycin II (cf. section 3.2.20 / **176**) (Scheme 114). Initially, this would involve benzyl group cleavage and conversion of the primary alcohol to the corresponding methyl ester followed by TBDPS cleavage, oxidation of the ensuing primary alcohol **212** and subsequent two-carbon extension with 2-(triphenylphosphoranylidene)propionaldehyde to give aldehyde **213**. After fragment assembly with phosphonate **43** cleavage of the acetate ester followed by TFA treatment to remove the dimethoxybenzyl (DMB) group will furnish Nocamycin II (**176**).

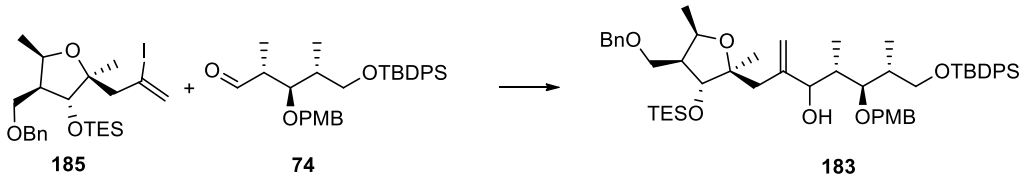



**Scheme 114:** Projected synthesis of Nocamycin II (**176**) from tricyclic ketal **180**.

## Optimization Potential in the Fragment Assembly Step

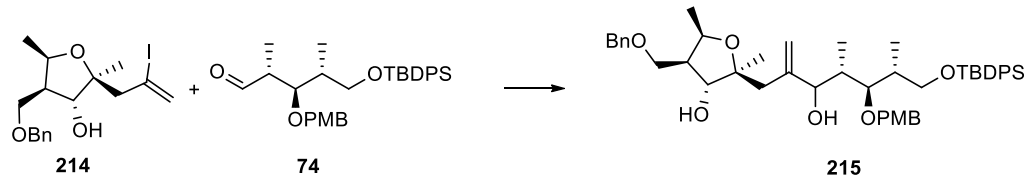
As discussed in section 3.2.23, the fragment assembly of vinyl iodide **185** with aldehyde **74** by means of vinyllithium addition left some room for improvement (Scheme 115). Based on the observations described in 3.1.5.2, improvements in the lithium-iodine exchange step on vinyl iodide **185** in our view are key to increasing the yield of the reaction. Therefore, *t*BuLi should be investigated as a lithium base for the lithium-iodine exchange instead of *n*BuLi. Should this not lead to an improvement in the yield of **183**, deuterium quench experiments should be performed, in order to determine if deuterium is incorporated elsewhere in the starting material. In particular, any decomposition products formed after longer reaction time or at elevated temperatures (if present) would be of interest.

In terms of selectivity, it is assumed that the vinyllithium addition could be improved by addition of HMPA as co-solvent. HMPA is capable to form cation-ligand complexes[180] and therefore prevents lithium cations from chelation with the substrate. The latter is expected to leads to product **183** with the undesired stereochemistry.




**Scheme 115:** Addition of vinyl iodide fragment **185** to aldehyde **74**.

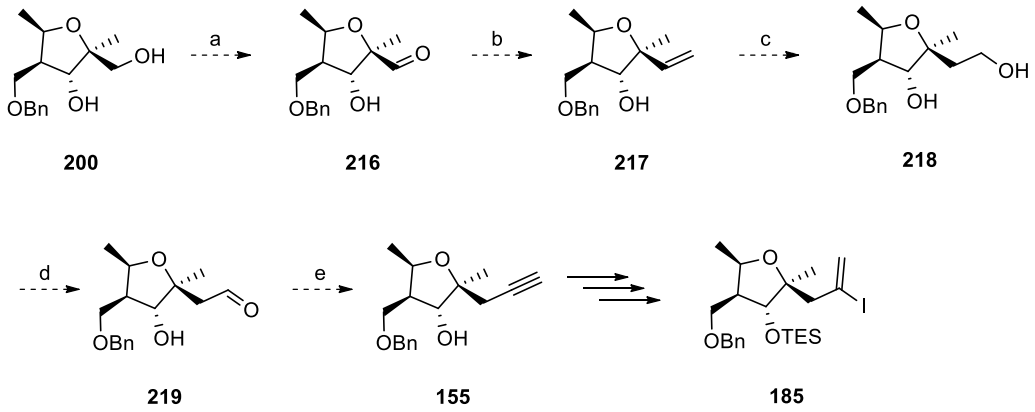
In case that the issue of incomplete lithium-iodine exchange on vinyl iodide **185** could not be resolved, the use of the dianion derived from vinyl iodide **214** should be explored in the addition to aldehyde **74** (Scheme 116).




**Scheme 116:** Alternative strategy for the vinyl lithium addition to aldehyde **74** with a free hydroxy group on vinyl iodide **214**.

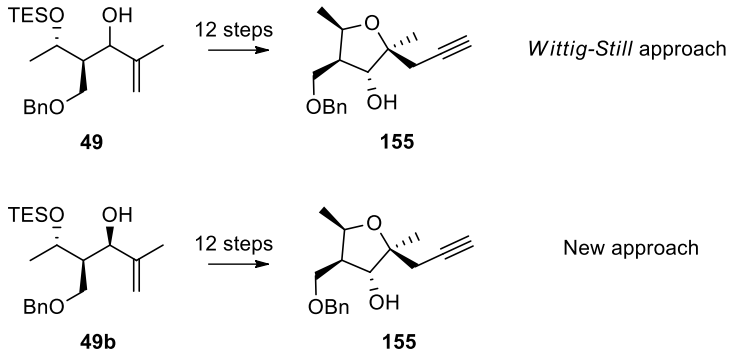
## Alternative Synthesis of Vinyl Iodide Fragment 185

Inspired by the successful synthesis of diol **200** as part of the iodide displacement approach described in section 3.2.26.1 we have conceived an alternative strategy towards the vinyl iodide **185** (Scheme 117). Thus **200** would be converted into aldehyde **216** by TEMPO oxidation. A *Wittig*[181] reaction followed by hydroboration of alkene **217** is then envisioned to lead to diol **218**. After another TEMPO oxidation, the aldehyde **219** would be converted to alkyne **155** by means of a *Corey-Fuchs*[161] reaction. Alkyne **155** intercepts the established synthesis of **185** (cf. section 3.2.22, Scheme 96).




**Scheme 117:** a) cat. TEMPO, $PhI(OAc)_2$; b) methyltriphenylphosphoniumbromide; c) $BH_3$•THF then $H_2O_2$/NaOH; d) cat. TEMPO, $PhI(OAc)_2$; e) $CBr_4$, $PPh_3$ then *n*BuLi.

While the new strategy would encompass the same number of steps as the one depicted in Scheme 118 (from alcohol **49**) it would benefit from a higher diastereoselectivity for the installation of the tertiary hydroxyl group and would not suffer from the moderate yield of the *Wittig-Still* rearrangement (64%) (Scheme 118). At the same time, however, the new approach would have to start from isomerically pure allylic alcohol **49b** which would result in a loss of material.




**Scheme 118:** Comparison of the two strategies for the synthesis of vinyl iodide **185**.

# 5. Experimental Section

## 5.1. General Methods

All non-aqueous reactions were performed under an argon atmosphere using flame-dried glassware and standard syringe/septa techniques.

$CH_2Cl_2$ (DCM), THF and $Et_2O$ used for reactions were distilled under argon prior to use (DCM from $CaH_2$, THF and $Et_2O$ from Na/benzophenone). All other absolute solvents were purchased as anhydrous grade from Fluka (puriss.; dried over molecular sieves; $H_2O$ <0.005%) and used without further purification unless otherwise stated. Solvents for extractions, flash column chromatography (FC) and thin layer chromatography (TLC) were purchased as commercial grade and distilled prior to use. All other commercially available reagents were used without further purification unless otherwise stated. Reactions were magnetically stirred and monitored by TLC performed on Merck TLC aluminum sheets (silica gel 60 F254). Spots were visualized with UV light (λ = 254 nm) or through staining with $Ce_2(SO_4)_3$/phosphomolybdic acid/$H_2SO_4$ (CPS), vanillin/$H_2SO_4$/EtOH or $KMnO_4/K_2CO_3$. Chromatographic purification of products (FC) was performed using Fluka silica gel 60 for preparative column chromatography (particle size 40-63 μm).

**Melting points** were obtained in open capillary tubes using a Büchi melting point apparatus B-540 and are uncorrected.

**$^1$H- and $^{13}$C-NMR spectra** were recorded in $CDCl_3$, $CD_3OD$ or $C_6D_6$ on a Bruker AV-400 400 MHz or on a Bruker AV-500 500 MHz spectrometer at room temperature. Chemical shifts (δ) are reported in ppm and are referenced to chloroform (δ 7.26 ppm for $^1$H, δ 77.16 ppm for $^{13}$C), MeOH (δ 3.31 ppm for $^1$H, δ 49.00 ppm for $^{13}$C) or benzene (δ 7.16 ppm for $^1$H, δ 128.06 ppm for $^{13}$C). All $^{13}$C-NMR spectra were measured with complete proton decoupling. Data for NMR spectra are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, *J* = coupling constant in Hz.

**Infrared spectra** (IR) were recorded on a Jasco FT/IR-6200 instrument. Resonance frequencies are given as wavenumbers in $cm^{-1}$.

**Optical rotations** were measured on a Jasco P-1020 polarimeter at the sodium D line with a 10 or 100 mm path length cell and are reported as follows: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: (concentration (g/100 mL), and solvent).

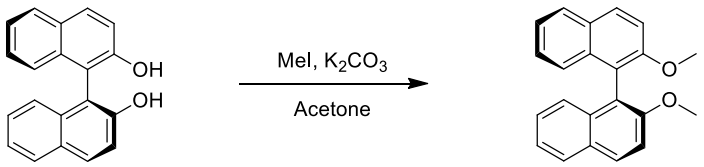
**High resolution mass spectra** (HRMS) were recorded on a Bruker maXis (ESI) or on a Micromass (Waters) AutoSpec Ultima spectrometer (EI), respectively, by the ETH Zürich MS

service (Louis Bertschi, Rolf Häfliger and Oswald Greter under the direction of Dr. Xiangyang Zhang).

For analytical **HPLC** the following combination of devices by VWR HITACHI was used: column oven L-2350, PDA detector L-2455, autosampler L-2200, pump L-2130. A reversed phase Waters Symmetry C18 column (3.5 μm, 4.6x100 mm) or chiral, normal phase Daicel Chiralpak AD-H (6 μm, 4.6x150 mm) were used. For preparative HPLC a device by Gilson equipped with a Waters SymmetryPrep C18 column (5 μm, 19x100 mm, room temperature) was used.

# 5.2. Tetramic Acid Part of Streptolydigin

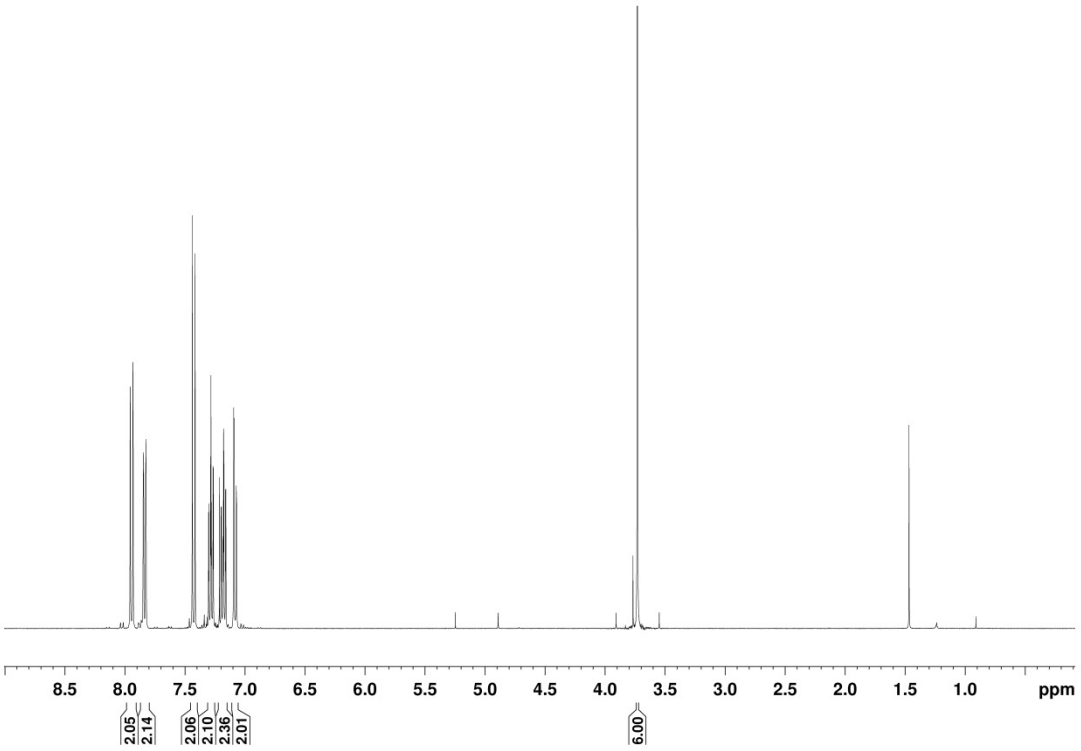
## 5.2.1. Synthesis of the Succinimide Fragment 10




**(*S*)-BINOL (20)** **220**

**Bis methylether 220:** To a solution of (S)-BINOL (7.80 g, 27.24 mmol, 1.00 equiv.) in 234 ml Acetone, potassium carbonate (12.42 g, 89.89 mmol, 3.30 equiv.) and methyliodide (6.78 ml, 108.96 mmol, 4.00 equiv.) were added. The reaction mixture was refluxed (oil bath 80°C) for 18 h. Afterwards the reaction mixture was concentrated under reduced pressure and to the resulting solid was added 280 ml of water and stirred for 2 h. Afterwards the solid was filtered off and washed with water. The solid was dissolved in DCM and dried over $MgSO_4$. Concentration under reduced pressure gave 8.45 gg (98 %) of a yellowish solid.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.1, 2 H), 7.87 (d, *J* = 8.2, 2 H), 7.46 (d, *J* = 9.1, 2 H), 7.34-7.29 (m, 2 H); 7.23-7.19 (m, 2 H), 7.11 (d, *J* = 8.5, 2 H), 3.77 (s, 6 H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 134.14, 129.53, 128.05, 126.42, 125.39, 123.63, 114.39.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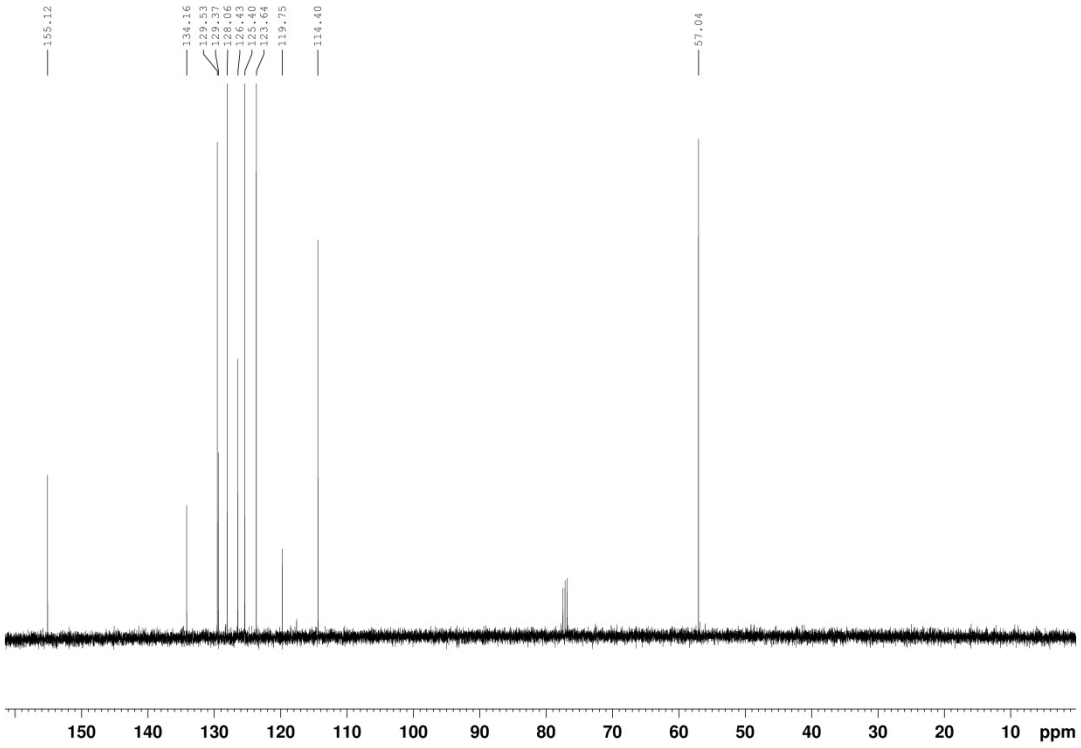
2.01
6.00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123.64
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114.40
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90
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70
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40
30
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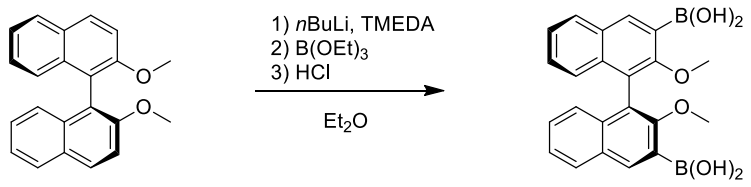
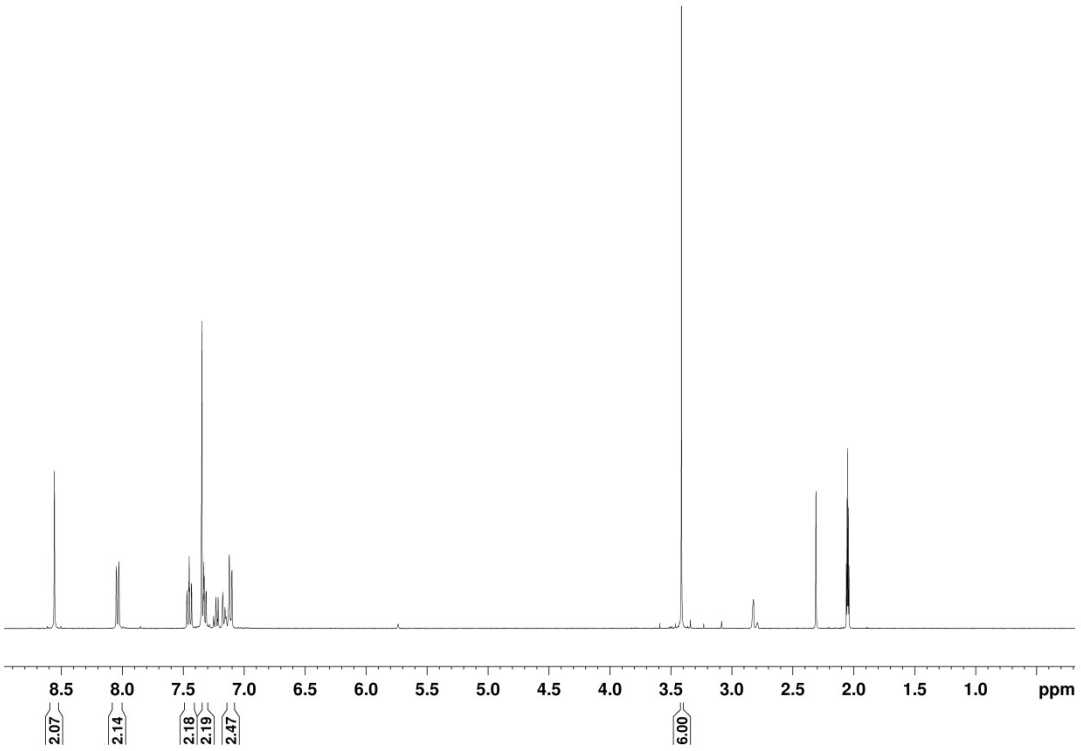
10
ppm




**41** **21**

**Bis boronic acid 21:** To a solution of freshly distilled TMEDA (10.8 ml, 72.2 mmol, 2.84 equiv.) in 420 ml dry ether, n-BuLi (46.7 ml, 74.8 mmol, 2.94 equiv.) (1.6 M in hexane) was added. The solution was stirred for 30 min at r.t. Afterwards solid **220** (8.00 g, 25.4 mmol, 1.00 equiv.) was added in one portion. The reaction mixture was stirred at r.t. for 3 h. The resulting brown suspension was cooled to -78 °C and $B(OEt)_3$ (26.6 ml, 156.5 mmol, 6.15 equiv.) was added over 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was cooled to 0 °C and 1 M HCl (208 ml) was added. The reaction mixture was stirred for 2 h at r.t. The phases were separated and the organic phase was washed twice with 1 M HCl (150 ml) and aq. sat. NaCl (150 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting light brown solid was recrystallized from toluene to give 6.78 g (66 %) of the desired product as white crystals.

**$^1$H-NMR** (400 MHz, Acetone) δ 8.56 (s, 2 H); 8.04 (d, *J* = 8.2, 2 H); 7.47-7.43 (m, 2H); 7.33-7.31 (m, 2 H); 7.11 (d, J = 8.5, 2 H); 3.41 (s, 6 H); **$^{13}$C-NMR** (101 MHz, Acetone) δ 206.11, 139.06, 129.75, 129.66, 128.17, 126.33, 125.67, 61.76.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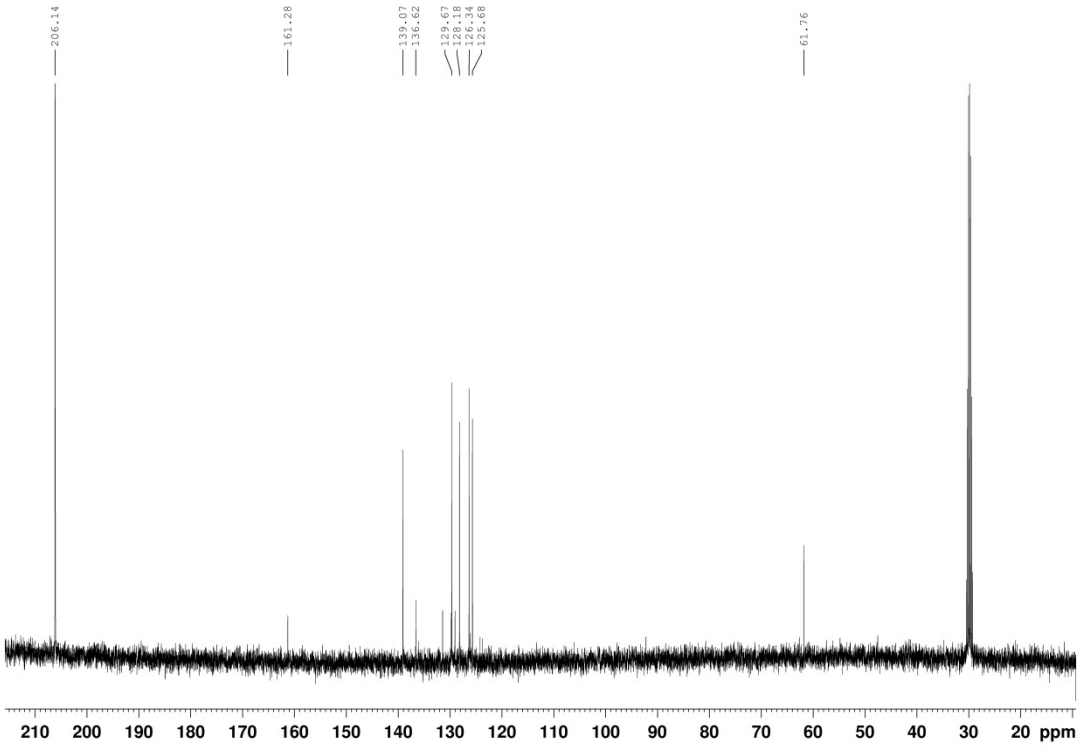
6.00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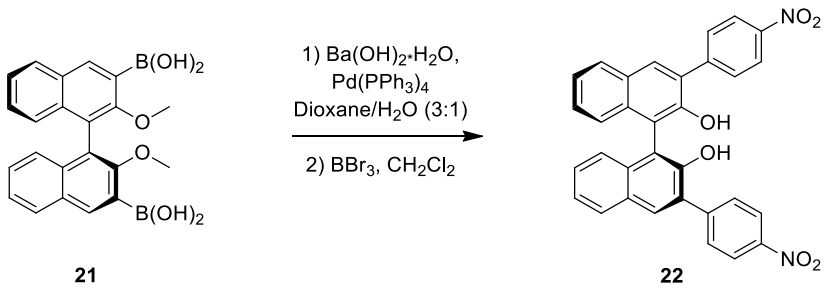
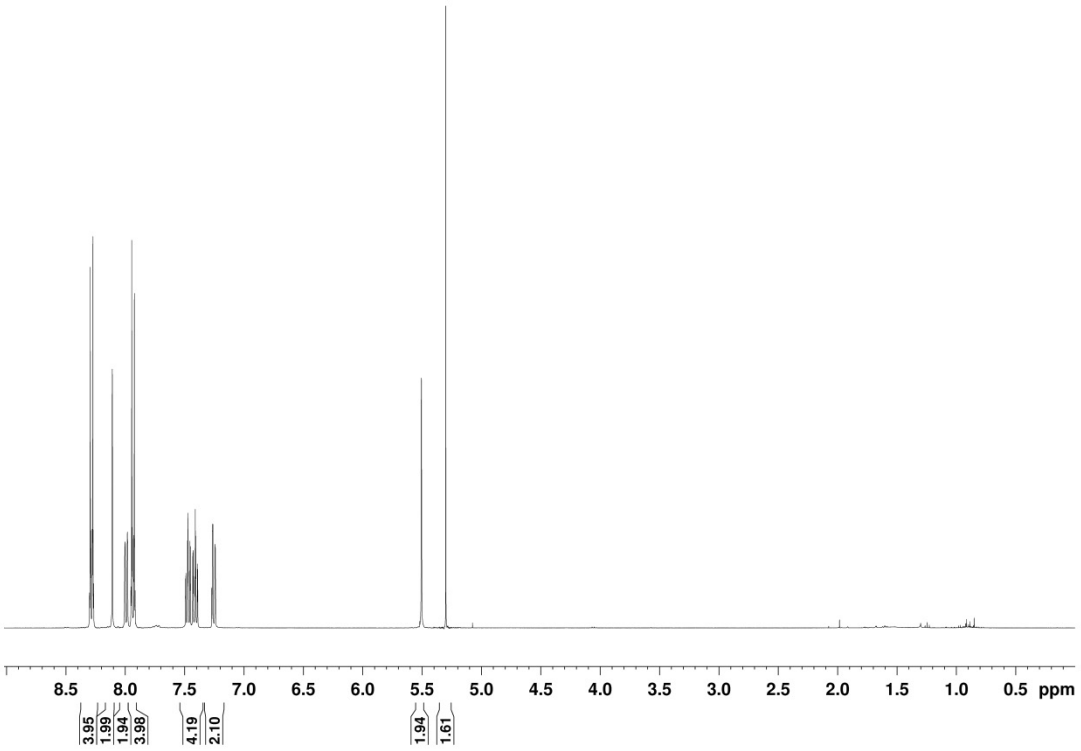
ppm




**21** **22**

**Bis nitrophenol 22:** To a suspension of **21** (0.150 g, 0.373 mmol, 1.00 equiv.), $Ba(OH)_2*8H_2O$ (0.355 g, 1.12 mmol, 3.02 equiv.) and $Pd(PPh_3)_4$ (0.0319 g, 0.0276 mmol, 0.07 equiv.) in degassed dioxane/water (2.4 ml, 3:1), 1-bromo-4-nitrobenzene (0.188 g, 0.933 mmol, 2.50 equiv.) was added. The reaction mixture was refluxed for 25 h. Afterwards the dioxane was removed and the resulting residue was redissolved in methylene chloride, washed with 1 M HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was dissolved in dry DCM (16 ml) and $BBr_3$ (1 M in DCM, 1.678 ml, 4.5 equiv.) was added at 0 °C. The reaction mixture was stirred overnight and afterwards quenched with by drop wise addition of water (16 ml) during 10 min at 0 °C. The phases where separated and the aqueous layer extracted twice with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:5, d = 2.5 cm, h = 17 cm) gave 173.3 mg (87 %) of a yellow solid.

**TLC**: $R_f$ = 0.20 (EtOAc/hexane 1:5, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 8.37 – 8.27 (m, 4H), 8.10 (s, 2H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.96 – 7.89 (m, 4H), 7.53 – 7.36 (m, 4H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.39 (s, 2H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 150.1, 147.3, 144.4, 133.4, 132.5, 130.6, 129.5, 129.0, 128.6, 125.2, 124.1, 123.6, 112.0; **IR** (thin film): ν 3503, 3058, 2361, 2327, 1619, 1595, 1513, 1441, 1401, 1342, 1241, 1199, 1168, 1128, 1108, 1065, 1015, 851, 749, 709, 619; **HRMS** (ESI): calculated for $C_{32}H_{20}N_2NaO_6$ $[M+Na]^+$: 551.1214, found 551.1217; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: + 14.20 (c = 1.00 in $CHCl_3$).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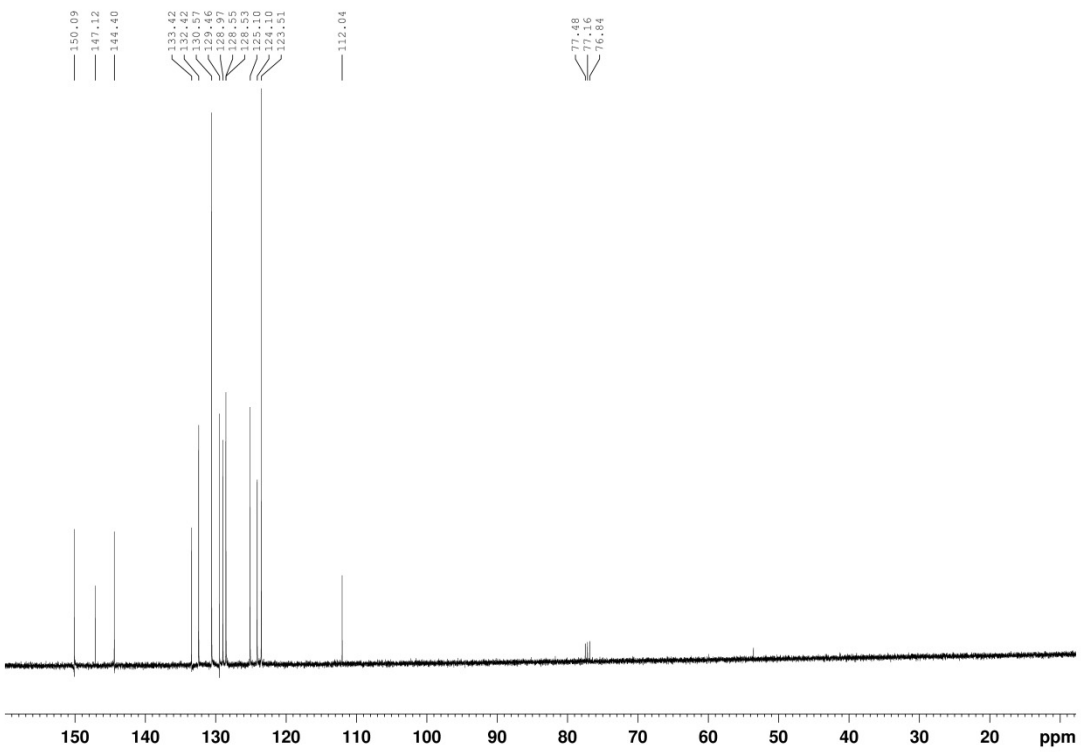
1.61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112.04
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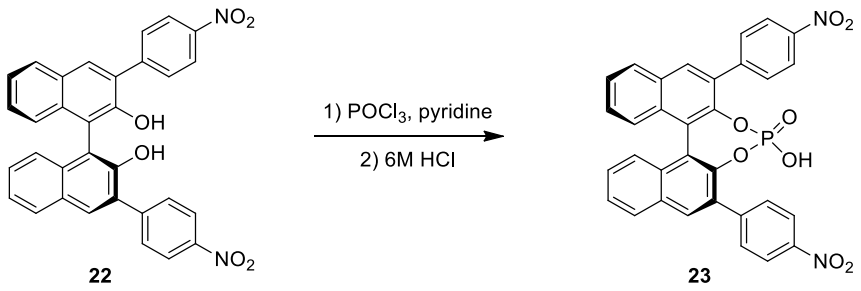
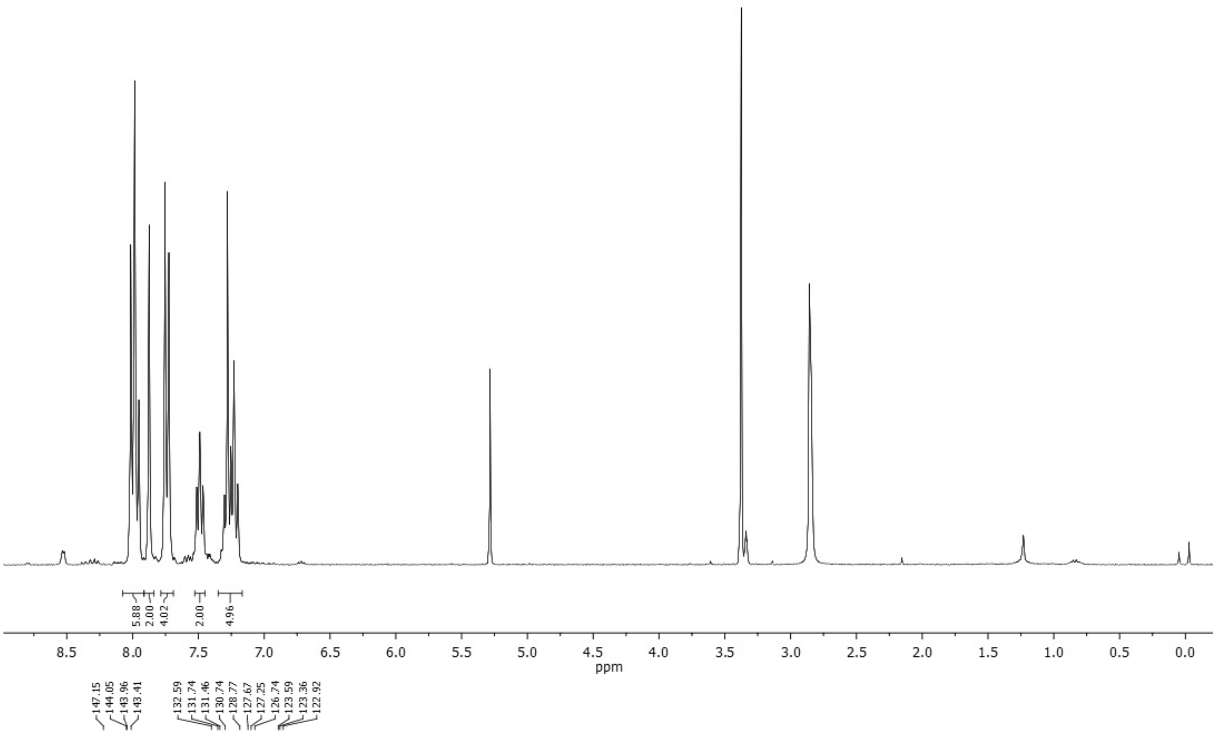



**22** **23**

**Phosphodiester 23:** To a solution of **22** (0.150 g, 0.283 mmol, 1.00 equiv.) in pyridine (1.2 ml), freshly distilled phosphorous oxychloride (37.0 µl, 0.400 mmol, 1.41 equiv.) was added at room temperature. After stirring at rt. for 3 h, the reaction mixture was quenched by addition of water (20.0 µl) at 0 °C and afterwards stirred for 1 h at rt. After evaporation of pyridine under reduced pressure, 6 M HCl (3 ml) was added to the residue at 0 °C. Afterwards the mixture was refluxed for 2 h. After cooling to 0 °C, the resulting solids were collected by filtration, washed with water to give crude material. The crude material was dissolved in DCM and poured into hexane to give the desired product as a yellow solid (129.1 mg; 77 %)

**TLC**: $R_f$ = 0.85 ($CH_2Cl_2$, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 9.2 Hz, 6H), 7.86 (s, 2H), 7.72 (d, *J* = 8.8 Hz, 4H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.22 (m, 4H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 147.1, 144.0, 143.9, 143.4, 132.6, 131.7, 131.5, 130.7, 128.8, 127.7, 127.2, 126.7, 123.6, 123.4, 122.9; **$^{31}$P-NMR** (162 MHz, $CDCl_3$): δ 2.15; **IR** (thin film): ν 3060, 2360, 1596, 1515, 1449, 1427, 1398, 1343, 1246, 1184, 1101, 999, 972, 847, 828, 747, 720, 694; **HRMS** (ESI): calculated for $C_{32}H_{20}N_2O_8P$, $[M+H]^+$ 591.0952, found 591.095; $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$: + 301.39 (c = 0.515 in $CHCl_3$).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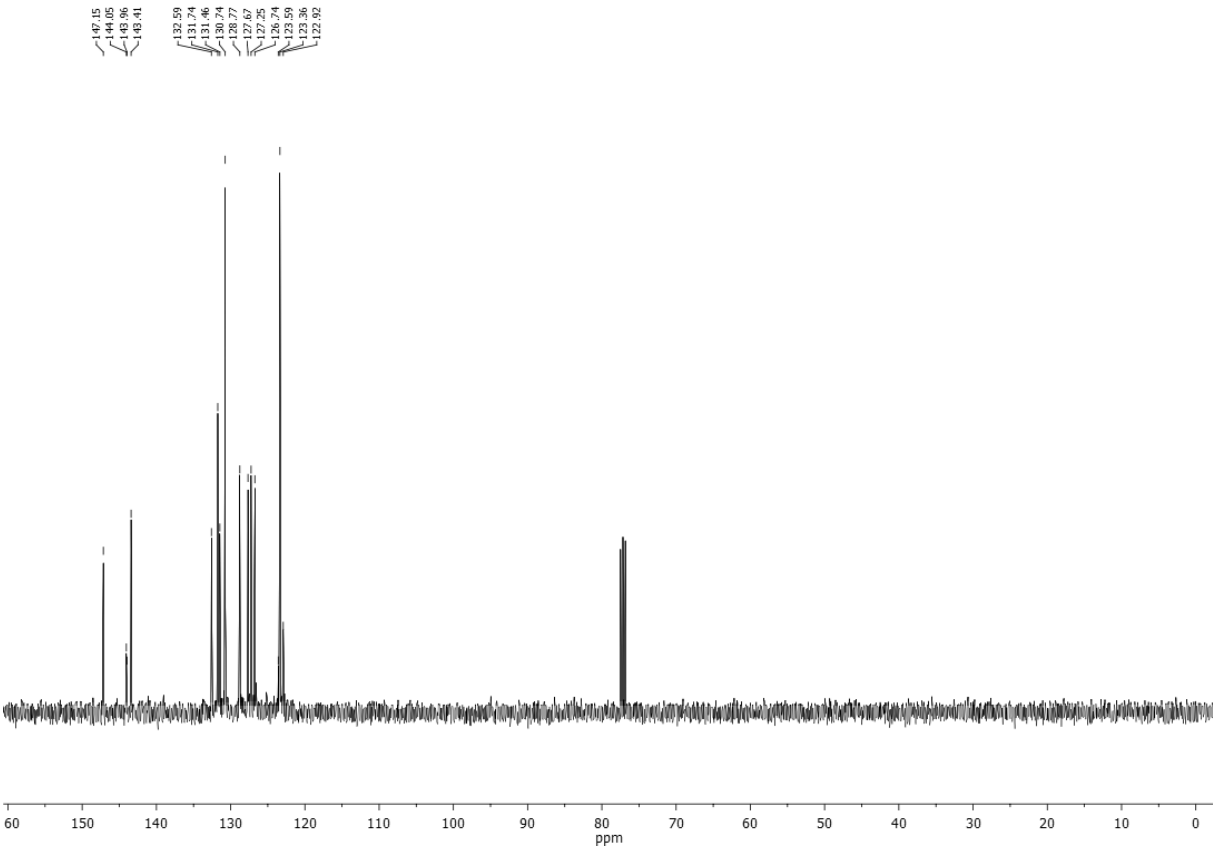
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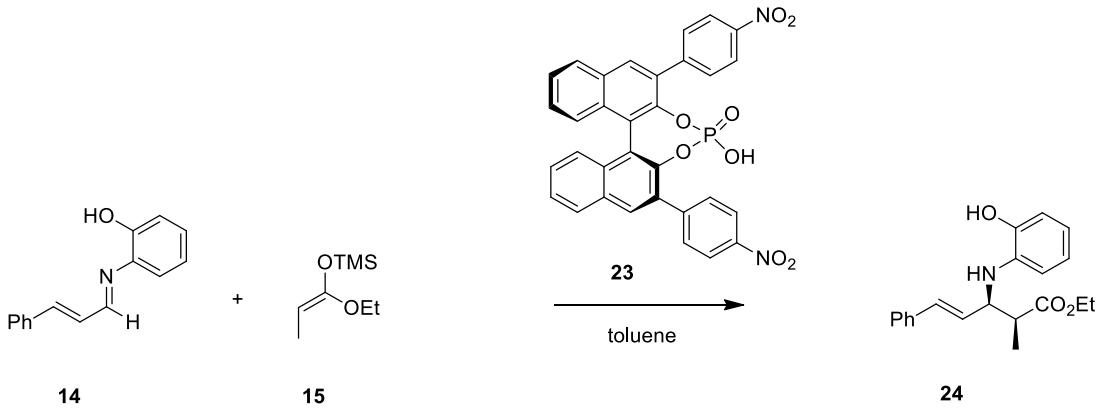
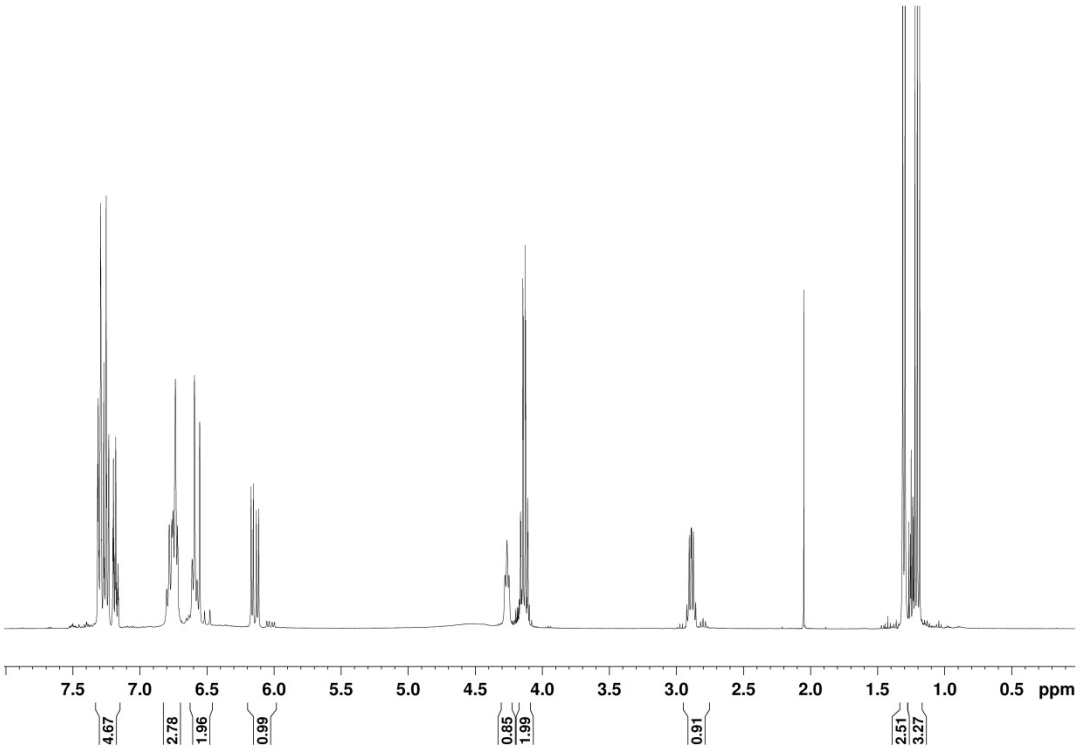



**14** **15** **24**

***Mannich* product 24:** To a suspension of **14** (0.600 g, 2.69 mmol, 1.00 equiv.) and **23** (0.170 g, 0.287 mmol, 0.11 equiv.) in toluene (18 ml) at -78 °C, **15** (0.851 ml, 3.98 mmol, 1.48 equiv.) was added dropwise over 5 min. The reaction mixture was stirred at -78 °C for 24 h (reaction completed?). Afterwards the reaction was quenched by addition of 10 ml aqu. sat. $NaHCO_3$ and aqu. sat. KF. After filtration over celite, the filtrate was extracted with EtOAc. The org. phase was washed 2 x with 20 ml 2 M HCl and 1 x with brine (until full TMS deprotection -> TLC) and afterwards dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($CH_2Cl_2$/MeOH 100:1, d = 4.5 cm, h = 15 cm)(catalyst washout with DCM/MeOH 10:1) gave the desired product (694 mg (79 %)) as an orange oil.

**TLC**: $R_f$ = 0.50 (EtOAc/hexane 1:3, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.34-7.18 (m, 5 H); 6.80-6.70 (m, 3 H), 6.67-6.62 (m, 1 H); 6.55 (d, J = 15.9, 1 H, *syn*); 6.44 (d, J = 15.8, 1 H, *anti*); 6.15 (dd, J = 15.9, 6.7, 1 H, *syn*); 6.01 (dd, J = 15.8, 7.5, 1 H, *anti*); 4.22-4.18 (m, 1 H); 4.15 (q, J = 7.2, 2 H); 2.88 (dq, J = 7.1, 5.1, 1 H, *syn*); 2.76 (dq, J = 8.1, 7.1, 1 H, *anti*); 1.30 (d, J = 7.1, 3 H, *syn*); 1.23 (t, J = 7.1, 3 H, *syn*); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 174.7, 145.2, 136.8, 135.5, 132.8, 132.2, 129.1, 128.6, 128.4, 127.7, 126.6, 121.3, 119.2, 115.4, 114.9, 114.8, 61.1, 61.0, 59.2, 45.1, 44.6, 14.6, 14.3, 13.2, 13.1; **IR** (thin film): ν 3366, 2977, 2937, 1685, 1521, 1457, 1419, 1390, 1362, 1300, 1244, 1171, 1052, 1007, 972, 916, 868, 752, 695, 629; **HRMS** (ESI): calculated for $C_{20}H_{24}NO_3$, $[M+H]^+$ 326.1751, found 326.1756; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -97.36 (c = 0.125 in $CHCl_3$); **Chiral HPLC**: HPLC: Daicel Chiralcel OD-H, Hexane/*i*-PrOH=97:3, Flow rate 0.5 mL/min, UV=244 nm, tR=40.27 min (major isomer, 2*S*, 3*R*), tR=47.02 min (minor isomer, 2*R*, 3*S*).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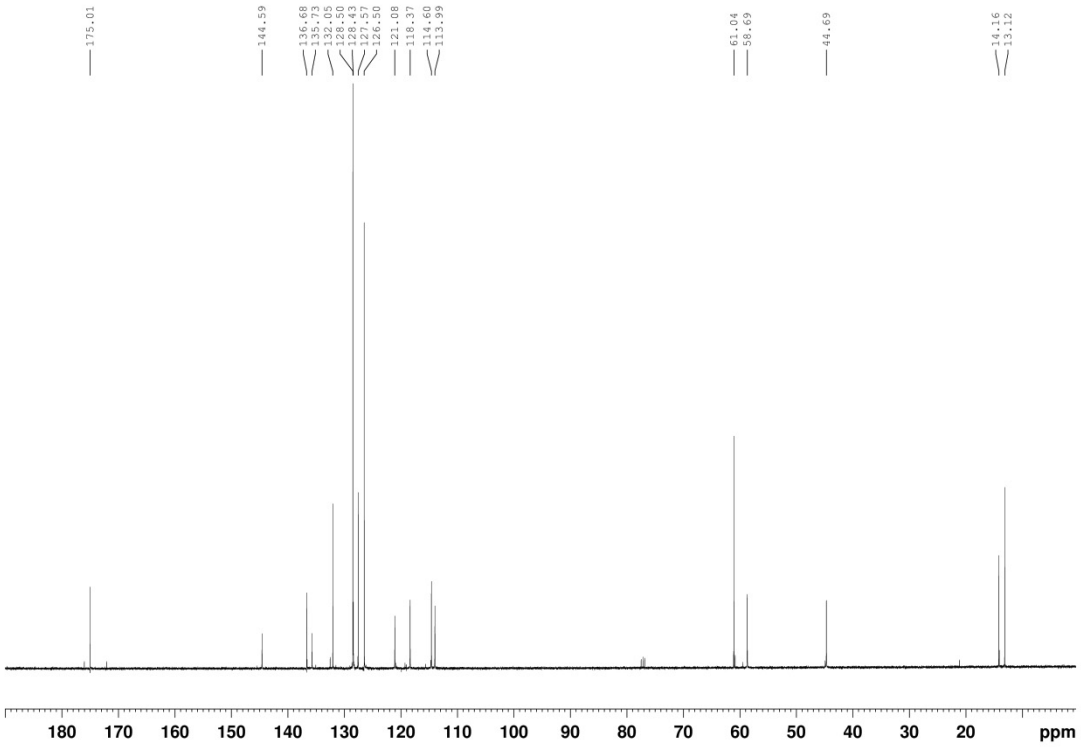
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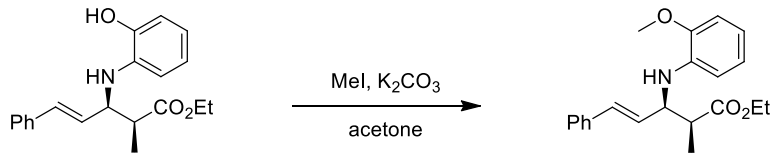
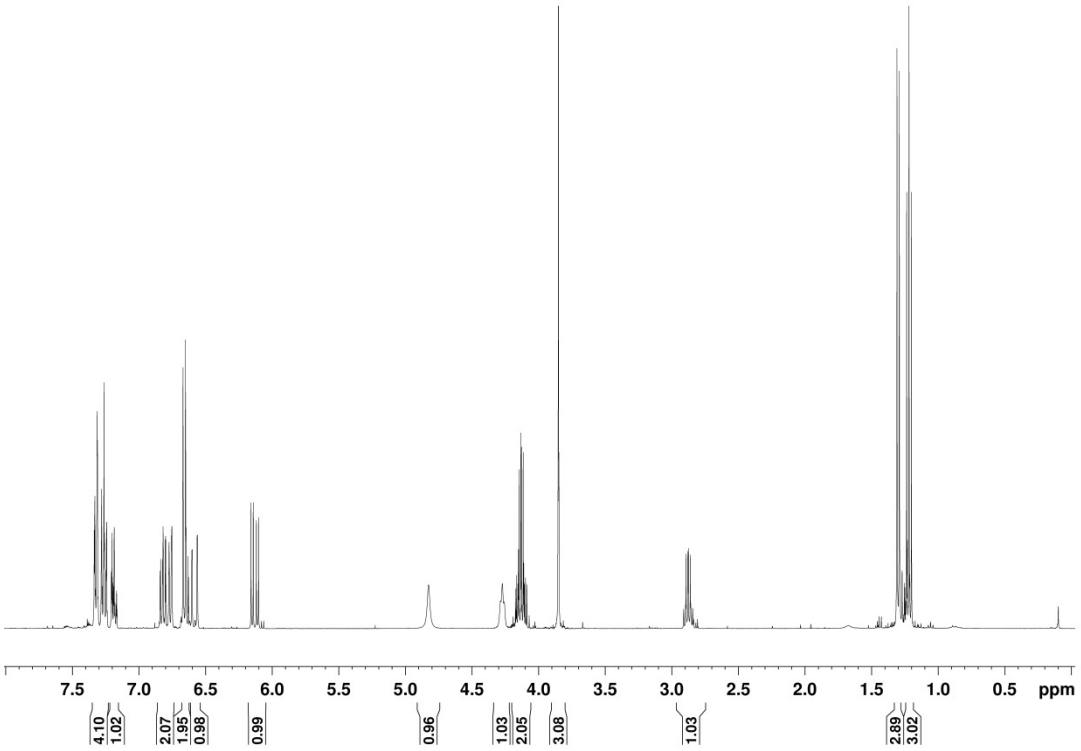



**24** **25**

**Methyl phenol 25:** Methyl iodide (2.22 mL, 35.6 mmol, 10.0 eq.) was added to a suspension of **24** (1.16 g, 3.56 mmol, 1.00 eq.) and $K_2CO_3$ (2.84 g, 20.6 mmol, 5.78 eq.) in freshly distilled acetone (59 mL). The green mixture was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with $NH_4Cl$ (aq. sat. 100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under vacuum. The orange crude product was purified by flash column chromatography (hexane/DCM, 3:1 then DCM) to give the title compound **25** (1.12 g, 3.29 mmol, 92%) as an orange oil.

**TLC**: $R_f$ = 0.66 (EtOAc/hexane 1:3, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 – 7.07 (m, 1H), 6.77 – 6.65 (m, 2H), 6.59 – 6.53 (m, 2H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.04 (dd, *J* = 15.9 Hz, 6.7 Hz, 1H), 4.73 (m, 1H), 4.23 – 4.14 (m, 1H), 4.11 – 3.99 (m, 2H), 3.76 (s, 3H), 2.78 (qd, *J* = 7.1 Hz, 5.7 Hz, 1H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 174.1, 147.0, 137.1, 136.8, 131.9, 128.6, 128.5 (2 C), 127.5, 126.5 (2 C), 121.2, 116.8, 111.0, 109.7, 60.7, 57.9, 55.6, 44.7, 14.3, 13.4; **IR** (thin film): ν 3413, 2978, 2936, 1728, 1600, 1510, 1455, 1430, 1371, 1340, 1242, 1220, 1178, 1049, 1027, 966, 859, 736, 693; **HRMS** (ESI): calculated for $C_{21}H_{25}NNaO_3$, $[M+H]^+$ 362.1727, found 362.1728; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -64.96 (c = 0.115 in $CHCl_3$).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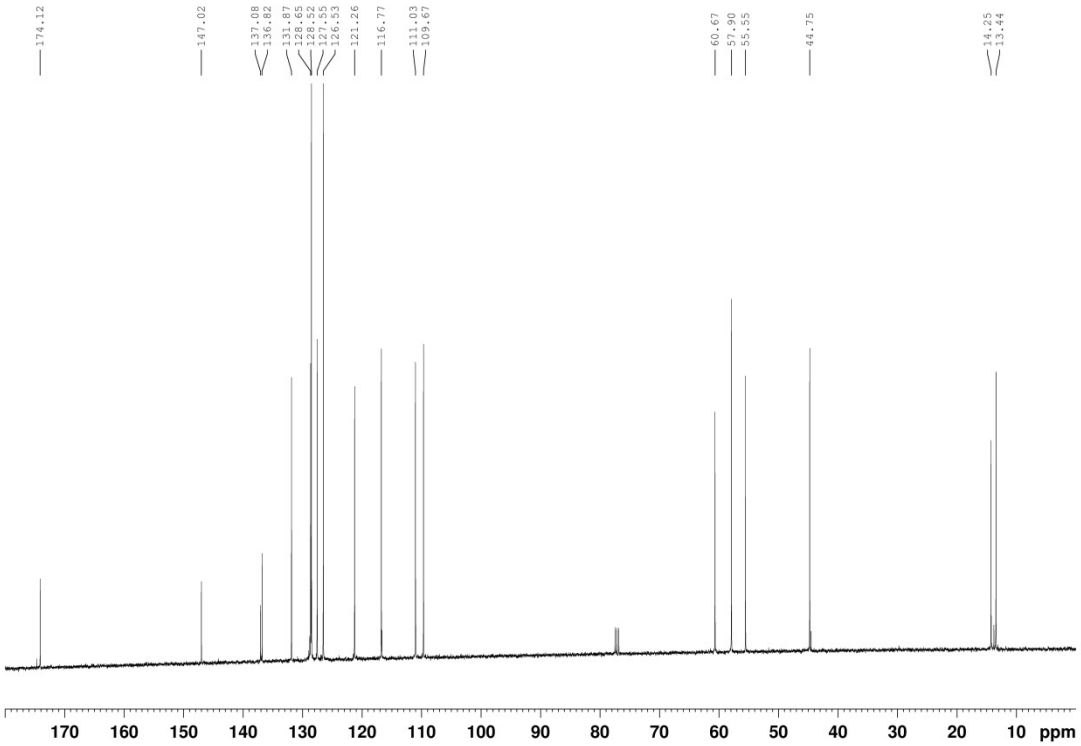
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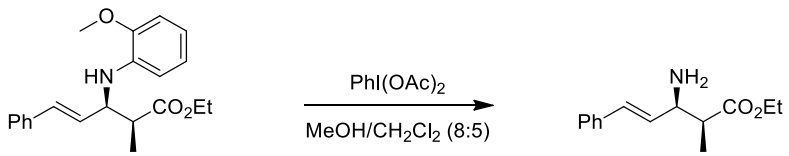
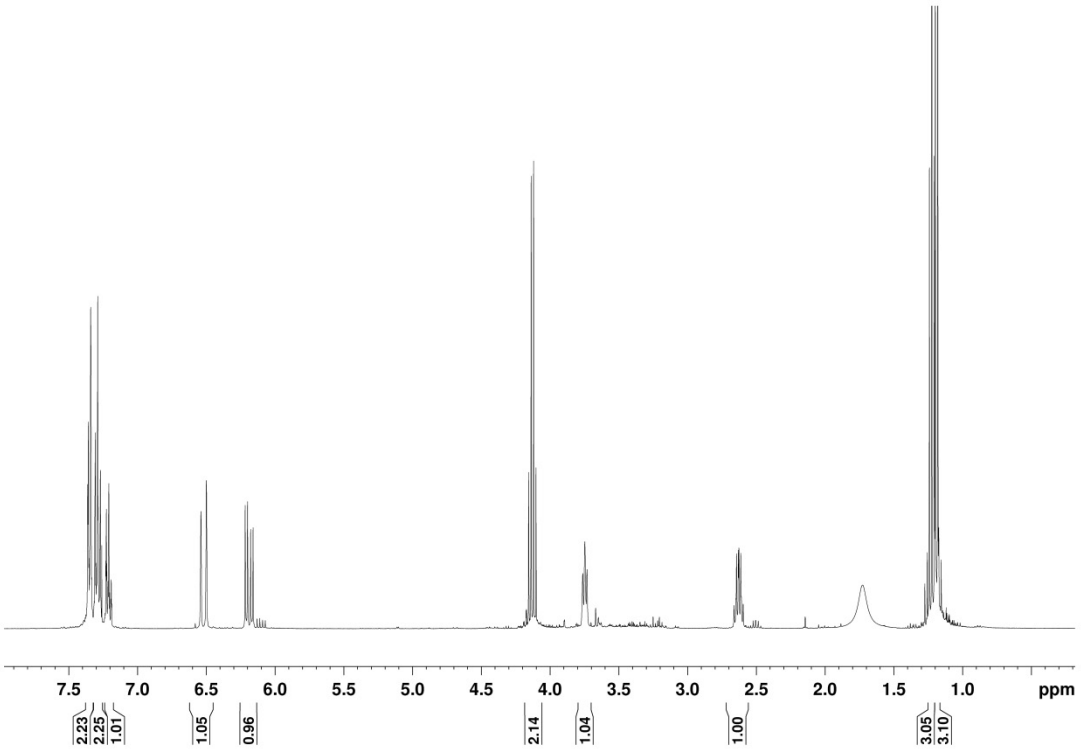



**25** **26**

**Amine 26:** A dry flask under argon atmosphere was charged with $PhI(OAc)_2$ (4.24 g, 13.1 mmol, 4.00 eq.) dissolved in MeOH (95.0 mL) and cooled to 0°C. At this temperature, a solution of **25** (1.116 g, 3.29 mmol, 1.0 eq.) in MeOH:$CH_2Cl_2$ (57.6 mL : 95 mL) was added dropwise over 30 min and then, the orange solution was stirred at room temperature for 21 h. Afterwards the reaction was quenched by addition of HCl (1 M, 49.3 mL), and the resulting orange solution was stirred at room temperature for 2 h. Then, the reaction was extracted with DCM (3 x 50 mL) and the combined organic phases were extracted with HCl (1 M, 5 x 80 mL). The combined aqueous phases were brought to pH= 9 by addition of $NaHCO_3$ (aq. sat.) and extracted with DCM (5 x 150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum to obtain the title compound **26** as an orange oil (445 mg, 1.91 mmol, 58%).

**TLC**: $R_f$ = 0.66 ($CH_2Cl_2$/MeOH 9:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.19 (dd, *J* = 15.9 Hz, 7.0 Hz, 1H), 6.10 (dd, *J* = 15.8, 7.8 Hz, 1H, d2), 4.13 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 6.1 Hz, 1H), 3.66 (m, 1H, d2), 2.63 (qd, *J* = 7.1 Hz, 5.1 Hz, 1H), 2.52 (d, *J* = 7.2 Hz, d2), 1.73 (brs, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 174.9, 136.9, 131.6, 130.5, 128.6, 127.6, 126.4, 60.5, 57.0, 56.1, 46.5, 45.8, 14.7, 14.3, 12.5; **IR** (thin film): ν 3363, 3026, 2979, 2935, 1725, 1598, 1494, 1448, 1371, 1339, 1251, 1177, 1094, 1063, 1027, 966, 859, 746, 693; **HRMS** (ESI): calculated for $C_{14}H_{20}NO_2$, $[M+H]^+$ 234.1489, found 234.1492; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -14.27 (c = 0.110 in $CHCl_3$).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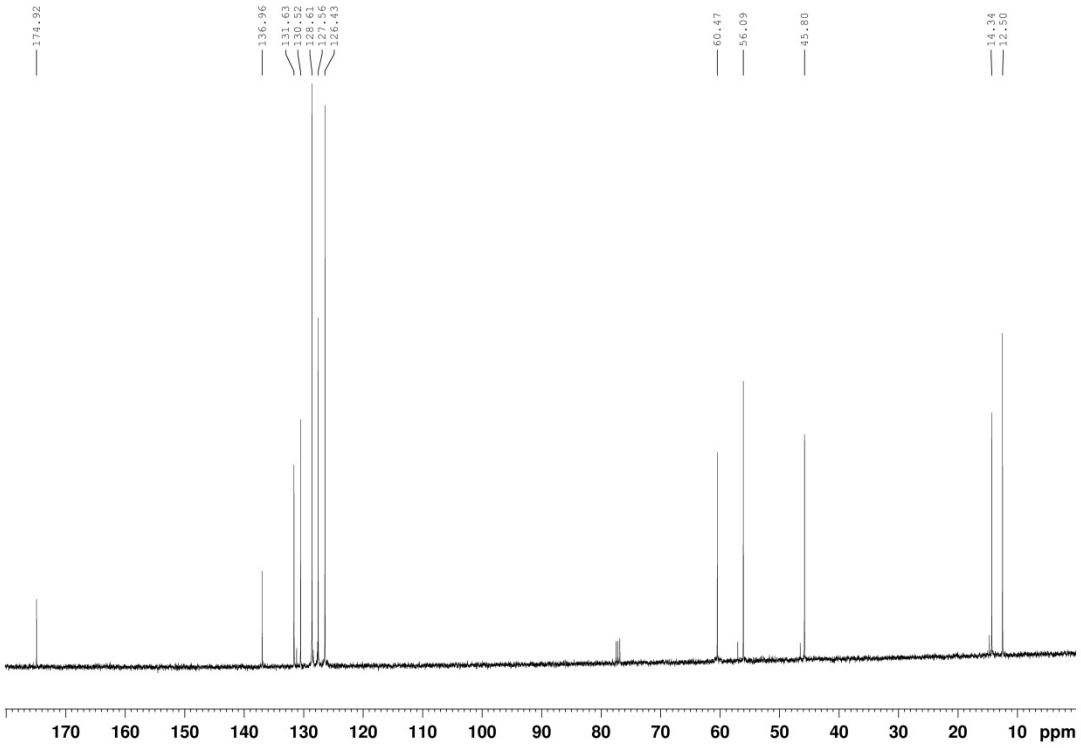
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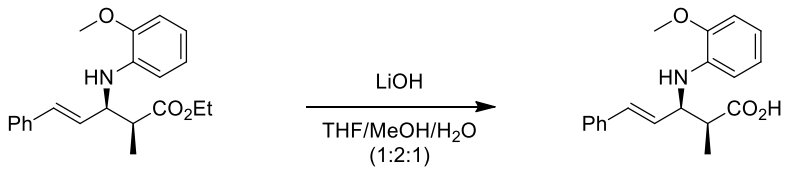
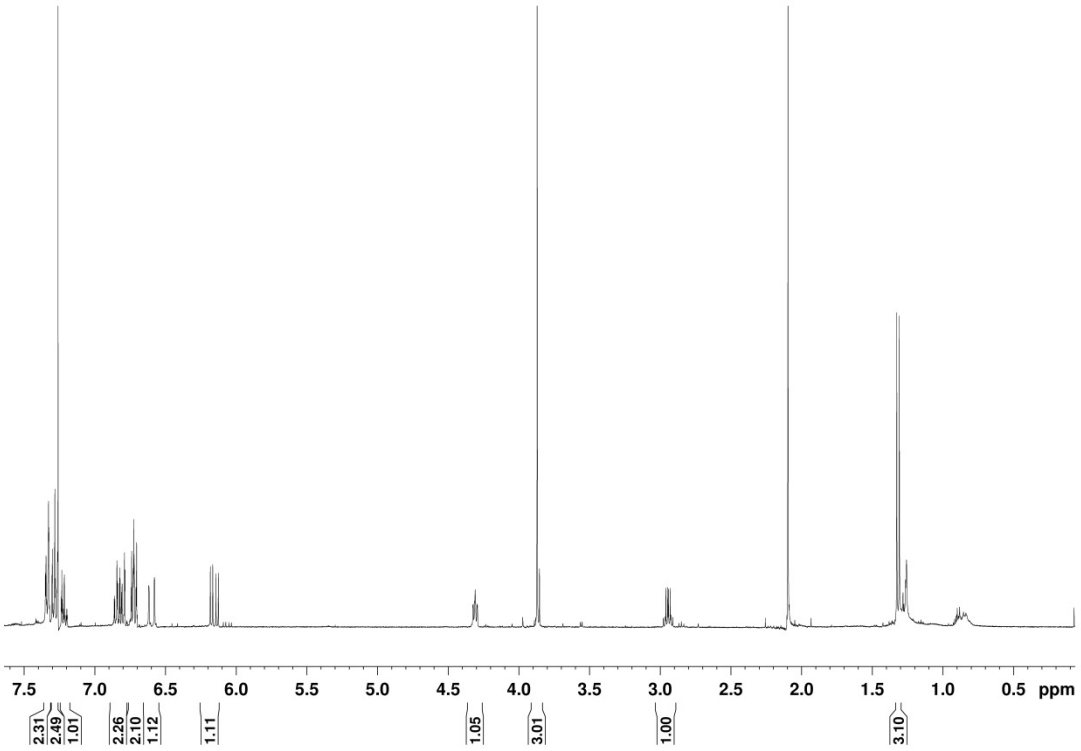



**25** **28**

**Acid 28:** To a solution of **25** (0.291 g, 0.857 mmol, 1.00 equiv.) in 46.0 ml MeOH/ THF/ $H_2O$ (2:1:1), LiOH monohydrate (0.360 g, 8.57 mmol, 10.0 equiv.) were added at 0 °C. The reaction mixture was stirred at 0 °C for 15.5 h. Afterwards the temperature was raised to 10 °C and the reaction mixture was stirred at this temperature for 22 h. Finally the reaction mixture was stirred at rt for additional 4 h. The reaction mixture was acidified with 2 M HCl to pH 1. THF and MeOH were removed under reduced pressure. The aqueous phase was extracted 3 times with EtOAc (50 ml) and the combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($CH_2Cl_2$/MeOH (100:1) -> $CH_2Cl_2$/MeOH/$CH_3COOH$ (100:3:1) d = 4.5 cm; h = 12 cm; to give 255 mg (95 %) of the desired product as brown oil.

**TLC**: $R_f$ = 0.13 (EtOAc/hexane/(AcOH 1%) 1:3, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2 H); 7.30-7.27 (m, 2 H); 7.23-7.19 (m, 1 H); 6.86-6.79 (m, 2 H); 6.74-6.70 (m, 2 H); 6.60 (d, *J* = 15.9, 1 H); 6.15 (dd, *J* = 15.9, 6.8, 1 H); 4.32-4.29 (m, 1 H); 3.87 (s, 3 H); 2.94 (dq, J = 7.2, 5.1, 1 H); 1.32 (d, *J* = 7.2, 3 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 177.17, 136.51, 136.07, 133.13, 128.68 (2 C), 127.97, 127.30, 126.73 (3 H), 121.35, 118.76, 112.74, 110.07, 58.48, 55.72, 43.62, 12.92; **IR** (thin film): ν 3410, 2925, 1705, 1601, 1511, 1456, 1430, 1342, 1243, 1221, 1177, 1120, 1028, 967, 742, 684; **HRMS** (ESI): calculated for $C_{19}H_{20}NNa_2O_3$ ($[M+2Na]^+$, 356.1233, found 356.1230; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -59.27 (c = 0.152 in $CHCl_3$).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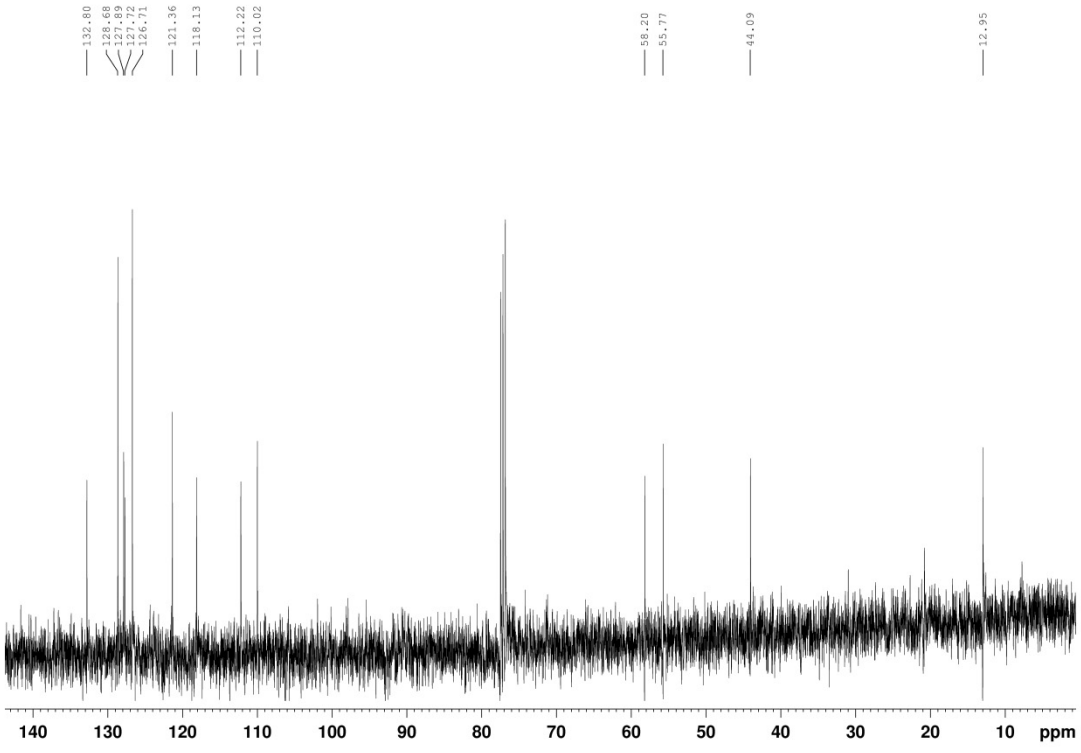
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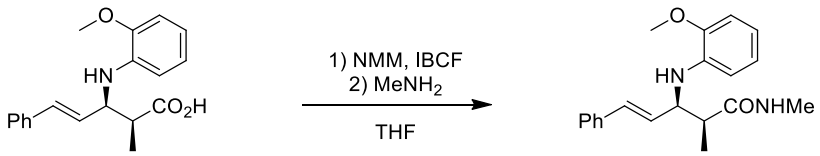
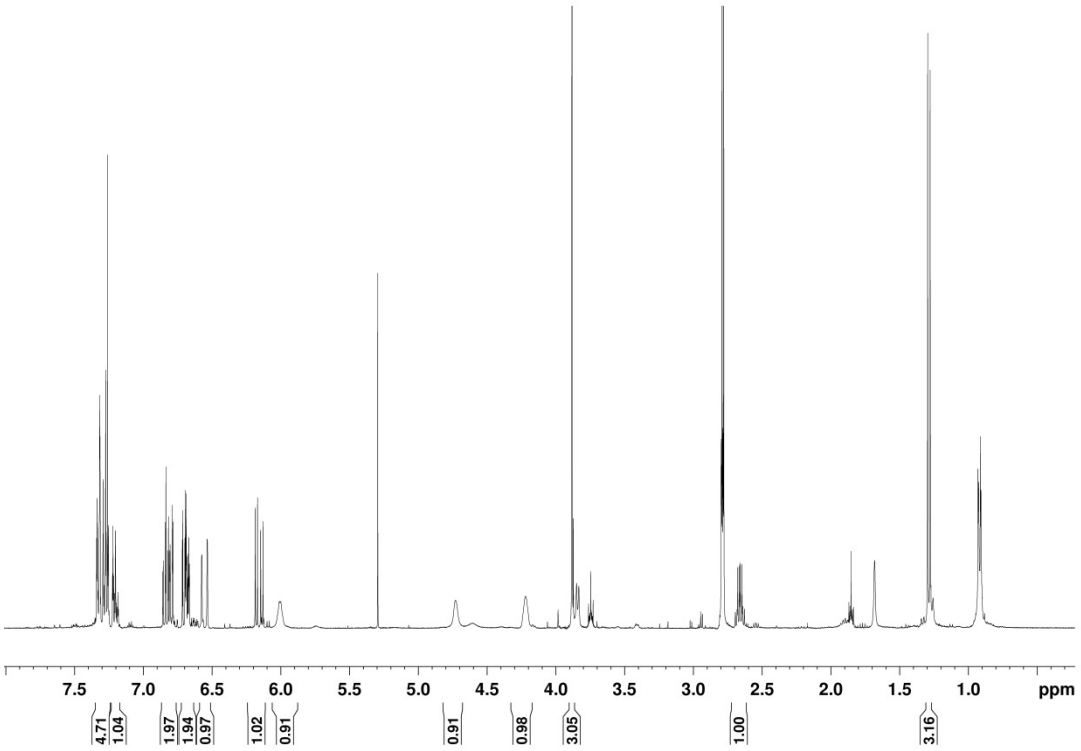



**28** **13**

**Methylamide 13:** To a solution of **28** (0.255 g, 0.819 mmol, 1.00 equiv.) in 22.5 ml THF, NMM (0.090 ml, 0.819 mmol, 1.00 equiv.) and IBCF (0.107 ml, 0.819 mmol, 1.00 equiv.) were added at -20 °C. The reaction mixture was stirred at 0 °C for 5 min and afterwards 40 % methylamine solution (0.107 ml, 0.123 mmol, 1.50 equiv.) was added. The reaction mixture was stirred at rt for 1.5 h and then quenched with 20 ml aq. sat. $NaHCO_3$. After stirring 30 min at room temperature, the aqueous phase was extracted with DCM and the comb. org. layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($CH_2Cl_2$/MeOH (50:1), h = 10 cm; d = 4.5 cm) gave 243.8 mg (92 %) of the desired compound as dark-red oil.

**TLC**: $R_f$ = 0.25 ($CH_2Cl_2$/MeOH 50:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.34-7.32 (m, 2 H); 7.29-7.25 (m, 2 H); 7.22-7.18 (m, 1 H); 6.86-6.78 (m, 2 H); 6.72-6.66 (m, 2 H); 6.55 (d, *J* =15.9, 1 H); 6.16 (dd, *J* =15.9, 6.6, 1 H); 6.01 (brd, *J* = 3.7, 1 H); 4.73 (brs, 1 H); 4.25-4.19 (m, 1 H); 3.88 (s, 3 H); 2.78 (d, *J* = 4.9, 3 H); 2.66 (dq, *J* = 7.1, 5.1, 1 H); 1.29 (d, *J* = 7.1, 3 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 174.8, 147.4, 136.8, 132.0, 128.7, 128.6 (2 C), 127.7, 126.6 (2 C), 121.4, 117.5, 111.6, 109.8, 58.4, 55.7, 45.7, 26.4, 19.2, 14.0; **IR** (thin film): ν 3322, 2932, 1647, 1599, 1510, 1456, 1340, 1244, 1221, 1176, 1126, 1028, 969, 744m, 693; **HRMS** (ESI): calculated for $C_{20}H_{24}N_2NaO_2$ ($[M+Na]^+$, 347.1730, found 347.1730; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -22.93 (c = 0.340 in $CHCl_3$).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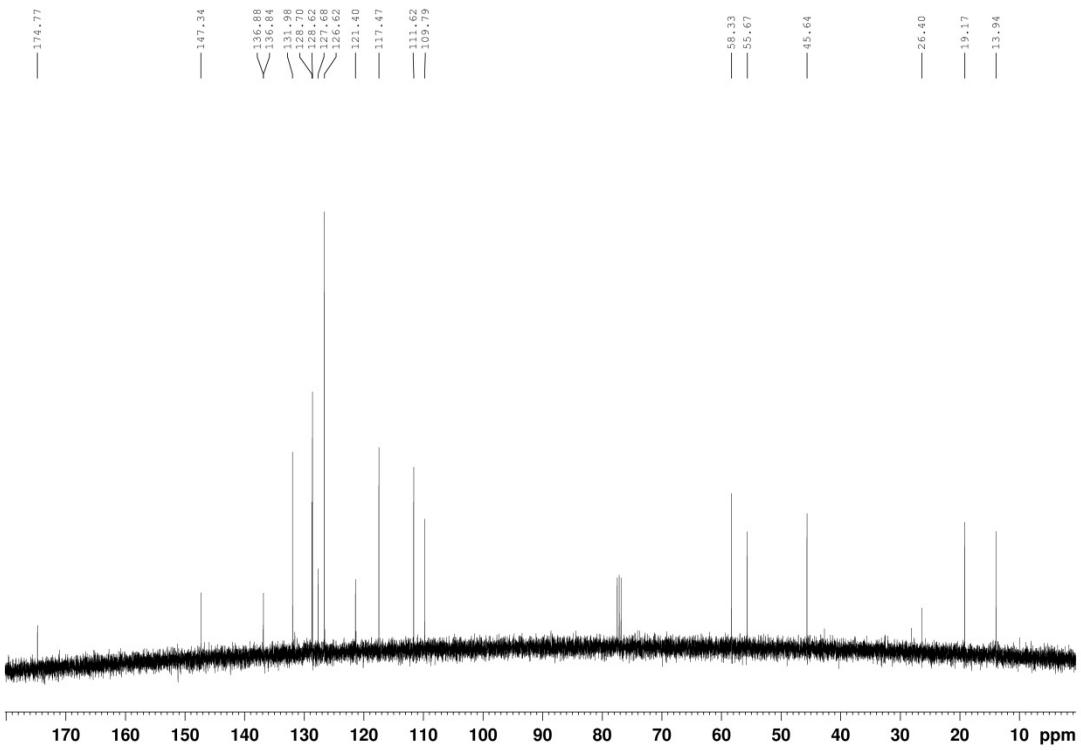
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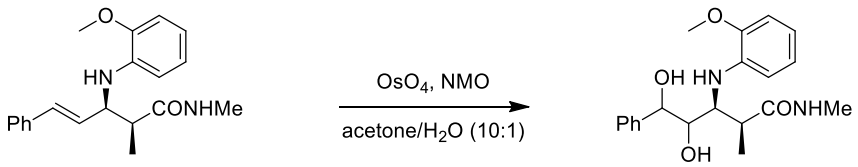
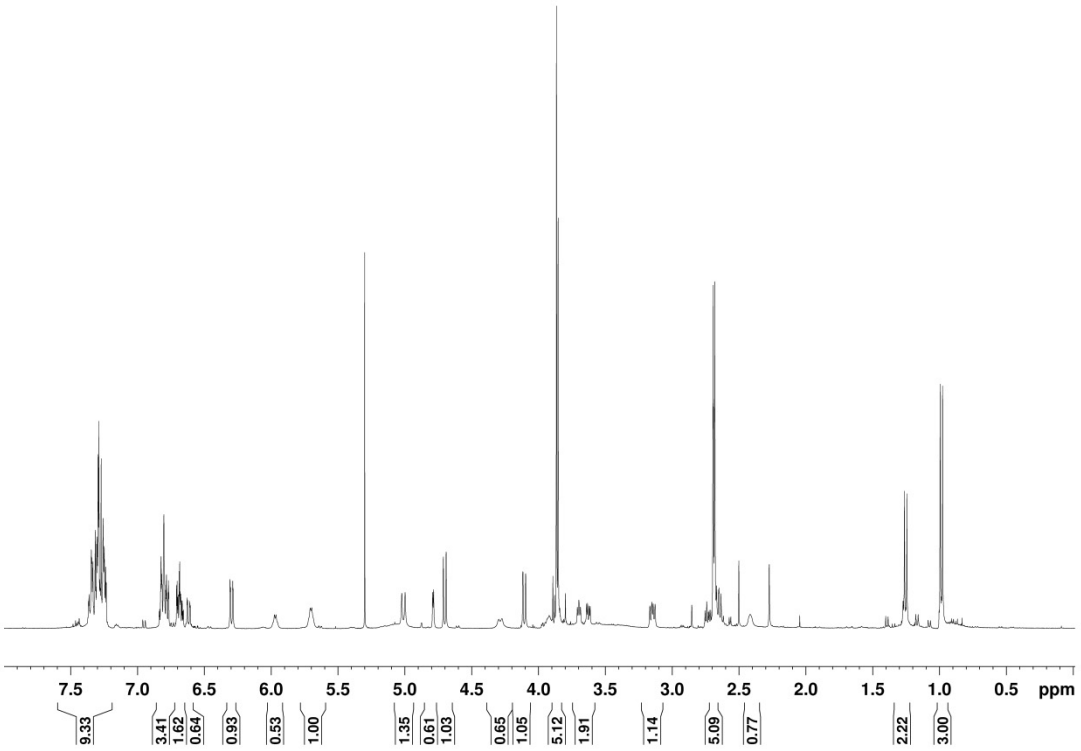



**13** **29**

**Diol 29:** To a solution of **13** (0.050 g, 0.154 mmol, 1.00 equiv.) in 1.55 ml Acetone/water (10:1) $OsO_4$ (0.024 ml, 0.0039 mmol, 0.03 equiv.), NMO (0.0361, 0.308 mmol, 2.00 equiv.) and 2,6-lutidine (0.036 ml, 0.308 mmol, 2.00 equiv.) were added at rt. The reaction mixture turned brown. The reaction mixture was heated to 45 °C for 24 h. The reaction mixture was then quenched by addition of 2 ml aqu. sat. sodiumthiosulfare solution. The aqueous phase was extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($CH_2Cl_2$/MeOH/ (100:1 -> 20:1)) gave 49 mg (88 %) of the desired product as brown foam. Mixture of diastereoisomers 1:1.6

**Major isomer:** $^1$**H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.23 (m, 5 H); 6.84-6.76 (m, 2 H); 6.71-6.60 (m, 1 H); 6.29 (dd, *J* = 7.9, 1.3, 1 H); 5.70 (q, *J* = 4.4, 1 H); 5.01 (d, *J* = 10, 1 H); 4.70 (d, *J* = 8.3, 1 H); 4.11 (d, 8.3, 1 H); 3.86 (s, 3 H); 3.63 (dd, J = 7.8, 2.9, 1 H); 3.15 (dd, *J* = 9.8, 5.8, 3 H); 2.69 (d, *J* = 4.9, 3 H); 0.97 (d, *J* = 7.1, 3 H); $^{13}$**C-NMR** (100 MHz, $CDCl_3$): δ 176.72, 147.18, 140.28, 136.44, 128.52, 127.63, 126.42, 121.40, 116.95, 110.79, 110.11, 75.79, 73.69, 55.65, 54.71, 42.89, 226.50, 14.70.

**Minor isomer:** $^1$**H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.23 (m, 5 H); 6.84-6.76 (m, 2 H); 6.71-6.60 (m, 1 H); 6.62 (dd, *J* = 8.0, 1.3, 1 H); 5.97 (q, *J* = 4.7, 1 H); 5.01 (d, *J* = 10, 1 H); 4.79 (d, *J* = 2.8, 1 H); 4.28 (d, 9.6, 1 H); 3.85 (s, 3 H); 3.70 (dd, J = 4.8, 4.4, 1 H); 3.15 (dd, *J* = 9.8, 5.8, 3 H); 2.69 (d, *J* = 4.9, 3 H); 1.25 (d, *J* = 7.2, 3 H); **Minor isomer:** $^{13}$**C-NMR** (100 MHz, $CDCl_3$): δ 176.56, 147.03, 142.28, 136.98, 128.39, 128.24, 126.42, 121.62, 117.46, 111.63, 109.97, 77.66, 73.14, 57.42, 55.65, 43.50, 26.50, 14.39.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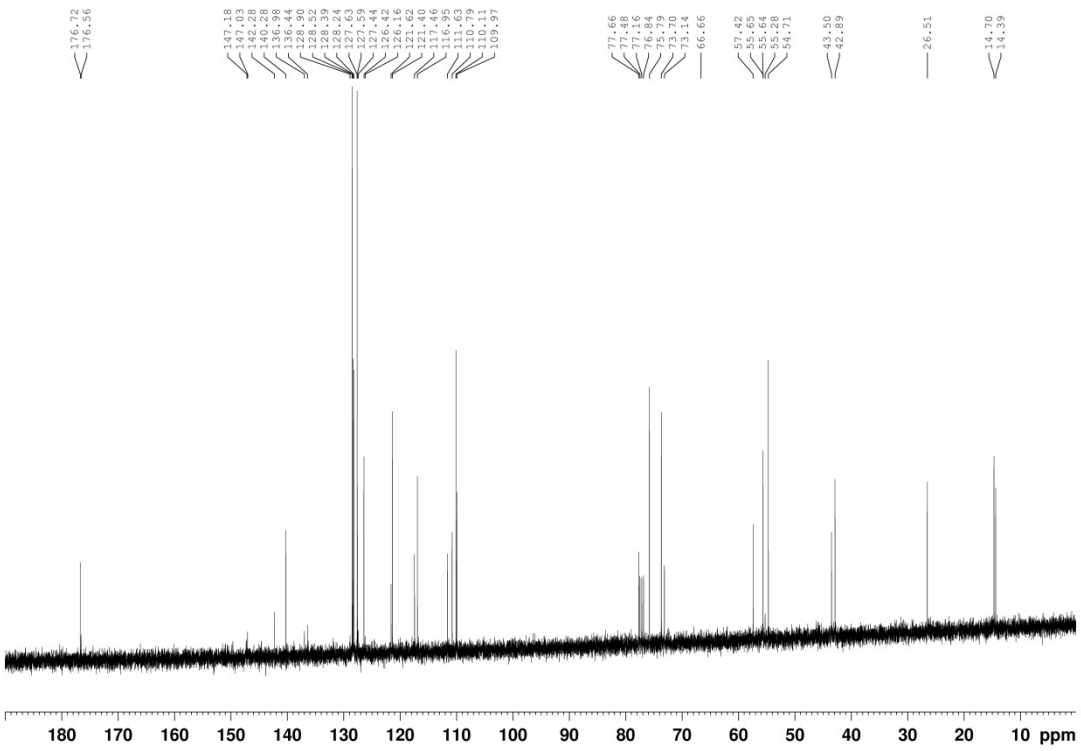
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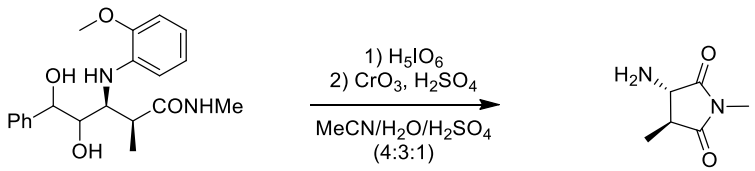
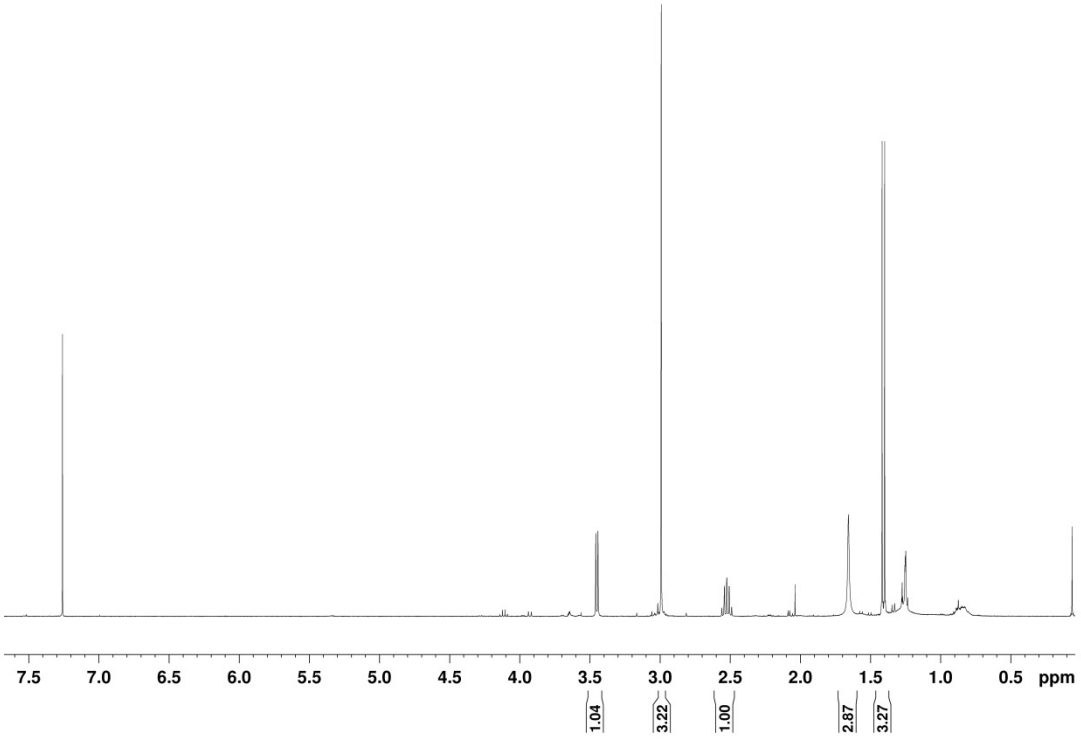



**29** **10**

**Succinimide 10:** To a solution of **29** (0.049 g, 0.137 mmol, 1.00 equiv.) in 8.0 ml MeCN /water/sulfuric acid (0.5 M) (4:3:2), periodic acid (0.031 g, 0.137 mmol, 1.00 equiv.) was added at rt. The reaction mixture was stirred at rt for 40 min. Afterwards again periodic acid (0.156 g, 0.684 mmol, 5.00 equiv.) was added and the reaction mixture stirred at rt for 1 h 10 min. Then 0.4 ml of jones reagent (2 M) was added. The reaction mixture was stirred at rt for 3h. The reaction was quenched by addition of 2-propanol. The reaction mixture was extracted several times with $CH_2Cl_2$. The Aqueous phase was then set to pH ~9 with aqu. sat. $NaHCO_3$ and extracted twice with EtOAc and several times with chloroform/isopropanol (3:1) until the signal of the desired product, disappeared in the MS and TLC of the aqueous phase. Concentration under reduced pressure and purification over silica ($CH_2Cl_2$/MeOH (20:1)) gave 2.3 mg (12 %) of the desired product.

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 3.45 (d, *J* = 6.2 Hz, 1H), 2.99 (s, 3H), 2.53 (m, 1H), 1.66 (brs, 2H), 1.41 (d, *J* = 7.3 Hz, 3H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 178.5, 177.9, 58.4, 44.5, 25.0, 13.9.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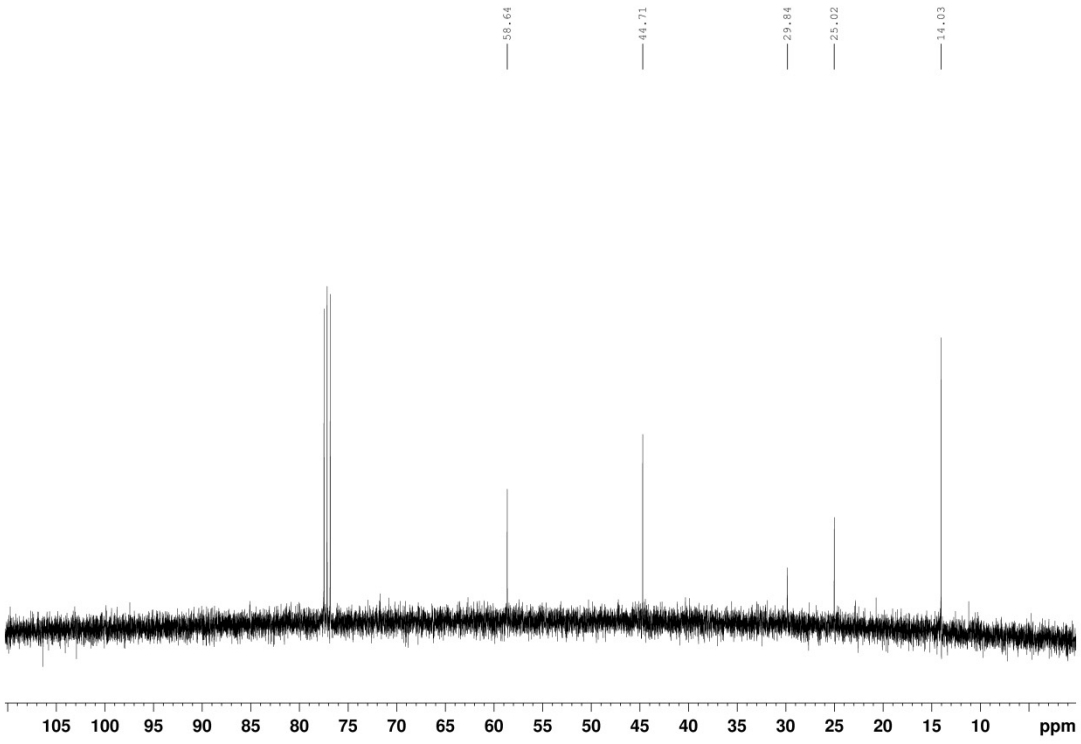
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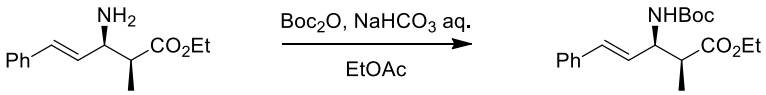
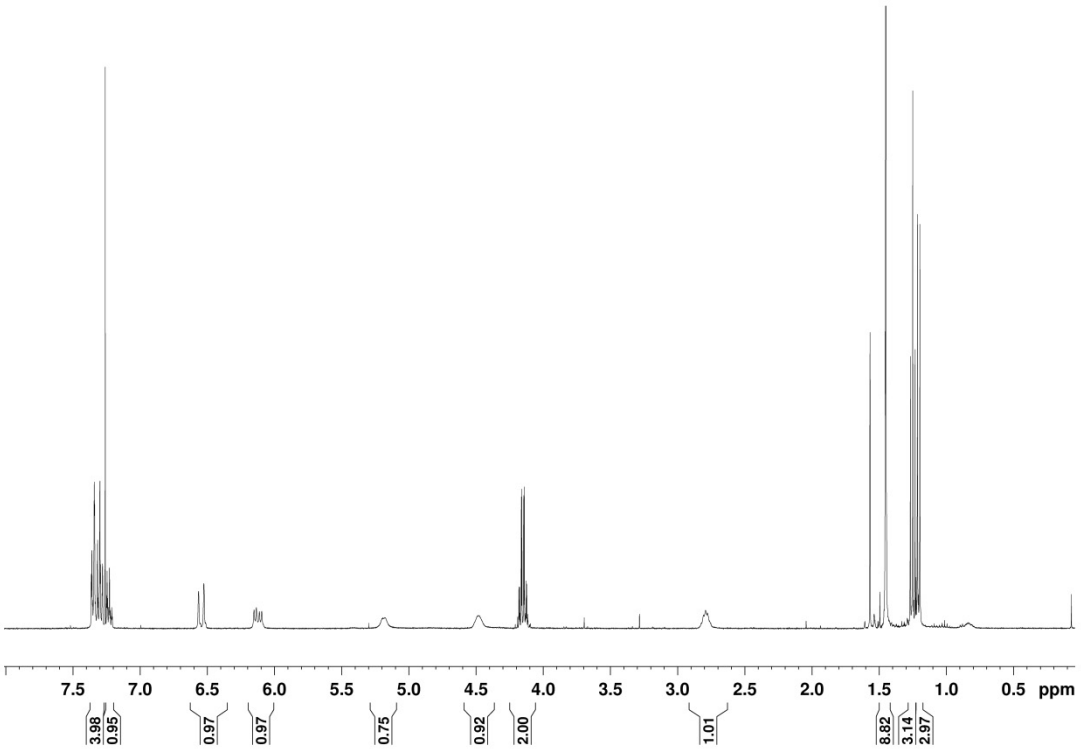



**26** **36**

**Carbamate 36: 26** (445 mg, 1.91 mmol, 1.00 eq.) was dissolved in $NaHCO_3$ (aq. sat., 19.2 mL) and ethyl acetate (19.2 mL). Then, $Boc_2O$ (499 mg, 2.29 mmol, 1.20 eq.) was added to the biphasic reaction mixture which was vigorously stirred at rt for two days. The organic phase was separated, washed with $H_2O$ (3 x 15 mL), with brine (1 x 15 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product, a yellow oil, was purified by flash column chromatography (hexane/EtOAc, 4:1) to afford the title compound **36** as a pale yellow solid (456 mg, 1.37 mmol, 72%).

**TLC**: $R_f$ = 0.47 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 8.3 Hz, 1.3 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.17 (brs, 1H), 4.48 (brs, 1H), 4.15 (qd, *J* = 7.1 Hz, 1.9 Hz, 2H), 2.79 (brs, 1H), 1.45 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 174.1, 155.2, 136.7, 132.3, 128.7, 128.4, 127.8, 126.6, 79.7, 60.8, 55.1, 44.3, 43.9, 28.5, 28.12, 14.6, 14.4, 13.8; **IR** (thin film): ν 3363, 2975, 232, 2362, 1725, 1682, 1508, 1450, 1391, 1366, 1298, 1256, 1239, 1156, 1068, 1038, 974, 750, 694; **HRMS** (ESI): calculated for $C_{19}H_{27}NNaO_4$ $[M+Na]^+$ 356.1832, found 356.1841; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -26.99 (c = 0.920 in $CHCl_3$).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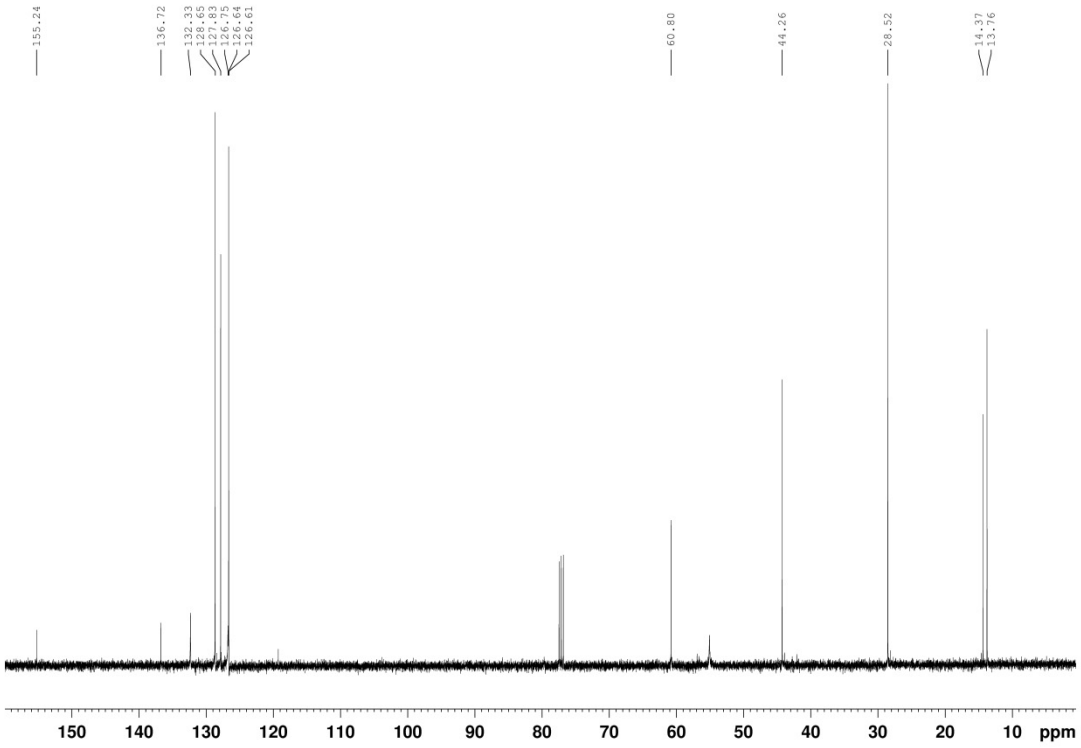
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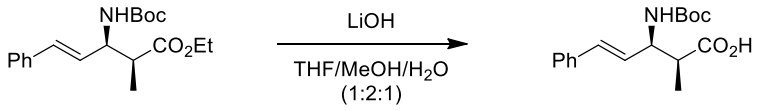
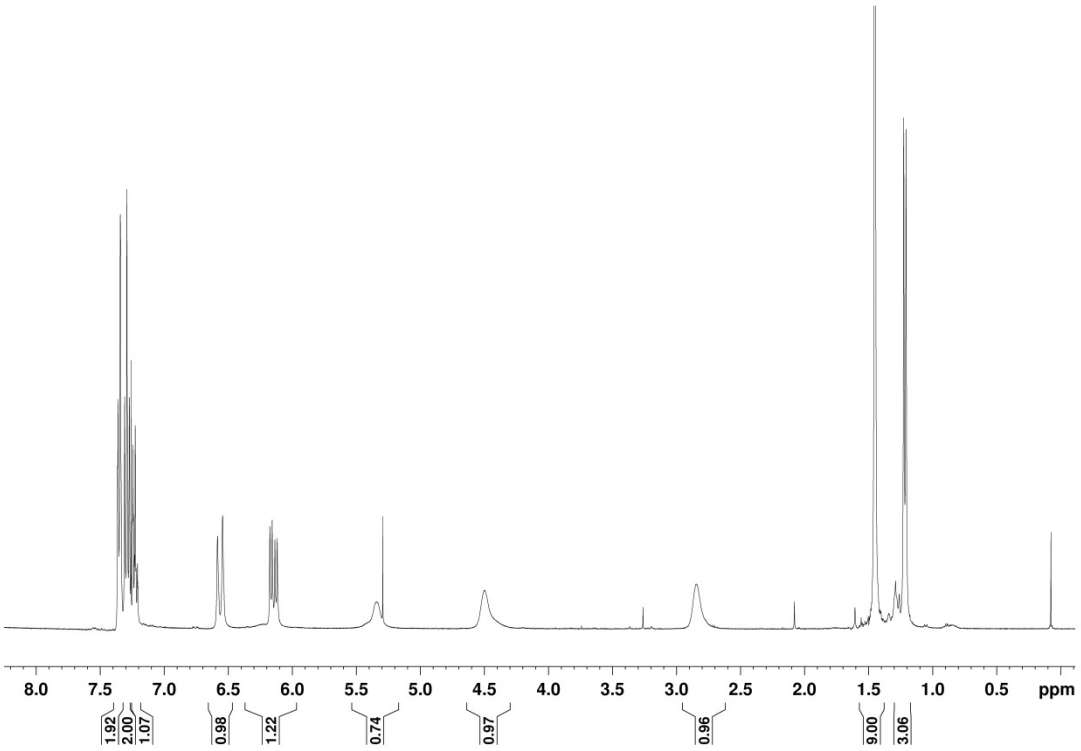



**36** **37**

**Acid 37: 36** (0.456 g, 1.37 mmol, 1.00 eq.) was dissolved in MeOH/THF/$H_2O$ (2:1:1, 14.7 mL) and cooled to 0°C. At this temperature, LiOH monohydrate (896 mg, 21.3 mmol, 15.6 eq.) was added and the reaction was slowly warmed up to rt, then stirred at rt for 24 h. The pale orange reaction mixture was acidified by addition of acetic acid (2 M) until a pH = 4 was reached. After evaporation of THF and MeOH, the aqueous phase was extracted with EtOAc (3 x 35 mL) and the combined organic layer was washed with brine (30 mL). The organic phase was dried over $MgSO_4$, concentrated under vacuum and the resulting crude product was purified by flash column chromatography (DCM/MeOH, 100:5) to obtain the title compound **37** as a white solid (418 mg, 1.37 mmol, 100%).

**TLC**: $R_f$ = 0.52 ($CH_2Cl_2$/MeOH 20:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H), 7.32 – 7.26 (m, 2H), 7.25 – 7.19 (m, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.15 (dd, *J* = 15.8 Hz, 7.2 Hz, 1H), 5.32 (brs, 1H), 4.50 (brs, 1H), 2.85 (brs, 1H), 1.45 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 179.6, 155.4, 136.6, 132.9, 128.7 (2C), 127.9, 126.7 (2C), 126.1, 80.0, 54.9, 43.9, 28.5 (3C), 13.7; **IR** (thin film): ν 3366, 2977, 2937, 1685, 1521, 1457, 1390, 1369, 1300, 1244, 1171, 1052, 972, 916, 868, 772, 752, 695, 629; **HRMS** (ESI): calculated for $C_{17}H_{23}NNaO_4$ $[M+Na]^+$, 328.1519, found 328.1524; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -46.79 (c = 0.865 in $CHCl_3$).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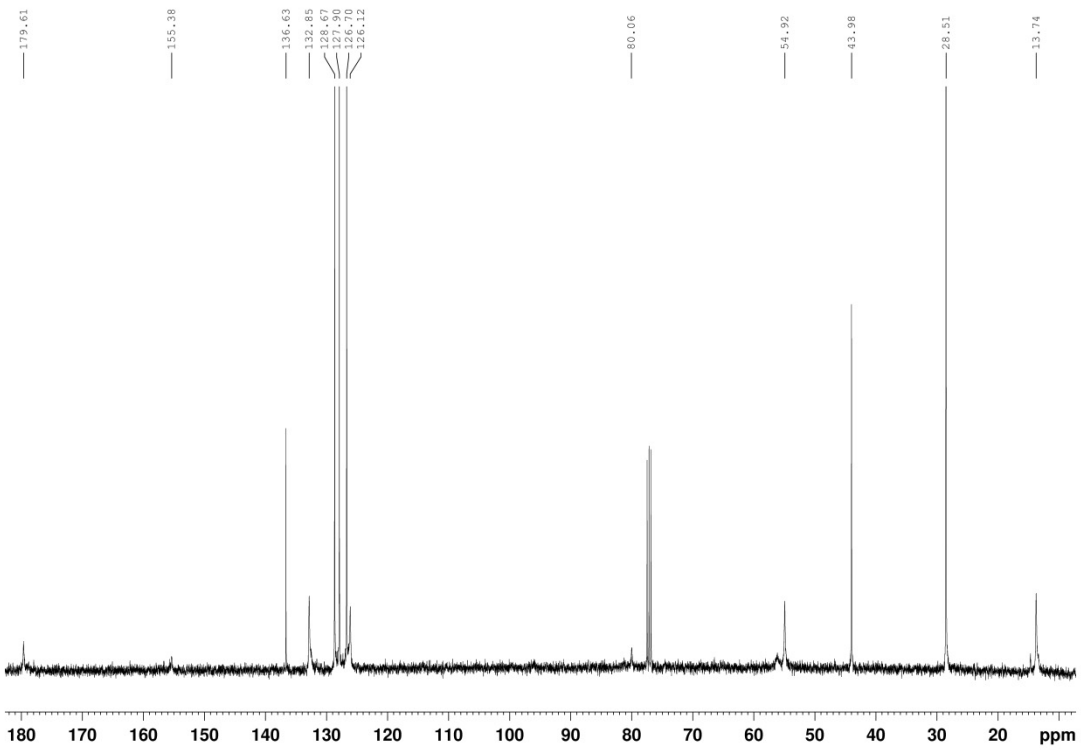
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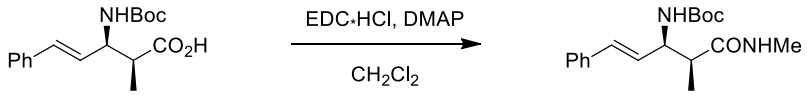
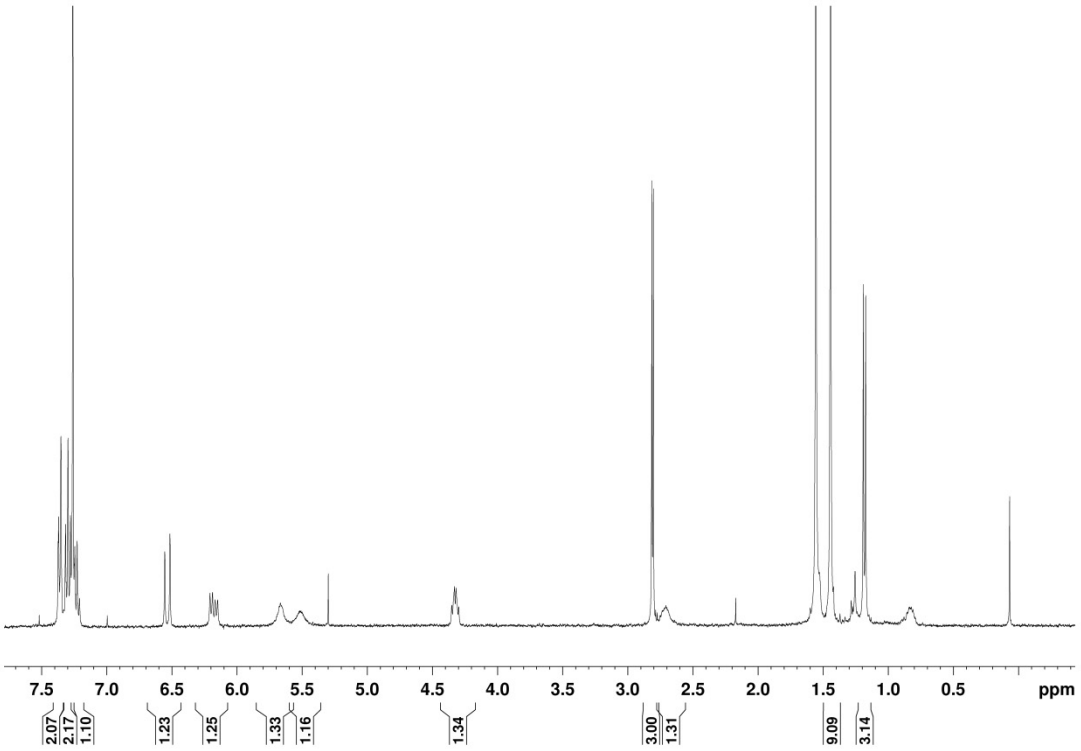



**37** **34**

**Methylamide 34:** A dry flask under argon atmosphere was charged with **37** (71.0 mg, 1.83 mmol, 1.00 eq.) dissolved in DCM (18.2 mL). Then, EDC·HCl (420 mg, 2.19 mmol, 1.20 eq.) and DMAP (22.3 mg, 0.183 mmol, 0.10 eq.) were added to the reaction at rt. Afterwards, methylamine (33% in ethanol, 273 µL, 2.19 mmol, 1.20 eq.) was added to the reaction mixture and the white suspension was stirred at rt for 5 h. The white suspension was washed with HCl (1M, 2 x 25 mL), $NaHCO_3$ (aq. sat, 2 x 25 mL) and brine (25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum to obtain the title compound **34** as a white solid (561 mg, 1.76 mmol, 96%).

**TLC**: $R_f$ = 0.52 ($CH_2Cl_2$/MeOH 10:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 15.8, 7.6 Hz, 1H), 5.69 (brs, 1H), 5.51 (brs, 1H), 4.36 – 4.28 (m, 1H), 2.81 (d, *J* = 4.8 Hz, 3H), 2.78 (d, *J* = 4.8 Hz, 3H), 2.71 (brs, 1H), 1.44 (s, 9H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 7.5 Hz, 3H); **$^{13}$C-NMR** (101 MHz, DMSO) δ 173.9, 155.2, 136.7, 129.7, 129.2, 128.6, 127.3, 126.0, 77.7, 54.6, 44.9, 28.2, 25.4, 14.9, 14.4; **IR** (thin film): ν 3341, 2972, 2022, 1679, 1637, 1531, 1449, 1363, 1304, 1236, 1172, 1063, 1005, 970, 912, 867, 750; **HRMS** (ESI): calculated for $C_{18}H_{26}N_2NaO_3$ $[M+Na]^+$, 341.1836, found 341.1837; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -29.67 (c = 0.205 in $CHCl_3$).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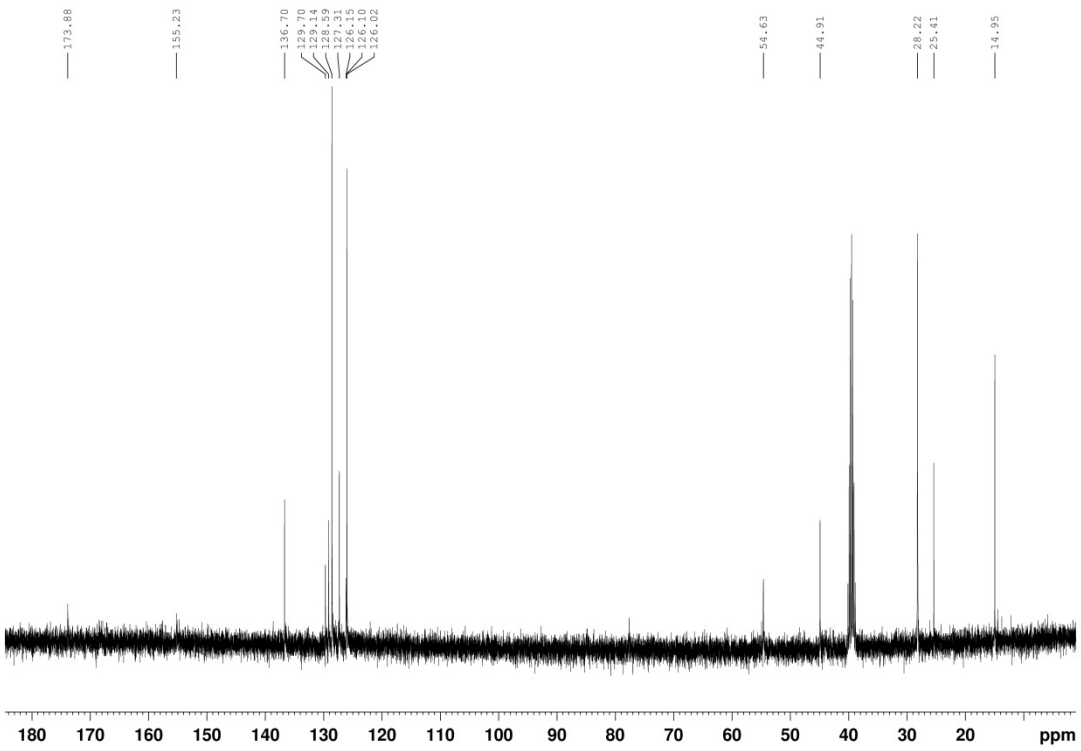
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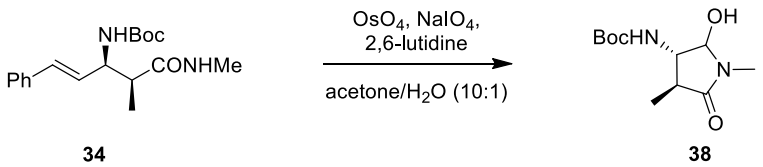
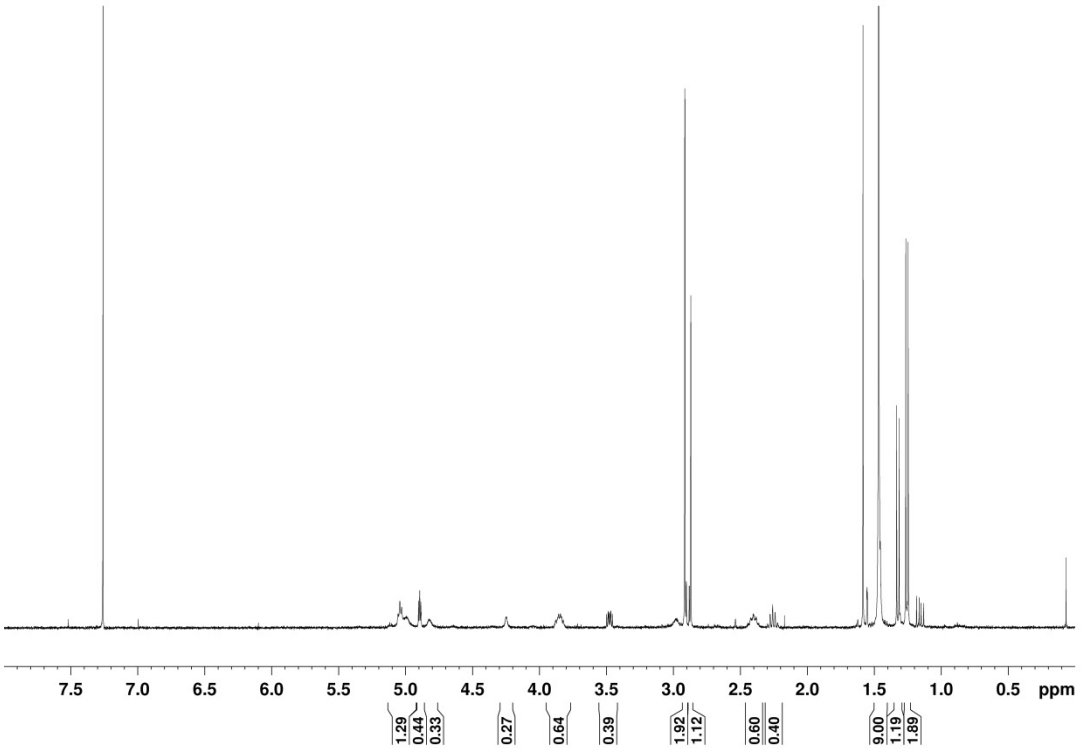



**34** **38**

**Hemiaminal 38:** To a solution of **34** (20.0 mg, 0.063 mmol, 1.00 eq.) in acetone/$H_2O$ (10:1, 1.25mL) at rt, 2,6-lutidine (15.0 µL, 0.126 mmol, 2.00 eq.), $OsO_4$ (2.5% in *t*BuOH, 6.00 µL, 0.600 µmol, 0.01 eq.) were added and the white suspension was stirred at rt for 5 min. Afterwards, $NaIO_4$ (53.7 mg, 0.251 mmol, 4.00 eq.) was added to the reaction mixture which was stirred at rt for 15 h. The reaction was quenched by addition of sodium thiosulfate (aq. sat. 1.50mL) and stirred at rt for 5 min. Afterwards, the reaction mixture was extracted with DCM (5 x 15 mL) and the combined organic phases were washed with brine (20 mL) before being dried over $MgSO_4$ and concentrated under vacuum. The resulting yellow crude oil was purified by flash column chromatography (DCM/MeOH, 20:1) to obtain the title compound **38** as a white solid (11.6 mg, 0.047 mmol, 76%).

**TLC**: $R_f$ = 0.21 ($CH_2Cl_2$/MeOH 10:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 5.05 (m, 1H), 4.99 (brs, 1H), 4.92 – 4.88 (m, 1H), 4.81 (brs, 1H), 3.90 – 3.80 (m, 1H), 3.52 – 3.43 (m, 1H), 2.95 – 2.91 (m, 3H), 2.90-2.88 (m, 3H), 2.45 – 2.35 (m, 1H), 2.26 (m, 1H), 1.47 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 7.1 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 175.9, 174.5, 156.6, 156.1, 88.4, 82.5, 80.8, 80.1, 61.4, 55.4, 42.2, 40.3, 28.4, 27.6, 26.8, 15.2, 13.5; **IR** (thin film): ν 3318, 2978, 2934, 2361, 2334, 1675 8, 1521, 1456, 1393, 1366, 1277, 1252, 1166, 1078, 1045, 1020, 975, 753; **HRMS** (ESI): calculated for $C_{11}H_{20}N_2NaO_4$ $[M+Na]^+$, 267.1315, found 267.1320; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -46.73 (c = 0.720 in $CHCl_3$).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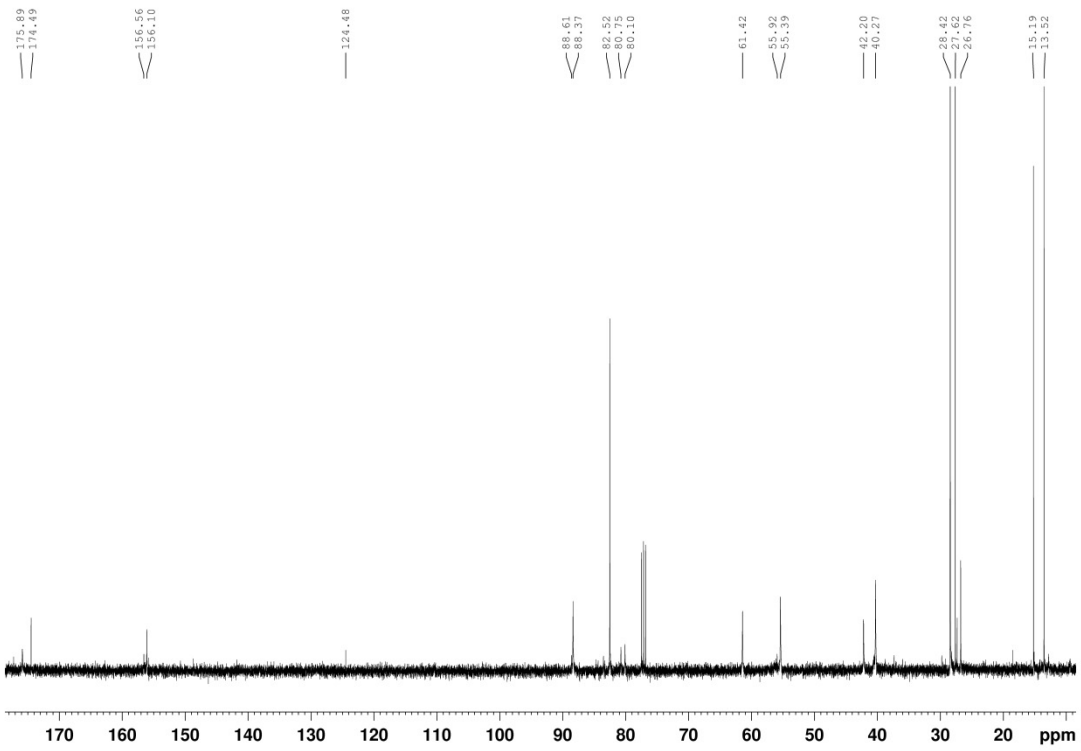
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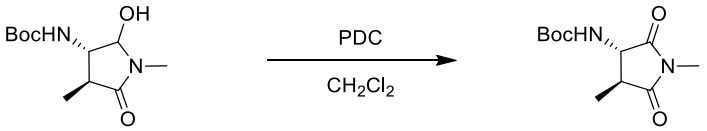
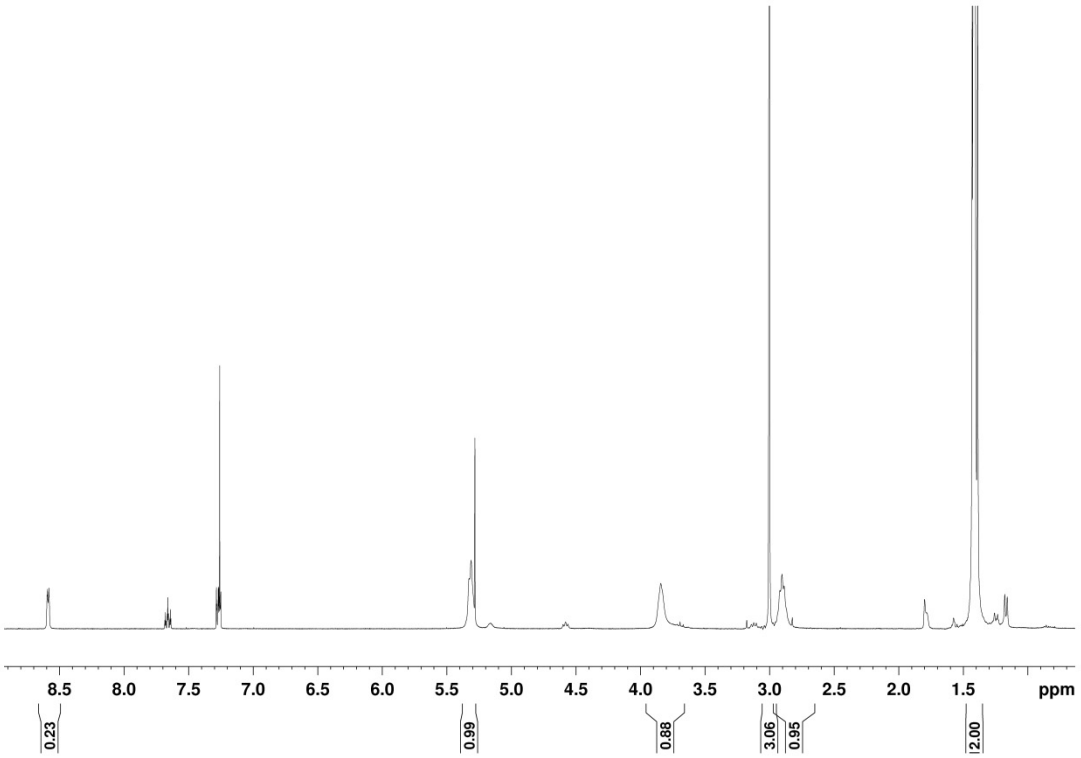



**38** **39**

**Succinimide 39:** A dry flask under argon atmosphere was charged with **38** (268 mg, 1.09 mmol, 1.00 eq.) dissolved in DCM (34.0 mL) and pyrridinium dichromate (1.24 g, 3.29 mmol, 3.00 eq.) was added to the reaction solution. Afterwards, the reaction was stirred at rt for 18 h. The brown reaction mixture was diluted with water (25 mL) and extracted with DCM (5 x 30 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$ before being concentrated under vacuum. The resulting brown crude oil was purified by flash column chromatography (DCM/MeOH, 30:1) to obtain the title compound **39** a pale yellow solid (244 mg, 1.007 mmol, 92 %).

**TLC**: $R_f$ = 0.59 ($CH_2Cl_2$/MeOH 10:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 8.58 (s, 1H, NH), 5.31 (brs, 1H), 3.84 (brs, 1H), 3.00 (s, 3H), 2.90 (brs, 1H), 1.42 (s, 9H), 1.39 (d, *J* = 7.4 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 177.4, 175.1, 155.5, 81.0, 58.0, 53.1, 42.4, 39.6, 28.3, 25.1, 14.0, 11.8; **IR** (thin film): ν 3343, 2976, 2937, 2363, 1776, 1698, 1526, 1435, 1366, 1341, 1281, 1250, 1160, 1044, 1006, 951, 863, 819, 761, 615; **HRMS** (ESI): calculated for $C_{11}H_{18}N_2NaO_4$ $[M+Na]^+$ 265.1159, found 265.1163; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -43.14 (c = 0.780 in $CHCl_3$).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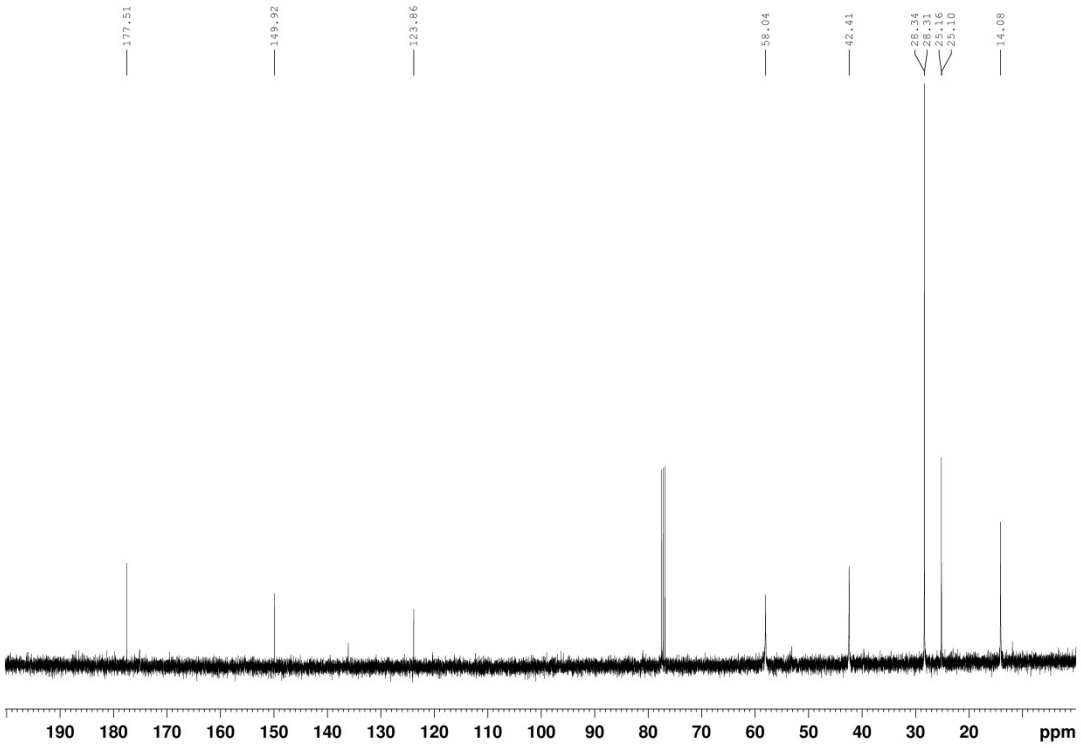
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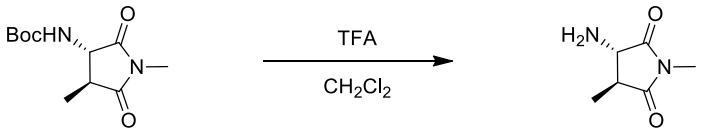
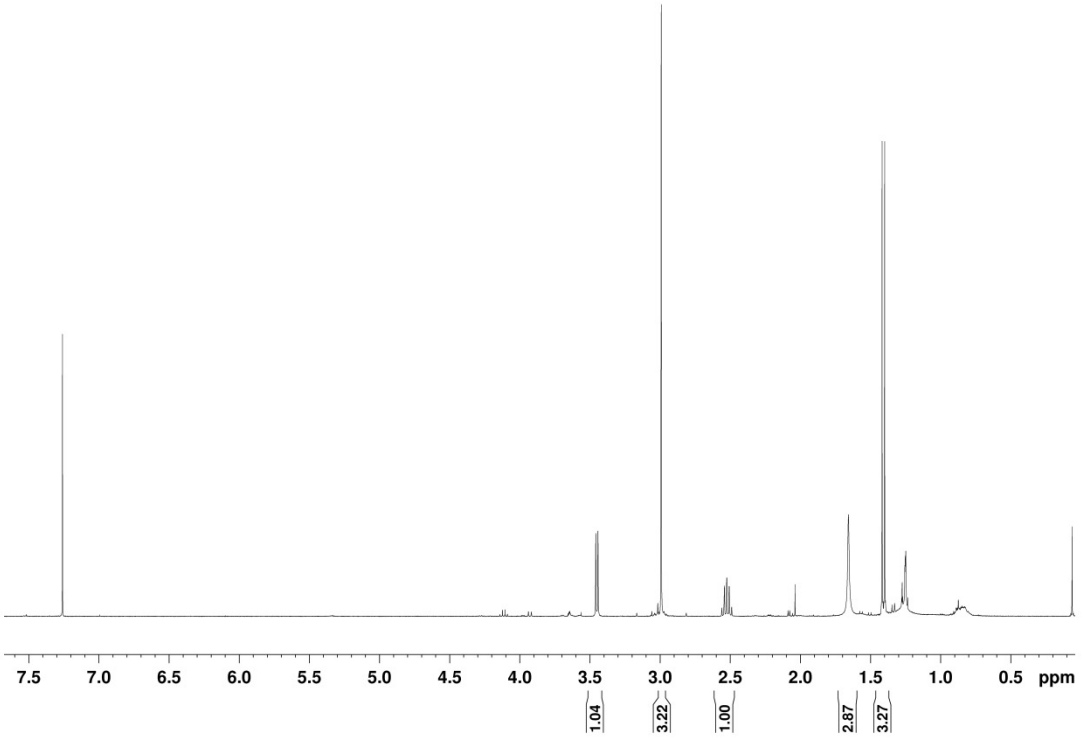



**39** **10**

**Amine 10: 39** (230 mg, 0.943 mmol, 1.00 eq.) was dissolved in DCM/TFA (3:1, 9.6 mL) and stirred at rt for 1.5 h under argon atmosphere. Afterwards the reaction mixture was concentrated under reduced pressure and coevaporated 4 times with chloroform. The crystalline solid was dissolved in EtOAc, filtered over basic alumina and concentrated under vacuum to give the title compound **10** as a pale yellow solid (98.3 mg, 0.691 mmol, 73%).

**TLC**: $R_f$ = 0.10 ($CH_2Cl_2$/MeOH 10:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 3.45 (d, *J* = 6.2 Hz, 1H), 2.99 (s, 3H), 2.53 (m, 1H), 1.66 (brs, 2H), 1.41 (d, *J* = 7.3 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 178.5, 177.9, 58.4, 44.5, 25.0, 13.9; **IR** (thin film): ν 3366, 3021, 2977, 2361, 1778, 1698, 1436, 1377, 1276, 1217, 1138, 1044, 1009, 772, 749; **HRMS** (ESI): calculated for $C_6H_{11}N_2O_2$ $[M+Na]^+$ 143.0815, found 143.0819; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -135.24 (c = 0.535 in $CHCl_3$).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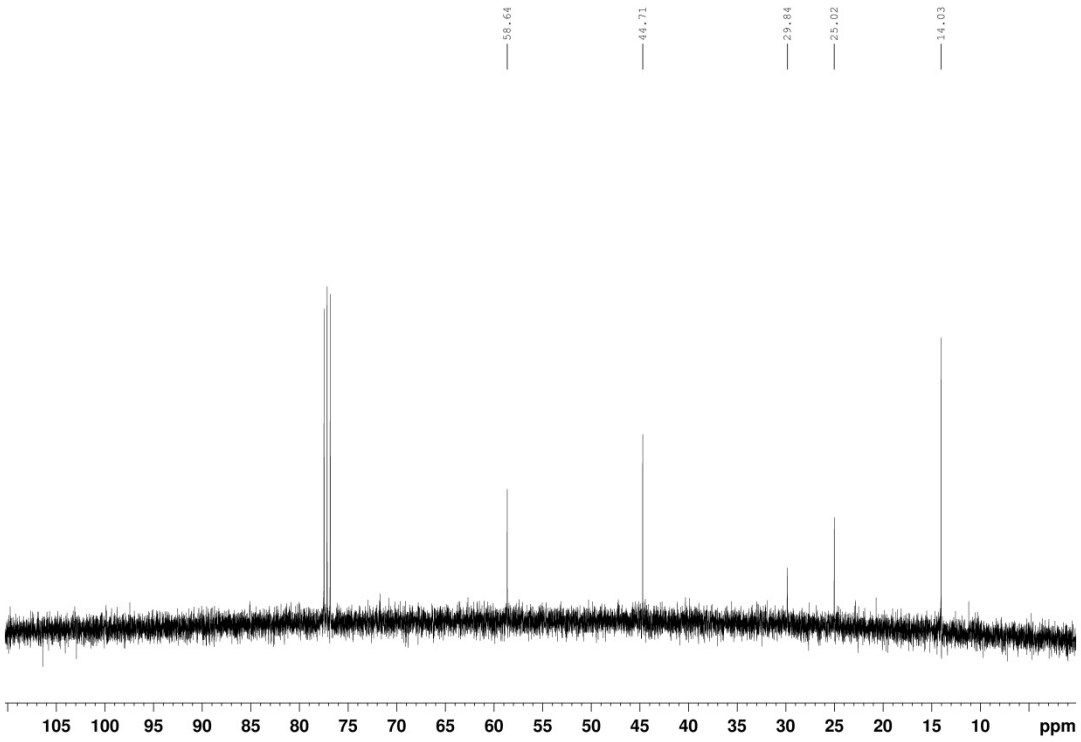
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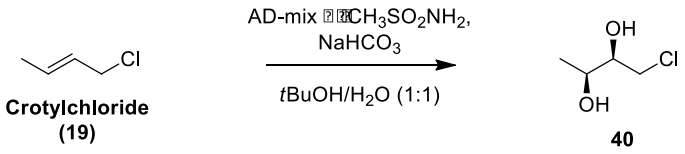
ppm

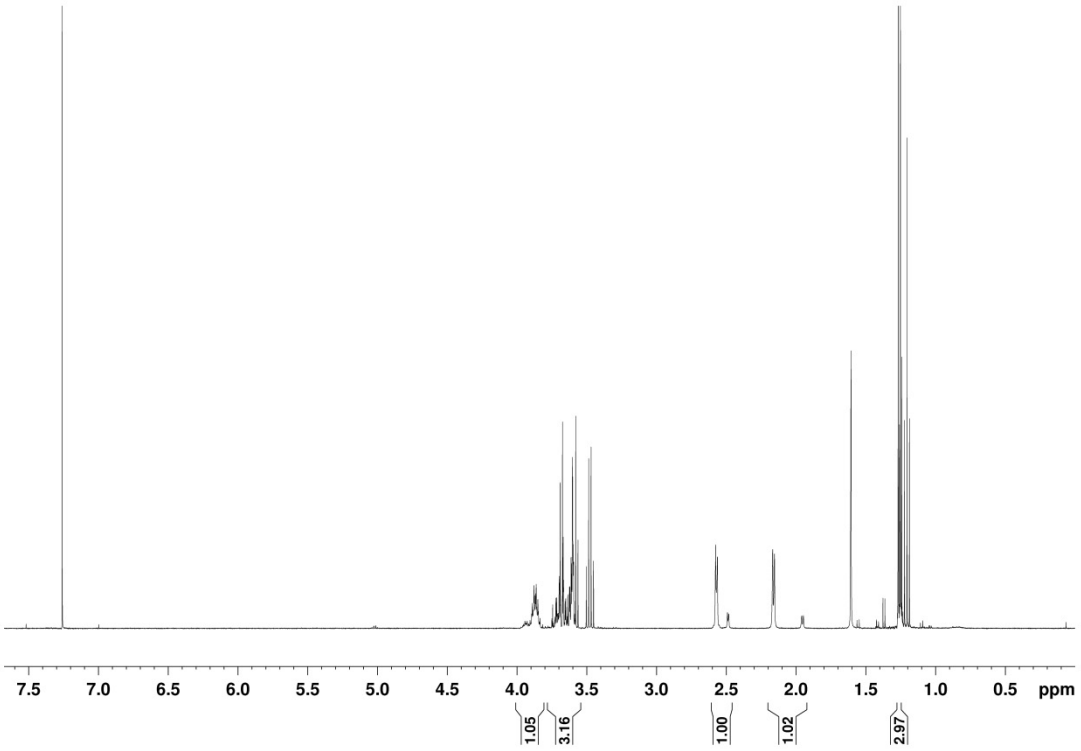
## 5.2.2. Synthesis of Protected *L*-Rhodinose 11




Crotylchloride (19) — 40

**Diol 40:** AD-mix-α (16.9 g, 21.6 mmol, 1.80 equiv.) and $NaHCO_3$ (3.05 g, 36.1 mmol, 3.00 equiv.), methanesulfonamide (1.15 g, 12.0 mmol, 1.00 equiv.) were added to 60 ml water and 60 ml t-BuOH. The solution was cooled to 0 °C (becoming a suspension) and then crotyl chloride (**19**) (E/Z ~ 6:1) (1.09 g, 12.0 mmol, 1.00 equiv.) was added. The reaction mixture was stirred at 0 °C for 4 d. The reaction was quenched by addition of 18 g $Na_2SO_3$ and stirred for 1 h at rt. The aqueous layer was extracted 3 x with 90 ml EtOAc. The combined org. layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($Et_2O$/pentane (9:1), d = 6 cm, 80 g silica) gave the desired product (1.26 g; 82 %, dr = 5.8:1) as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 3.89-3.83 (m, 1 H); 3.74-3.56 (m, 3 H); 2.57 (d, *J* = 5.0, 1 H *syn*); 2.49 (d, *J* = 3.7, 1 H *anti*); 2.16 (d, *J* = 5.0, 1 H *syn*); 1.95 (d, *J* = 4.9, *anti*); 1.26 (d, *J* = 6.4, 3 H *syn*); 1.2h (d, *J* = 6.4, 3 H *anti*); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 75.35, 68.16, 46.95, 19.66.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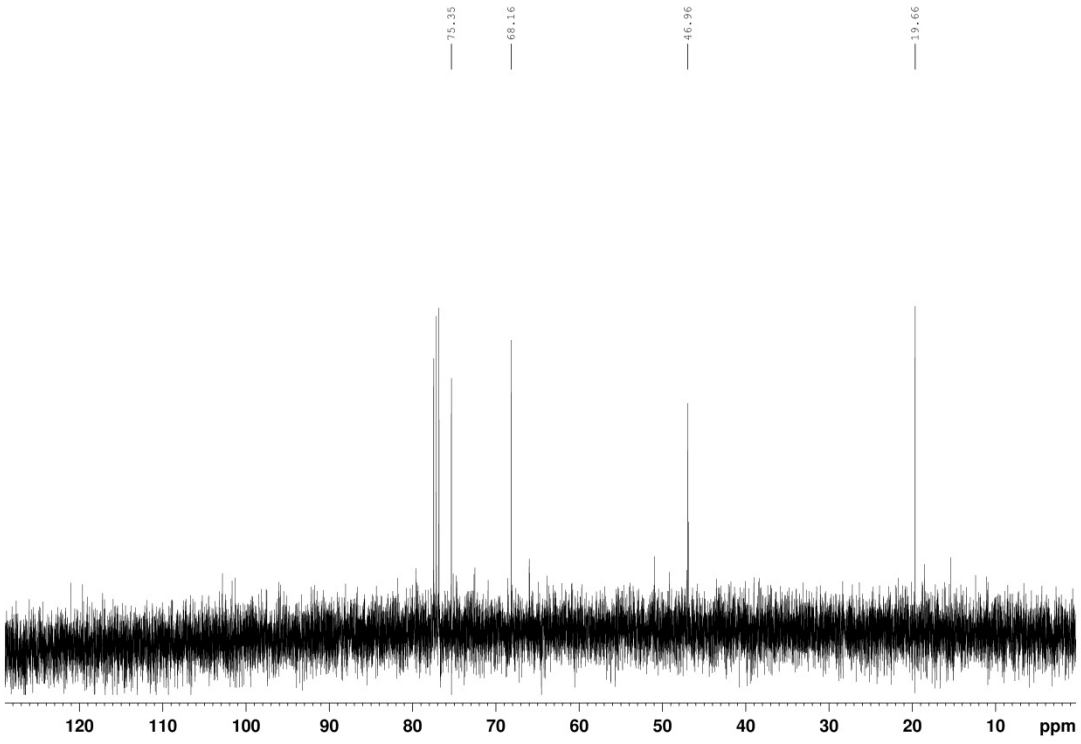
2.97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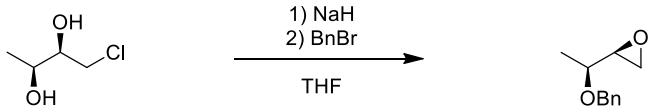
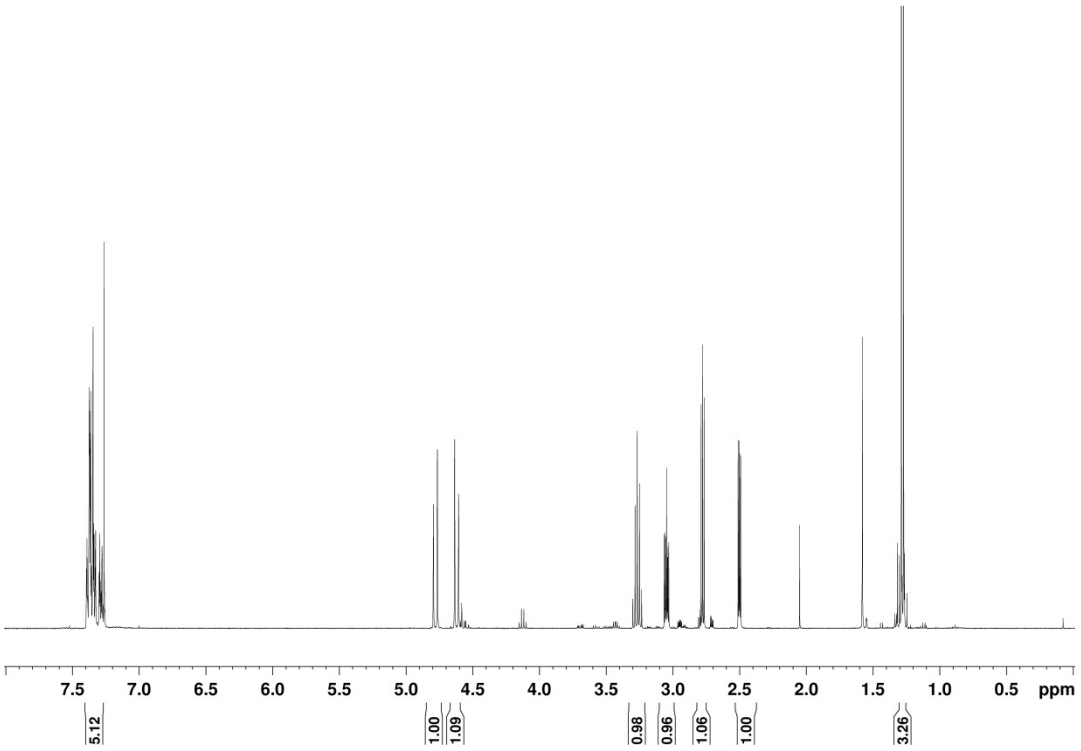
10
ppm




**40** **18**

**Epoxide 18:** To a solution of **40** (1.87 g, 15.0 mmol, 1.00 equiv.) in THF (140.0 ml) at 0 °C NaH (2.10 g, 52.5 mmol, 3.50 equiv.) was added. The solution was stirred for 2 h at 0 °C. Afterwards benzylbromide (3.57 ml, 30.0 mmol, 2.00 equiv.) was added neat. The reaction mixture was stirred at rt for 4 h. Then the reaction mixture was quenched with aqu. sat. $NaHCO_3$, extracted with $Et_2O$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:15)) gave 1.60 g (60 %) of the desired product as a yellow liquid.

**TLC**: $R_f$ = 0.17 (EtOAc/hexane 1:7, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ7.39-7.32 (m, 4 H); 7.30-7.27 (m, 1 H); 4.78 (d, *J* = 11.9, 1 H); 4.62 (d, *J* = 11.9, 1 H); 3.27 (quint, *J* = 6.6, 1 H); 3.05 (ddd, *J* =6.6, 4.2, 2.8, 1 H); 2.78 (dd, *J* =4.7, 4.2, 1 H); 2.50 (dd, *J* = 4.7, 2.8, 1 H); 1.28 (d, *J* = 6.6, 3 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 138.7, 128.5, 127.8, 127.6, 76.5, 71.3, 55.6 43.2, 17.5; **IR** (thin film): ν 3062, 3031, 2981, 2931, 2868, 1496, 1454, 1374, 13.26, 1287, 1255, 1204, 1103, 1069, 1028, 961, 908, 839, 738, 698; **HRMS** (ESI): calculated for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994, found 178.0989; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -10.05 (c = 1.02 in $CHCl_3$).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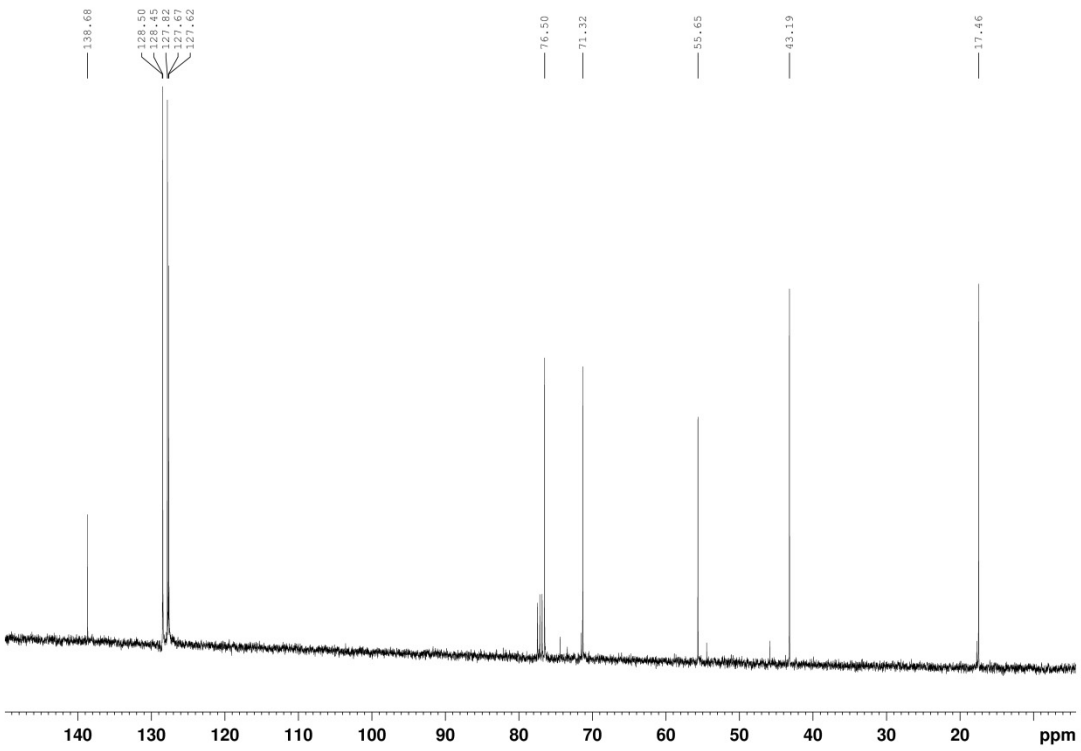
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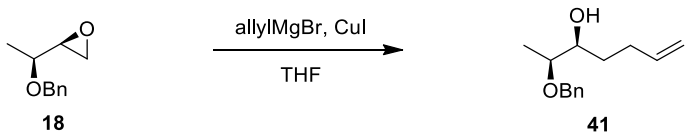
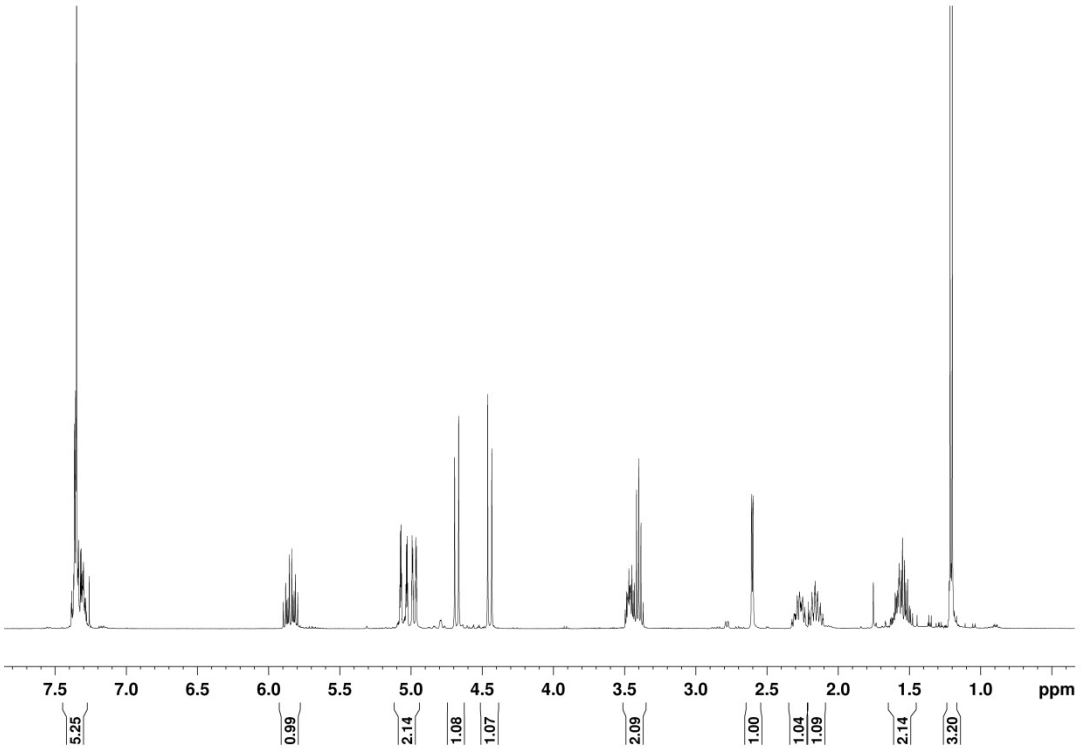



**18** **41**

**Alcohol 41:** To a suspesion of copper(I)iodide (0.0107 g, 0.0561 mmol, 0.10 equiv.) in THF (2.50 ml) at -40 °C, allylmagnesiumbromide (1.68 ml, 1.68 mmol, 3.00 equiv.) was added. The solution was stirred for 10 min at -40 °C. Afterwards a solution of **18** (0.100 g, 0.561 mmol, 1.00 equiv.) in 3.10 ml THF was added drop wise during 14 min (temperature never under over -30 °C). The reaction mixture was allowed to warm up to -25 °C. The reaction was stirred at -25 °C for 2.5 h. Then the reaction mixture was quenched with aqu. sat. $NH_4Cl$ and extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:7)) gave 102 mg (83 %) of the desired product as a colorless liquid.

**TLC**: $R_f$ = 0.13 (EtOAc/hexane 1:7, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5 H); 5.85 (ddt, *J* = 17.1, 10.3, 6.6, 1 H); 5.05 (dq, *J* = 17.1, 1.6, 1 H); 4.98 (dm, *J* = 10.3, 1 H); 4.68 (d, *J* = 12.6, 1 H); 4.45 (d, *J* = 12.6, 1 H); 3.49-3.43 (m, 1 H); 3.40 (quint, *J* = 6.2, 1 H); 2.60 (d, *J* = 3.8, 1 H); 2.32-2.23 (m, 1 H); 2.20-2.11 (m, 1 H); 1.64-1.48 (m, 2 H); 1.21 (d, *J* = 6.1, 3 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 138.6, 138.4, 128.6, 127.9, 127.8, 114.8, 78.4, 74.4, 71.1, 32.3, 29.9, 15.6; **IR** (thin film): ν 3440, 3065, 3031, 2975, 2933, 2869, 1640, 1496, 1453, 1375, 1332, 1305, 1269, 1206, 1072, 1027, 996, 910, 735, 697; **HRMS** (ESI): calculated for $C_{14}H_{20}O_2$ $[M]^+$ 220.1463, found 220.1458; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +26.53 (c = 0.92 in $CHCl_3$).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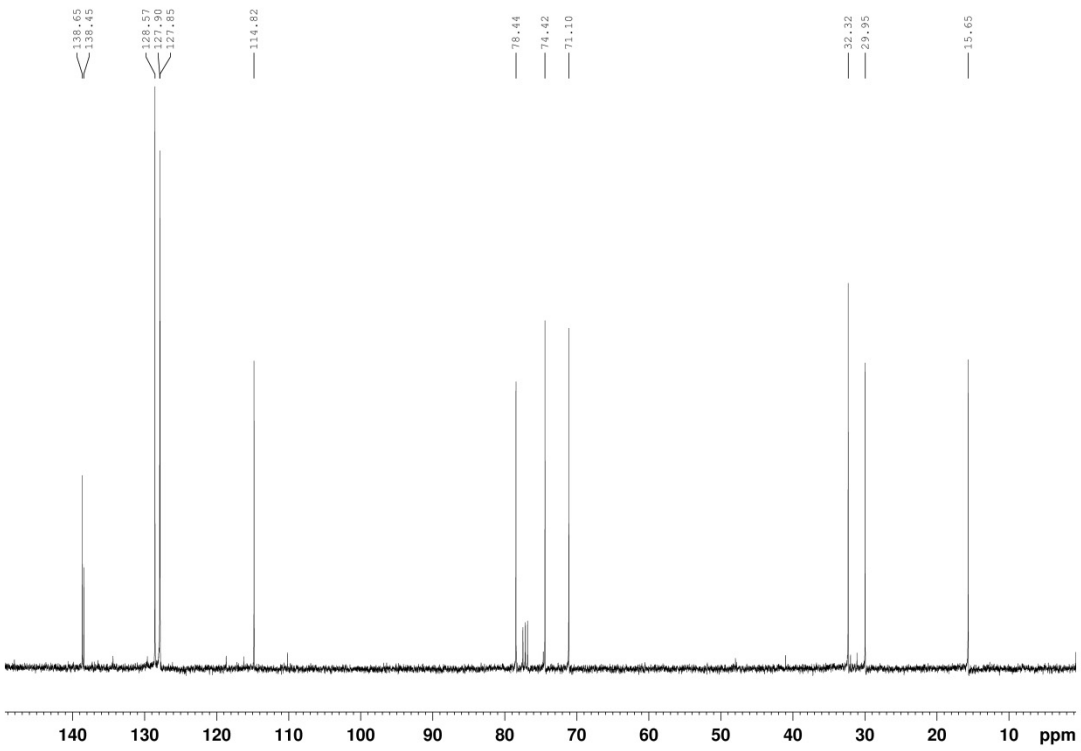
1.09
2.14
3.20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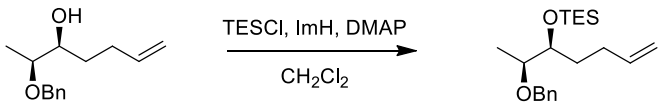
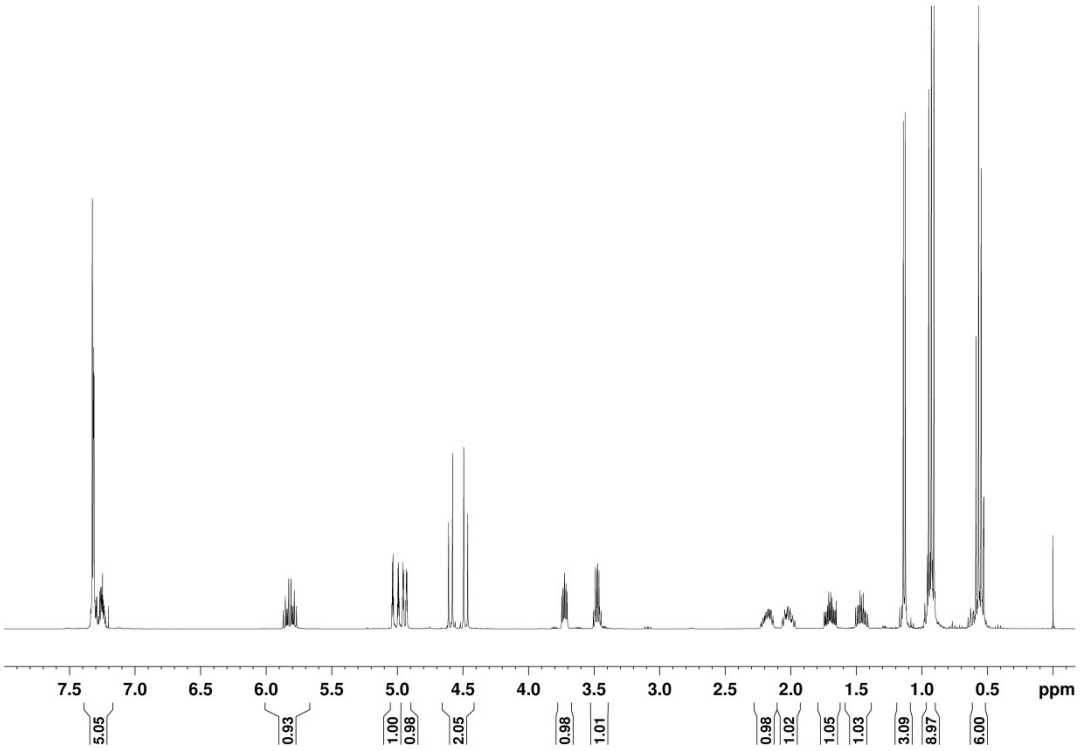
ppm




**41** **17**

**Silyl ether 17:** To a solution of **41** (1.46 g, 6.63 mmol, 1.00 equiv.) in $CH_2Cl_2$ (6.60 ml) at rt, Imidazole (1.03 g, 15.2 mmol, 2.30 equiv.) and DMAP (0.081 g, 0.663 mmol, 0.10 equiv.) were added. Afterwards TESCl (1.67 ml, 9.94 mmol, 1.50 equiv.) was added neat. (Reaction mixture turned from colorless to a white emulsion within minutes) The reaction mixture was stirred at rt overnight. Then the reaction mixture was diluted with hexane, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was filtered over a short path of silica (Eluent = EtOAc/hexane (1:10) to give 2.06 mg (93 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.58 (EtOAc/hexane 1:7, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.33-7.20 (m, 5 H); 5.82 (ddt, *J* = 17.1, 10.3, 3.6, 1 H); 5.01 (dq, *J* = 17.1, 1.6, 1 H); 4.94 (dm, *J* = 10.3, 1 H); 4.59 (d, *J* = 12.1, 1 H); 4.48 (d, *J* = 12.1, 1 H); 3.75-3.70 (m, 1 H); 3.47 (dq, *J* = 6.4, 6.3, 1 H); 2.23-2.13 (m, 1 H); 2.06-1.97 (m, 1 H); 1.74-1.65 (m, 1 H); 1.51-1.41 (m, 1 H); 1.13 (d, *J* = 6.4, 3 H); 0.93 (t, *J* = 7.8, 9H); 0.56 (q, *J* = 7.8, 6 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 139.1, 139.1, 128.4, 127.7, 127.5, 114.4, 77.4, 73.5, 71.0, 30.7, 30.3, 13.9, 7.0, 5.2; **IR** (thin film): ν 3066, 3031, 2953, 2876, 1641, 1496, 1455, 1414, 1374, 1239, 1082, 1004, 909, 821, 730, 686; **HRMS** (ESI): calculated for $C_{20}H_{34}NaO_2Si$ $[M]^+$ 357.2220, found 357.2220; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -6.07 (c = 1.05 in $CHCl_3$).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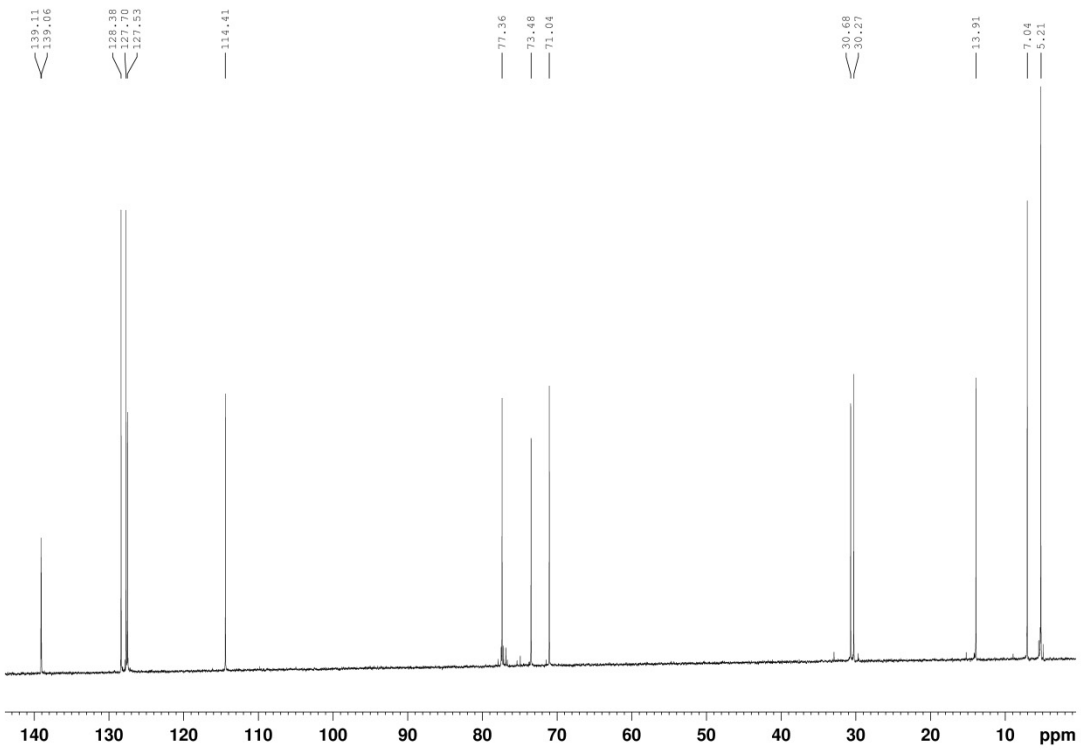
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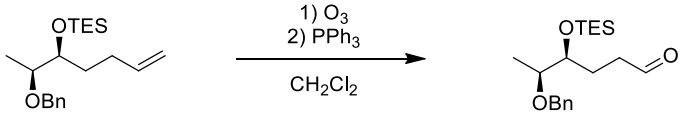
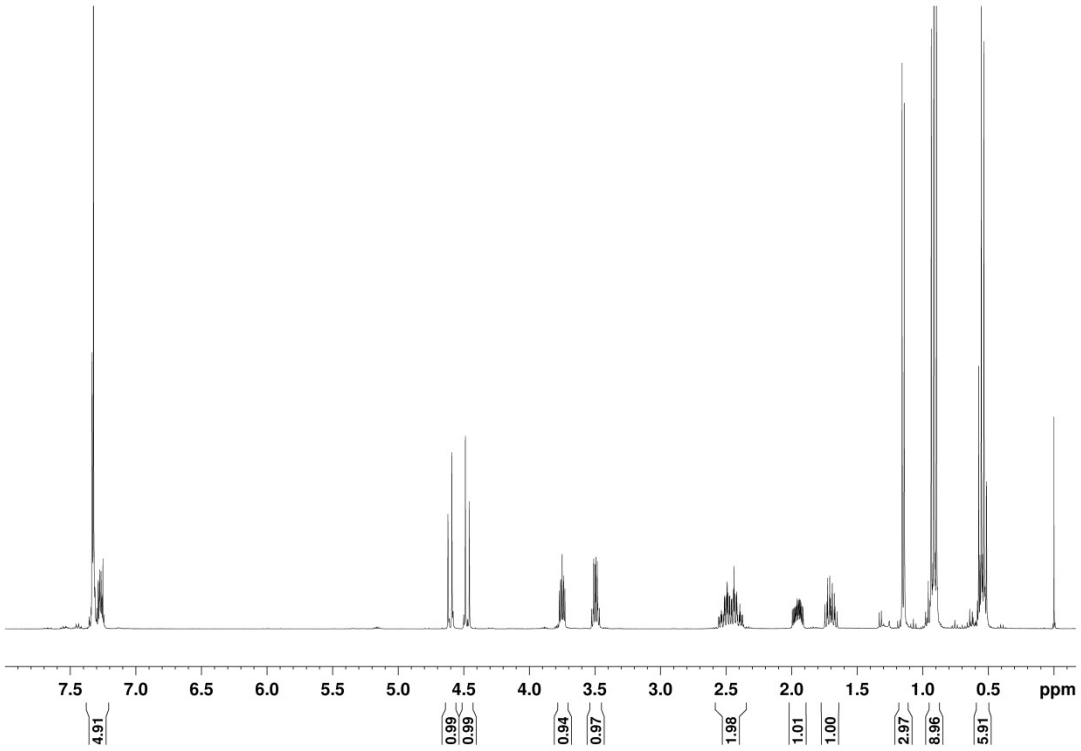



**17** **42**

**Aldehyde 42:** To a cooled (- 78 °C) solution of **17** (1.90 g, 5.68 mmol, 1.00 equiv.) in 380 ml DCM, ozone was bubbled through until a light blue color persisted in the solution. The excess of ozone was removed by exchanging with nitrogen gas. Afterwards triphenylphosphine (2.23 g, 8.52 mmol, 1.50 equiv.) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. Purification over silica gel (application of crude material on silica gel) (EtOAc/hexane 1:50 -> 1:5) gave 1.73 g (90 %) of the desired product as a colorless oil.

**TLC**: $R_f$ = 0.28 (EtOAc/hexane 1:7, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.8, 1 H); 7.33-7.25 (m, 5 H); 4.61 (d, *J* = 12.0, 1 H); 4.47 (d, *J* = 12.0, 1 H); 3.77-3.73 (m, 1 H); 3.49 (dq, *J* = 6.4, 6.3, 1 H); 2.56-2.37 (m, 2 H); 1.99-1.91 (m, 1 H); 1.75-1.65 (m, 1 H); 1.15 (d, *J* = 6.4, 3 H); 0.91 (t, *J* = 8.0, 9 H); 0.54 (q, *J* = 7.8, 6 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 202.8, 138.8, 128.4, 127.7, 127.6, 77.2, 73.0, 71.0, 40.6, 23.9, 13.6, 7.0, 5.1; **IR** (thin film): ν 2954, 2876, 2715, 1725, 1555, 1414, 1377, 1239, 1090, 1005, 893, 733, 697; **HRMS** (ESI): mass not found; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -4.80 (c = 1.04 in $CHCl_3$).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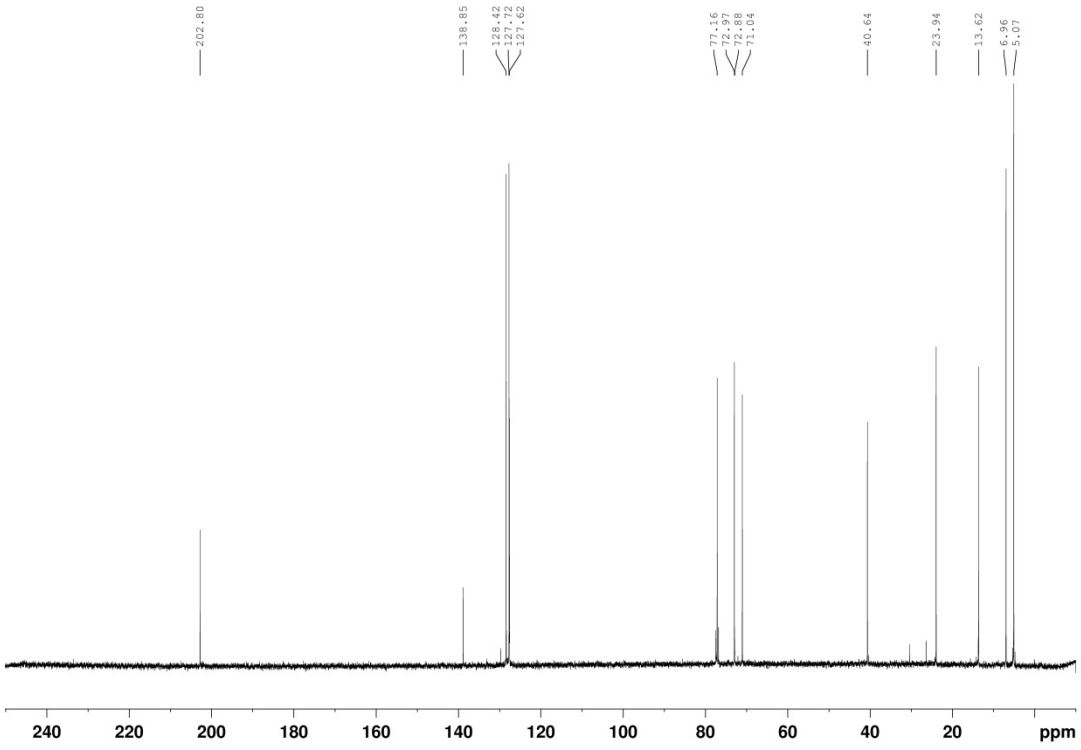
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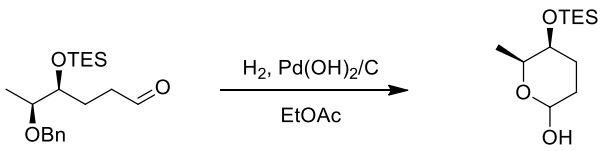
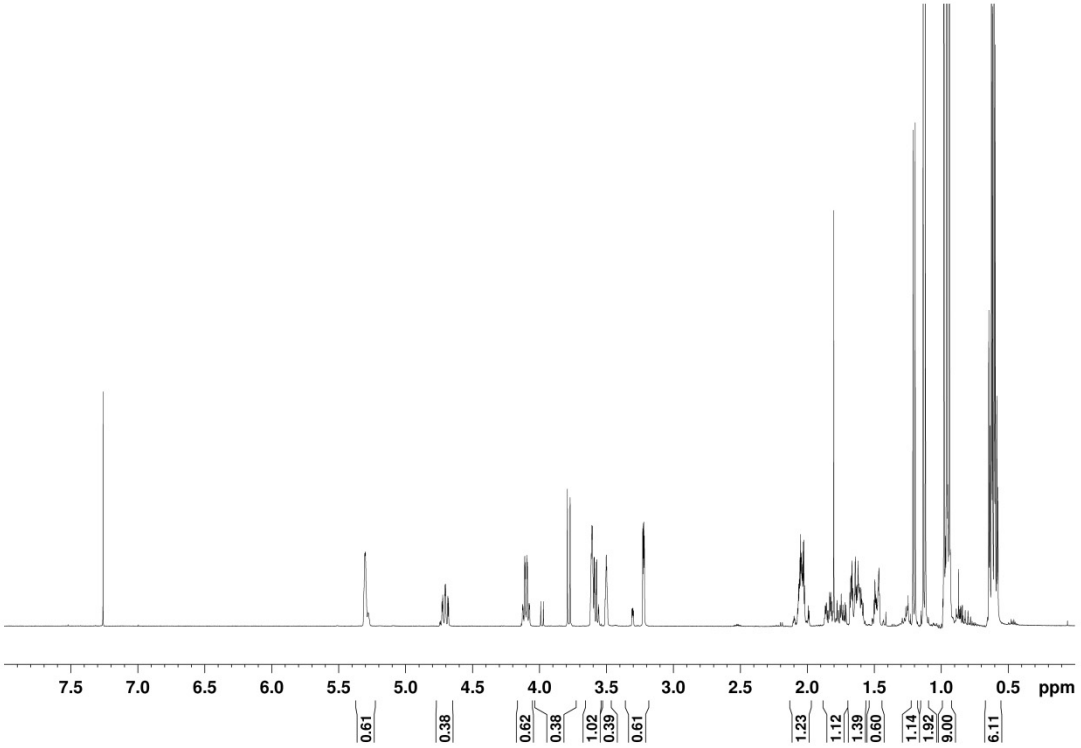



**42** **11**

**Hemiacetal 11:** To a solution of **42** (0.871 g, 2.59 mmol, 1.00 equiv.) in 26.0 ml EtOAc, palladiumhydroxide on carbon (0.217 g, 20 % w/w) was added. The reaction mixture was stirred under 5 bar hydrogen atm. for 60 min. The reaction mixture was filtered over celite and concentrated under reduced pressure. Purification over silica gel (EtOAc / hexane (1:8)) gave 433.0 mg (68 %) of the desired product as colorless oil.

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ 5.30 (brs, 0.5 H); 5.28 (brs, 0.1 H); 4.74-4.68 (m, 0.4 H); 4.10 (dq, *J* = 6.5, 1.3, 0.6 H); 3.98 (d, *J* = 7.9, 0.05 H); 3.78 (d, *J* = 7.9, 0.35 H); 3.61 (brs, 0.6 H); 3.58 (dq, *J* = 6.5, 1.3, 0.4 H); 3.50 (brs, 0.4H); 3.31-3.30 (m, 0.1 H); 3.23-3.22 (m, 0.5 H); 2.11-1.99 (m, 1.3 H); 1.87-1.71 (m, 0.7 H); 1.68-1.58 (m, 1.3 H); 1.50-1.46 (m, 0.7 H); 1.20 (d, *J* = 6.5, 1.2 H); 1.13 (d, *J* = 6.5, 1.8 H); 0.96 (t, *J* = 8.0, 9 H); ); 0.64-0.58 (m, 6 H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 96.5, 91.7, 74.8, 68.1, 67.3, 66.9, 30.7, 27.6, 25.9, 24.0, 17.7, 17.5, 7.0, 5.0.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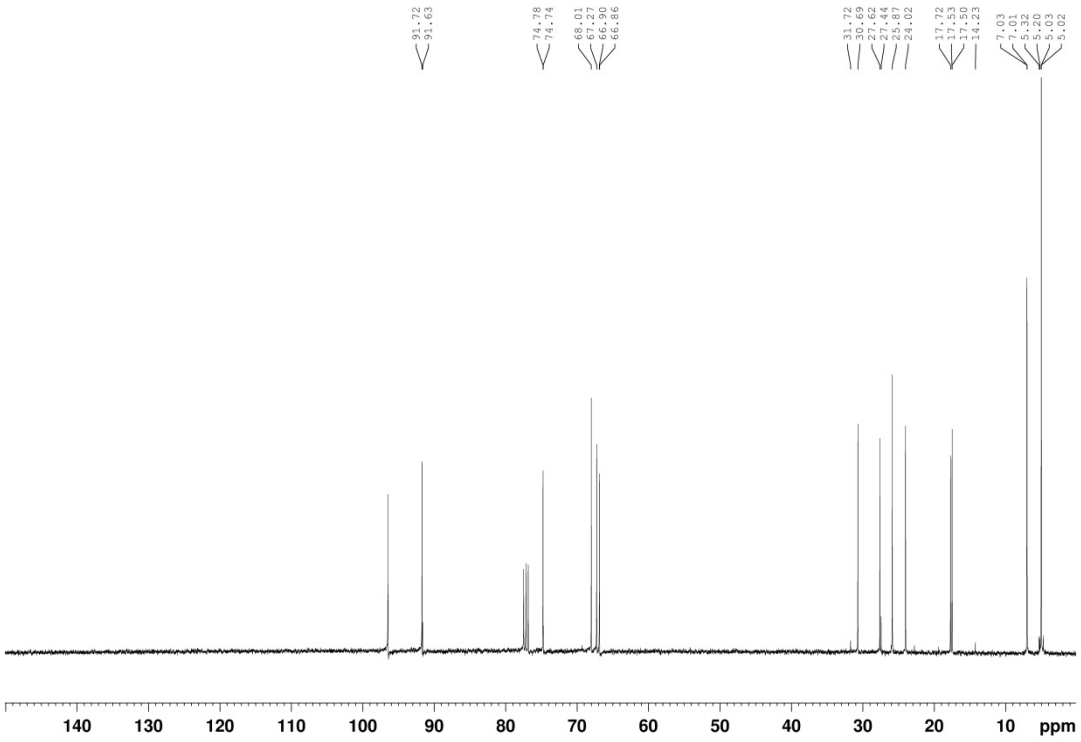
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27.44
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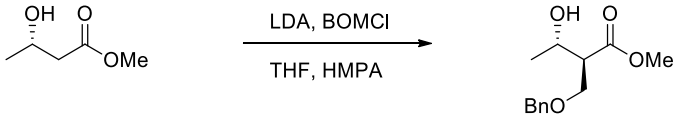
24.02
17.72
17.53
17.50
14.23
7.03
7.01
5.32
5.20
5.03
5.02
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

# 5.3. Bu-2313 B

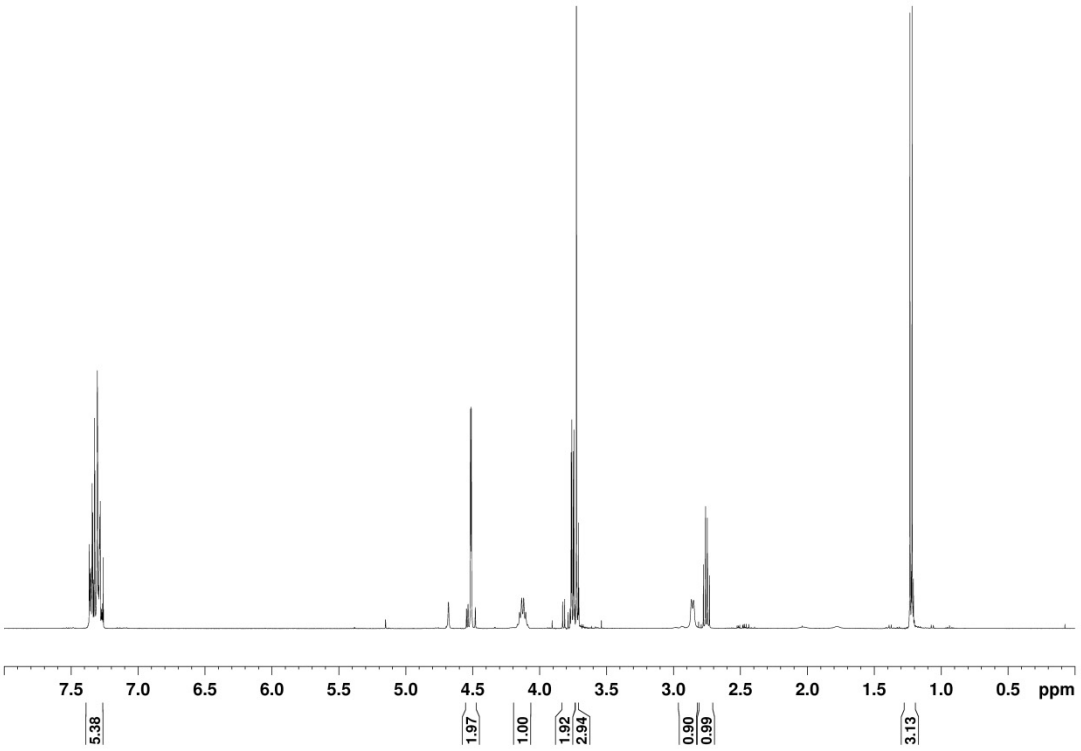
## 5.3.1. Epoxide Opening Strategy




**(*S*)-methyl 3-hydroxybutanoate** **221**

**Alkylation product 221:** To a solution of Diisopropylamine (37.54 ml, 267.84 mmol, 2.00 equiv.) in 610.0 ml THF at -78 °C, BuLi (175.77 ml, 281.23 mmol, 2.10 equiv.) was added dropwise over 5 min. The reaction mixture was stirred at -78 °C for 30 min, was then warmed up to 0 °C and re-cooled to -78 °C and stirred again for 30 min. Afterwards a solution of **(*S*)-methyl-3-hydroxybutyrate** (15.00 ml, 133.92 mmol, 1.00 equiv.) in 305 ml THF was added dropwise over 17 min at -78 °C. After 60 min a solution of freshly prepared benzylchloromethylether (25.98 ml, 187.49 mmol, 1.40 equiv.) in freshly distilled HMPA (42.12 ml, 133.92 mmol, 1.00 equiv.) was added dropwise over 5 min. The reaction mixture was stirred at -78 °C for 4 h. Afterwards the reaction was quenched by addition of 300 ml aqu. sat. $NH_4Cl$. The phases were separated and the aqu. phase extracted twice with ether. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc / hexane (1:2) gave 2.01 g (6.3 %) of the desired product and (16.7 g) of a mixture of the desired product and starting material. The starting material was distilled off by Kugelrohr distillation (56-58 °C, 11 torr) giving 10.44 g (33 %) of the desired product **221** as colorless liquid and 5.69 g (36 %) of recovered starting material.

**TLC**: $R_f$ = 0.21 (EtOAc/hexane 1:2, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 5H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.76 (d, *J* = 1.7 Hz, 1H), 3.75 (d, *J* = 2.0 Hz, 1H), 3.73 (s, 3H), 2.86 (d, *J* = 6.6 Hz, 1H), 2.75 (td, *J* = 6.3, 5.6 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 173.7, 137.8, 128.5, 127.9, 127.7, 73.4, 68.7, 66.5, 52.6, 52.0, 21.2; **IR** (thin film): ν 3460, 2971, 2871, 2360, 2327, 1733, 1454, 1436, 1363, 1263, 1198, 1172, 1096, 1049, 771, 738, 697; **HRMS** (ESI): calculated for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097, found 261.1097; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +6.20° (c = 1.00 in $CHCl_3$).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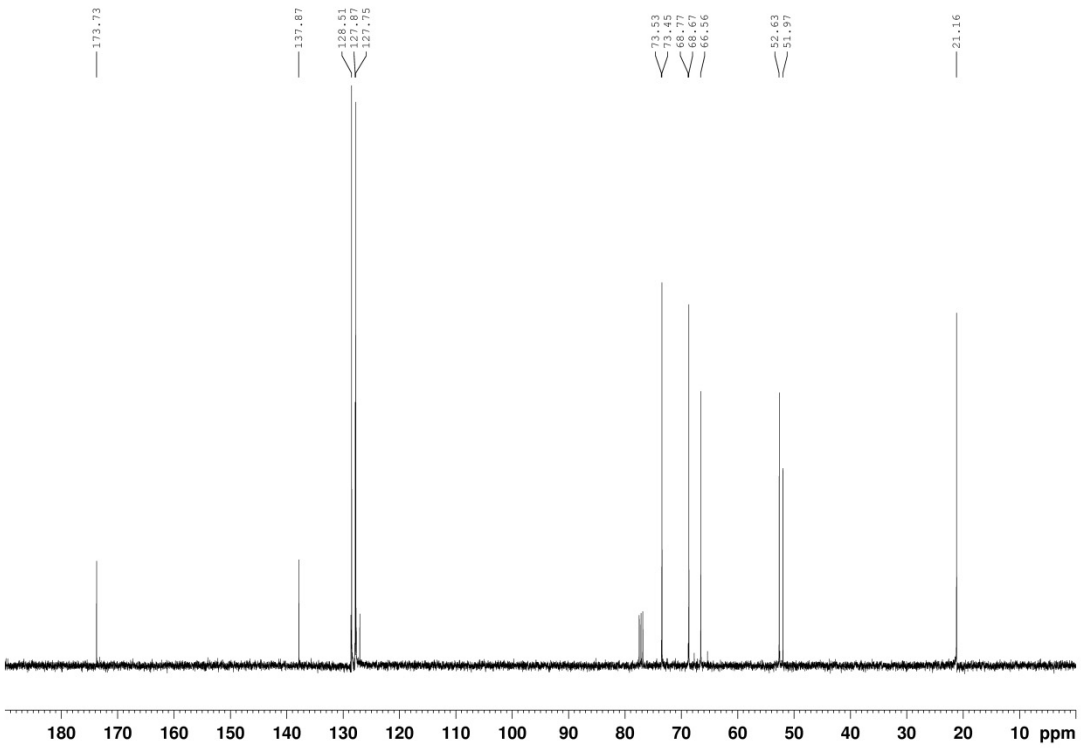
0.90
0.99
3.13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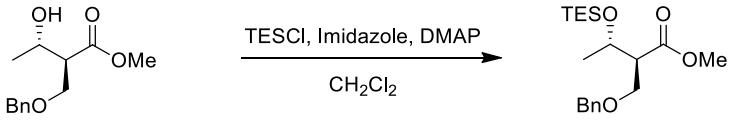
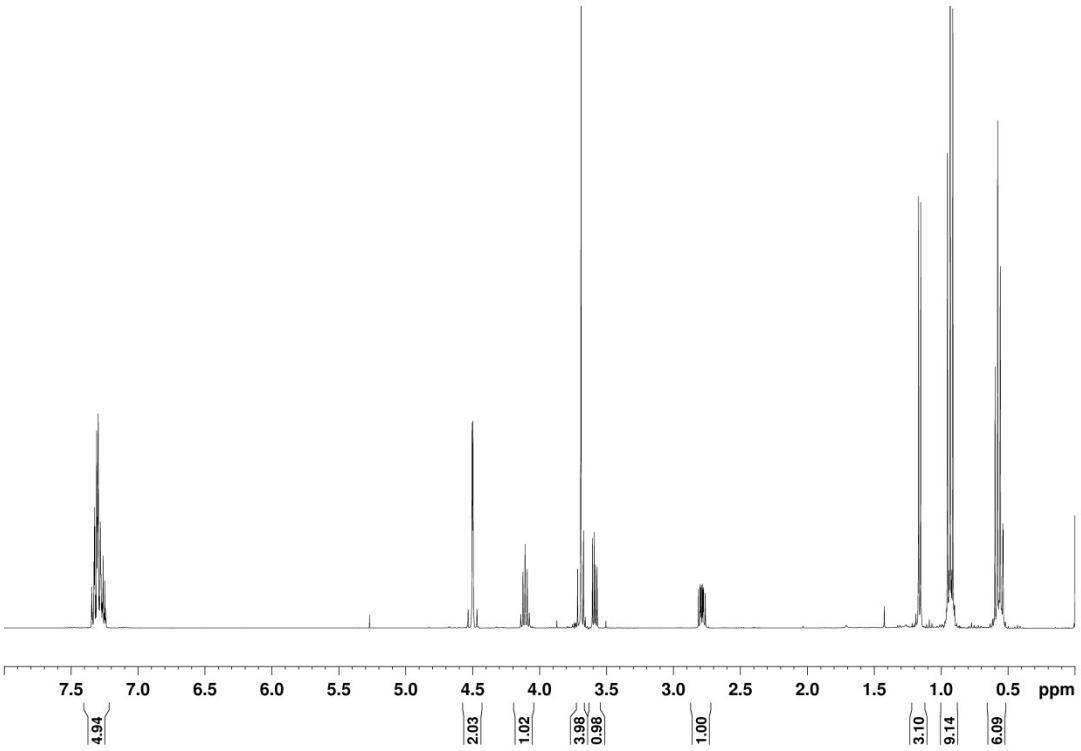
ppm




**221** **55**

**Silyl ether 55:** To a solution of **221** (10.79 g, 45.32 mmol, 1.00 equiv.) in $CH_2Cl_2$ (45.0 ml) at rt, Imidazole (7.09 g, 104.23 mmol, 2.30 equiv.) and DMAP (0.55 g, 4.53 mmol, 0.10 equiv.) were added. Afterwards TESCl (11.41 ml, 67.98 mmol, 1.50 equiv.) was added neat (Reaction mixture turned from colorless to a white emulsion within minutes). The reaction mixture was stirred at rt overnight. Then the reaction mixture was diluted with hexane, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($Et_2O$/pentane (1:30) → (1:15)) to give 15.18 g (95 %) of the desired product **55** as colorless liquid.

**TLC**: $R_f$ = 0.14 (EtOAc/hexane 1:30, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5 H); 4.52 (d, *J* = 12.1, 1 H); 4.48 (d, *J* = 12.1, 1 H); 4.11 (q, *J* = 6.3, 1 H); 3.71-3.67 (m, 1 H); 3.69 (s, 3 H); 3.59 (dd, *J* = 9.2, 5.1, 1 H); 2.81-2.76 (m, 1 H); 1.16 (d, *J* = 6.3, 3 H); 0.93 (t, *J* = 8.0, 9 H); 0.57 (q, *J* = 8.0, 6 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 173.2, 138.2, 128.4, 127.7, 73.3, 68.1, 67.5, 54.7, 51.6, 22.0, 6.9, 5.0; **IR** (thin film): ν 2954, 2912, 2874, 1738, 1457, 1437, 1376, 1240, 1198, 1171, 1100, 1004, 743; **HRMS** (ESI): calculated for $C_{19}H_{32}NaO_4Si$ $[M+Na]^+$: 375.1962, found 375.1953; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +8.04° (c = 1.00 in $CHCl_3$).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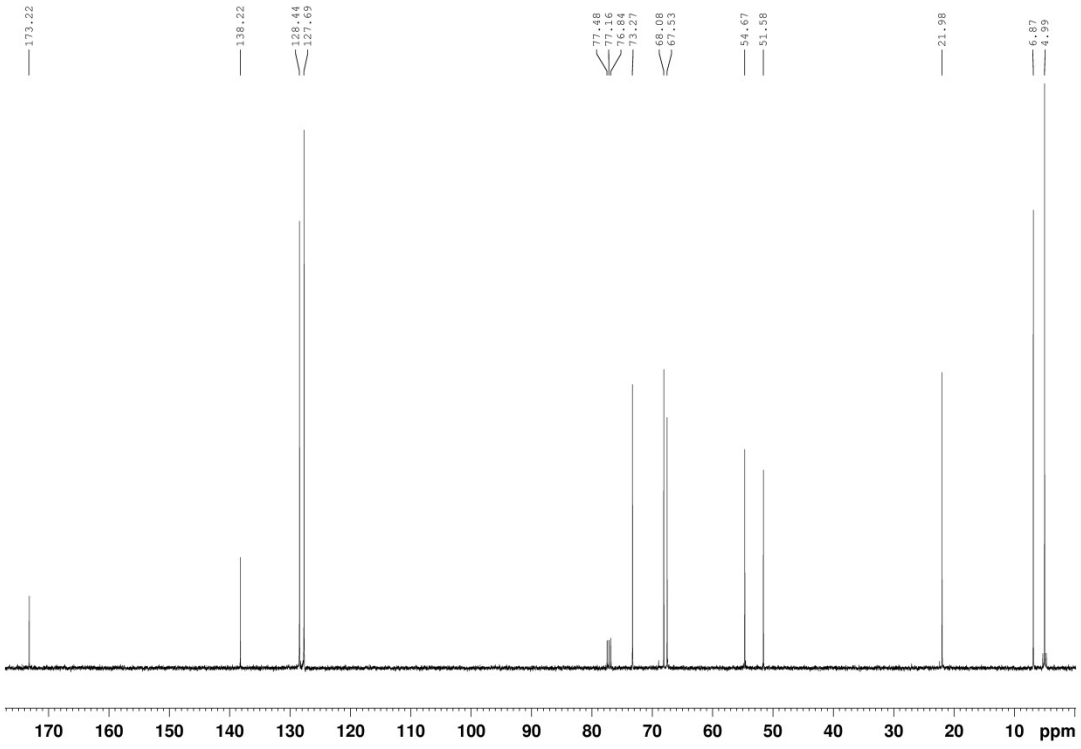
6.09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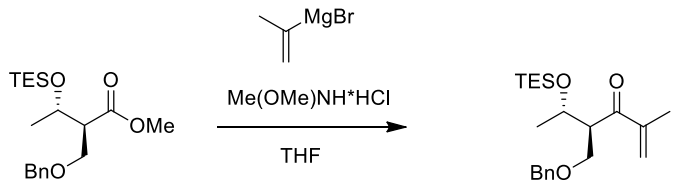
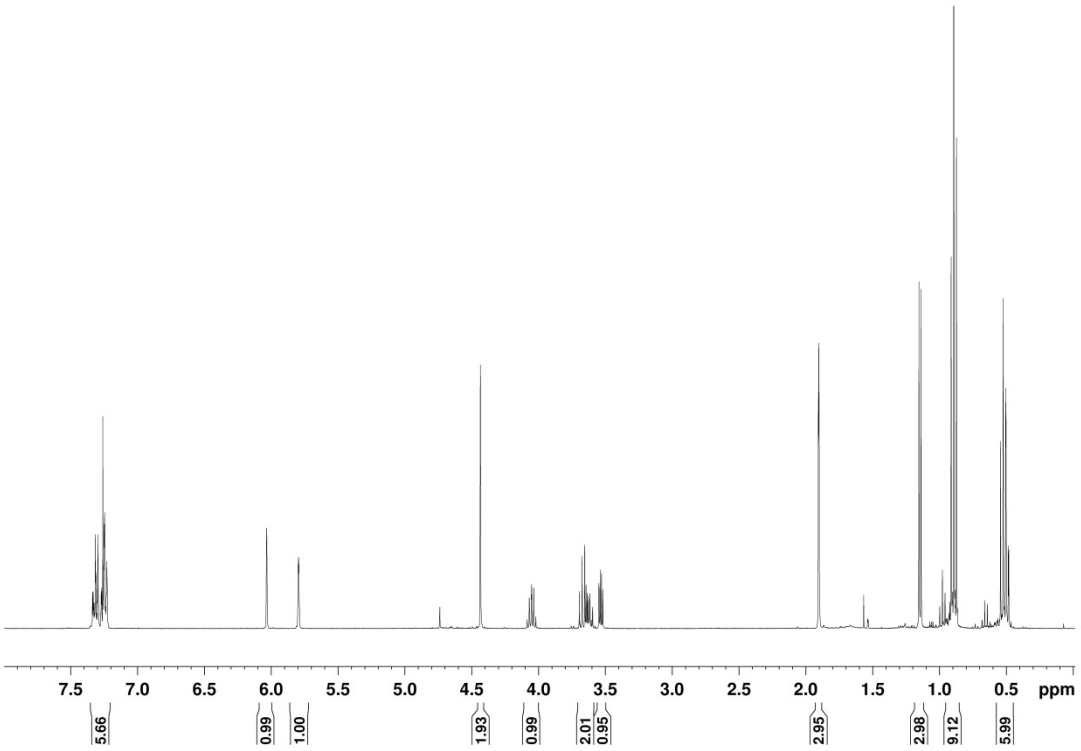



**55** **56**

**Ketone 56:** To a slurry of **55** (1.00 g, 2.84 mmol, 1.00 equiv.) and *Weinreb* amine (0.346 g, 3.54 mmol, 1.25 equiv.) in THF (28.3 ml) at -15 °C, feshly prepared isopropenylmagnesiumbromide (11.4 ml, 22.7 mmol, 8.00 equiv.) (2 M in THF) was added drop wise during 10 min (Temperature never over – 5 °C). The reaction mixture was stirred at -5 °C for 1 h. Afterwards the reaction mixture was allowed to heat up to rt and stirred overnight. Afterwards the reaction was quenched by addition of aqu. sat. $NH_4Cl$. The phases were separated and the aqu. phase extracted twice with ether. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20)) gave 200 mg (19.4 %) of the desired product as slightly yellow oil. Also 0.63 g of TES deprotected side product (**57**) was isolated.

The mixture containing the side products was submitted to a TES protection (see **55**). After purification over silica gel (EtOAc/hexane (1:20)) 501 mg (48.7 %) of the desired product was obtained.

**$^1$H-NMR** (400 MHz, CDCl3): δ 7.34-7.23 (m, 5 H); 6.03 (s, 1 H); 5.80-5.79 (m, 1 H); 4.43 (s, 2 H); 4.08-4.02 (m, 1 H); 3.69 (m, 2 H); 3.53 (dd, J = 7.7, 3.7, 1 H); 1.90 (s, 3 H); 1.15 (d, J = 6.2, 3 H); 0.89 (t, J = 7.9, 9 H); 0.51 (q, J = 7.9, 6 H); **$^{13}$C-NMR** (100 MHz, CDCl3): δ 203.6, 146.0, 138.4, 128.4, 127.6, 127.5, 125.5, 73.4, 69.4, 68.7, 54.2, 22.2, 17.9, 6.9, 5.0.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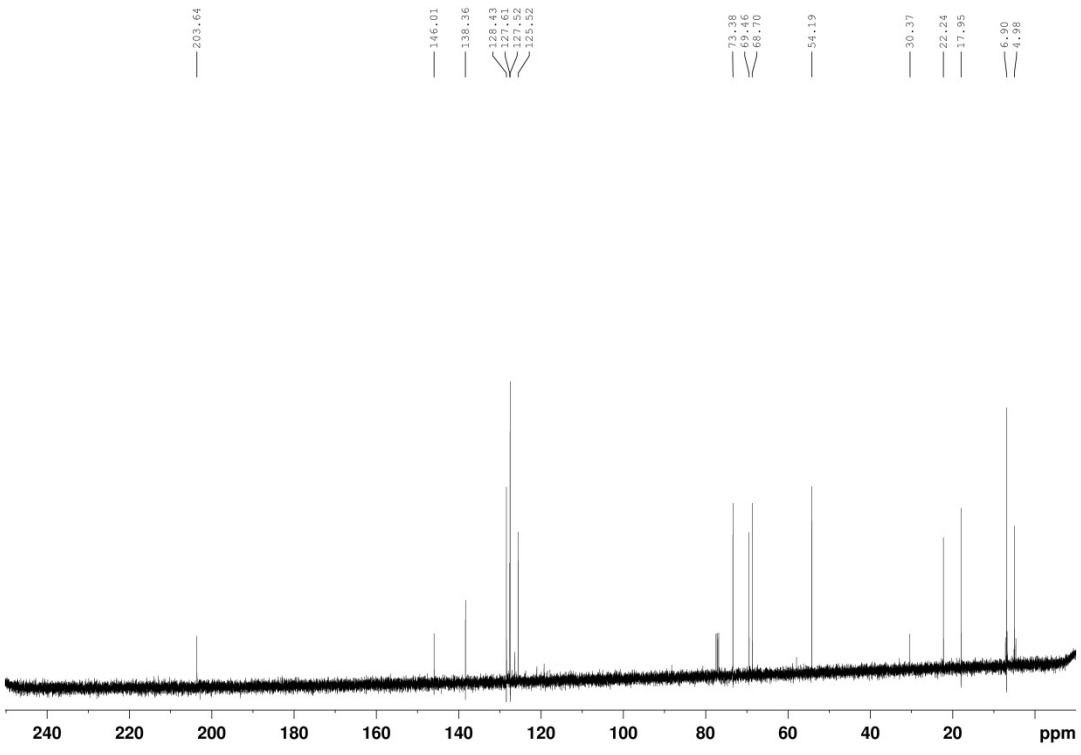
5.99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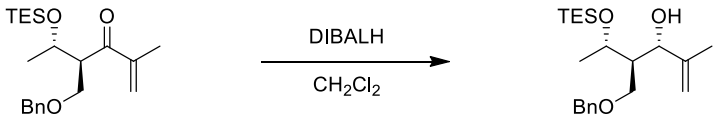
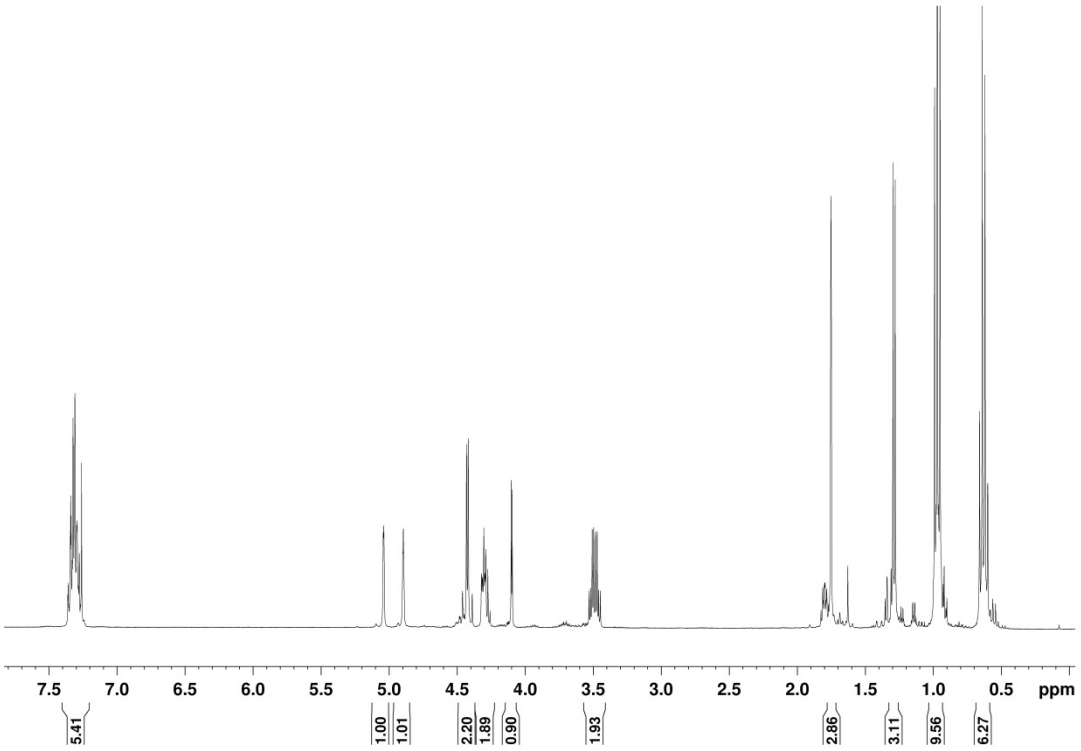



**56** **49a**

**Ketone 49a:** To a solution of **56** (0.020 g, 0.055 mmol, 1.00 equiv.) in 0.55 ml $CH_2Cl_2$ at -78 °C, diisobutylaluminium hydride (0.099 ml, 0.099 mmol, 1.80 equiv.) was added drop wise over 2 min. The reaction mixture was stirred at -78 °C for 2 h. (TLC showed conversion, but not complete). Additional DIBAL (0.05 ml) was added and the reaction mixture was stirred for another hour at -78 °C. Afterwards the reaction mixture was quenched with aqu. sat. sodium potassium tartrate. The aqu. phase was extracted with $CH_2Cl_2$, the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:20) gave 11 mg (54 %) of the desired product as colorless oil and a dr of 1:16.

Data from major isomer only

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5 H); 5.04 (s, 1 H); 4.87 (s, 1 H); 4.44 (d, *J* = 11.9, 1 H); 4.40 (d, *J* = 11.9, 1 H); 4.32-4.25 (m, 2 H); 4.10 (d, *J* = 3.1, 1 H); 3.51 (dd, *J* = 9.5, 4.4, 1 H); 3.46 (dd, *J* = 9.5, 5.0, 1 H); 1.82-1.76 (m, 1 H); 1.75 (s, 3 H); 1.29 (d, *J* = 6.3, 3 H); 0.97 (t, *J* = 7.9, 9 H); 0.63 (q, *J* = 7.9, 6 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 146.1, 138.5, 128.4 (2 C), 127.7 (2 C), 127.6, 112.5, 77.2, 73.4, 70.7, 69.9, 48.1, 23.1, 18.1, 6.9 (3 C), 5.1 (3 C).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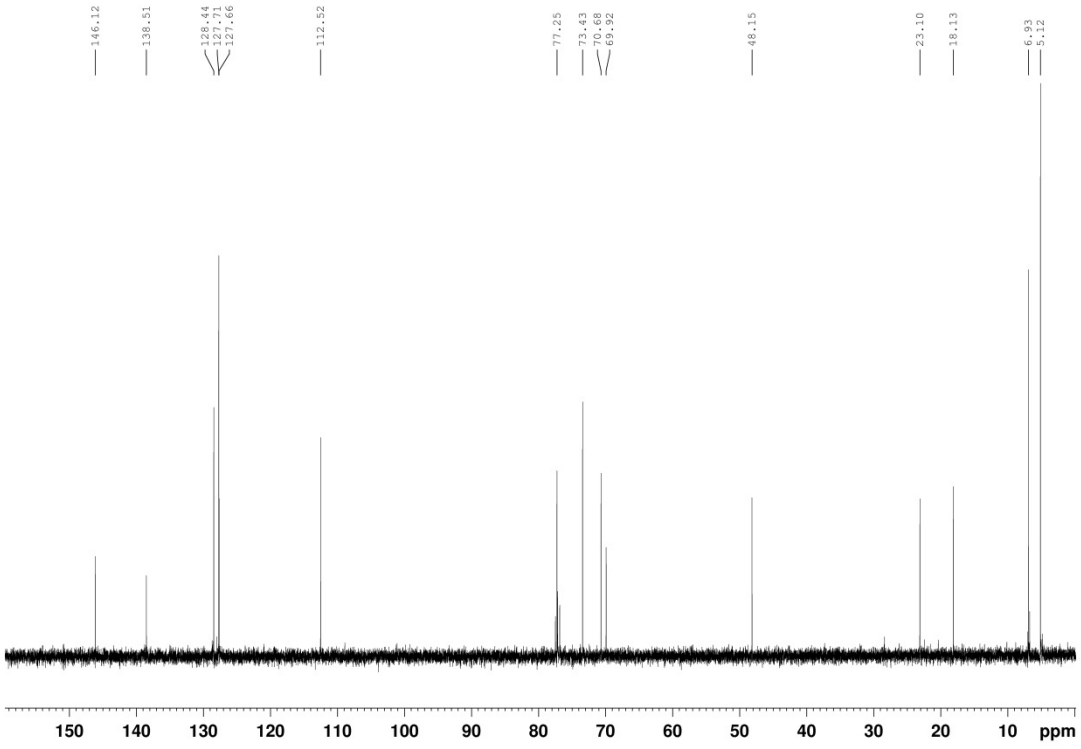
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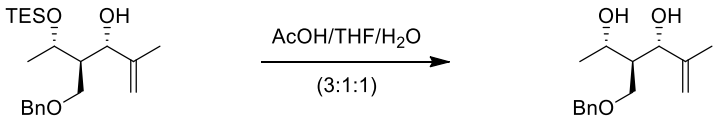
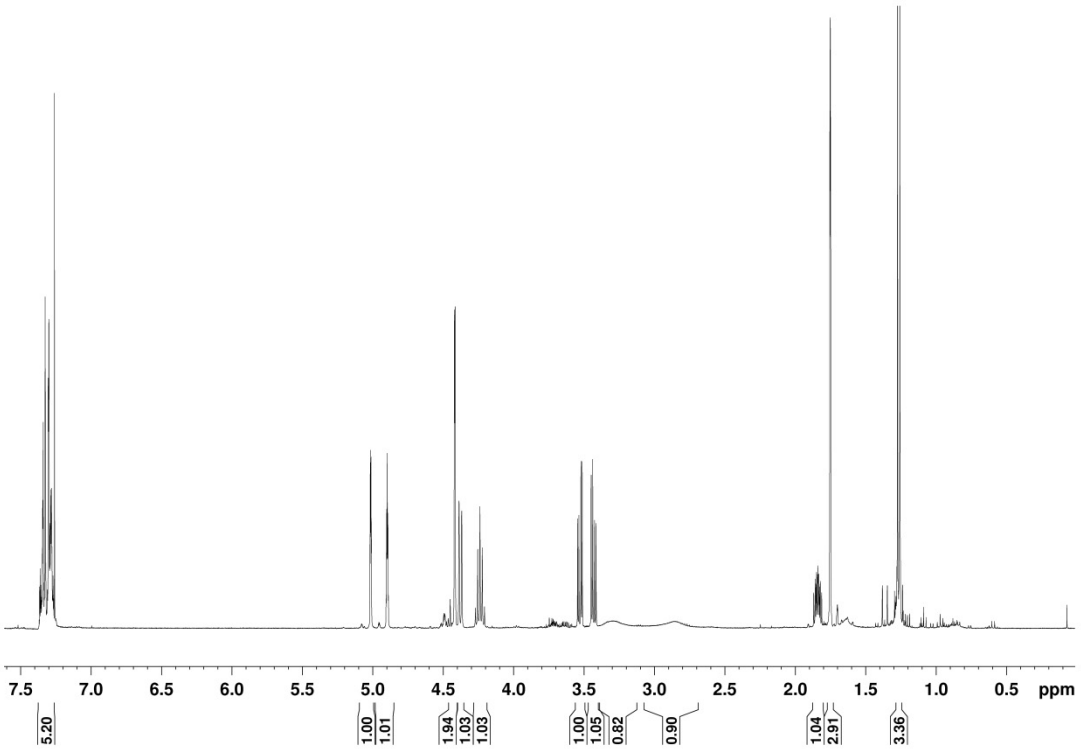



**49a** **222a**

**Diol 222a:** To a solution of **49a** (0.020 g, 0.055 mmol, 1.00 equiv.) in THF (0.40 ml), 0.40 ml water and 1.20 ml AcOH was added at rt. The reaction mixture was stirred at rt for 15 min. The reaction mixture was neutralized with $Na_2CO_3$, extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:2)) gave 11.3 mg (82 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5 H); 5.02-5.01 (m, 1 H); 4.90-4.89 (m, 1 H); 4.43 (d, *J* = 12.0, 1 H); 4.40 (d, *J* = 12.0, 1 H); 4.38 (d, *J* = 7.6, 1 H); 4.24 (quint, *J* = 6.4, 1 H); 3.53 (dd, *J* = 9.5, 3.8, 1 H); 3.43 (dd, *J* = 9.5, 4.5, 1 H); 3.29 (brs, 1 H); 2.85 (brs, 1 H); 1.87-1.81 (m, 1 H); 1.75 (s, 3 H); 1.27 (d, *J* = 6.4, 3 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 146.4, 138.0, 128.5 (2 C), 127.9, 127.8 (2 C), 113.1, 77.9, 73.7, 70.1, 68.9, 47.6, 21.2, 17.5.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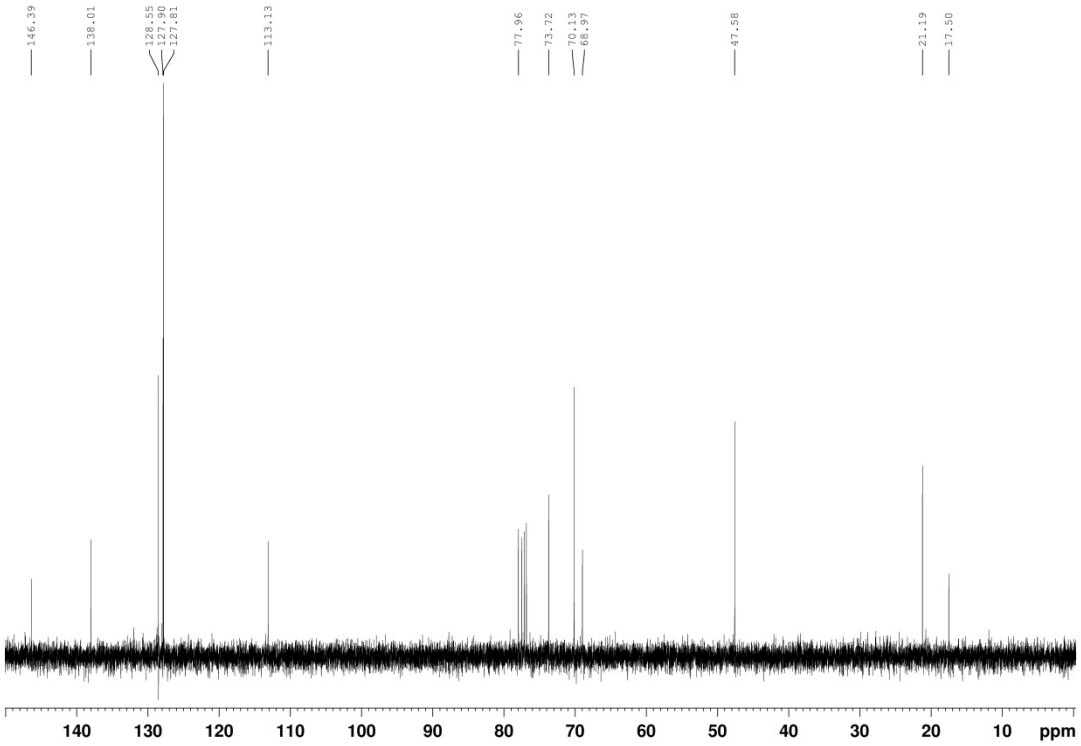
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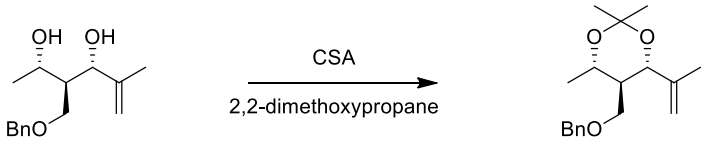
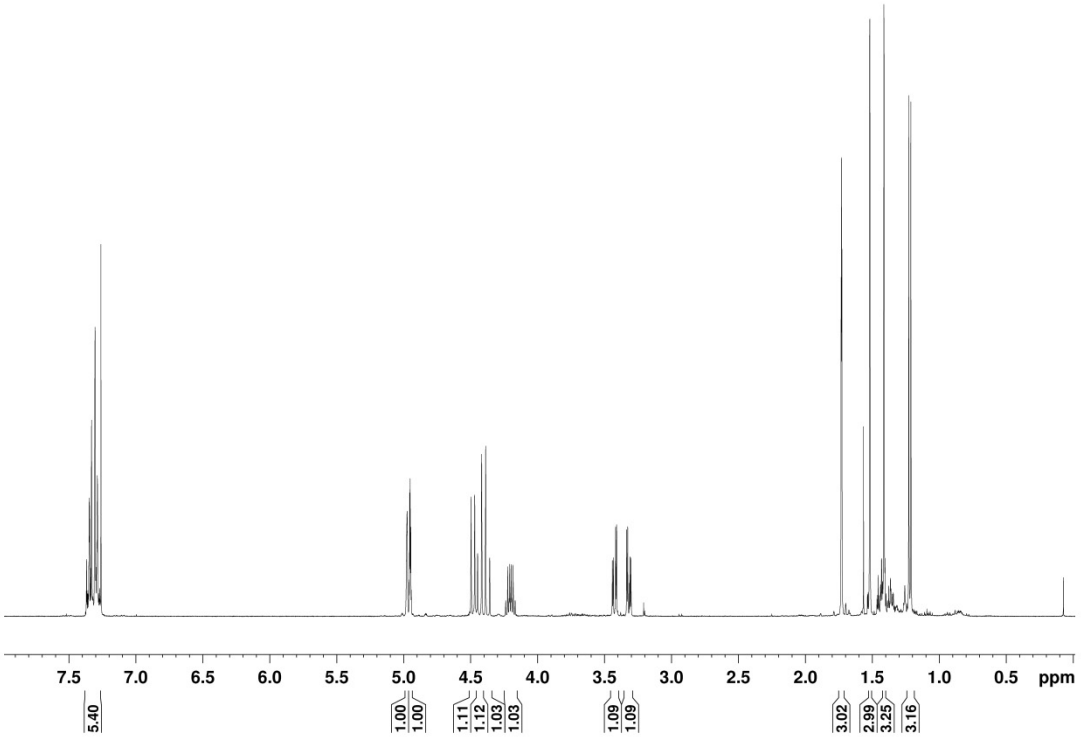



**222a** **58a**

**Acetonide 58a:** To a solution of **222a** (0.011 g, 0.044 mmol, 1.00 equiv.) in 1.00 ml 2,2-dimethoxypropane at rt, (+)-CSA (0.0009 mg, 0.0037 mmol, 0.09 equiv.) was added. The reaction mixture was stirred at rt for 27 min. The reaction mixture was quenched by addition of one drop of $NEt_3$. Filtration over a short pad of silica gel (EtOAc/hexane 1:2) gave 11.2 mg (87%) of the 1,3-syn-product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H); 4.97 (s, 1 H); 4.96-4.94 (m, 1 H); 4.48 (d, *J* = 10.8, 1 H); 4.43 (d, *J* = 12.1, 1 H); 4.37 (d, *J* = 12.1, 1 H); 4.20 (dq, *J* = 10.1, 6.1, 1 H); 3.42 (dd, *J* = 9.8, 2.8, 1 H); 3.32 (dd, *J* = 9.8, 3.0, 1 H); 1.73 (s, 3 H); 1.52 (s, 3 H); 1.46-1.37 (m, 1 H); 1.41 (s, 3 H); 1.22 (d, *J* = 6.1, 3 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 143.3, 138.5, 128.5 (2 C), 127.7, 127.6 (2 C), 98.2, 75.5, 73.5, 67.2, 66.6, 43.9, 30.3, 20.2, 20.0, 17.0.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1.0
0.5
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1.00
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1.03
1.03
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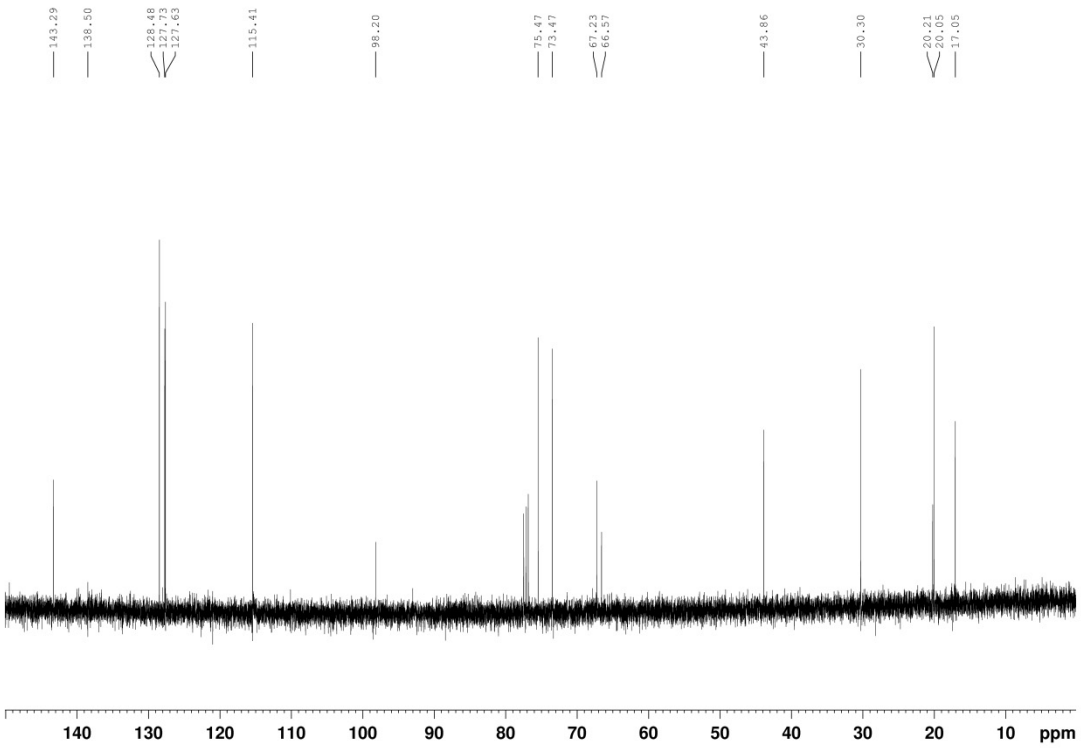
1.09
3.02
2.99
3.25
3.16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66.57
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70
60
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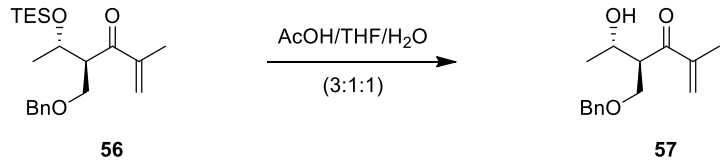
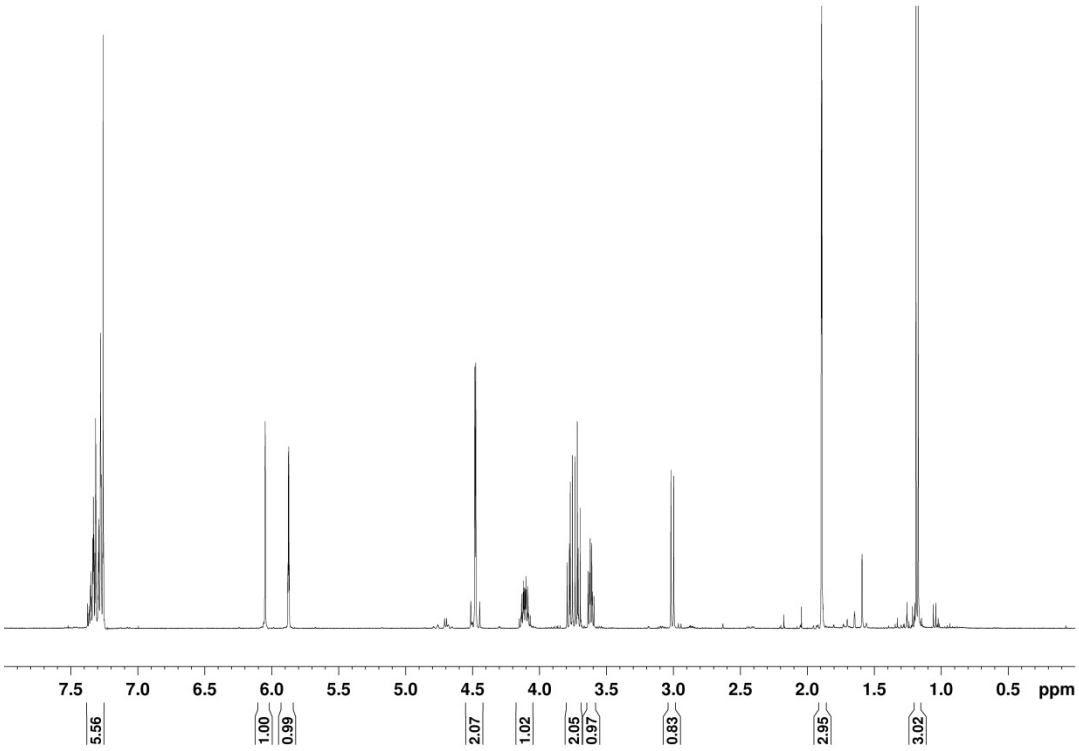
40
30
20
10
ppm

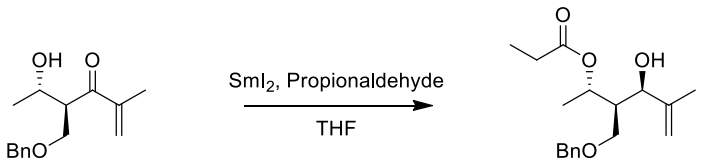



**56** **57**

**Alcohol 57:** To a solution of **56** (0.495 g, 1.36 mmol, 1.00 equiv.) in THF (3.00 ml), 3.00 ml water and 9.00 ml AcOH was added at rt. The reaction mixture was stirred at rt for 24 min. The reaction mixture was neutralized with $Na_2CO_3$, extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 271 mg (80 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5 H); 6.04 (s, 1 H); 5.87 (q, *J* = 1.4, 1 H); 4.50 (d, *J* = 12.1, 1 H); 4.46 (d, *J* = 12.1, 1 H); 4.11 (ddq, *J* = 6.5, 1.8, 1.8, 1 H); 3.77 (dd, *J* = 9.2, 6.6, 1 H); 3.71 (dd, *J* = 9.2, 6.6, 1 H); 3.64-3.60 (m, 1 H); 3.01 (d, *J* = 8.4, 1 H); 1.89 (s, 3 H); 1.18 (d, *J* = 6.5, 3 H).

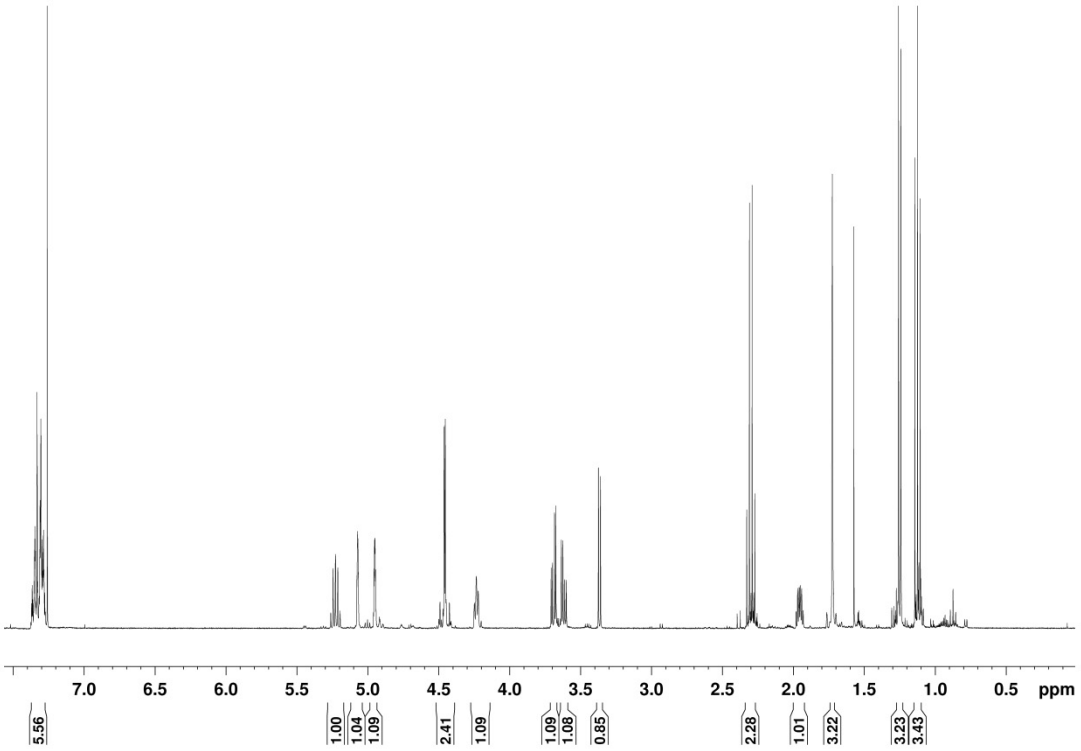





**57** **59**

**Alcohol 59:** The $SmI_2$-solution was prepared immediately before use according to the method of Imamoto[182]: A 20 mL microwave vial was heated to 600 °C and transferred hot into the glovebox where it was charged with Sm. Then $I_2$ was added (not in the glove box) followed by THF (10.8 mL). The brown mixture was transferred to a 80 °C oil bath. After 15 minutes at 80 °C, a dark blue solution was obtained. After 15 minutes more at 80 °C, the solution was allowed to cool to rt. A two-necked flask was flame-dried and vented with argon. To a solution of propionaldehyde in THF (7.0 mL) at -15 - -20 °C (ice/salt) was added the $SmI_2$ solution (5.4 mL, 0.5 equiv.) (dropwise). The initially blue color turned into a yellow within 25 seconds. Then **57** was added (in 5.0 mL THF, rinsed with twice 1.0 mL). The yellow solution was stirred at -15 - -20 °C for 48 min (full conversion on TLC). The reaction was quenched by addition of auq. sat. $NaHCO_3$ and diluted with EtOAc. The phases were separated and the aq. Phase was extracted with EtOAc (three times). Combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 315 mg (95 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H); 5.23 (quint, *J* = 6.6, 1 H); 5.07 (s, 1 H); 4.96-4.95 (m, 1 H); 4.48 (d, *J* = 11.8, 1 H); 4.44 (d, *J* = 11.8, 1 H); 4.25-4.20 (m, 1 H); 3.69 (dd, *J* = 9.5, 3.8, 1 H); 3.62 (dd, *J* = 9.5, 4.4, 1 H); 3.37 (d, *J* = 5.8, 1 H); 2.30 (q, *J* = 7.6, 2 H); 1.98-1.93 (m, 1 H); 1.73 (s, 3 H); 1.25 (d, *J* = 6.5, 3 H); 1.12 (t, *J* = 7.6, 3 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 137.8, 145.6, 128.6 (2 C), 128.1, 128.0 (2 C), 121.0, 111.9, 75.1, 73.8, 69.5, 68.0, 45.4, 28.0, 18.8, 17.6, 9.3.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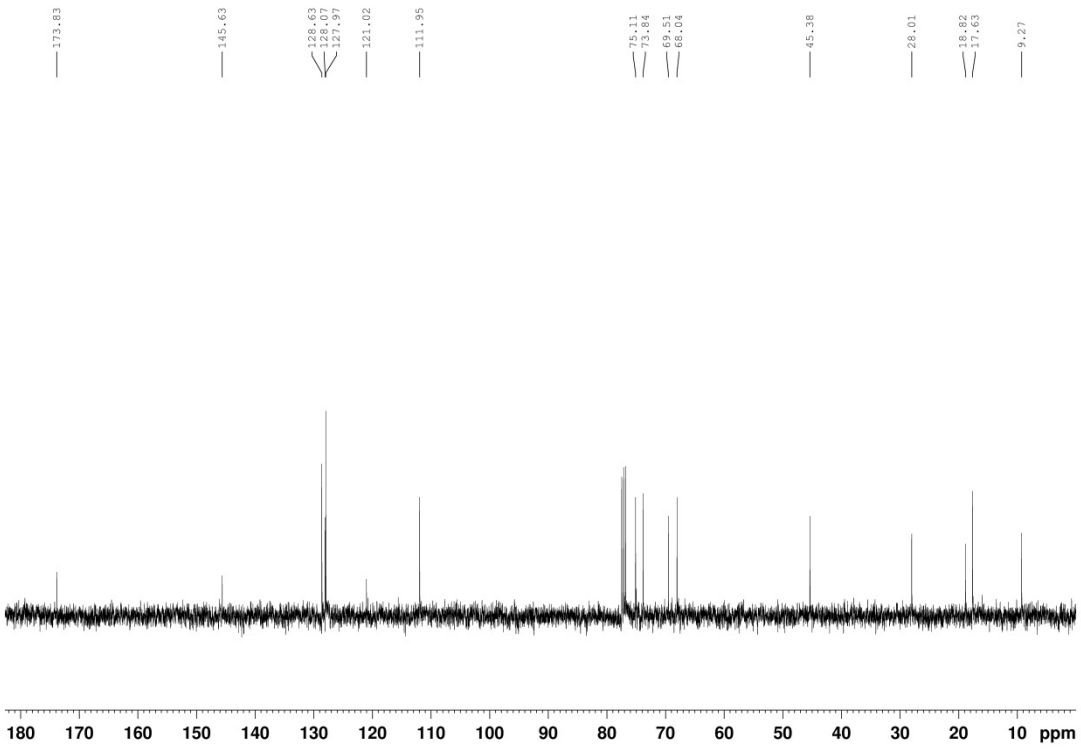
3.22
3.23
3.43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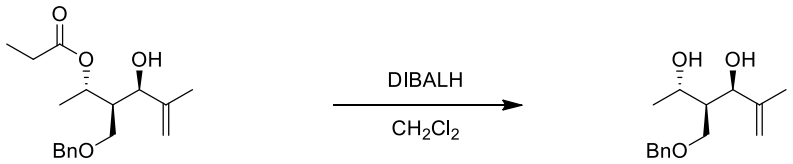
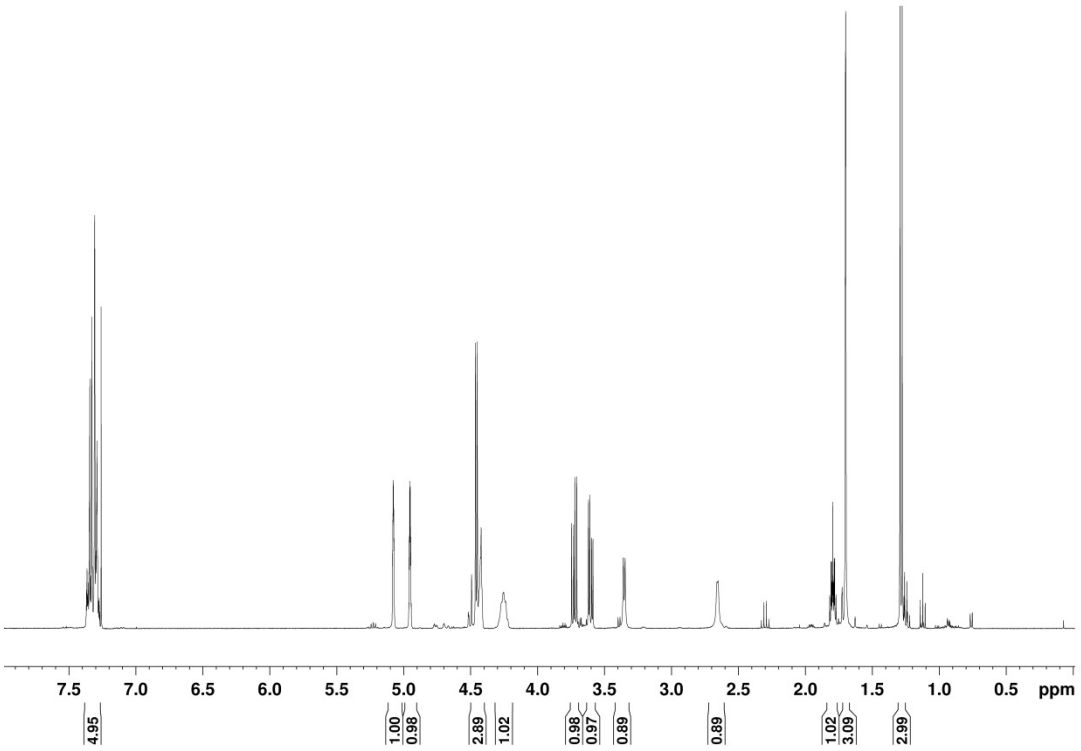
ppm




**59** **222b**

**Diol 222b:** To a solution of **59** (0.020 g, 0.065 mmol, 1.00 equiv.) in 1.00 ml $CH_2Cl_2$ at -78 °C, diisobutylaluminium hydride (0.136 ml, 0.163 mmol, 2.50 equiv.) was added drop wise. The reaction mixture was stirred at -78 °C for 1 h 23 min. Afterwards the reaction mixture was quenched with aqu. sat. sodium potassium tartrate. The aqu. phase was extracted with EtOAc, the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:2) gave 15.8 mg (96 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H); 5.07 (s, 1 H); 4.96-4.95 (m, 1 H); 4.48 (d, *J* = 11.7, 1 H); 4.44 (d, *J* = 11.7, 1 H); 4.44-4.41 (m, 1 H); 4.29-4.22 (m, 1 H); 3.73 (dd, *J* = 9.6, 5.7, 1 H); 3.60 (dd, *J* = 9.6, 3.8, 1 H); 3.35 (d, *J* = 5.4, 1 H); 2.65 (s, 1 H); 1.79 (ddt, *J* = 5.7, 5.7, 3.8, 1 H); 1.70 (s, 3 H); 1.28 (d, *J* = 6.4, 3 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 145.9, 137.8, 128.6 (2 C), 128.0, 127.9 (2 C), 111.1, 74.2, 73.8, 68.5, 67.2.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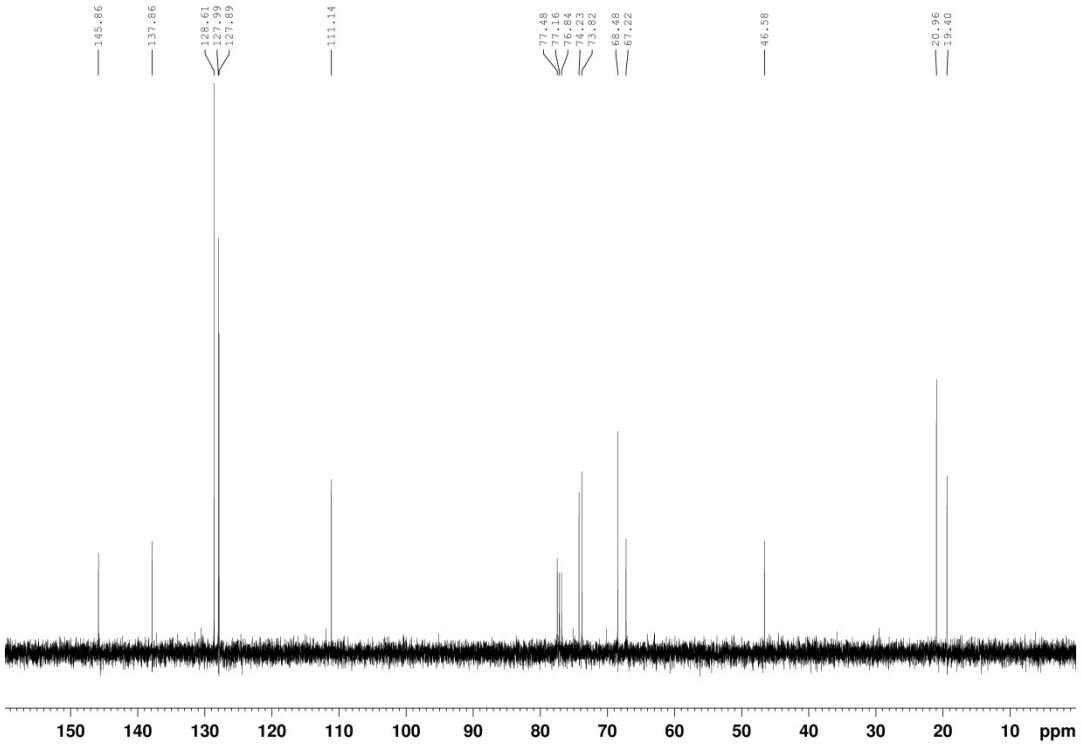
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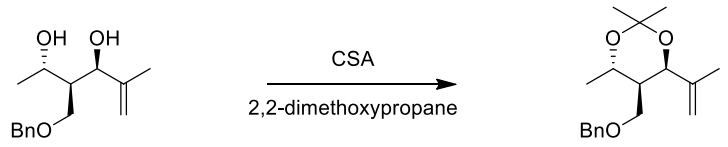
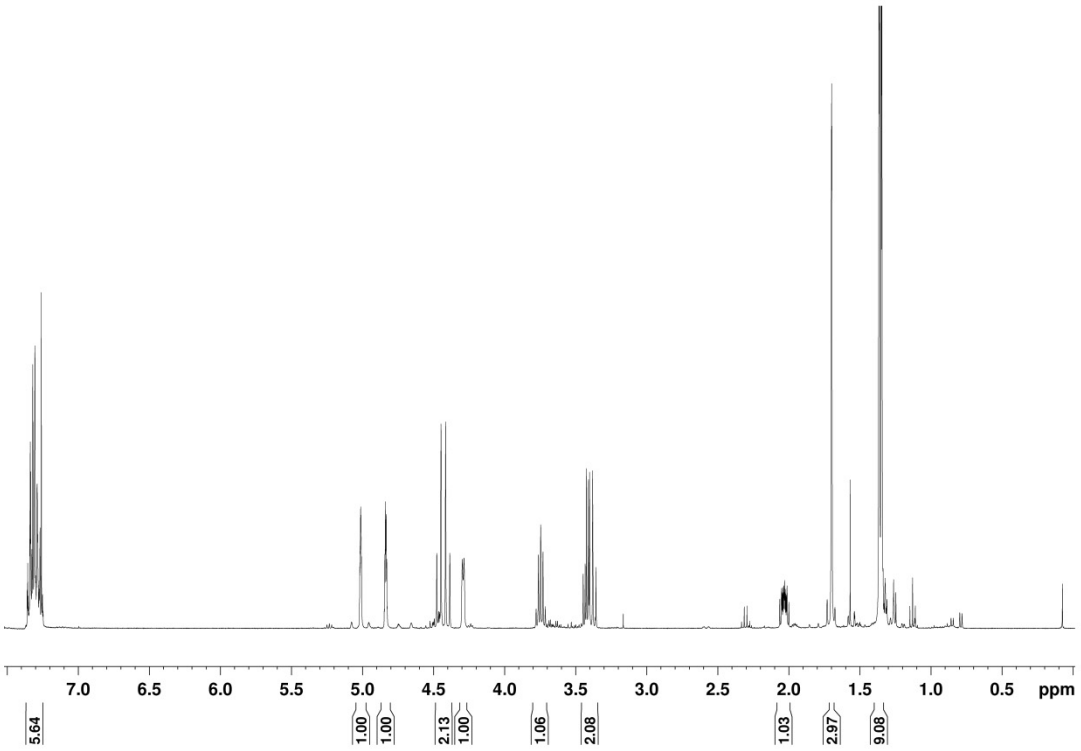
ppm




**222b** **58b**

**Acetonide 58b:** To a solution of **59** (0.020 g, 0.065 mmol, 1.00 equiv.) in 1.00 ml $CH_2Cl_2$ at -78 °C, diisobutylaluminium hydride (0.136 ml, 0.163 mmol, 2.50 equiv.) was added drop wise. The reaction mixture was stirred at -78 °C for 1 h 23 min. Afterwards the reaction mixture was quenched with aqu. sat. sodium potassium tartrate. The aqu. phase was extracted with EtOAc, the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:2) gave 15.8 mg (96 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H); 5.07 (s, 1 H); 4.96-4.95 (m, 1 H); 4.48 (d, *J* = 11.7, 1 H); 4.44 (d, *J* = 11.7, 1 H); 4.44-4.41 (m, 1 H); 4.29-4.22 (m, 1 H); 3.73 (dd, *J* = 9.6, 5.7, 1 H); 3.60 (dd, *J* = 9.6, 3.8, 1 H); 3.35 (d, *J* = 5.4, 1 H); 2.65 (s, 1 H); 1.79 (ddt, *J* = 5.7, 5.7, 3.8, 1 H); 1.70 (s, 3 H); 1.28 (d, *J* = 6.4, 3 H).**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 145.9, 137.8, 128.6 (2 C), 128.0, 127.9 (2 C), 111.1, 74.2, 73.8, 68.5, 67.2.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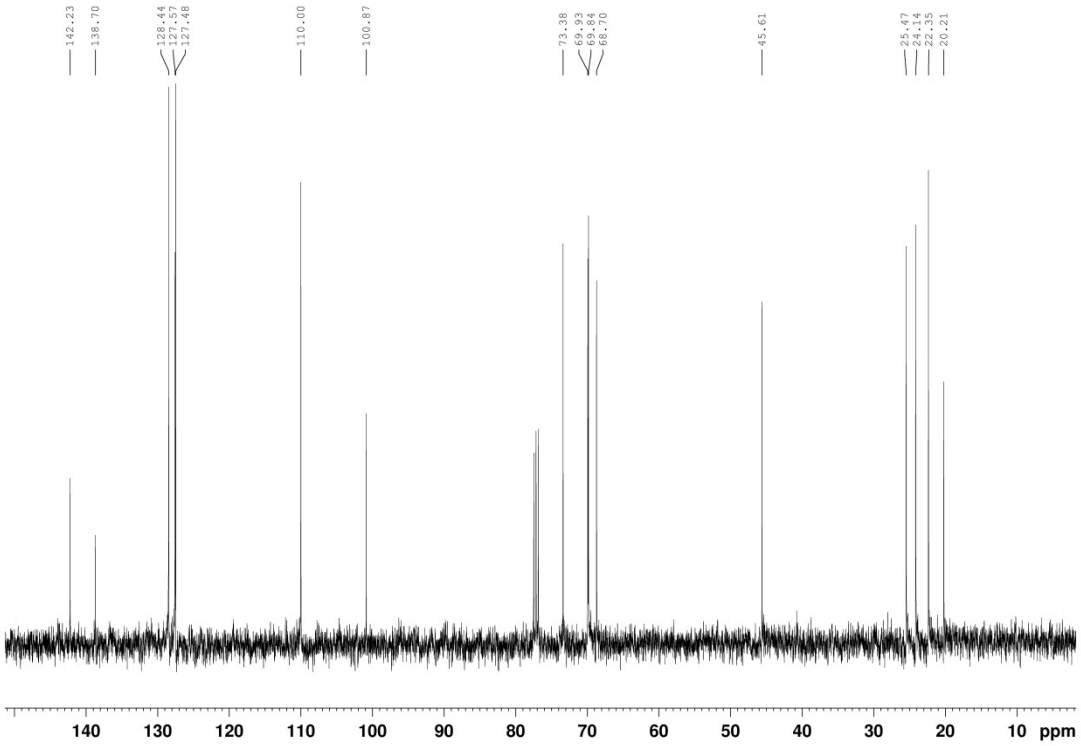
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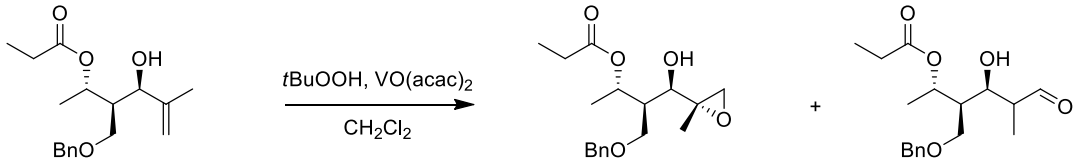


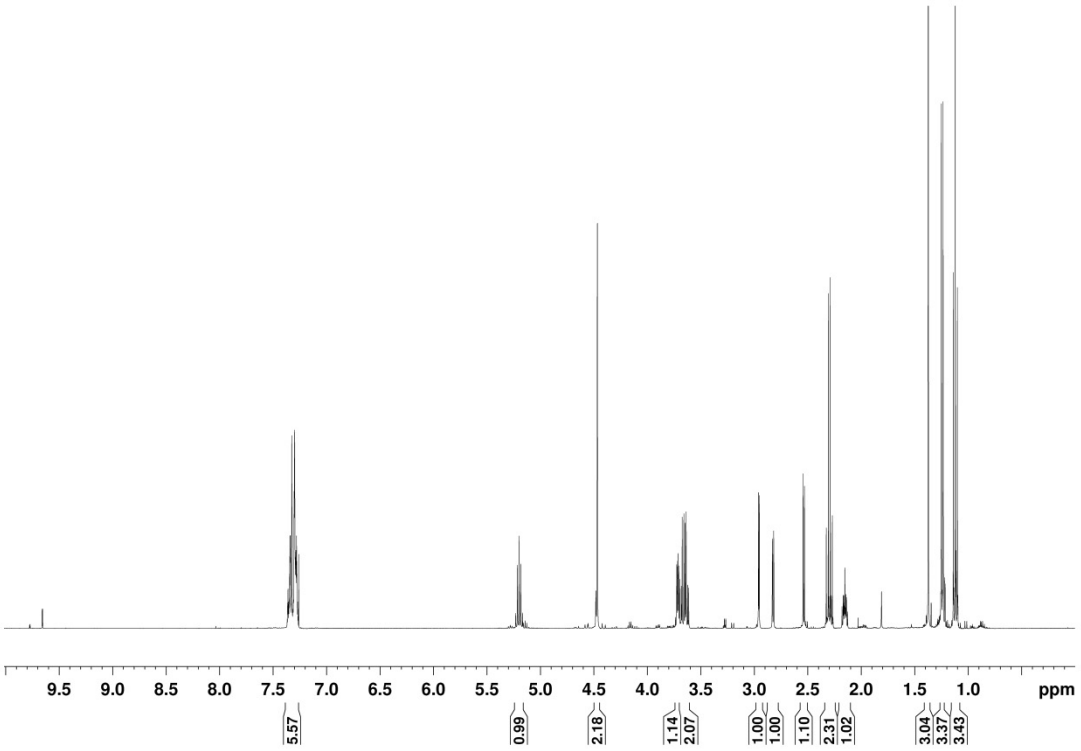

**59** **60** **62**

**Epoxide 60:** To a cooled solution (0 °C) of **59** (0.100 g, 0.326 mmol, 1.00 equiv.), in 5.00 ml DCM $VO(acac)_2$ (0.435 ml, 0.0033 mmol, 0.01 equiv. (2mg /ml stock solution)) and TBHP (0.089 ml, 5.5 M in nonane, 1.50 equiv.) were added. (reaction mixture turned red). After 4 min the reaction mixture was allowed to warm up to rt and stirred for 30 min. The reaction turned yellow/nearly colorless. The reaction mixture was cooled to 0 °C and additional $VO(acac)_2$ (0.435 ml, 0.0033 mmol, 0.01 equiv. (2mg /ml stock solution)) was added (reaction mixture tured red again). After 5 min the reaction mixture was allowed to warm up to rt and stirred for 1 h 20 min. The reaction mixture turned yellow again. The reaction mixture was cooled to 0 °C and additional $VO(acac)_2$ (0.435ml, 0.0033 mmol, 0.01 equiv. (2mg /ml stock solution)) was added (reaction mixture turned red again). After 5 min the reaction mixture was allowed to warm up to rt and stirred for 1 h. (reaction mixture turned yellow and TLC showed complete conversion). The reaction was cooled to 0 °C and afterwards quenched by addition of aqu. sat. $Na_2SO_3$ and diluted with DCM. The aqu. phase was extracted 3 times with DCM, the comb. org phases were washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure (crude product = 124.5 mg). Purification over silica gel (EtOAc/hexane (1:6)) gave 74.6 mg (63.5 %) of a mixture of the desired product (58 %) and the side product **62** (5.5 %).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5 H); 5.20 (quint, *J* = 6.4, 1 H); 5.47 (s, 2 H); 3.74-3.70 (m, 1 H); 3.68 (dd, *J* = 9.6, 6.4, 1 H); 3.63 (dd, *J* = 9.6, 4.1, 1 H); 2.95 (d, *J* = 2.8, 1 H); 2.82 (d, *J* = 4.8, 1 H); 2.54 (d, *J* = 4.8, 1 H); 2.30 (q, *J* = 7.6, 2 H); 2.15 (ddt, *J* = 6.3, 6.3, 4.3, 1 H); 1.37 (s, 3 H); 1.24 (d, *J* = 6.4, 3 H); 1.25 (t, *J* = 7.6, 3 H).

Distinguishable signals from side product **62**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 9.66 (d, *J* = 1.8, 1 H); 3.26 (d, *J* = 5.4, 1 H); 2.93 (d, *J* = 2.7, 1 H); 2.30 (q, *J* = 7.5, 2 H); 1.23 (d, *J* = 7.0, 3 H); 1.12 (t, *J* = 7.5, 3 H).**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 173.8, 137.6, 128.5 (2 C), 128.0, 127.8 (2 C), 73.6, 72.6, 69.8, 67.7, 58.1, 51.3, 45.1, 27.9, 17.7, 17.4, 9.2.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2.31
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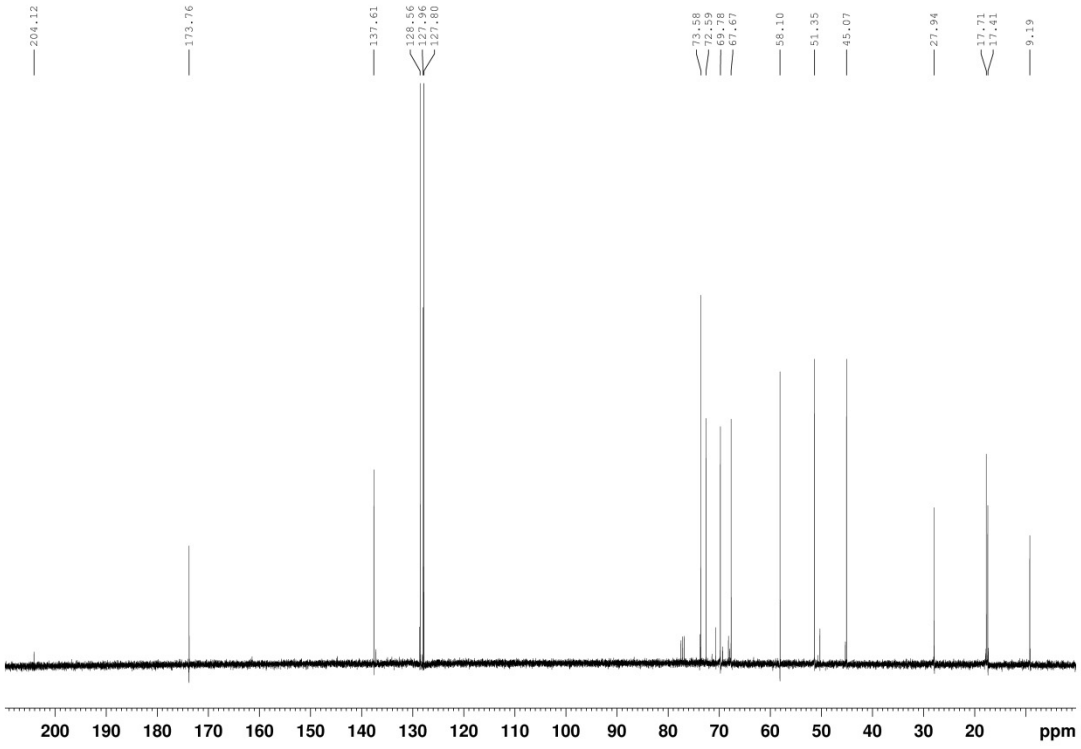
3.04
3.37
3.43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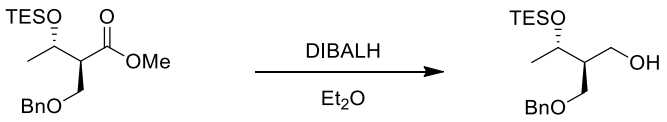
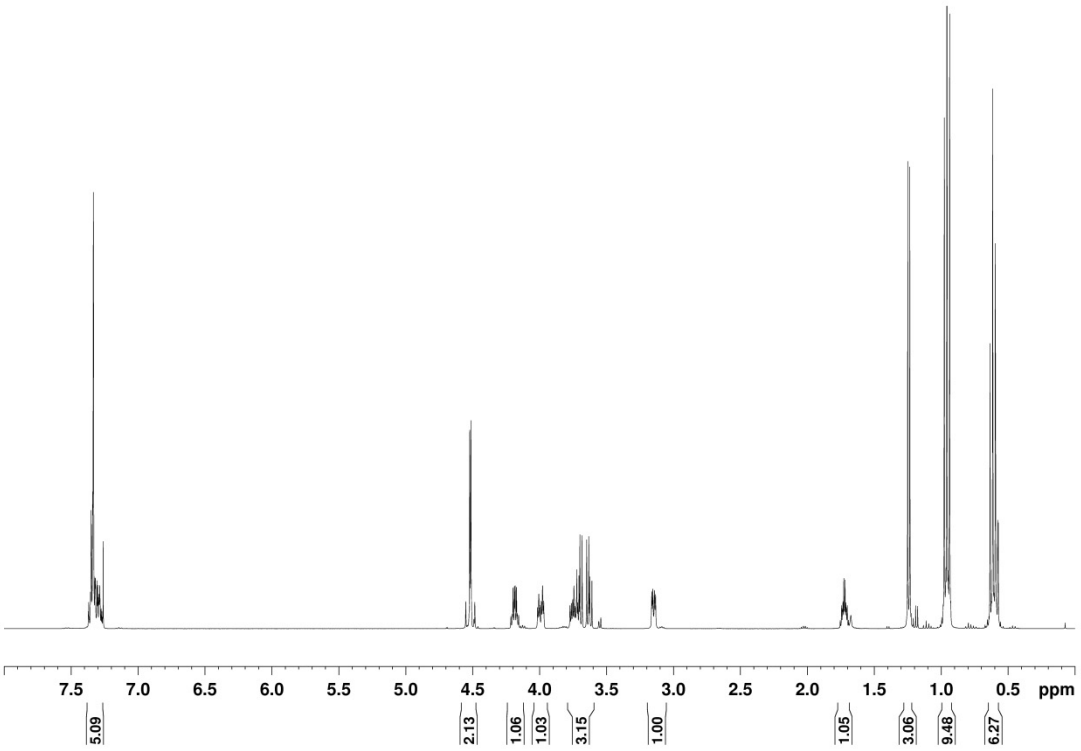



**55** **223**

**Primary alcohol 223:** To a solution of **55** (15.18 g, 43.05 mmol, 1.00 equiv.) in 215 ml $Et_2O$ at -78 °C, DIBALH (89.70 ml, 107.64 mmol, 2.50 equiv.) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h 40 min. Afterwards the reaction mixture was quenched by addition of EtOAc. Afterwards aqu. sat. sodium potassium tartrate was added and stirred for 1 h. The aqu. phase was extracted with EtOAc, the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4) gave 11.85 g (85 %) of the desired product **223** as colorless oil.

**TLC**: $R_f$ = 0.22 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 6H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.18 (qd, *J* = 6.3, 4.0 Hz, 1H), 4.02 – 3.95 (m, 1H), 3.78 – 3.71 (m, 1H), 3.70 (dd, *J* = 9.2, 6.5 Hz, 1H), 3.63 (dd, *J* = 9.2, 6.5 Hz, 1H), 3.13 (dd, *J* = 7.9, 3.3 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (dt, *J* = 8.4, 4.5 Hz, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 138.3, 128.5, 127.8, 127.7, 73.5, 70.5, 69.1, 62.4, 47.1, 22.1, 6.9, 4.9; **IR** (thin film): ν 3455, 2954, 2910, 2875, 1454, 1413, 1375, 1239, 1076, 1004, 973, 730; **HRMS** (ESI): calculated for $C_{18}H_{33}O_3Si$ $[M+H]^+$: 325.2193, found 325.2191; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +8.24° (c = 1.00 in $CHCl_3$).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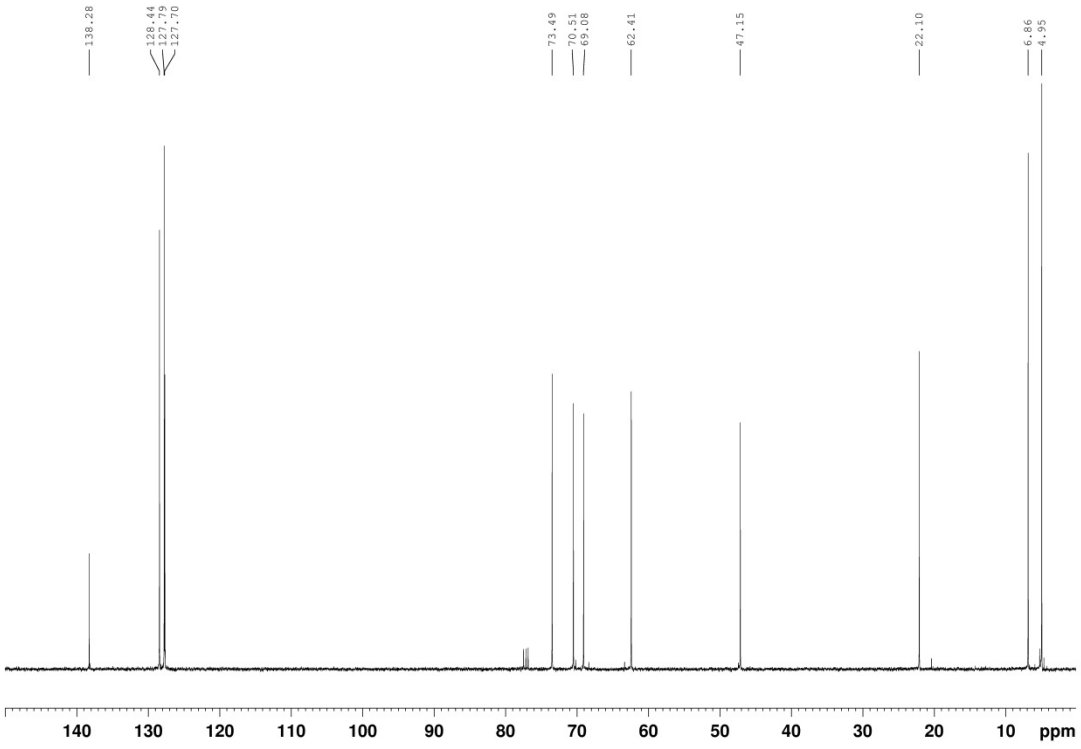
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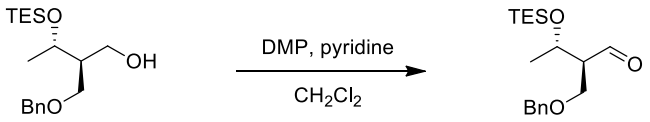
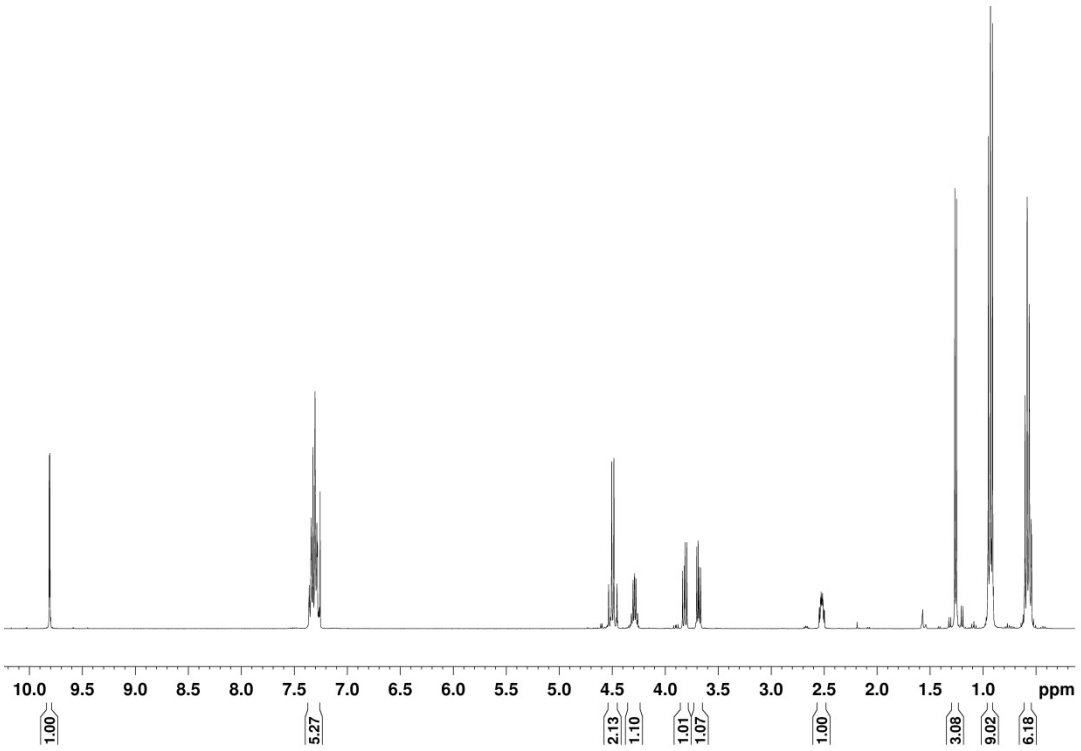



**223** **63**

**Aldehyde 63:** To a solution of **223** (0.355 g, 1.09 mmol, 1.00 equiv.) and pyridine (0.69 mL, 8.53 mmol, 7.80 equiv.) in $CH_2Cl_2$ (10.0 mL) was added Dess–Martin periodinane (0.60 g, 1.42 mmol, 1.30 equiv.). The reaction mixture was stirred for 3 h at RT before the addition of saturated aqueous $NaHCO_3$ solution (20 mL) and a saturated aqueous sodium thiosulfate solution (5 mL). After stirring for additional 5 min, the reaction mixture was diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20 → 1:10)) gave 0.331 g (94 %) of the desired product **63** as a colorless oil.

**TLC**: $R_f$ = 0.27 (EtOAc/hexane 1:10, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 9.81 (d, *J* = 2.6 Hz, 1H), 7.37 – 7.27 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.29 (qd, *J* = 6.4, 4.9 Hz, 1H), 3.82 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.69 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.53 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.62 – 0.54 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 204.0, 138.0, 128.5, 127.9, 127.8, 73.5, 67.0, 66.7, 59.3, 22.4, 6.9, 5.1; **IR** (thin film): ν 2955, 2909, 2876, 1726, 1455, 1378, 1362, 1242, 1102, 1006, 740, 698; **HRMS** (ESI): calculated for $C_{18}H_{31}O_3Si$ $[M+H]^+$: 323.2037, found 323.2037; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +15.37° (c = 1.00 in $CHCl_3$).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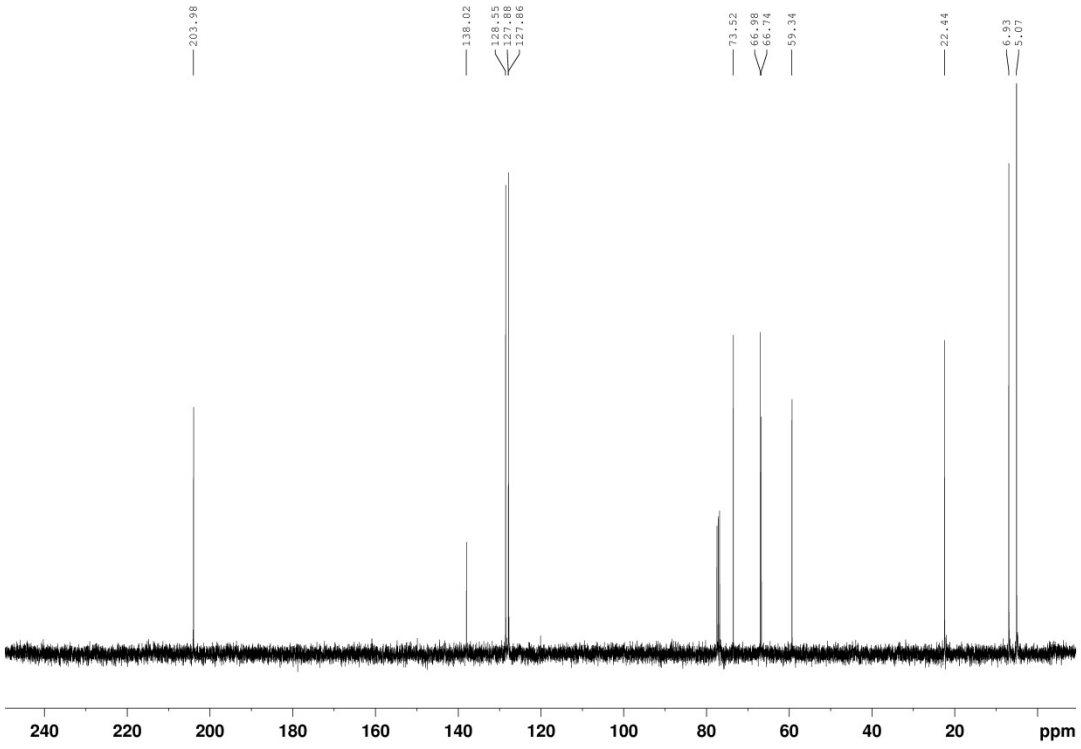
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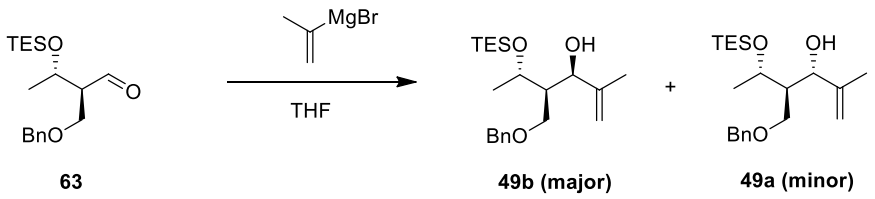
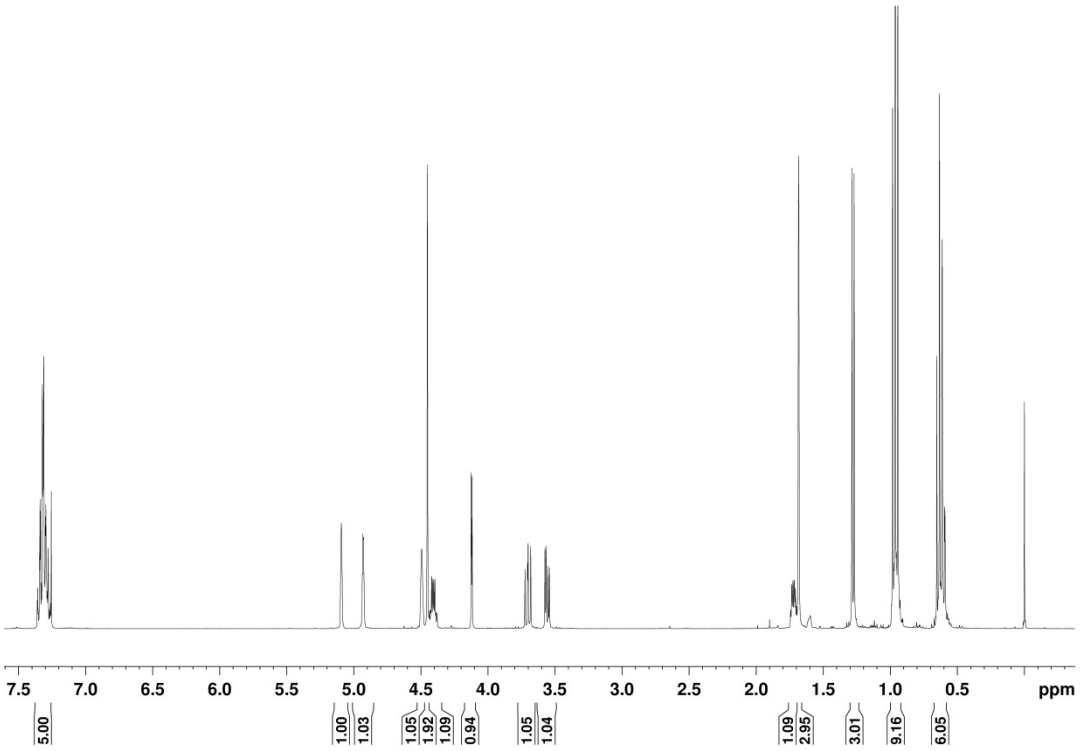



**63** **49b (major)** **49a (minor)**

**Allyl alcohol 49:** To a solution of **63** (10.85 g, 33.64 mmol, 1.00 equiv.) in 67.28 ml THF was added freshly prepared isopropylmagnesiumbromide (1.0 M in THF, 9.77 ml, 67.28 mmol, 2.00 equiv.) dropwise over 22 min at - 78 °C (careful, Grignard reagent can freeze!). The reaction mixture was stirred at - 78 °C for 26 min. Then the cooling bath was removed and after 6 min the reaction mixture was quenched with aqu. sat. $NaHCO_3$ (100 ml). The layers were separated and the aqu. phase was extracted 3 times with $Et_2O$. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20)) gave 9.19 g (74 %, dr = 10:1, major isomer) and 1.44 g (12 %, dr = 1:8, minor isomer) of the desired product **49** as colorless oil.

**Major Isomer (NMR shown): TLC**: $R_f$ = 0.27 (EtOAc/hexane 1:10, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.22 (m, 5H), 5.10 (s, 1H), 4.93 (dd, *J* = 1.4, 0.7 Hz, 1H), 4.50 (s, 1H), 4.46 (s, 2H), 4.43 – 4.40 (m, 1H), 4.13 (d, *J* = 2.4 Hz, 1H), 3.71 (dd, *J* = 9.4, 7.7 Hz, 1H), 3.56 (dd, *J* = 9.5, 3.9 Hz, 1H), 1.69 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.62 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 146.1, 138.5, 128.4, 127.7, 127.6, 112.5, 77.2, 73.4, 70.7, 69.9, 48.1, 23.10, 18.1, 6.9, 5.1; **IR** (thin film): ν 3493, 2954, 2913, 2876, 1454, 1414, 1376, 1239, 1102, 973, 900, 728, 697; **HRMS** (ESI): calculated for $C_{21}H_{36}NaO_3Si$ $[M+Na]^+$: 387.2326, found 387.2325; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +14.75° (c = 1.00 in $CHCl_3$).

**Minor Isomer (NMR not shown):** **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5 H); 5.04 (s, 1 H); 4.87 (s, 1 H); 4.44 (d, *J* = 11.9, 1 H); 4.40 (d, *J* = 11.9, 1 H); 4.32-4.25 (m, 2 H); 4.10 (d, *J* = 3.1, 1 H); 3.51 (dd, *J* = 9.5, 4.4, 1 H); 3.46 (dd, *J* = 9.5, 5.0, 1 H); 1.82-1.76 (m, 1 H); 1.75 (s, 3 H); 1.29 (d, *J* = 6.3, 3 H); 0.97 (t, *J* = 7.9, 9 H); 0.63 (q, *J* = 7.9, 6 H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 146.1, 138.5, 128.4, 127.7, 127.6, 112.5, 77.2, 73.4, 70.7, 69.9, 48.1, 23.1, 18.1, 6.9, 5.1.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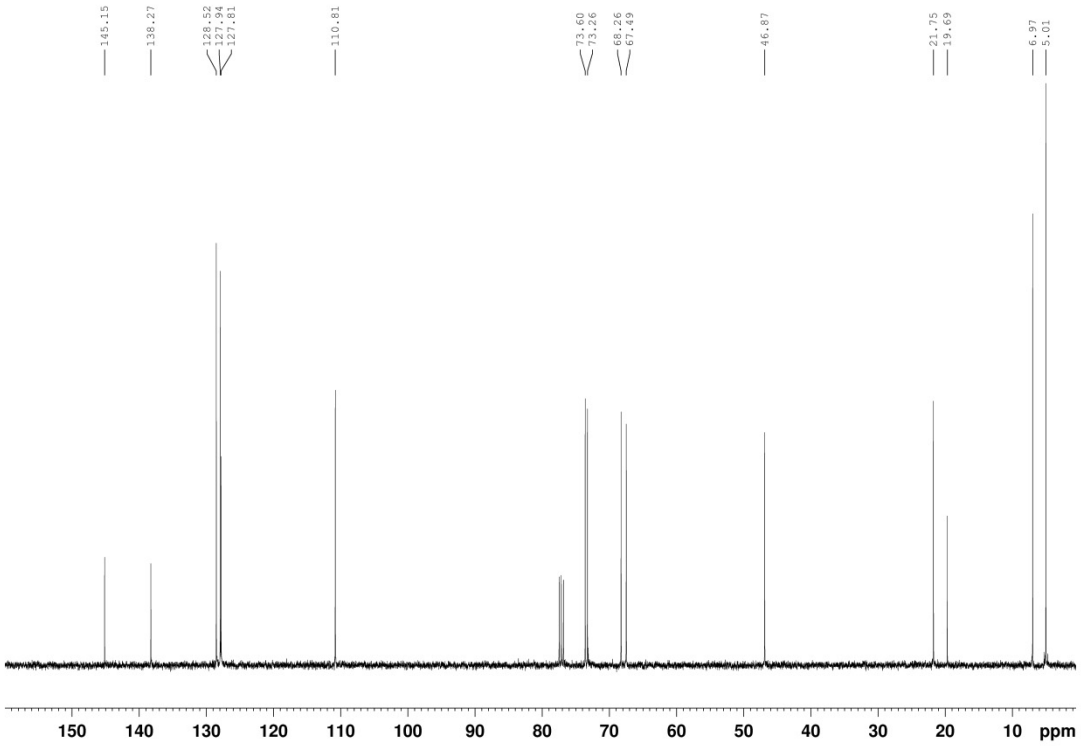
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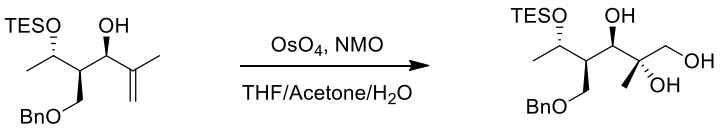
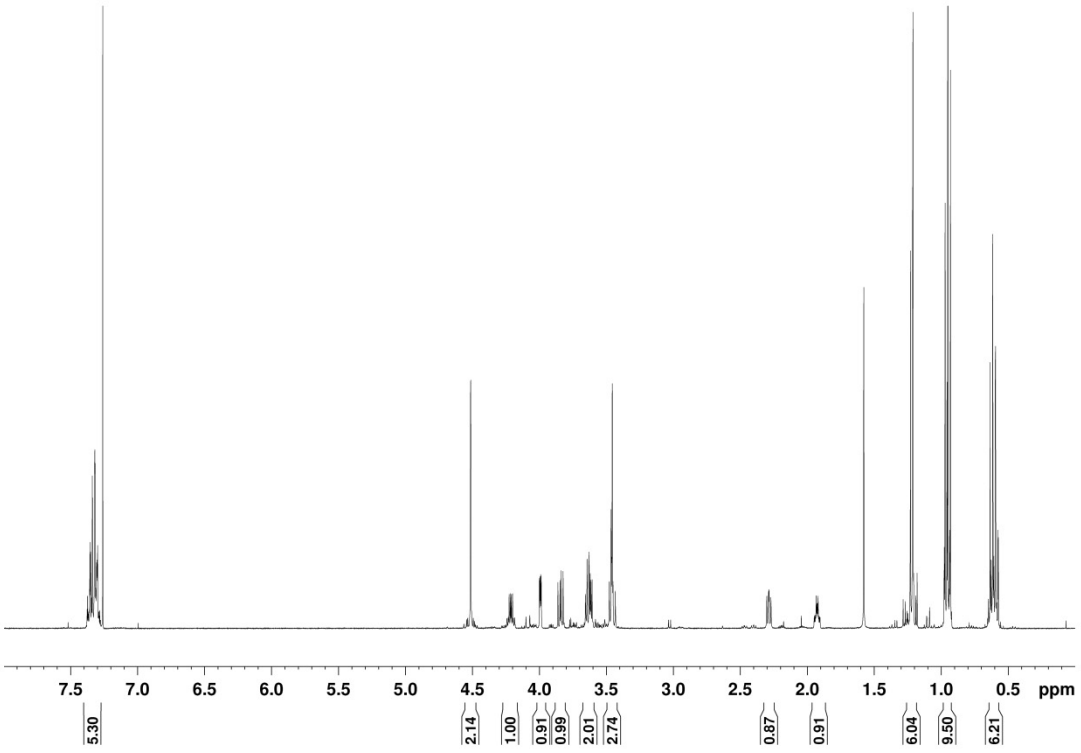
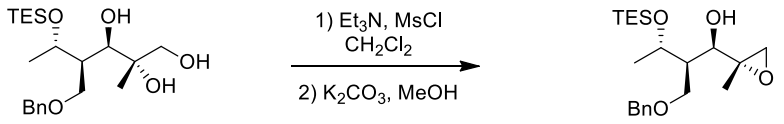



**49b** **64**

**Triol 64:** To a solution of **49b** (0.237 g, 0.650 mmol, 1.00 equiv.) in 25.0 ml THF/acetone/water (5:5:1) were added NMO (0.114 g, 0.975 mmol, 1.50 euqiv.) and $OsO_4$ (0.099 ml (4 % in water), 0.0163 mmol, 0.03 equiv.) at rt. The reaction mixture was stirred at rt for 4 h 45 min and then quenched by addition of aqu. sat. $Na_2S_2O_3$. After stirring for 10 min EtOAc was added and the phases were separated. The aqu. phase was extracted 3 times with EtOAc. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:1)) gave 204.4 mg (79 %) of the desired product as colorless oil/solid.

**$^1$H-NMR** (400 MHz, CDCl3) δ 7.39 – 7.27 (m, 2H), 4.51 (s, 1H), 4.21 (qd, J = 6.3, 3.9 Hz, 1H), 3.99 (dd, J = 3.2, 1.8 Hz, 1H), 3.84 (dd, J = 9.4, 6.1 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.49 – 3.42 (m, 1H), 2.31 (t, J = 5.9 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.22 (d, J = 6.5 Hz, 1H), 1.21 (s, 1H), 0.95 (t, J = 7.9 Hz, 2H), 0.66 – 0.56 (m, 1H).

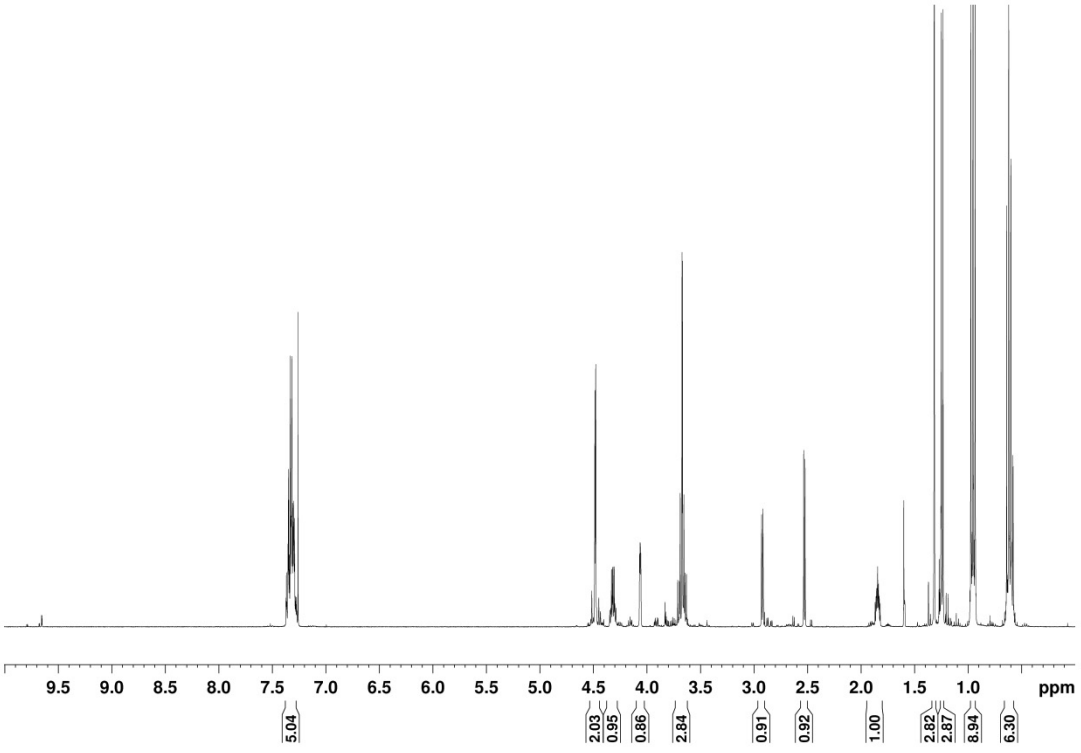


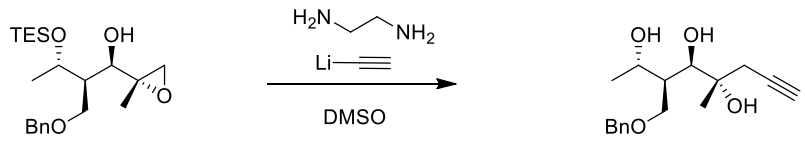



**64** **65**

**Epoxide 65:** To a solution of **64** (0.894 g, 2.24 mmol, 1.00 equiv.) and $NEt_3$ (2.46 ml, 22.42 mmol, 10.0 equiv.) in DCM (22.0 ml) at -40 °C, MsCl (0.191 ml, 2.47 mmol, 1.10 equiv.) was added drop wise. The reaction mixture was stirred at -40 °C for 45 min and then the $CH_2Cl_2$ was evaporated under reduced pressure. The salts were precipitated by addition of $Et_2O$ and the org. phase was washed with water and brine. The org. phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in 22.0 ml MeOH and afterwards $K_2CO_3$ (0.930 g, 6.73 mmol, 3.00 equiv.) was added in one portion at 0 °C. The reaction mixture was stirred at rt for 30 min and then diluted with $Et_2O$. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:8)) gave 578.9 mg (68 %) of the desired product as colorless oil (~5% aldehyde (H-shift product) impurity visible in NMR).

**$^1$H-NMR** (400 MHz, CDCl3) δ 7.38 – 7.27 (m, 5H), 4.50 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.32 (qd, J = 6.3, 3.9 Hz, 1H), 4.06 (dd, J = 2.8, 1.9 Hz, 1H), 3.72 – 3.63 (m, 3H), 2.92 (d, J = 5.1 Hz, 1H), 2.53 (d, J = 5.1 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.32 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.65 – 0.57 (m, 6H).

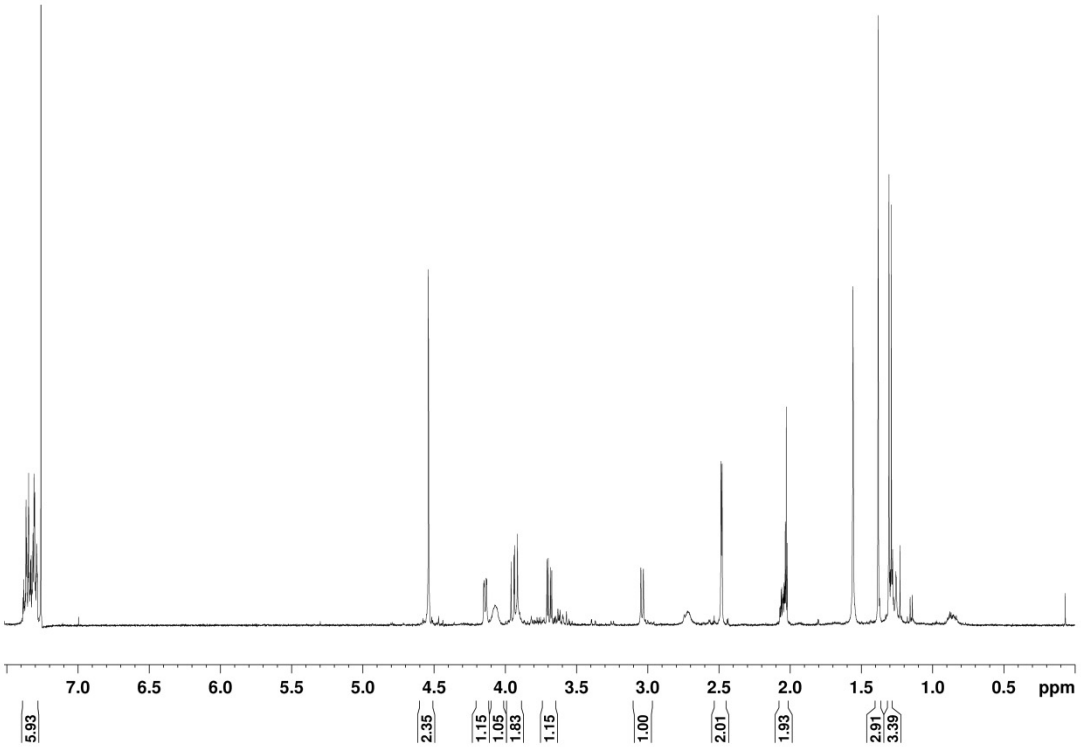





**65** **68**

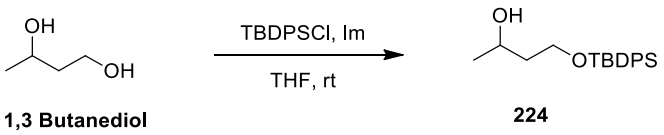
**Alkyne 68:** To a solution of **65** (0.020 g, 0.0525 mmol, 1.00 equiv.) in 0.10 ml DMSO at rt was added lithium acetylide ethylenediamine complex (0.040 g, 0.525 mmol, 10.00 equiv.). The reaction mixture was stirred at rt for 7 h. The reaction was quenched by addition of aqu. sat. $NH_4Cl$ and was diluted with $Et_2O$. The phases were separated and the aqu. phase was extracted 3 times with $Et_2O$. The comb. org. phases were washed with brine, washed over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:1)) gave 1.7 mg (10 %) of **68**.

**$^1$H-NMR** (400 MHz, CDCl3) δ 7.39 – 7.28 (m, 5H), 4.54 (s, 2H), 4.18 – 4.11 (m, 1H), 4.07 (s, 1H), 3.95 (d, J = 8.3 Hz, 1H), 3.93 (d, J = 8.3 Hz, 1H), 3.69 (dd, J = 9.9, 3.7 Hz, 1H), 3.04 (d, J = 7.1 Hz, 1H), 2.72 (s, 1H), 2.48 (d, J = 2.7 Hz, 2H), 2.08 – 2.01 (m, 2H), 1.38 (s, 3H), 1.30 (d, J = 6.5 Hz, 3H).



## 5.3.2. *Julia* Olefination Strategy

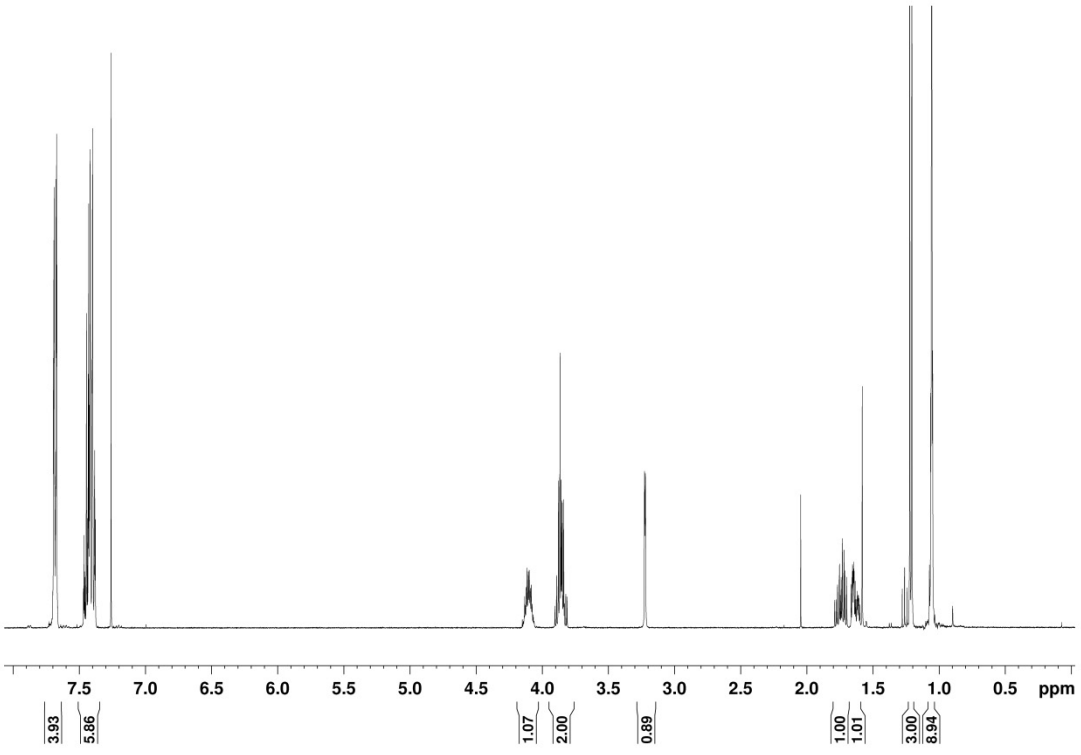
### 5.3.2.1. Synthesis of Sulfone 73

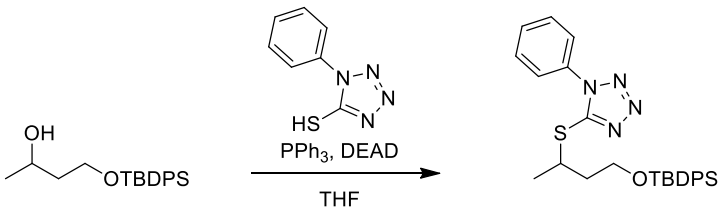



**1,3 Butanediol** **224**

**Silyl ether 224:** To a solution of 1,3-butanediol (0.995 g, 11.09 mmol, 1.00 equiv.) in 111 ml $CH_2Cl_2$ at 0 °C, imidazole (0.937 g, 13.76 mmol, 1.24 equiv.) and TBDPSCl (2.86 ml, 10.98 mmol, 0.99 equiv.) were added. The reaction mixture was stirred at rt overnight, then quenched with aqu. sat. $NH_4Cl$ and extracted with hexane/$Et_2O$ (4:1). The combined org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:19 -> 1:4)) gave 3.11 g (85 %) of the desired product as colorless oil.

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H), 7.48 – 7.37 (m, 6H), 4.16 – 4.05 (m, 1H), 3.92 – 3.79 (m, 2H), 3.22 (d, *J* = 2.4 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.67 – 1.59 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.06 (s, 9H).

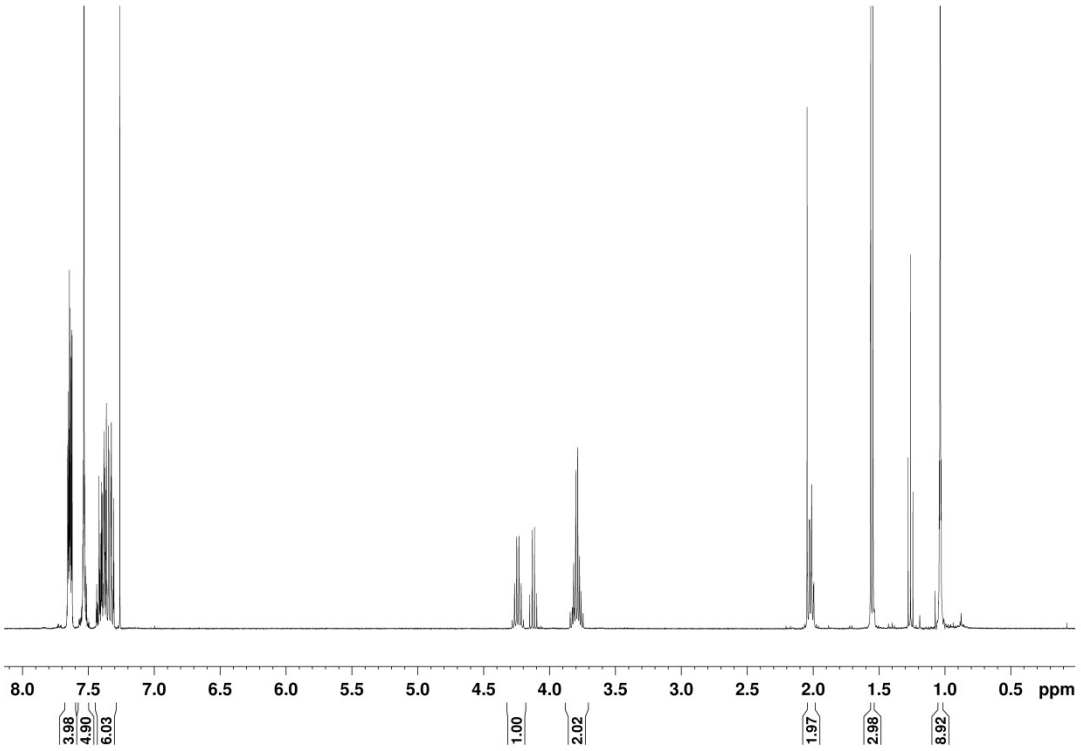





**224** **225**

**Sulfide 225:** To a solution of **224** (1.00 g, 3.04 mmol, 1.00 equiv.) in THF (30 ml), 1-phenyl-1H-tetrazole-5-thiol (1.22 g, 6.08 mmol, 2.00 equiv.) and triphenylphosphine (1.20 g, 4.56 mmol, 1.50 equiv.) were added in one portion at rt. The reaction mixture was then cooled to 0 °C and afterwards DEAD (0.93 g, 5.33 mmol, 1.75 equiv.) was added dropwise. The reaction mixture was allowed to warm up to rt and stirred overnight. The reaction was then quenched by addition of aqu. sat. $NaHCO_3$ (30 ml). The phases were separated and the aqu. phase extracted 3x with $Et_2O$. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20)) gave 1.20 g (80.8%) of the desired product as colorless oil and 0.25 g (17 %) of a side product with the same mass as the desired product. It is assumed that the TBDPS protecting group is migrated to the secondary alcohol and the primary sulfide was therefore formed.

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 4H), 7.53 (s, 5H), 7.45 – 7.29 (m, 6H), 4.29 – 4.19 (m, 1H), 3.86 – 3.74 (m, 2H), 2.05 – 1.99 (m, 2H), 1.55 (d, $J$ = 6.8 Hz, 3H), 1.04 (s, 9H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 135.74, 135.71, 133.64, 130.13, 129.82, 127.84, 127.79, 124.17, 61.13, 41.91, 38.88, 26.97, 21.79, 19.29.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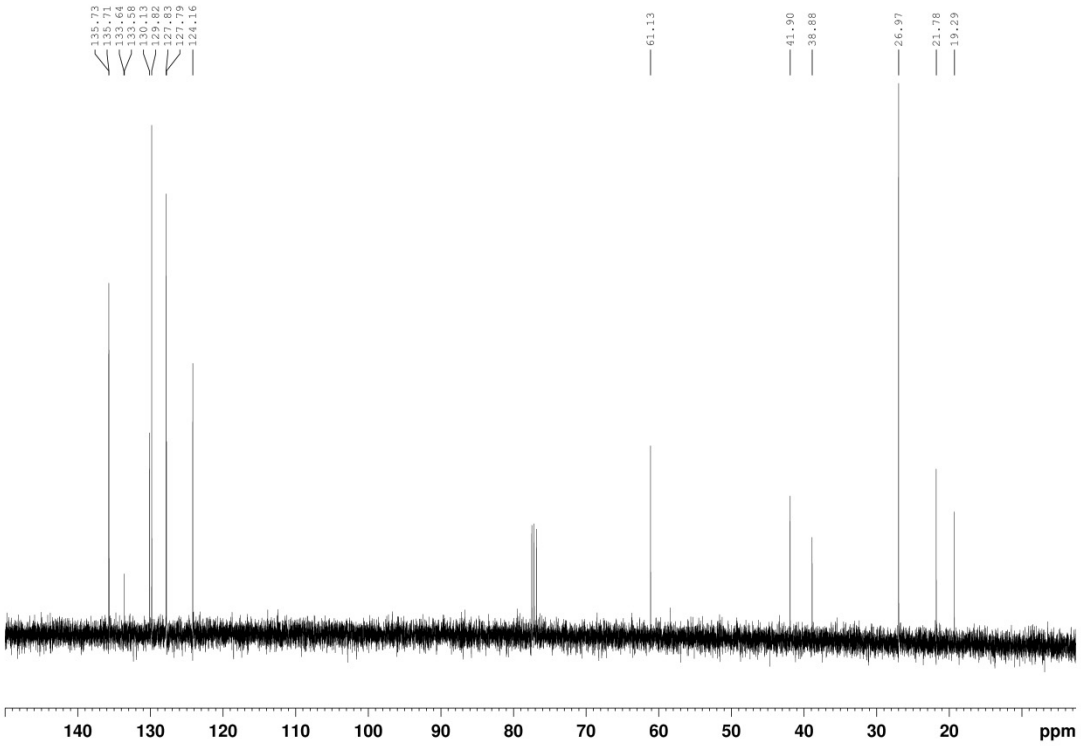
6.03
1.00
2.02
1.97
2.98
8.92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135.71
133.64
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130.13
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127.79
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61.13
41.90
38.88
26.97
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19.29
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120
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90
80
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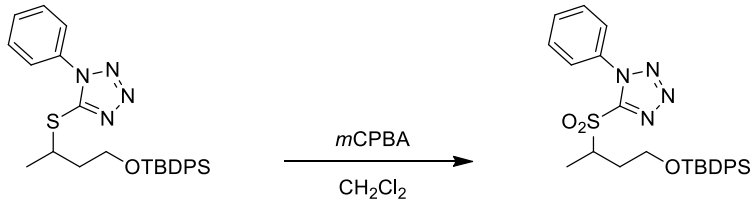
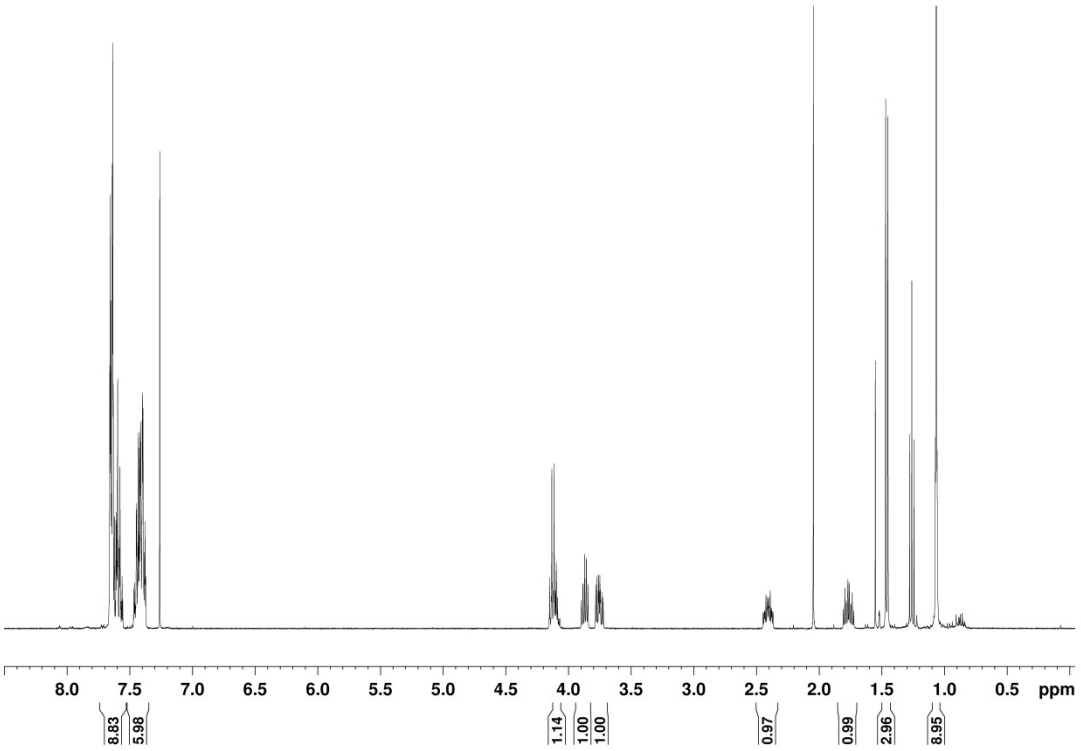
60
50
40
30
20
ppm




**225** **77**

**Sulfone 77:** To a solution of **225** (1.00 g, 2.05 mmol, 1.00 equiv.) in 20 ml $CH_2Cl_2$, *m*CPBA (1.24 g, 7.16 mmol, 3.50 equiv.) was added in one portion at rt and the reaction mixture was stirred for 4 h (white emulsion). The reaction mixture was diluted with EtOAc, washed with aqu. sat. $Na_2SO_3$ and aqu. sat. $NaHCO_3$. The org. phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 839 mg (78 %) of the desired product as viscous colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.53 (m, 9H), 7.48 – 7.34 (m, 6H), 4.17 – 4.06 (m, 1H), 3.91 – 3.83 (m, 1H), 3.79 – 3.71 (m, 1H), 2.46 – 2.35 (m, 1H), 1.82 – 1.71 (m, 1H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H), **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 135.69, 135.67, 131.58, 130.06, 129.73, 128.00, 127.99, 125.58, 60.06, 58.97, 31.37, 27.00, 19.33, 12.71.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7.5
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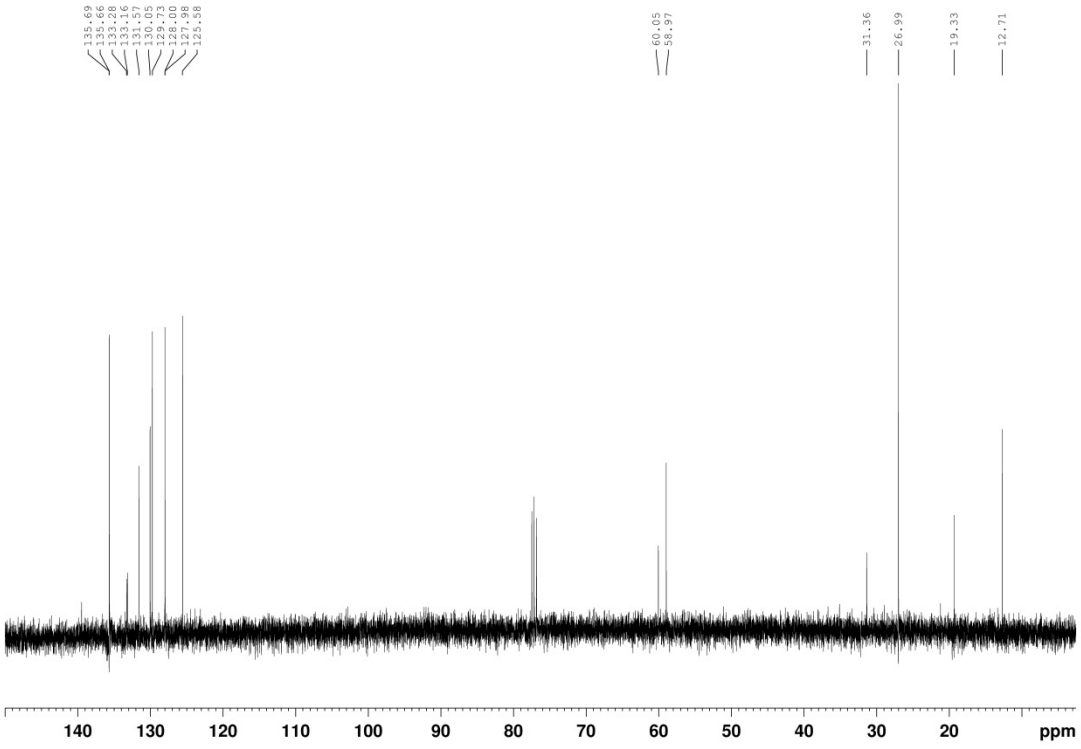
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
8.83
5.98
1.14
1.00
1.00
0.97
0.99
2.96
8.95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60.05
58.97
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26.99
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140
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100
90
80
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50
40
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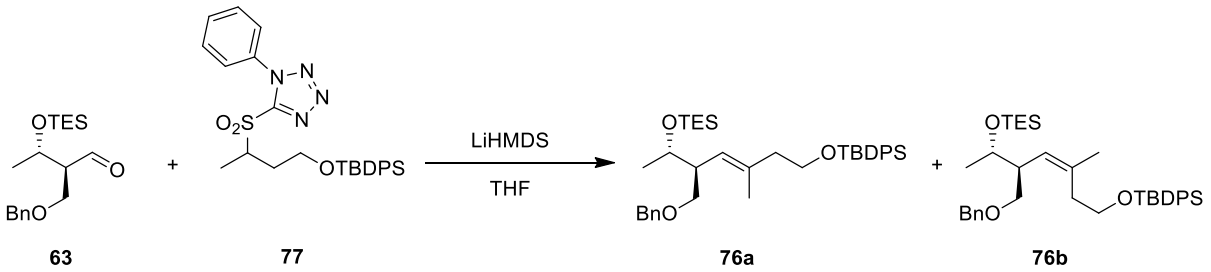
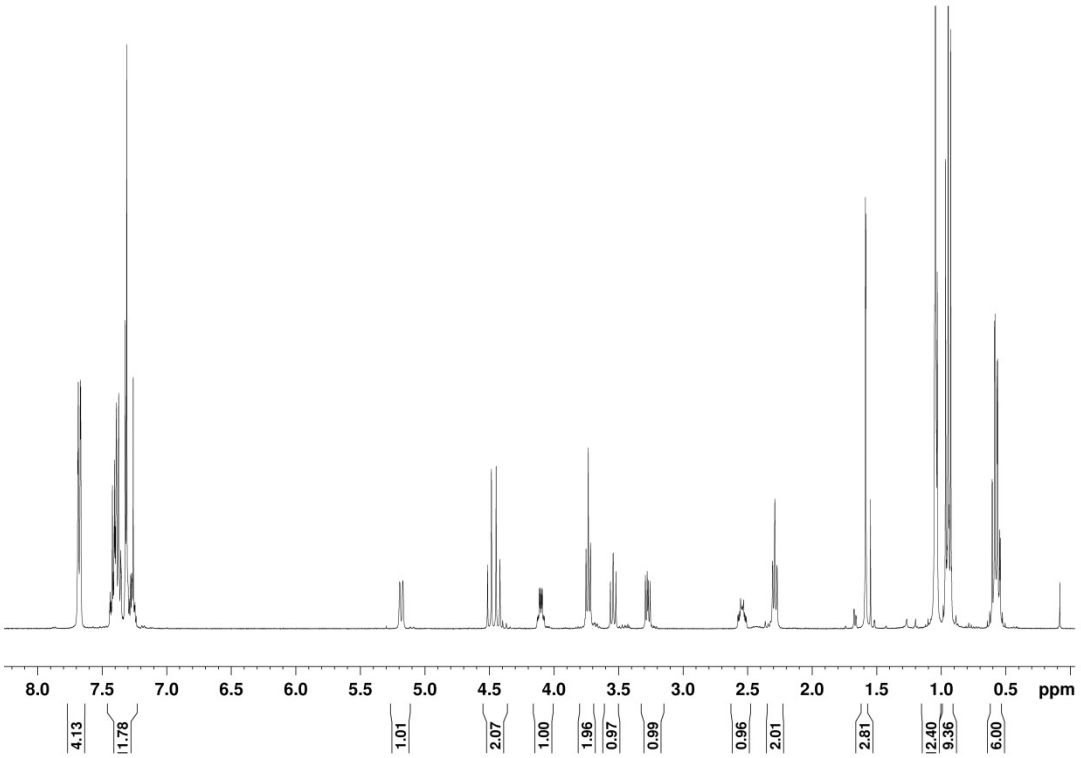
20
ppm




**Alkenes 76a + 76b:** To a solution of **77** (0.581 g, 1.12 mmol, 1.00 equiv.) in 6.00 ml THF, LiHMDS (1.30 ml, 1.30 mmol, 1.40 equiv., 1 M in THF) was added at -78 °C. After the reaction mixture was stirred at – 78 °C for 30 min, a solution of **63** (0.300 g, 0.930 mmol, 1.00 equiv.) in 9.00 ml THF was added drop wise during 6 min to the reaction mixture. After 50 min at – 78 °C the reaction mixture was quenched by addition of aqu. sat. NaCl. The layers were separated and the aqu. phase was extracted 3 times with $Et_2O$. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:40)) gave 0.371 g (64.6 %) of the desired product mixture as colorless oil. Separation of the isomers: (Toluene/hexane (1:1)): 0.150 g (E), 0.120 g (Z), 70 mg (mix fractions).

Analytical data of *Z*-isomer **76b** on page 231

***E*-Isomer 76a: $^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.45 – 7.22 (m, 11H), 5.18 (dd, *J* = 9.7, 1.1 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.10 (qd, *J* = 6.3, 2.8 Hz, 1H), 3.73 (t, *J* = 6.9 Hz, 2H), 3.57 – 3.51 (m, 1H), 3.27 (dd, *J* = 9.0, 5.7 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.29 (t, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.06 – 1.02 (m, 12H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.62 – 0.53 (m, 6H); **13C NMR** (101 MHz, CDCl3) δ 138.90, 135.74, 135.74, 134.98, 134.22, 129.65, 128.42, 127.75, 127.74, 127.72, 127.52, 123.83, 77.48, 77.16, 76.85, 73.15, 71.16, 67.46, 63.29, 45.90, 43.22, 27.00, 21.88, 19.32, 16.96, 7.12, 5.24.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1.5
1.0
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ppm
4.13
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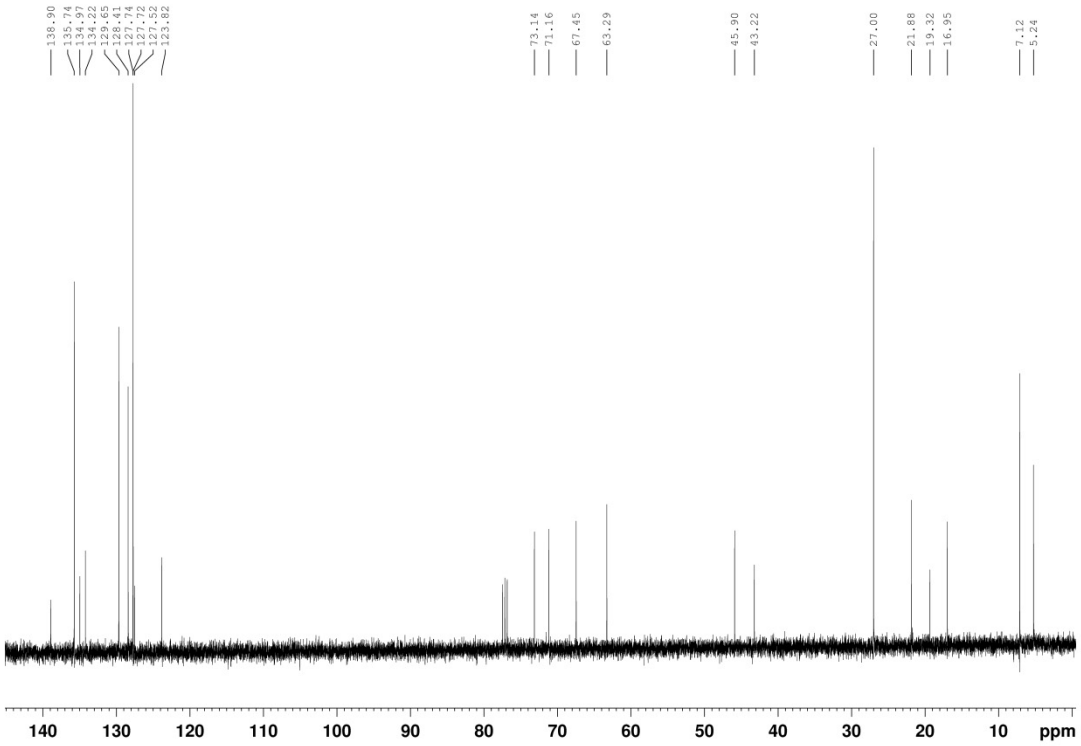
2.07
1.00
1.96
0.97
0.99
0.96
2.01
2.81
2.40
9.36
6.00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73.14
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43.22
27.00
21.88
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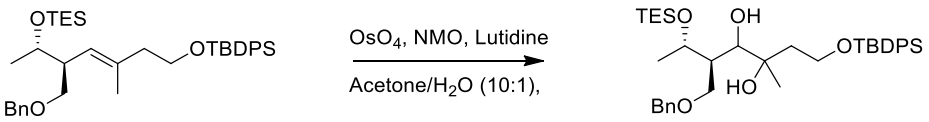
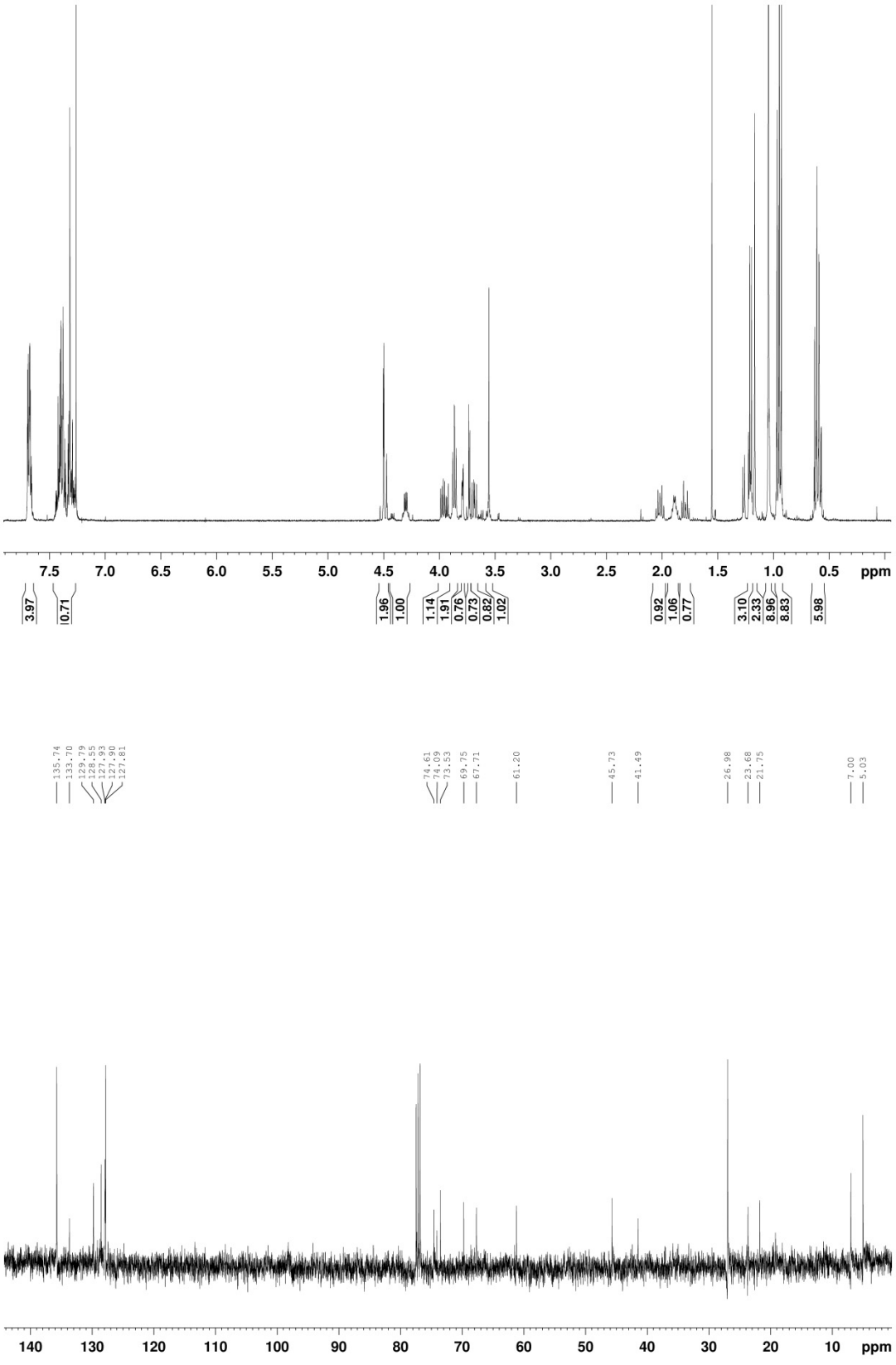
30
20
10
ppm




**76a** **85a**

**Diol 85a (from 76a):** To a solution of **76a** (0.012 g, 0.0194 mmol, 1.00 equiv.) in 0.20 ml Acetone/water (10:1) $OsO_4$ (0.00012 ml, 0.0005 mmol, 0.03 equiv.), NMO (0.0034 g, 0.0292 mmol, 1.50 equiv.) and 2,6-lutidine (0.005 ml, 0.0389 mmol, 2.00 equiv.) were added at 0 °C. The reaction mixture was stirred at 0 °C for 3 h (TLC and MS did not show any conversion). The reaction mixture was allowed to warm up to rt and stirred for 30 min (TLC and MS did not show any conversion). Additional $OsO_4$ (0.03 equiv.) were added and the reaction mixture was stirred at rt for 4 d (TLC and MS showed little conversion). The reaction mixture was heated to 45 °C and stirred for 3 d (TLC and MS showed full conversion). The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfare solution. The aqueous phase was extracted with EtOAc. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 7.3 mg (57 %) of the desired product as a mixture of diastereoisomers (4.5:1) as colorless oil.

**Major Isomer:** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.46 – 7.25 (m, 11H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 9.7 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.00 – 3.91 (m, 1H), 3.87 (d, *J* = 6.2 Hz, 1H), 3.86 (d, *J* = 6.7 Hz, 1H), 3.79 (dd, *J* = 3.4, 1.5 Hz, 1H), 3.73 (d, *J* = 3.4 Hz, 1H), 3.69 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.56 (s, 1H), 2.02 (dt, *J* = 13.9, 6.8 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.79 (dt, *J* = 14.2, 6.1 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.17 (s, 3H), 1.04 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.64 – 0.56 (m, 6H); $^{13}$**C NMR** (101 MHz, $CDCl_3$) δ 135.71, 133.68, 129.78, 128.59, 127.93, 127.86, 74.56, 74.05, 73.56, 69.73, 67.77, 61.15, 45.65, 41.45, 27.03, 23.59, 21.68, 6.90, 4.93.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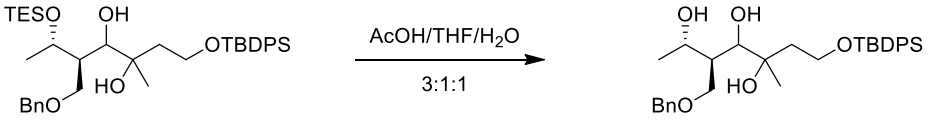
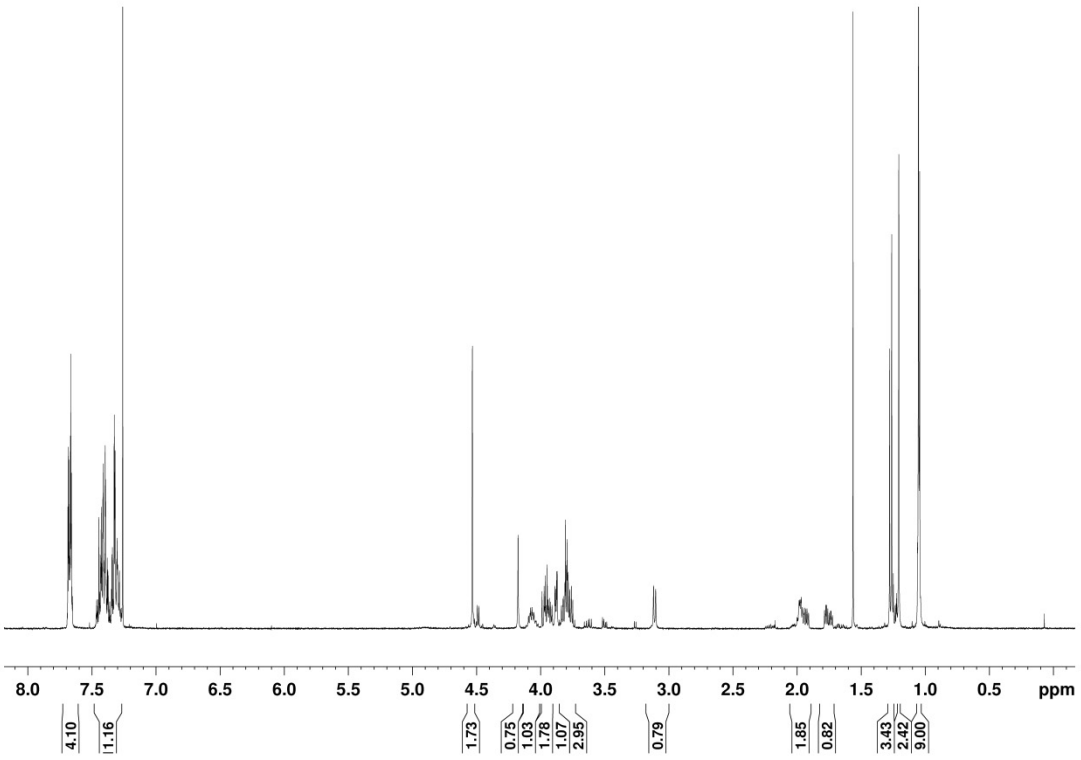
3.97 0.71 1.96 1.00 1.14 1.91 0.76 0.73 0.82 1.02 0.92 1.06 0.77 3.10 2.33 8.96 8.83 5.98
135.74 133.70 129.79 128.55 127.93 127.90 127.81
74.61 74.09 73.53 69.75 67.71 61.20 45.73 41.49 26.98 23.68 21.75 7.00 5.03
140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

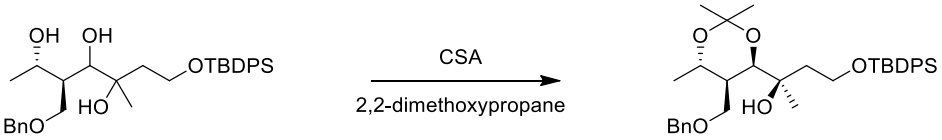



**85a** **226a**

**Triol 226a:** To a solution of **85a** (0.007 g, 0.0108 mmol, 1.00 equiv.) in THF (0.05 ml), 0.05 ml water and 0.15 ml AcOH was added at rt. The reaction mixture was stirred at rt for 20 min. The reaction mixture was neutralized with aqu. sat. $NaHCO_3$, extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:1)) gave 5.5 mg (94 %) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.48 – 7.27 (m, 11H), 4.53 (s, 2H), 4.18 (s, 1H), 4.12 – 4.02 (m, 1H), 4.00 – 3.90 (m, 2H), 3.88 (dd, $J$ = 5.3, 1.8 Hz, 1H), 3.84 – 3.74 (m, 3H), 3.11 (d, $J$ = 6.7 Hz, 1H), 2.05 – 1.86 (m, 2H), 1.76 (ddd, $J$ = 14.6, 6.0, 4.2 Hz, 1H), 1.27 (d, $J$ = 6.5 Hz, 3H), 1.21 (s, 3H), 1.05 (s, 9H).

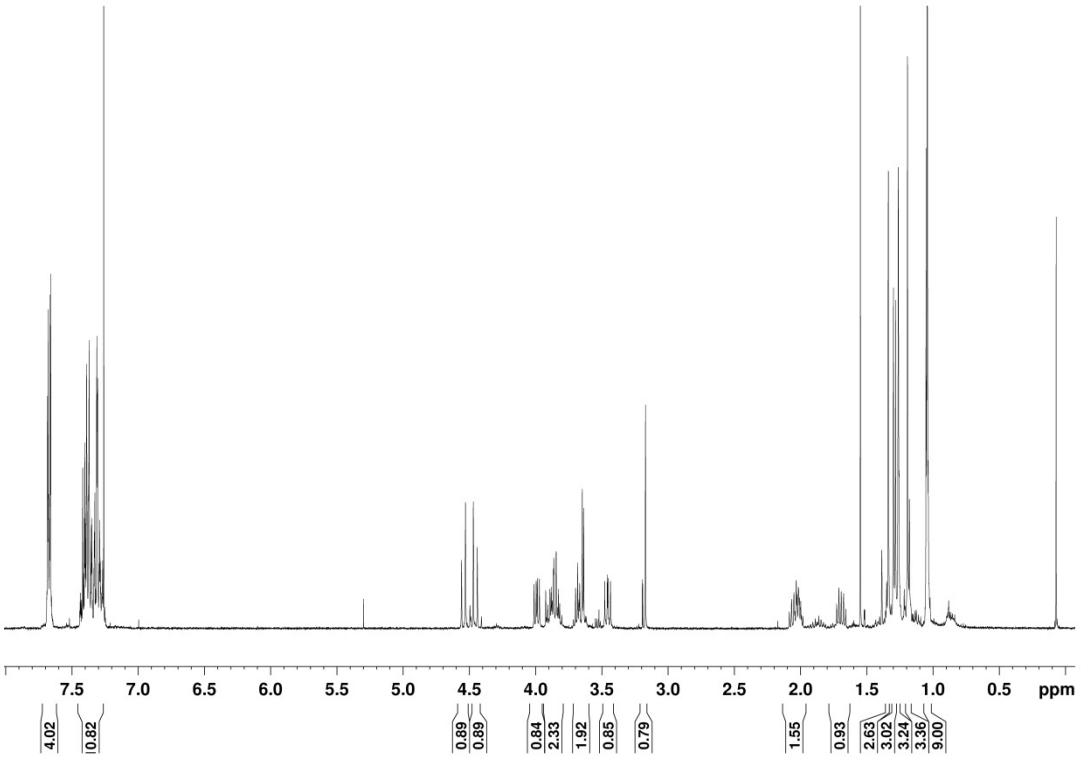





**226a** **86a**

**Acetonide 86a:** To a solution of **226a** (0.0055 g, 0.0102 mmol, 1.00 equiv.) in 0.30 ml 2,2-dimethoxypropane at rt, (+)-CSA (0.0002 mg, 0.0009 mmol, 0.09 equiv.) was added. The reaction mixture was stirred at rt for 16 min. The reaction mixture was quenched by addition of one drop of $NEt_3$. Direct purification over a short pad of silica gel (EtOAc/hexane 1:6) gave 5.8 mg (98%) of the **1,3-anti-product** as colorless oil.

**Major Isomer:** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 4H), 7.46 – 7.26 (m, 11H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.99 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.94 – 3.79 (m, 2H), 3.71 – 3.66 (m, 1H), 3.64 (d, *J* = 4.1 Hz, 1H), 3.46 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.17 (s, 1H), 2.10 – 1.97 (m, 2H), 1.74 – 1.65 (m, 1H), 1.34 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 1.04 (s, 9H); $^{13}$**C NMR** (101 MHz, $CDCl_3$) δ 138.19, 135.75, 133.88, 129.74, 128.55, 127.79, 127.75, 127.61, 101.21, 73.40, 73.19, 72.94, 69.62, 68.37, 60.84, 45.64, 41.46, 27.03, 25.69, 24.01, 23.13, 22.35, 19.26.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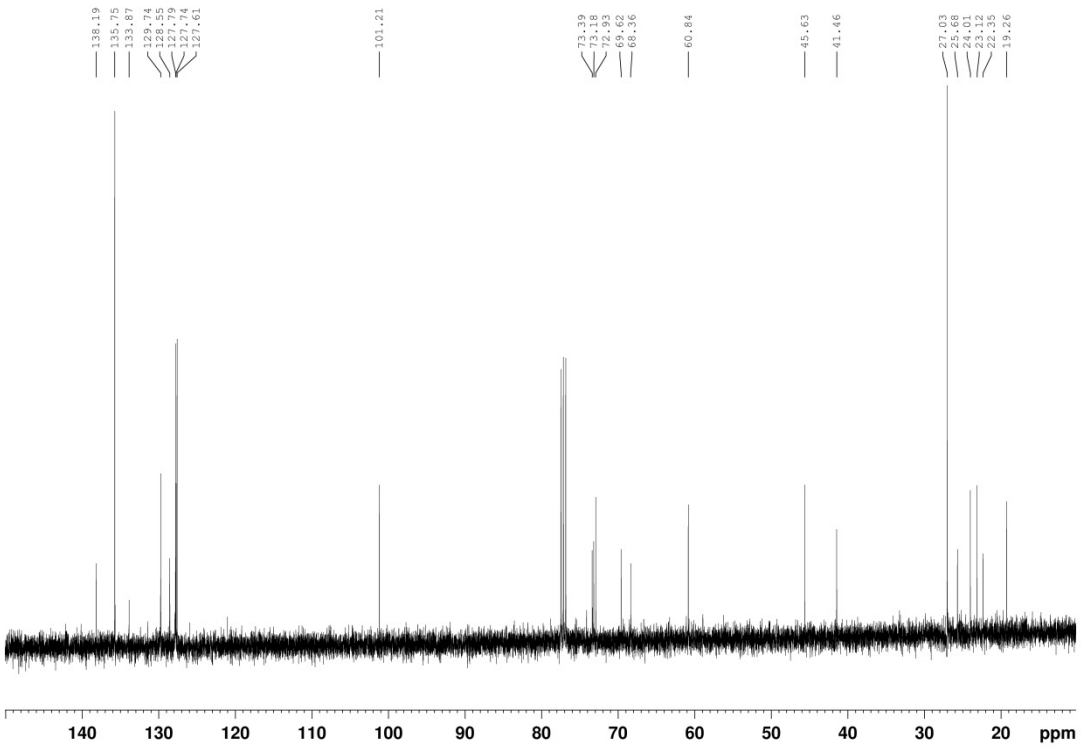
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25.68
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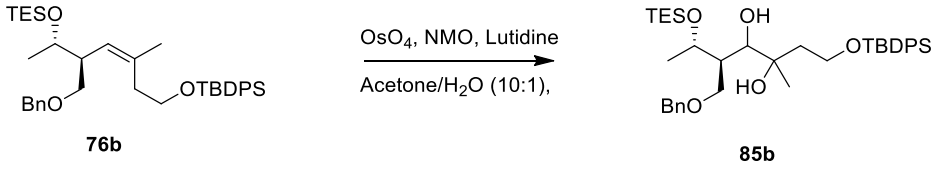
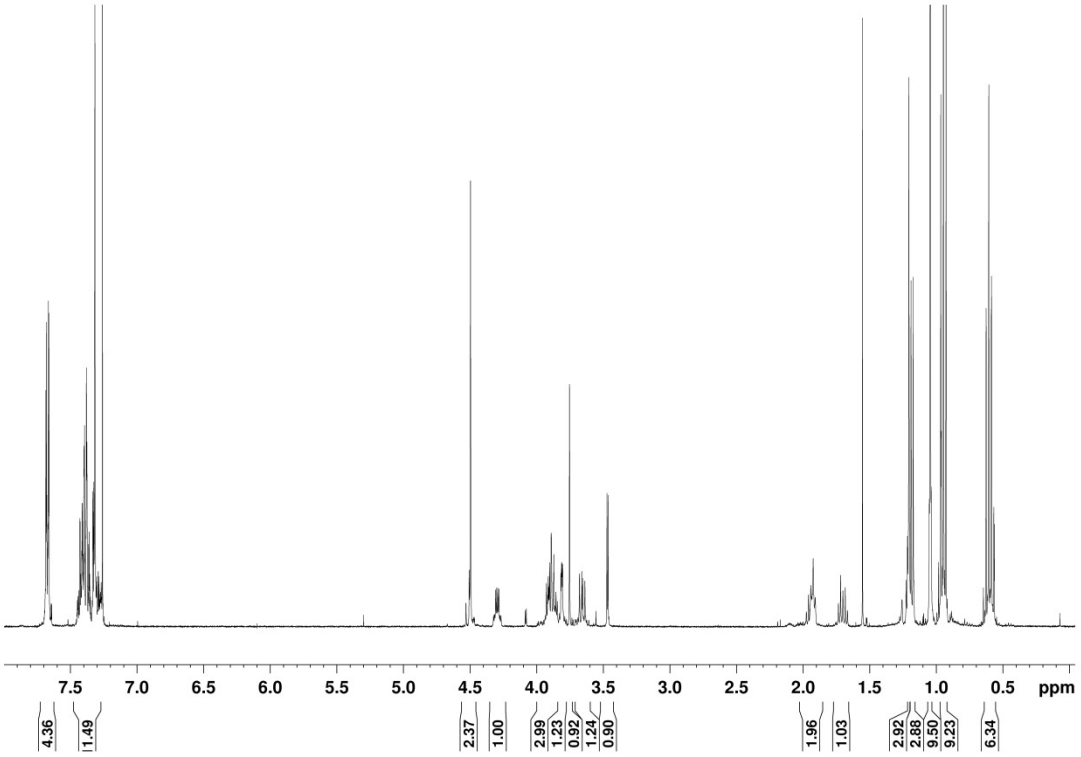
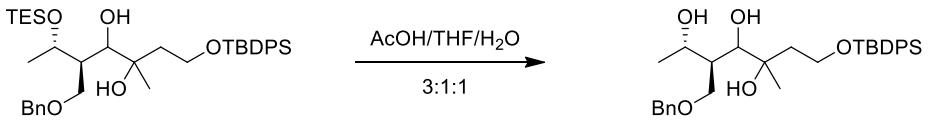



**Diol 85b:** To a solution of **76b** (0.010 g, 0.0162 mmol, 1.00 equiv.) in 0.20 ml Acetone/water (10:1) $OsO_4$ (0.00010 ml, 0.0004 mmol, 0.03 equiv.), NMO (0.0028 g, 0.0243 mmol, 1.50 equiv.) and 2,6-lutidine (0.004 ml, 0.0324 mmol, 2.00 equiv.) were added at rt. The reaction mixture was stirred at rt for 3 d (TLC and MS showed approx. 30 % conversion). The reaction mixture was heated to 45 °C and stirred for overnight (TLC and MS showed full conversion). The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfate solution. The aqueous phase was extracted with EtOAc. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 7.9 mg (75 %) of the desired product as a mixture of diastereoisomers (1:7) as colorless oil.

**Major Isomer:** $^1$**H-NMR** (400 MHz, $CDCl_3$): δ 7.71 – 7.64 (m, 4H), 7.47 – 7.24 (m, 11H), 4.50 (s, 2H), 4.30 (qd, *J* = 6.3, 3.1 Hz, 1H), 3.96 – 3.84 (m, 3H), 3.82 (dd, *J* = 3.1, 1.8 Hz, 1H), 3.77 (s, 1H), 3.66 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.48 (d, *J* = 3.3 Hz, 1H), 1.99 – 1.90 (m, 2H), 1.76 – 1.65 (m, 1H), 1.21 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.66 – 0.56 (m, 6H);

For analytical data of pure isomer **85b** see page 202.

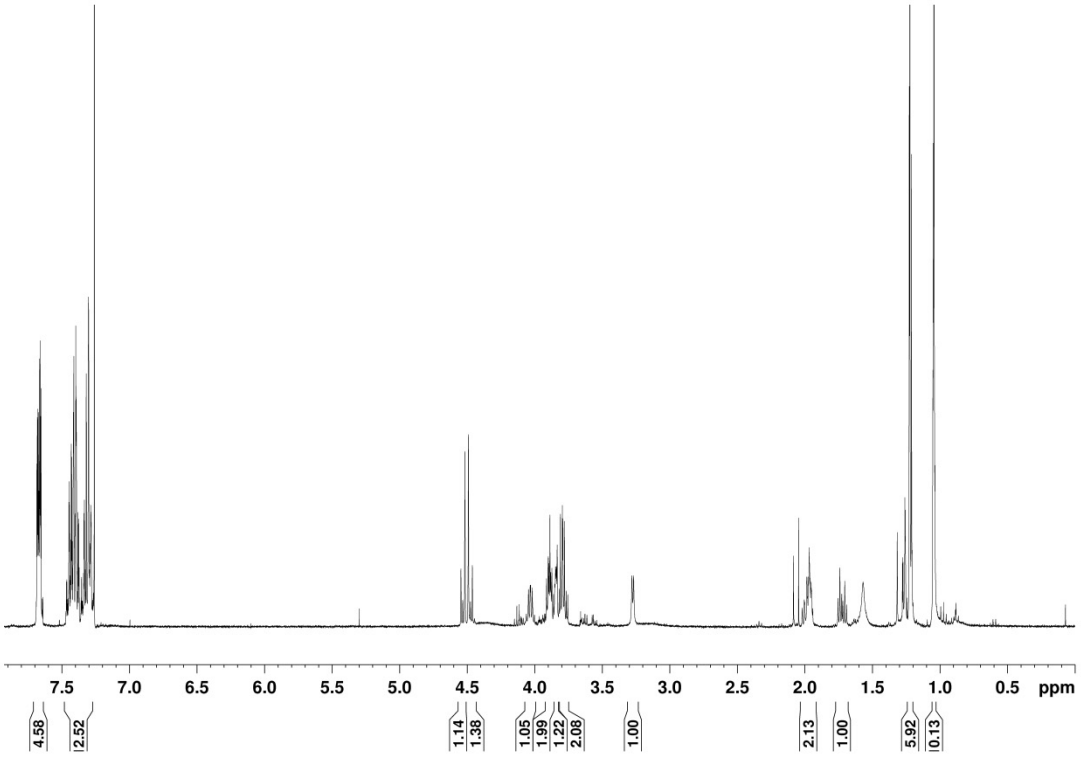


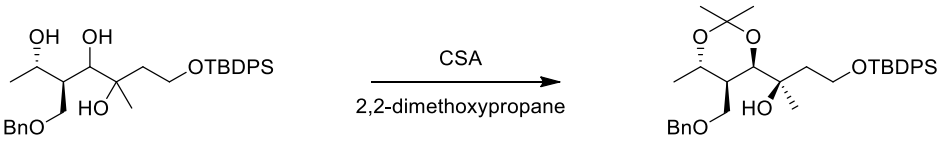



**85b** **226b**

**Triol 226b:** To a solution of **85b** (0.0079 g, 0.0128 mmol, 1.00 equiv.) in THF (0.05 ml), 0.05 ml water and 0.15 ml AcOH was added at rt. The reaction mixture was stirred at rt for 20 min. The reaction mixture was neutralized with aqu. sat. $NaHCO_3$, extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:1)) gave 6.0 mg (87 %) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 4H), 7.49 – 7.27 (m, 11H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.92 – 3.74 (m, 5H), 3.27 (d, *J* = 5.0 Hz, 1H), 2.03 – 1.93 (m, 2H), 1.72 (dt, *J* = 14.3, 5.5 Hz, 1H), 1.22 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H).

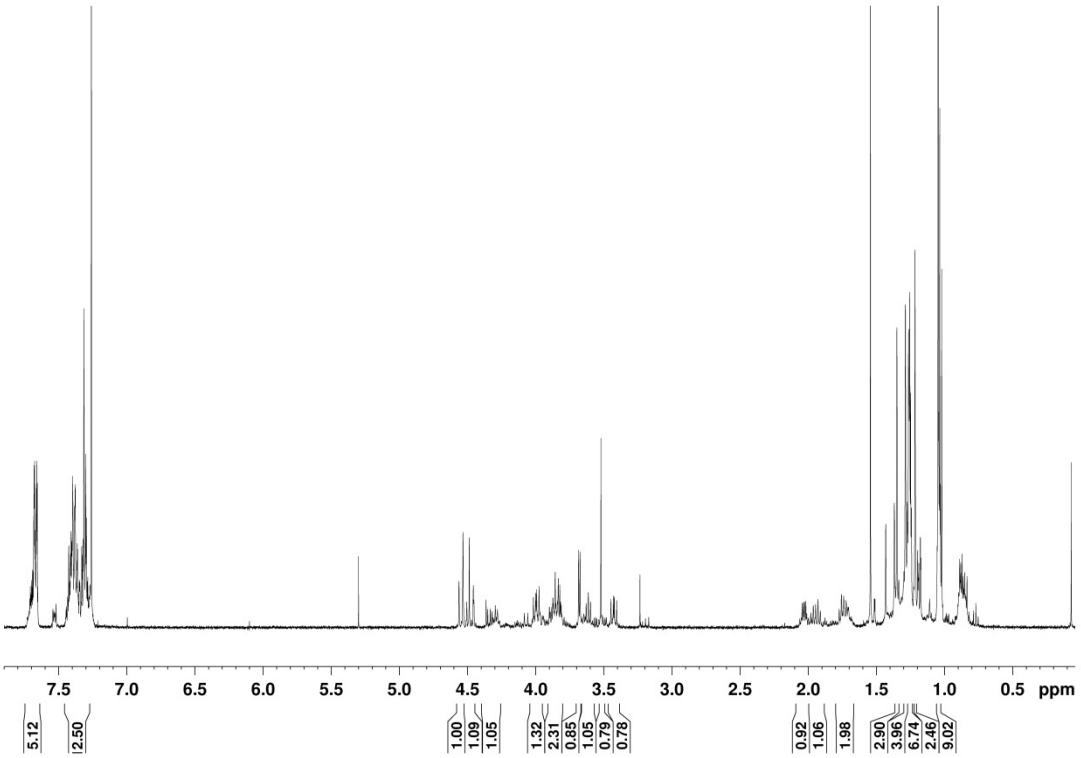





**226b** **86b**

**Acetonide 86b:** To a solution of **226b** (0.0060 g, 0.0112 mmol, 1.00 equiv.) in 0.30 ml 2,2-dimethoxypropane at rt, (+)-CSA (0.0002 mg, 0.0010 mmol, 0.09 equiv.) was added. The reaction mixture was stirred at rt for 12 min. (TLC showed full conversion). The reaction mixture was quenched by addition of one drop of $NEt_3$. Direct purification over a short pad of silica gel (EtOAc/hexane 1:6) gave 5.0 mg (77%) of the **anti-product** as colorless oil.

**Major Isomer:** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.45 – 7.29 (m, 11H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.40 – 4.24 (m, 1H), 4.00 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.91 – 3.78 (m, 2H), 3.68 (d, *J* = 4.1 Hz, 1H), 3.52 (s, 1H), 3.43 (dd, *J* = 9.7, 6.9 Hz, 1H), 2.07 – 2.00 (m, 1H), 1.99 – 1.87 (m, 1H), 1.79 – 1.67 (m, 1H), 1.46 – 1.16 (m, 12H), 1.05 (s, 9H); $^{13}$**C NMR** (101 MHz, $CDCl_3$) δ 137.98, 135.72, 133.64, 129.83, 128.58, 128.55, 127.92, 127.85, 127.82, 127.68, 101.26, 73.47, 73.16, 69.45, 68.03, 60.78, 45.79, 40.48, 27.01, 26.98, 25.41, 24.39, 23.90, 22.10, 19.25, 7.49, 2.41.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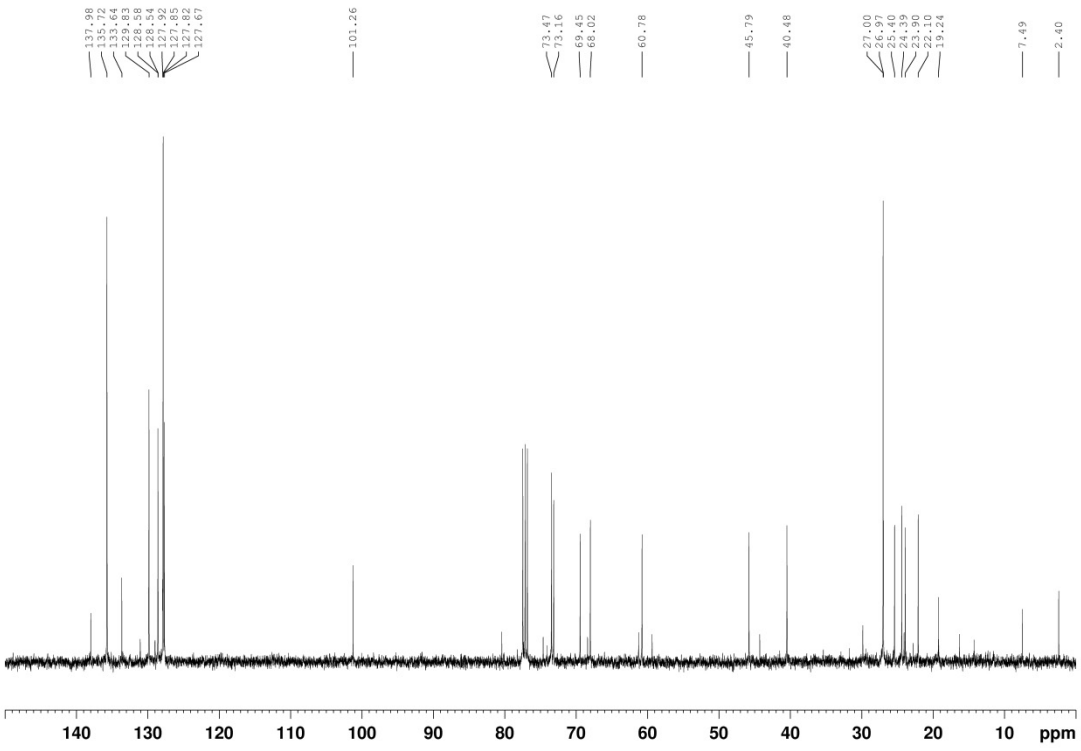
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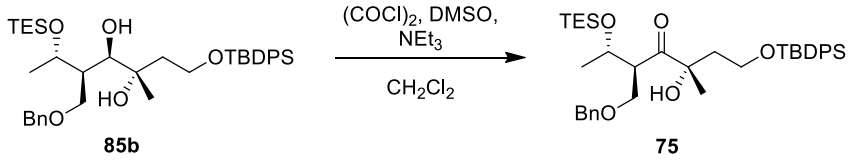
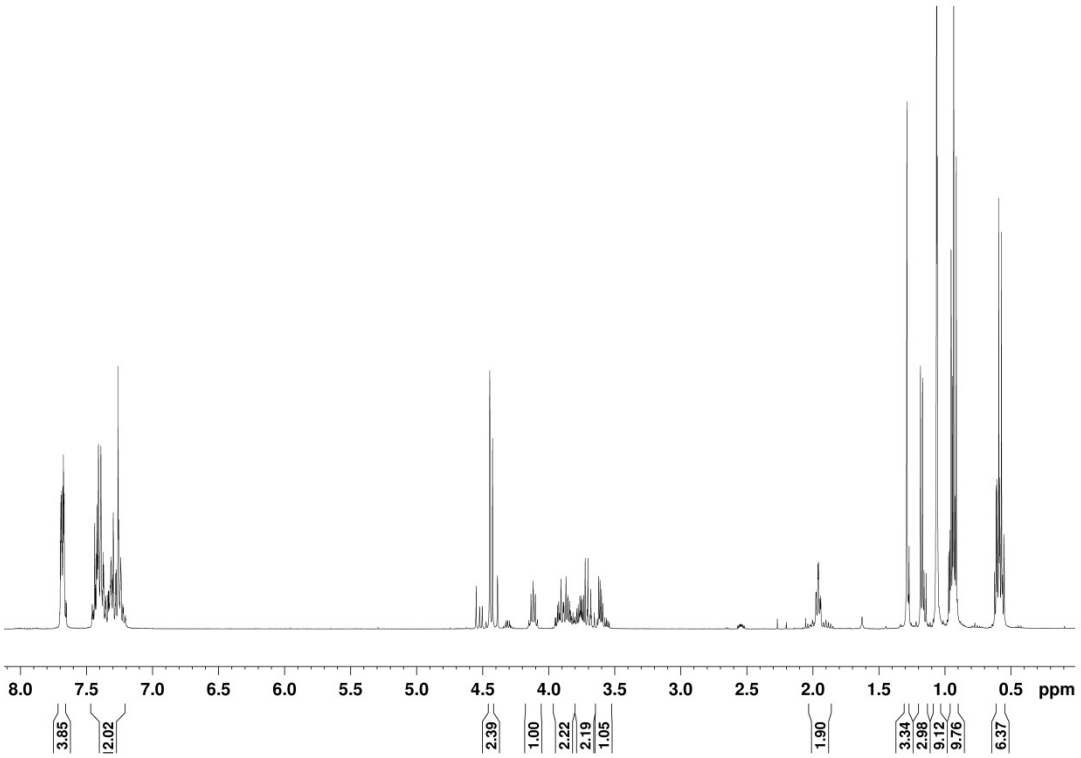



**Ketone 75:** To a solution of oxalylchloride (0.111 ml, 1.29 mmol, 5.00 equiv.) in 1.00 ml $CH_2Cl_2$ at -78 °C, DMSO in $CH_2Cl_2$ (0.50 ml) (0.183 ml, 2.58 mmol, 10.0 equiv.) was added drop wise. After 15 min, a solution of **85b** (0.168 g, 0.258 mmol, 1.00 equiv.) in $CH_2Cl_2$ (1.00 ml) was added. The reaction mixture was stirred at – 78 °C for 20 min , then $NEt_3$ (0.538 ml, 3.87 mmol, 15.0 equiv.) was added drop wise. The cooling bath was removed and the reaction mixture was allowed to warm up to rt. Water and $CH_2Cl_2$ were then added. The phases were separated and the aqueous layer was extracted with $CH_2Cl_2$. The comb. org. phases were washed with aqu. sat. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 129.8 mg (77 %) of the desired product as orange oil.

**Major isomer $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.64 (m, 4H), 7.47 – 7.19 (m, 11H), 4.45 (s, 2H), 4.12 (p, *J* = 6.2 Hz, 1H), 3.98 – 3.52 (m, 5H), 2.08 – 1.83 (m, 2H), 1.29 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.06 (d, *J* = 1.7 Hz, 9H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.65 – 0.54 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 215.13, 138.06, 135.67, 135.66, 133.45, 129.84, 128.54, 128.47, 127.85, 127.71, 127.63, 79.28, 73.48, 73.42, 68.81, 68.20, 60.99, 53.87, 53.74, 39.40, 26.92, 24.24, 21.85, 21.75, 19.19, 6.91, 5.07, 4.98.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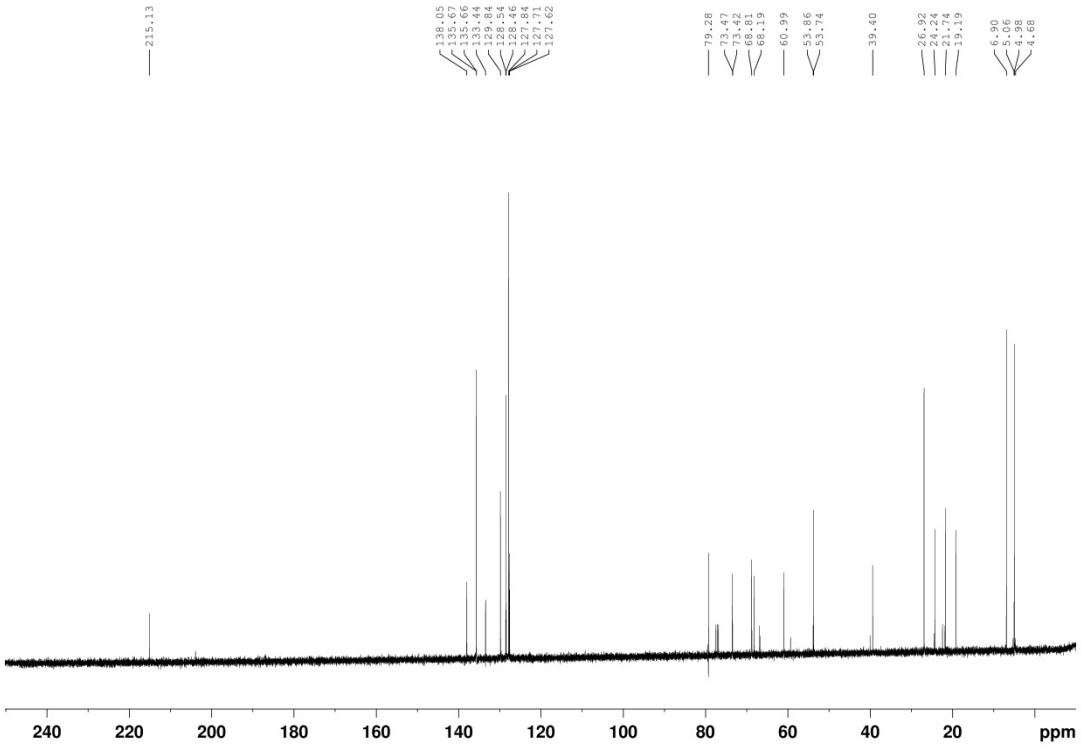
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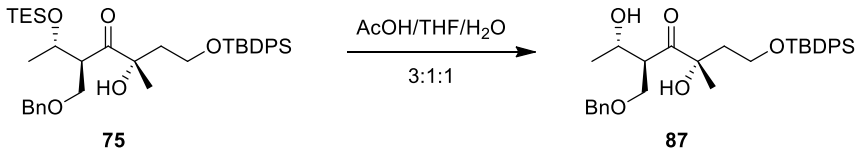
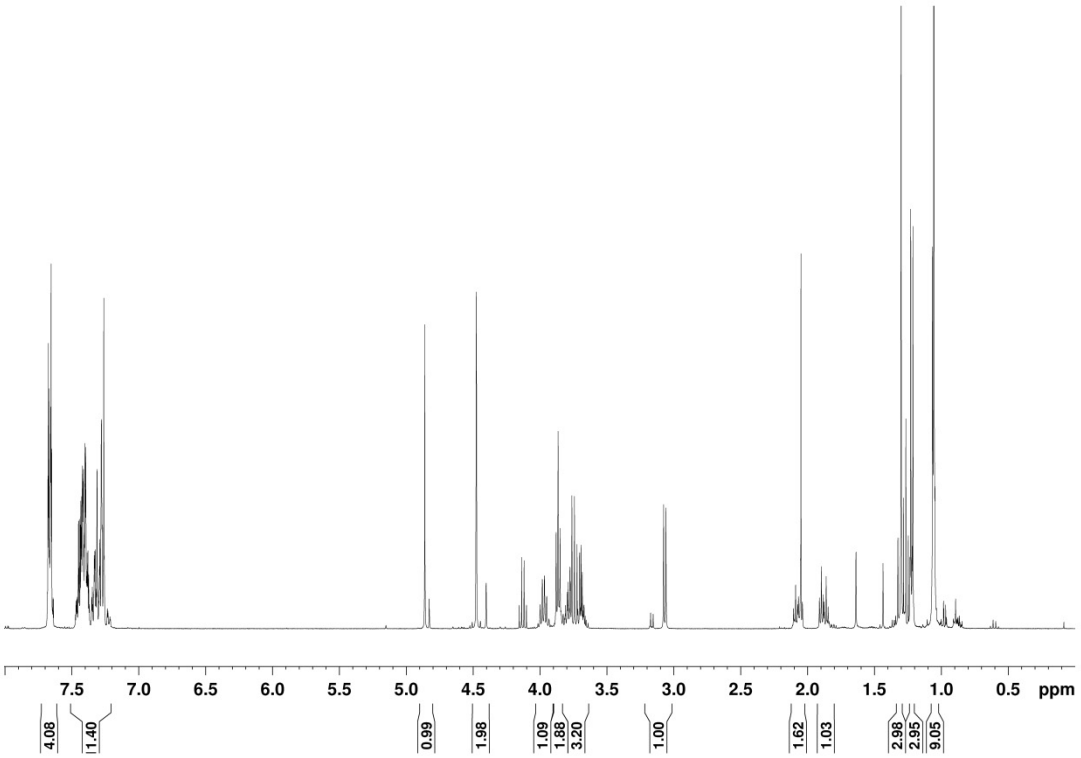



**75** **87**

**Alcohol 87:** To a solution of **75** (0.129 g, 0.199 mmol, 1.00 equiv.) in THF (0.30 ml), 0.0.30 ml water and 0.920 ml AcOH were added at rt. The reaction mixture was stirred at rt for 1 h. The reaction mixture was neutralized with aqu. sat. $NaHCO_3$, extracted with EtOAc and the comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:3)) gave 93.3 mg (87 %) of the desired product as colorless oil.

**Major isomer $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 4H), 7.50 – 7.20 (m, 11H), 4.86 (s, 1H), 4.48 (s, 2H), 4.02 – 3.92 (m, 1H), 3.87 (t, *J* = 5.9 Hz, 2H), 3.83 – 3.63 (m, 3H), 3.07 (d, *J* = 7.1 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.88 (dt, *J* = 14.4, 5.8 Hz, 1H), 1.30 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 217.50, 137.80, 135.69, 135.66, 132.87, 132.73, 130.08, 128.54, 127.98, 127.87, 127.76, 80.07, 73.59, 69.62, 67.74, 61.45, 52.67, 38.90, 26.93, 24.93, 22.09, 19.13.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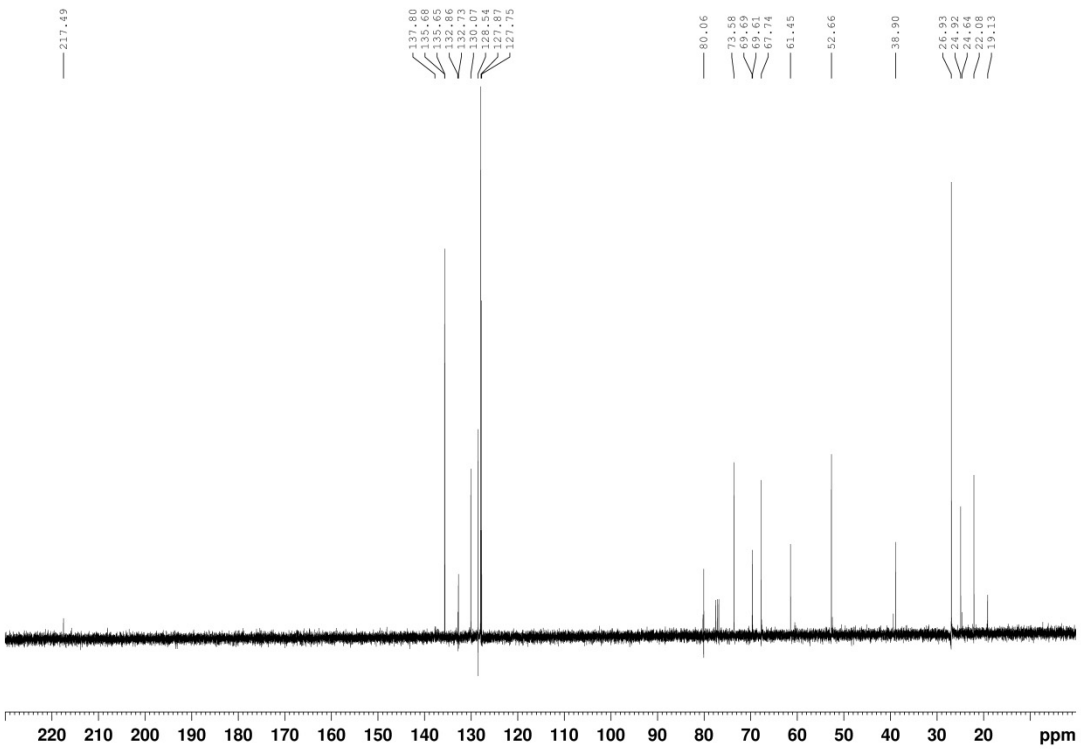
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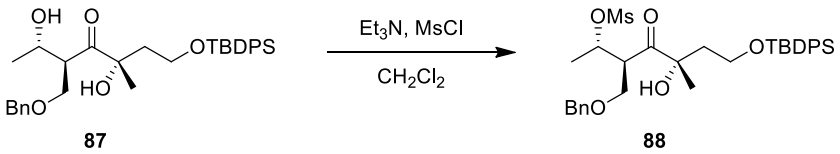
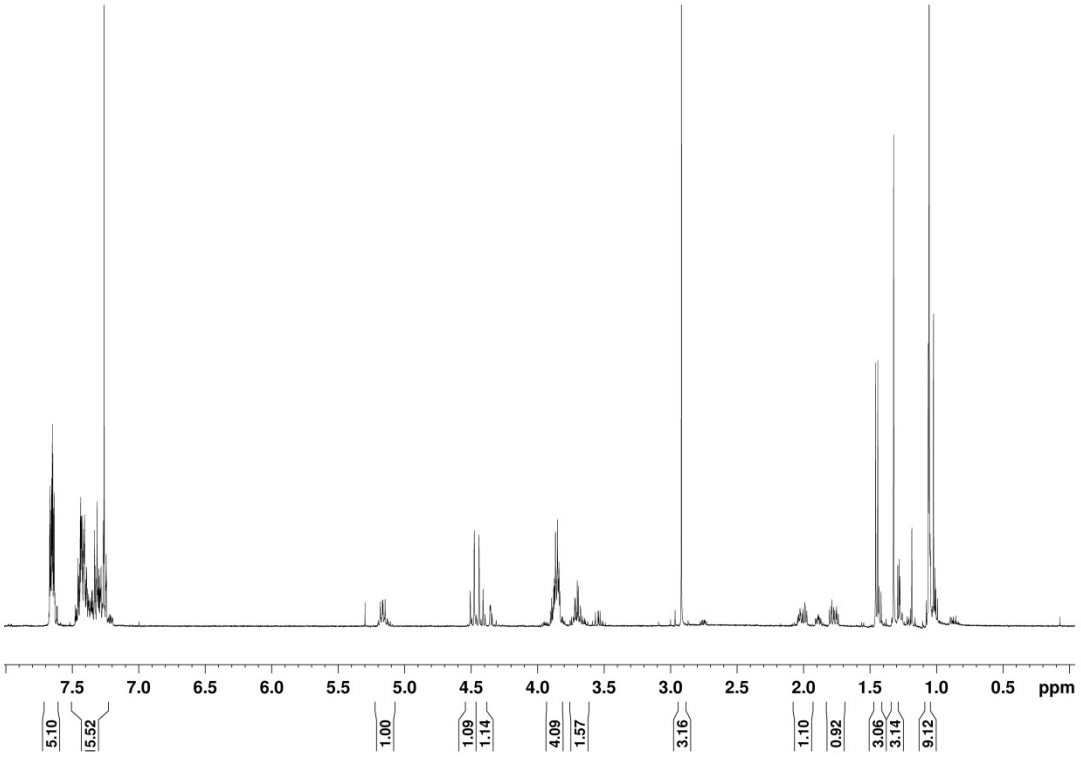
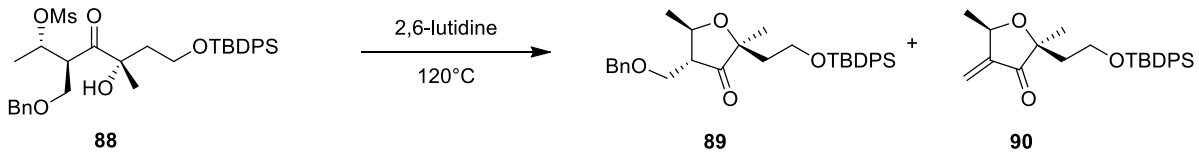



**87** **88**

**Mesylate 88:** To a solution of **87** (0.023 g, 0.043 mmol, 1.00 equiv.) and $NEt_3$ (0.060 ml, 0.430 mmol, 10.0 equiv.) in DCM (0.80 ml) at -40 °C, MsCl (0.010 ml, 0.129 mmol, 3.00 equiv.) was added. The reaction mixture was stirred at -40 °C for 20 min and then quenched by addition of MeOH (~0.12 ml). The reaction mixture was allowed to warm up to rt and then water was added. The layers were separated and the aqu. phase was extracted with DCM. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure to give 34.5 mg of crude product.

**Major isomer $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H), 7.49 – 7.17 (m, 11H), 5.24 – 5.07 (m, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.93 – 3.80 (m, 4H), 3.77 – 3.58 (m, 2H), 2.92 (s, 3H), 2.06 – 1.94 (m, 1H), 1.77 (ddd, *J* = 14.4, 6.9, 5.1 Hz, 1H), 1.45 (d, *J* = 6.4 Hz, 3H), 1.32 (s, 3H), 1.06 (s, 9H).





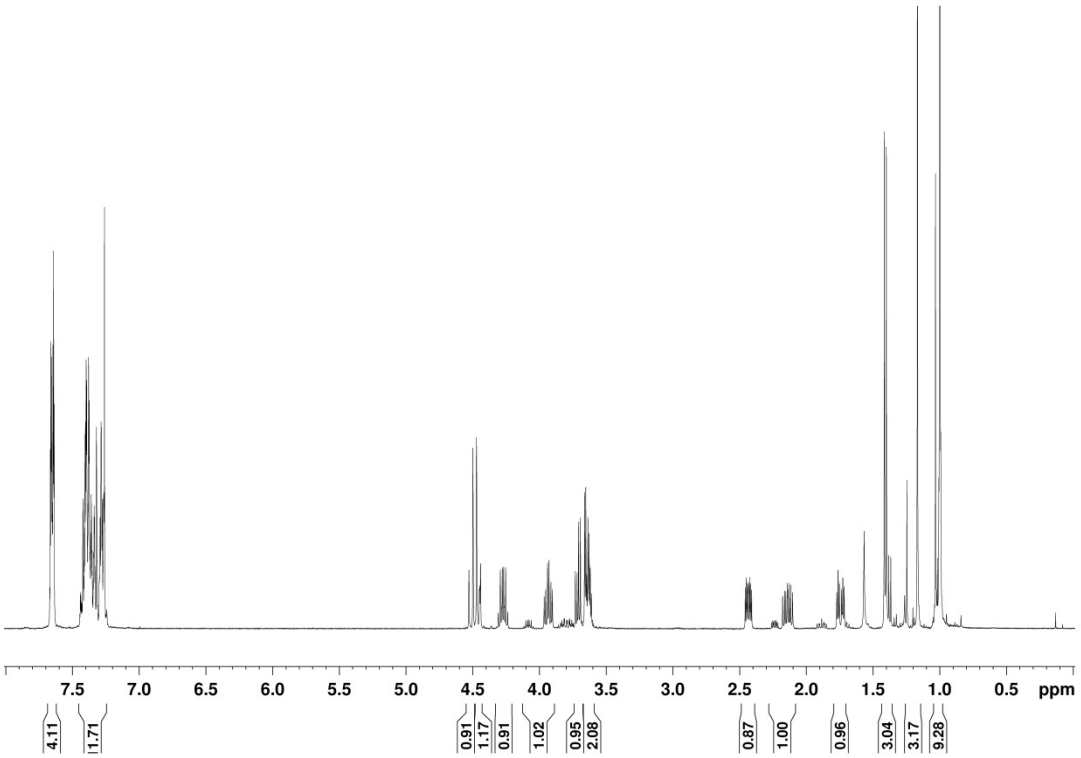

**88** **89** **90**

**Tetrahydrofuran 89:** A solution of crude **88** in 3.00 ml 2,6-lutidine was heated to 120 °C for 3 h. After cooling to rt, water was added and the aqu. phase was extracted 3 times with DCM. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Crude product: 76.4 mg. Purification over silica gel (EtOAc/hexane (1:10)) gave 49 mg of a mixture consisting 34 mg (40.8 %) isomerized product and 15 mg (22.7 %) of the benzyl elimination product 1.

After further unsuccessful purification over silica gel trials, the mixture was separated by means of preparative HPLC giving 24.7 mg (31 %) of the isomerized product **89** and 10 mg (15 %) of the elimination product **90**.

**Major isomer 89** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H), 7.45 – 7.24 (m, 11H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.33 – 4.22 (m, 1H), 3.93 (td, *J* = 10.1, 4.5 Hz, 1H), 3.71 (dd, *J* = 9.8, 5.5 Hz, 1H), 3.68 – 3.58 (m, 2H), 2.43 (ddd, *J* = 10.1, 5.4, 3.4 Hz, 1H), 2.14 (ddd, *J* = 14.4, 9.9, 5.8 Hz, 1H), 1.78 – 1.71 (m, 1H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.17 (s, 3H), 1.00 (s, 9H); $^{13}$**C NMR** (101 MHz, CDCl3) δ 216.82, 138.30, 135.79, 135.65, 133.90, 133.51, 129.78, 129.73, 128.49, 127.79, 127.71, 127.50, 81.38, 73.46, 72.44, 66.32, 59.34, 54.44, 40.75, 27.00, 26.89, 21.64, 20.53, 19.22.

**90** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 4H), 7.45 – 7.34 (m, 6H), 6.08 (d, *J* = 2.8 Hz, 1H), 5.35 (d, *J* = 2.4 Hz, 1H), 4.85 – 4.71 (m, 1H), 3.81 (ddd, *J* = 10.3, 8.8, 5.8 Hz, 1H), 3.65 (ddd, *J* = 10.5, 6.8, 4.1 Hz, 1H), 2.22 – 2.12 (m, 1H), 1.81 (ddd, *J* = 14.2, 5.8, 4.1 Hz, 1H), 1.42 (d, *J* = 6.3 Hz, 3H), 1.22 (s, 3H), 0.98 (s, 9H); $^{13}$**C NMR** (101 MHz, $CDCl_3$) δ 205.58, 145.35, 135.78, 135.71, 133.96, 133.78, 129.69, 129.65, 127.71, 117.98, 81.48, 72.14, 59.42, 40.37, 26.83, 22.58, 20.74, 19.17.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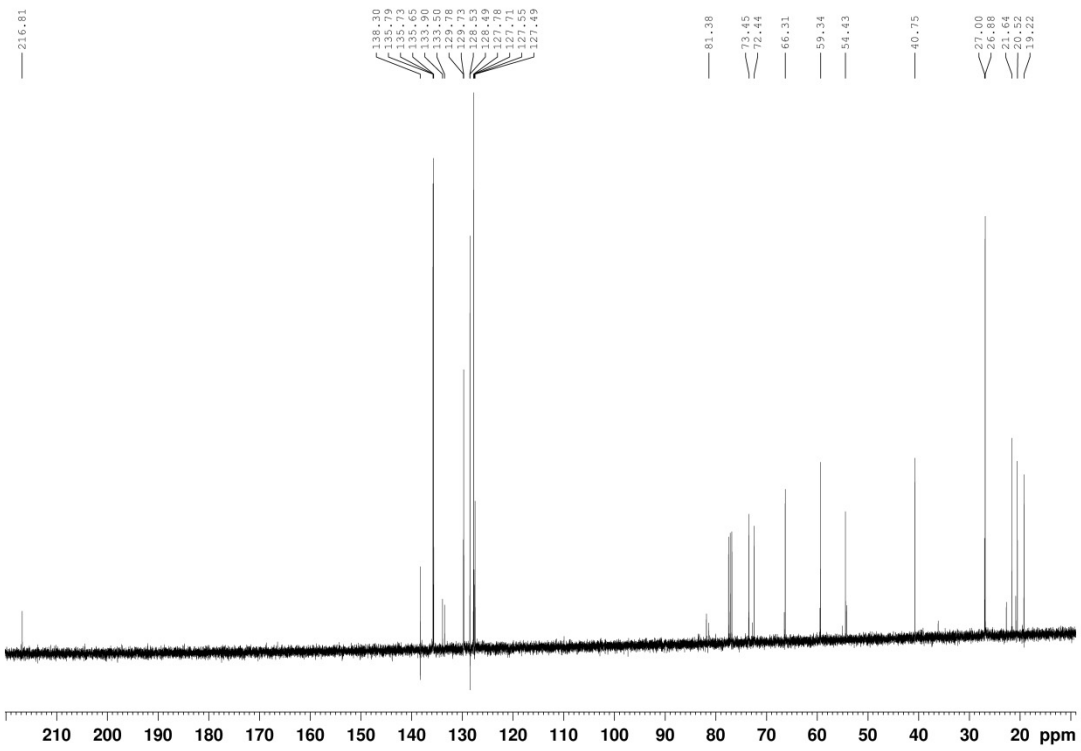
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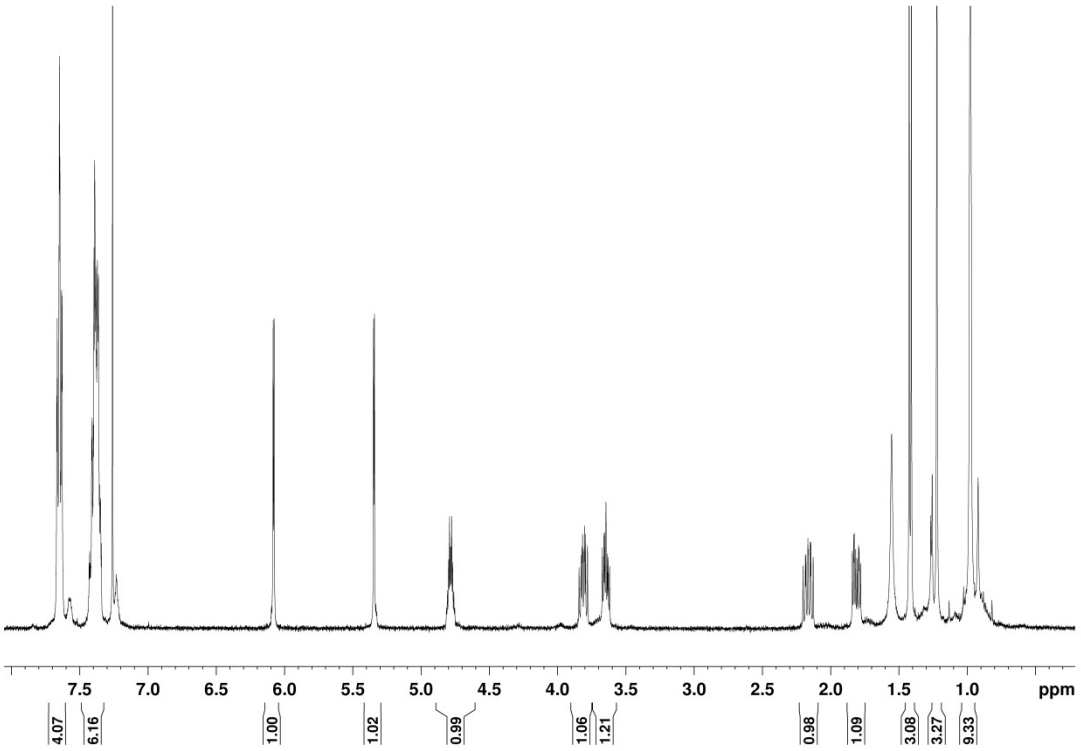
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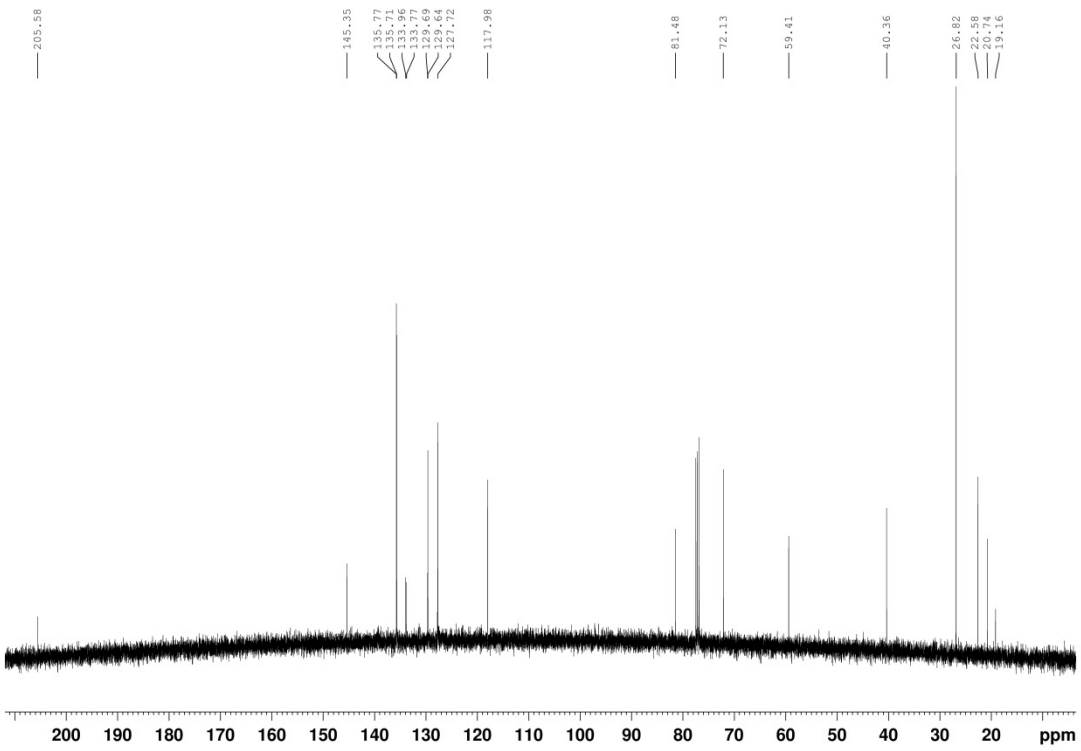
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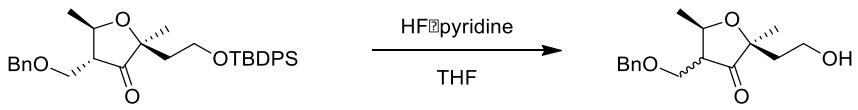
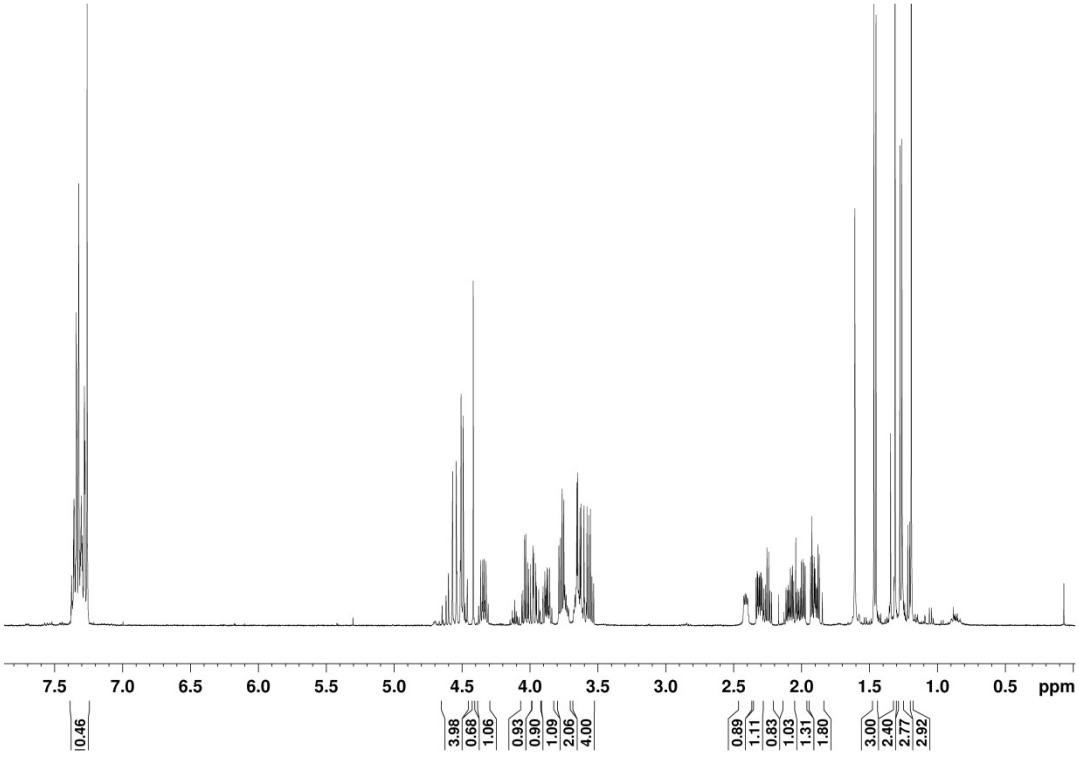


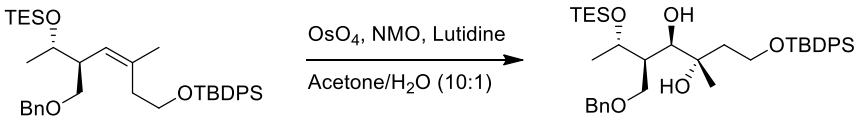

**89** **91**

**Alcohol 91: 89** (0.020 g, 0.0387 mmol, 1.00 equiv.) was dissolved in THF (1.00 mL) and cooled to 0 °C. HF-pyridine (0.0249 mL, 0.193 mmol, 5.00 equiv,) was added and the reaction solution stirred at rt for 6 h (no full conversion). Additional HF-pyridine (0.025 ml) was added and the reaction stirred for another 8 h. The reaction solution was poured into aqu. sat. $NaHCO_3$ (1 mL) and stirred for 1 h. The resulting mixture was filtered through Celite and washed with $CH_2Cl_2$. The aqueous layer was extracted with $CH_2Cl_2$, and then the combined org phases were dried over $MgSO_4$, filtered, and concentrated. Purification over silica gel (EtOAc/hexane 1:2) gave 7.2 mg of the desired product as a diastereomeric mixture (1:1) as colorless oil.

**Both isomers $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 10H), 4.66 – 4.45 (m, 4H), 4.42 (s, 1H), 4.34 (dq, *J* = 9.9, 6.0 Hz, 1H), 4.16 – 3.93 (m, 2H), 3.93 – 3.83 (m, 1H), 3.80 – 3.70 (m, 2H), 3.69 – 3.51 (m, 4H), 2.41 (dd, *J* = 7.5, 3.8 Hz, 1H), 2.34 – 2.28 (m, 1H), 2.25 (td, *J* = 8.7, 5.0 Hz, 1H), 2.12 – 2.05 (m, 1H), 2.01 (ddd, *J* = 14.8, 7.5, 3.8 Hz, 1H), 1.95 – 1.83 (m, 2H), 1.46 (d, *J* = 6.0 Hz, 3H), 1.31 (s, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.19 (s, 3H).



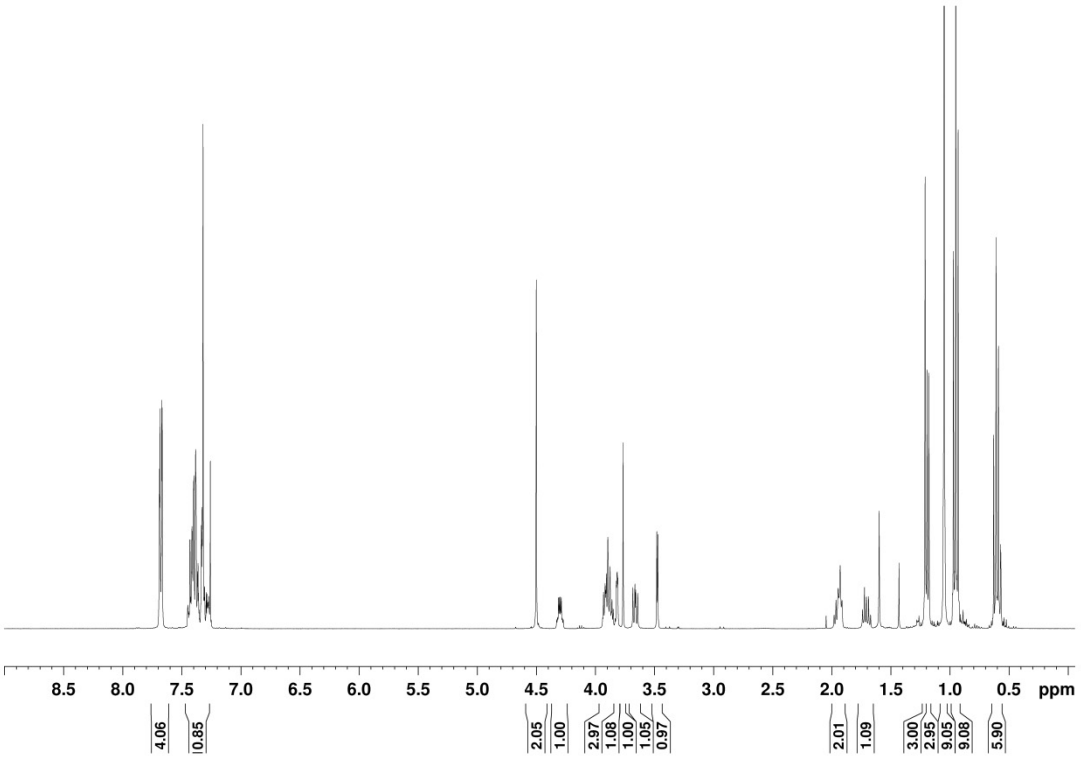
### 5.3.2.2. Synthesis of Sulfone 92




**76b** **85b**

**Diol 85b:** To a solution of **76b** (6.03 g, 9.77 mmol, 1.00 equiv.) in 97.70 ml Acetone/water (10:1) $OsO_4$ (1.49 ml, 0.244 mmol, 0.03 equiv.), NMO (1.72 g, 14.66 mmol, 1.50 equiv.) and 2,6-lutidine (2.27 ml, 19.54 mmol, 2.00 equiv.) were added at rt. The reaction mixture was heated to 45 °C for 24 h (TLC and MS showed incomplete conversion). Additional 1.49 ml $OsO_4$ and 1.72 g NMO were added and the reaction mixture heated again to 45 °C for 48 h. The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfate solution. The phases were separated and the aqueous phase was extracted 3 times with EtOAc. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 4.64 g (73 %; desired isomer) of **85b** as brown oil.

**TLC**: $R_f$ = 0.44 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.71 – 7.64 (m, 4H), 7.47 – 7.24 (m, 11H), 4.50 (s, 2H), 4.30 (qd, *J* = 6.3, 3.1 Hz, 1H), 3.96 – 3.84 (m, 3H), 3.82 (dd, *J* = 3.1, 1.8 Hz, 1H), 3.77 (s, 1H), 3.66 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.48 (d, *J* = 3.3 Hz, 1H), 1.99 – 1.90 (m, 2H), 1.76 – 1.65 (m, 1H), 1.21 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.66 – 0.56 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 138.15, 135.69, 133.46, 133.41, 129.88, 128.55, 127.91, 127.88, 127.82, 74.75, 74.23, 73.51, 69.76, 68.20, 61.27, 45.33, 40.24, 26.97, 24.05, 21.64, 19.20, 7.00, 5.05; **IR** (thin film): ν 3491, 2954, 2933, 2876, 1455, 1427, 1379, 1238, 1082, 1006, 969, 822, 735, 699, 613, 503; **HRMS** (ESI): calculated for $C_{38}H_{58}NaO_5Si_2$ $[M+Na]^+$: 673.3715, found 673.3713; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +11.55° (c = 1.03 in $CHCl_3$).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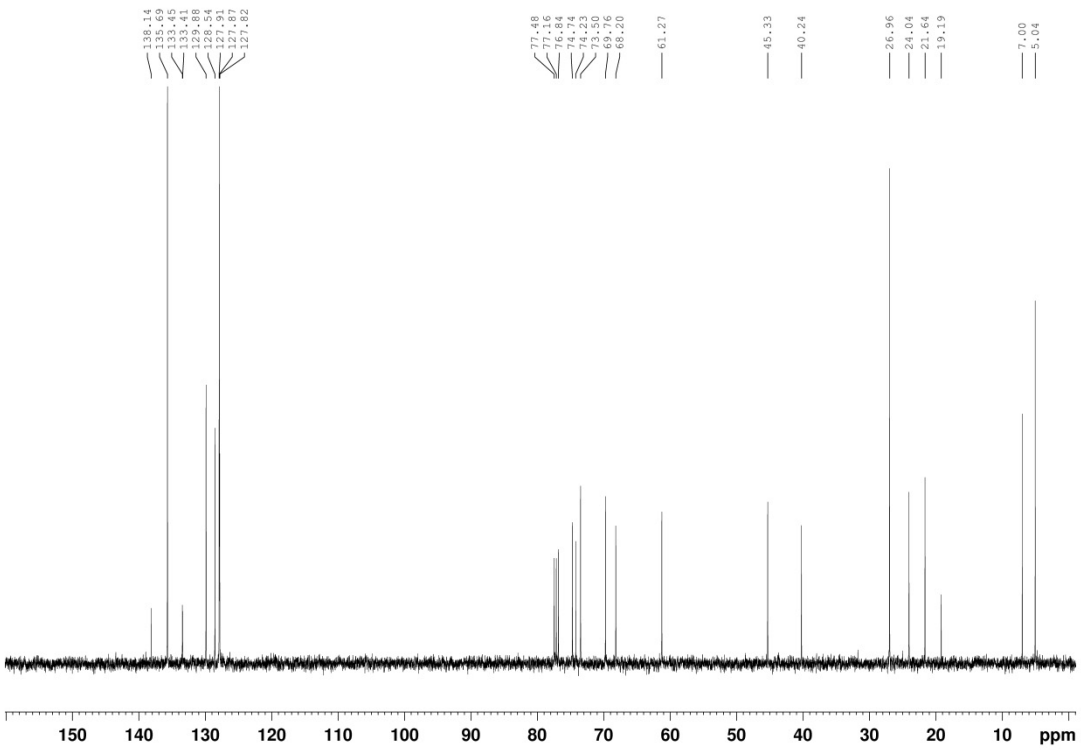
4.06 0.85 2.05 1.00 2.97 1.08 1.00 1.05 0.97 2.01 1.09 3.00 2.95 9.05 9.08 5.90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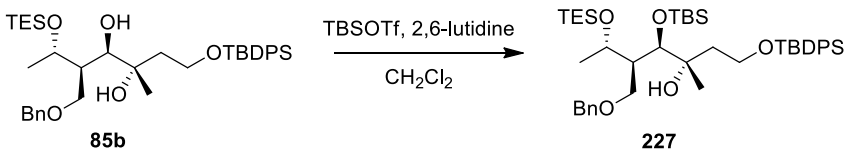
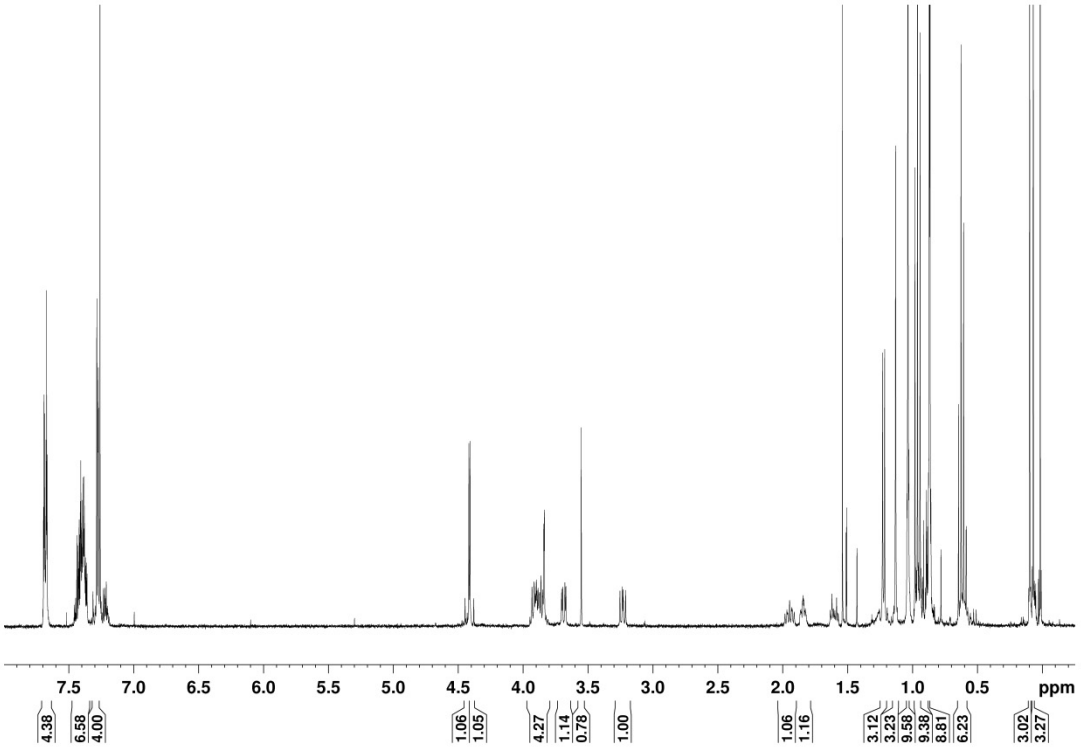
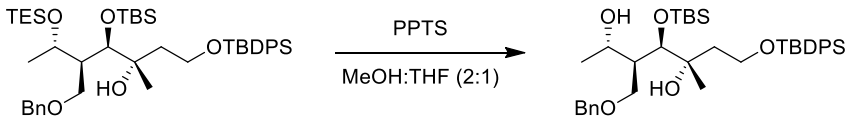
77.48 77.16 76.84 74.74 74.23 73.50 69.76 68.20
61.27
45.33
40.24
26.96 24.04 21.64 19.19
7.00 5.04
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm




**Silyl ether 227:** To a solution of **85b** (0.163 g, 0.250 mmol, 1.00 equiv.) in $CH_2Cl_2$ (1.25 mL), 2,6-Lutidine (0.087 mL, 0.751 mmol, 3.00 equiv.) was added and the solution was cooled -78 °C. TBSOTf (0.063 mL, 0.275 mmol, 1.10 equiv.) was added dropwise and the reaction was stirred for 1 h at -78 °C (TLC and MS showed incomplete conversion). Additional TBSOTf (1.1 equiv.) and lutidine (3.0 equiv.) were added and the reaction mixture stirred for 1h (again incomplete conversion). Additional TBSOTf (1.1 equiv.) and lutidine (3.0 equiv.) were added and the reaction mixture stirred for 1h. The reaction mixture was quenched by $NaHCO_3$(aq.) and the reaction was allowed to warm to rt. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:20) gave 189 mg (90 %) of the desired product as colorless oil with some TBSCl impurities.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.47 – 7.34 (m, 6H), 7.33 – 7.18 (m, 5H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 3.97 – 3.80 (m, 4H), 3.69 (dd, *J* = 10.0, 3.1 Hz, 1H), 3.55 (s, 1H), 3.23 (dd, *J* = 10.1, 7.4 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.89 – 1.78 (m, 1H), 1.60 (dt, *J* = 14.2, 5.2 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.13 (s, 3H), 1.04 (s, 9H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.87 (s, 9H), 0.67 – 0.57 (m, 6H), 0.10 (s, 3H), 0.07 (s, 3H);

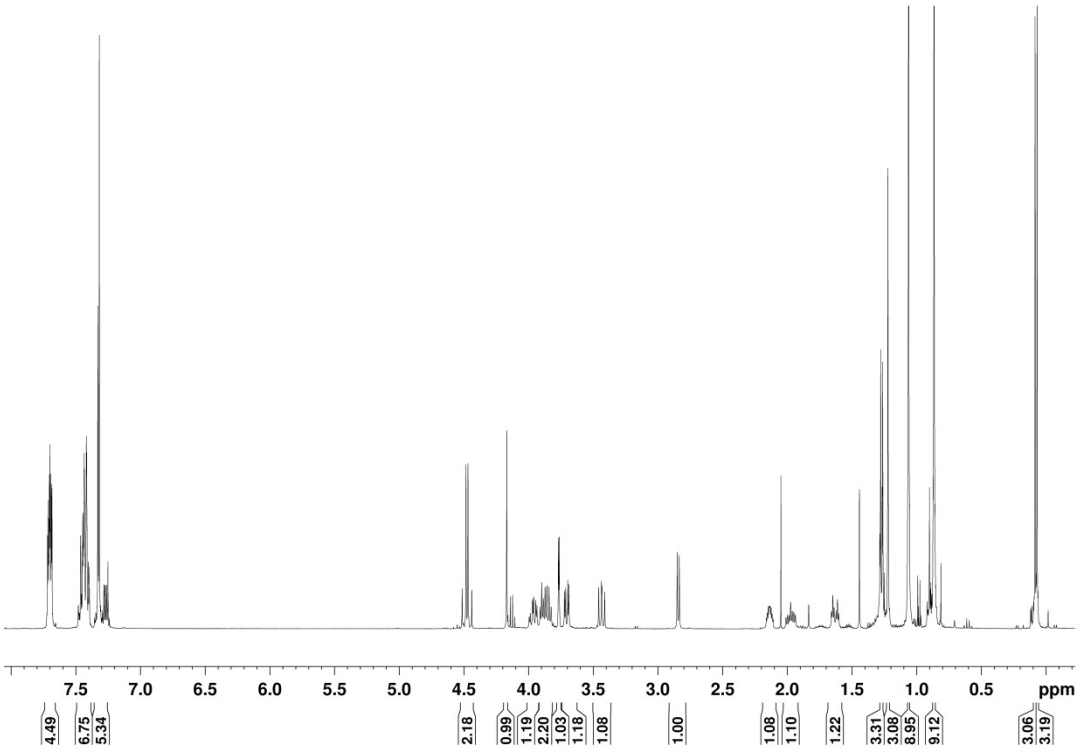





**227** **93**

**Alcohol 93:** To a solution of **227** (0.149 g, 0.195 mmol, 1.00 equiv.) in MeOH/THF (2:1) (1.94 ml) at rt was added PPTS (0.0489 g, 0.195 mmol, 1.00 equiv.) The reaction mixture was stirred at rt for 30 min and was than quenched by addition of aqu. sat. $NaHCO_3$. . The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4 or 1:10) gave 110.5 mg (87 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 4H), 7.48 – 7.37 (m, 6H), 7.36 – 7.20 (m, 5H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.16 (s, 1H), 3.95 (td, *J* = 10.2, 3.6 Hz, 1H), 3.91 – 3.80 (m, 2H), 3.75 (d, *J* = 2.5 Hz, 1H), 3.69 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.42 (dd, *J* = 10.0, 8.6 Hz, 1H), 2.83 (d, *J* = 6.5 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.96 (ddd, *J* = 14.6, 9.8, 5.0 Hz, 1H), 1.62 (dt, *J* = 14.4, 3.9 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.21 (s, 3H), 1.05 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.3, 135.7, 135.7, 132.8, 132.8, 130.0, 130.0, 128.4, 128.0, 127.9, 127.7, 77.8, 76.0, 73.4, 70.2, 69.2, 61.7, 46.2, 37.5, 26.9, 26.3, 22.1, 21.4, 19.1, 18.6, -3.8, -4.0.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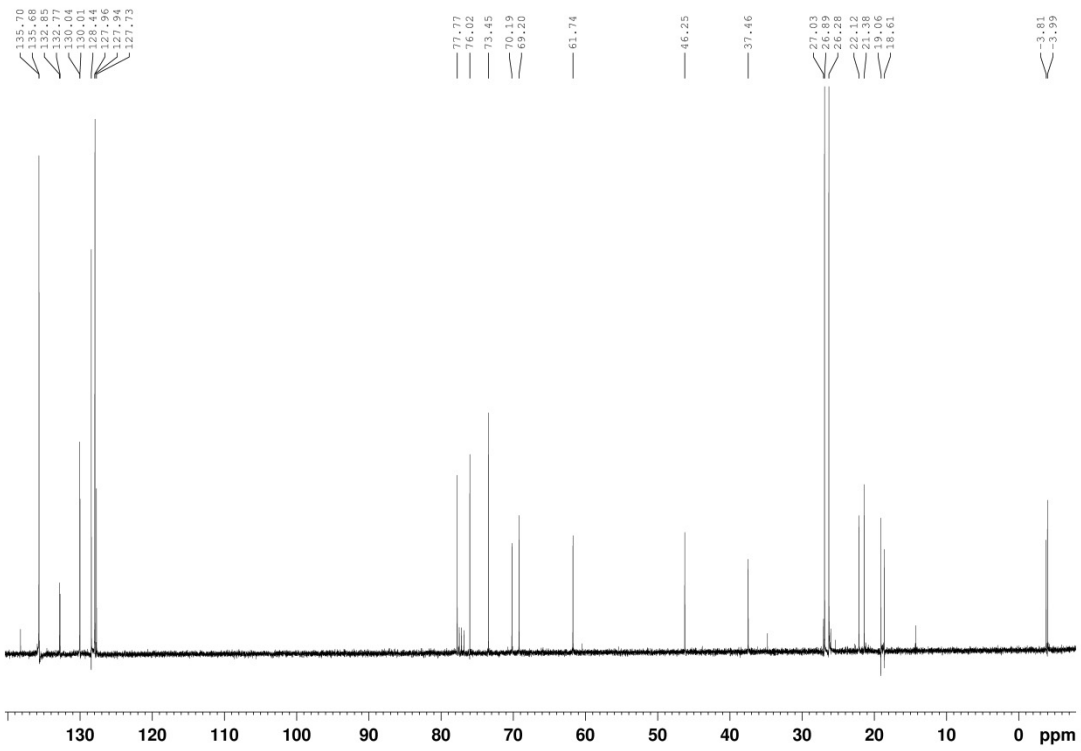
3.19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70.19
69.20
61.74
46.25
37.46
27.03
26.89
26.28
22.12
21.38
19.06
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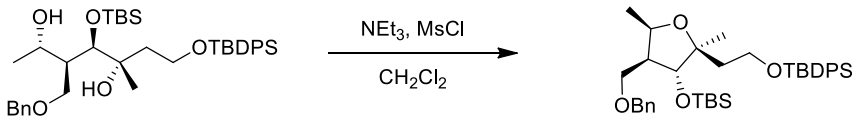
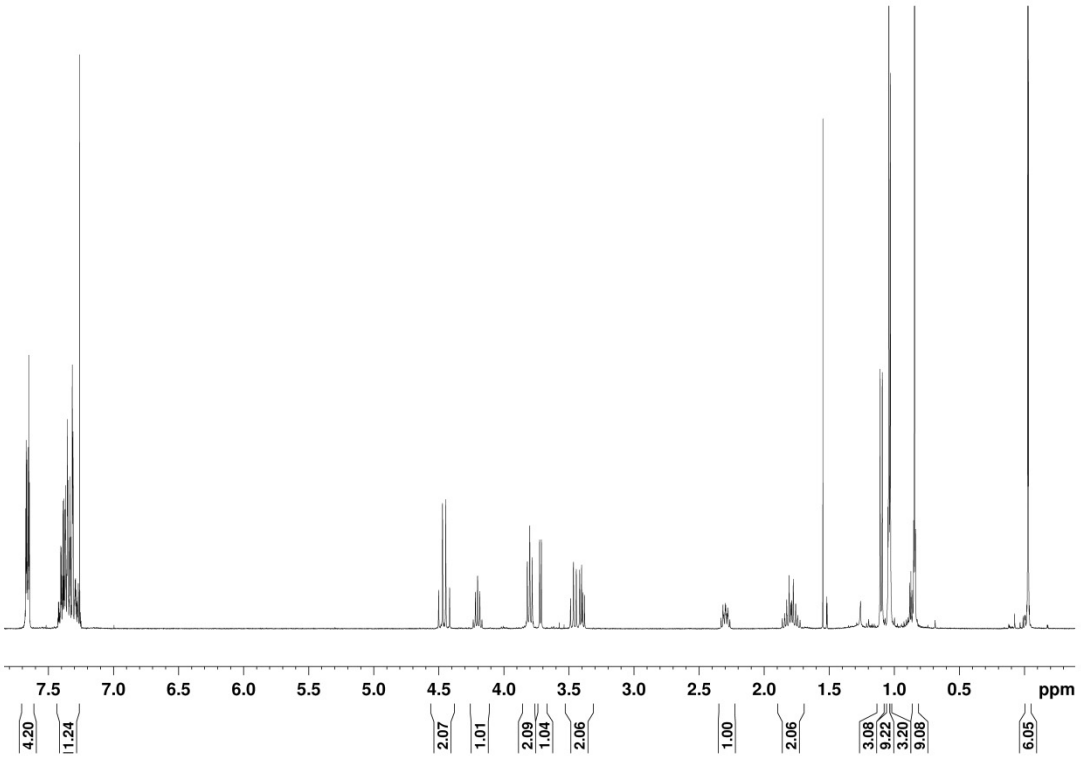



**93** **94**

**Tetrahydrofuran 94:** To a solution of **93** (0.110 g, 0.169 mmol, 1.00 equiv.) and $NEt_3$ (0.171 ml, 1.69 mmol, 10.0 equiv.) in DCM (3.50 ml) at -40 °C, MsCl (0.039 ml, 0.507 mmol, 3.00 equiv.) was added. The reaction mixture was stirred at -40 °C for 30 min and then quenched by addition of MeOH (~0.8 ml). The reaction mixture was allowed to warm up to rt and then water was added. The layers were separated and the aqu. phase was extracted with DCM. The comb. org. phases were washed with 1 M HCl and aqu. sat. $NaHCO_3$ then dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:20) gave 83.2 mg (78 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H), 7.43 – 7.24 (m, 11H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.20 (p, *J* = 6.7 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.72 (d, *J* = 5.6 Hz, 1H), 3.47 (dd, *J* = 8.9 Hz, 1H), 3.40 (dd, *J* = 9.3, 5.8 Hz, 1H), 2.30 (ddt, *J* = 8.6, 7.1, 5.7 Hz, 1H), 1.89 – 1.70 (m, 2H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H), 1.03 (s, 3H), 0.84 (s, 9H), -0.03 (s, 3H), -0.03 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.33, 135.70, 134.17, 134.16, 129.64, 128.49, 127.85, 127.75, 127.73, 127.68, 82.32, 79.90, 73.38, 72.22, 68.49, 60.74, 50.25, 43.84, 27.03, 25.89, 20.21, 19.28, 18.07, 16.97, -4.32, -4.41.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1.5
1.0
0.5
ppm
4.20
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2.09
1.04
2.06
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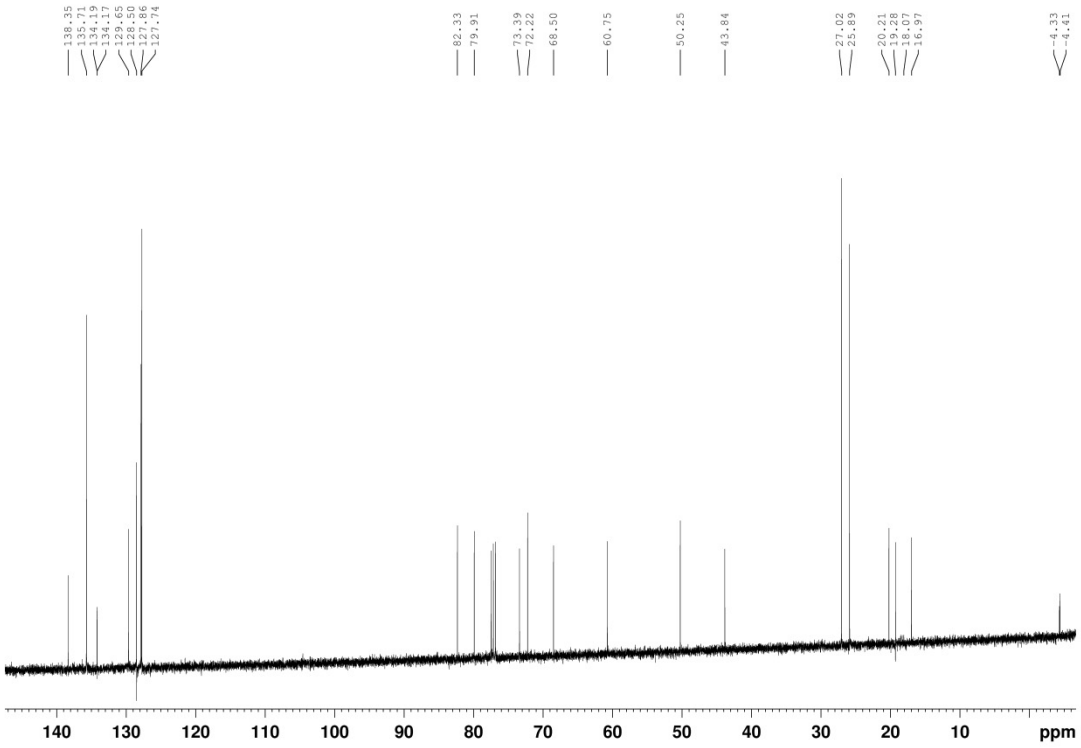
3.08
9.22
3.20
9.08
6.05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60.75
50.25
43.84
27.02
25.89
20.21
19.28
18.07
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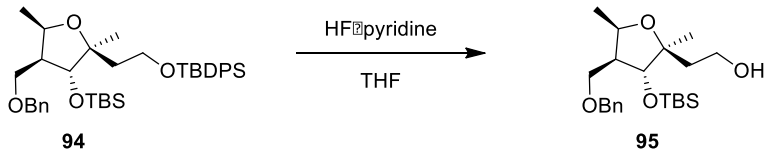
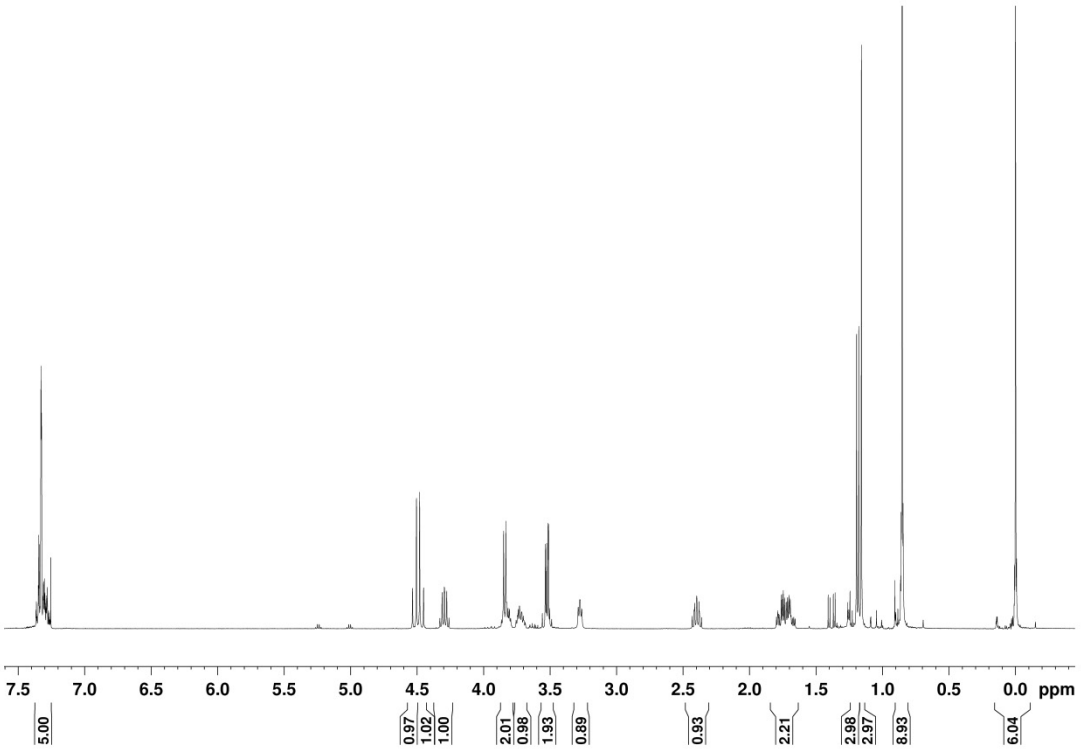
ppm




**94** **95**

**Alcohol 95:** To a solution of **94** (0.083 g, 0.131 mmol, 1.00 equiv.) in THF (1.30 ml) at 0 °C was added HF*py (0.227 ml, 70 % HF in pyridine). The reaction mixture was stirred at 0 °C for 40 min and then allowed to warm up to rt. The reaction mixture was stirred at rt for 1 h 30 min and then quenched by addition of aqu. sat. $NaHCO_3$. The phases were separated and the aqueous phase was extracted with $Et_2O$. The combined org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 34.1 mg (66 %) of the desired product as colorless oil which was contaminated with very small amounts of unknown material.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.30 (dq, *J* = 7.7, 6.6 Hz, 1H), 3.89 – 3.77 (m, 2H), 3.72 (dtd, *J* = 11.4, 6.3, 3.9 Hz, 1H), 3.57 – 3.49 (m, 2H), 3.25 (dd, *J* = 6.5, 4.5 Hz, 1H), 2.47 – 2.34 (m, 1H), 1.77 (ddd, *J* = 14.5, 6.2, 3.5 Hz, 1H), 1.69 (ddd, *J* = 14.5, 8.1, 3.9 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.16 (s, 3H), 0.86 (s, 9H), 0.00 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.17, 128.52, 127.93, 127.82, 84.37, 79.22, 73.45, 72.94, 68.23, 59.54, 49.03, 41.23, 25.85, 19.87, 18.04, 17.27, -4.31, -4.32.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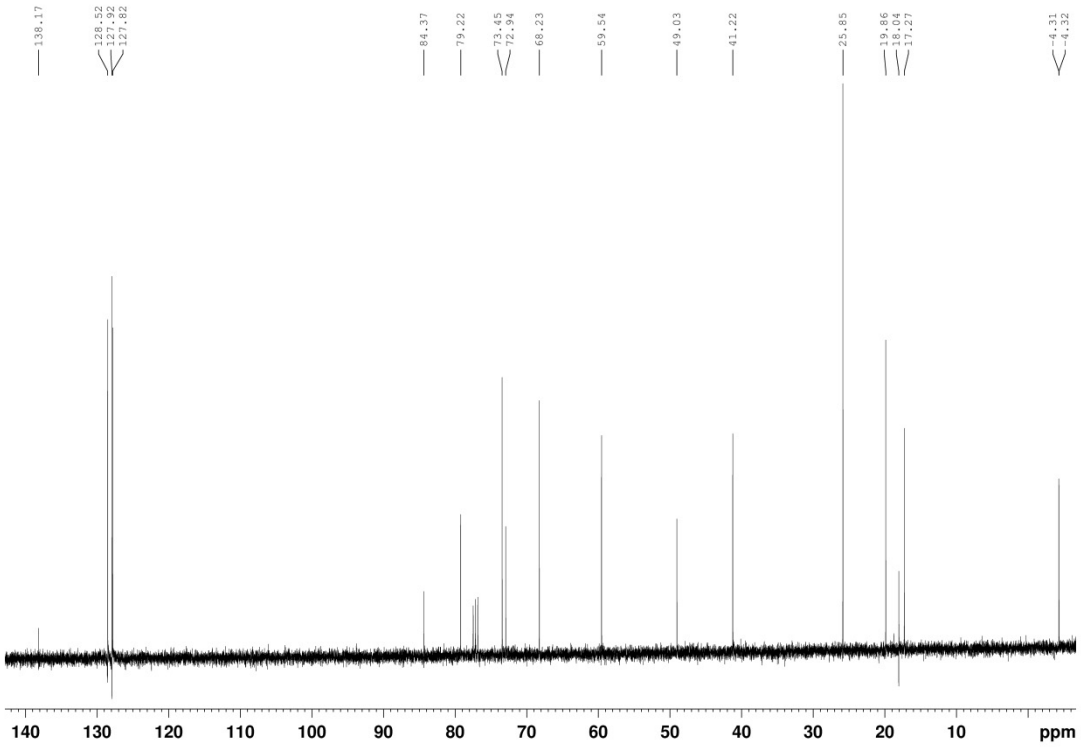
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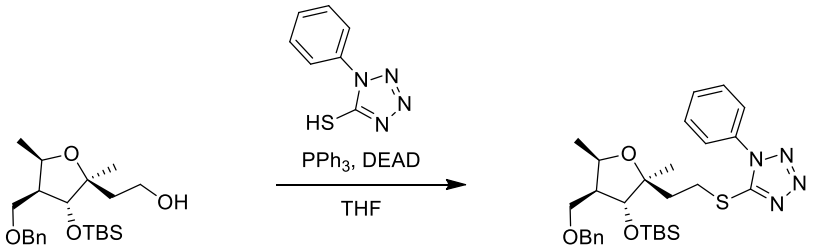
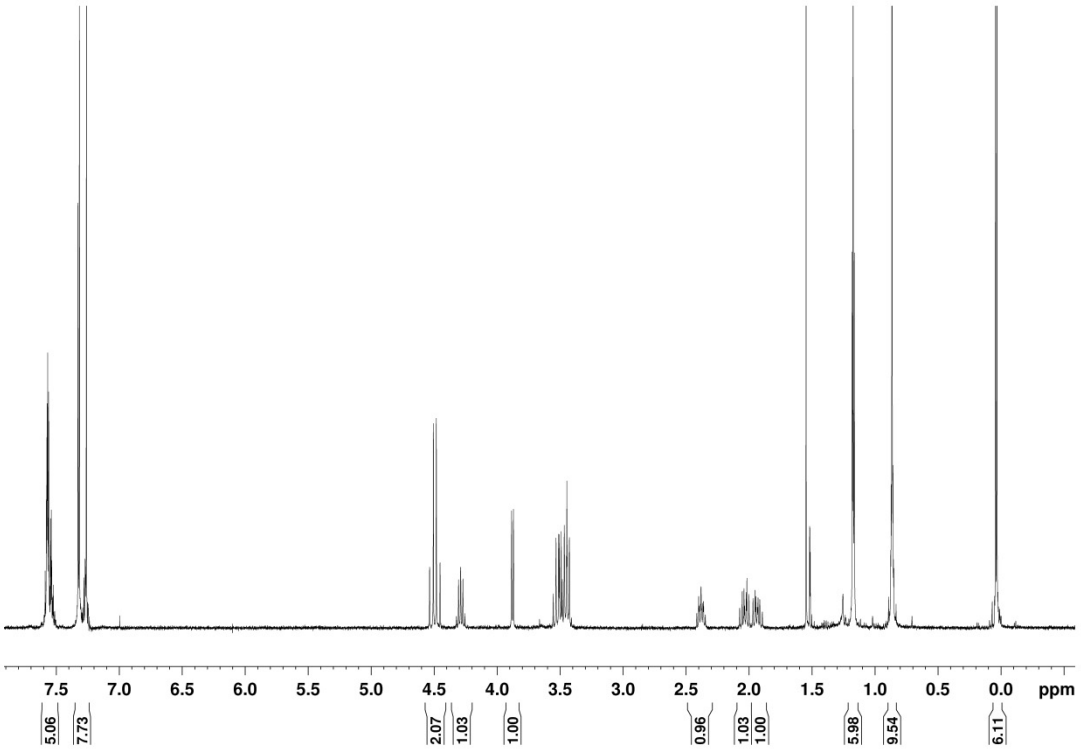



**95** **228**

**Sulfide 228:** To a solution of **95** (0.034 g, 0.0862 mmol, 1.00 equiv.) in THF (0.90 ml), 1-phenyl-1H-tetrazole-5-thiol (0.0307 g, 0.172 mmol, 2.00 equiv.) and triphenylphosphine (0.0339 g, 0.129 mmol, 1.50 equiv.) were added in one portion at rt. The reaction mixture was then cooled to 0 °C and afterwards DEAD (0.0237 ml, 0.151 mmol, 1.75 equiv.) was added drop wise. The reaction mixture was allowed to warm up to rt and stirred overnight. The reaction was then quenched by addition of aqu. sat. $NaHCO_3$. The phases were separated and the aqu. phase extracted 3x with $Et_2O$. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:8)) gave 42.4 mg (88%) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.49 (m, 5H), 7.36 – 7.22 (m, 5H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.29 (p, *J* = 6.6 Hz, 1H), 3.88 (d, *J* = 5.9 Hz, 1H), 3.57 – 3.42 (m, 4H), 2.38 (dq, *J* = 8.0, 5.9 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.99 – 1.88 (m, 1H), 1.18 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 154.59, 138.24, 133.92, 130.13, 129.87, 128.48, 127.92, 127.76, 123.93, 82.76, 78.77, 73.43, 72.63, 68.23, 50.05, 39.98, 28.44, 25.87, 20.14, 18.07, 17.01, -4.34, -4.36.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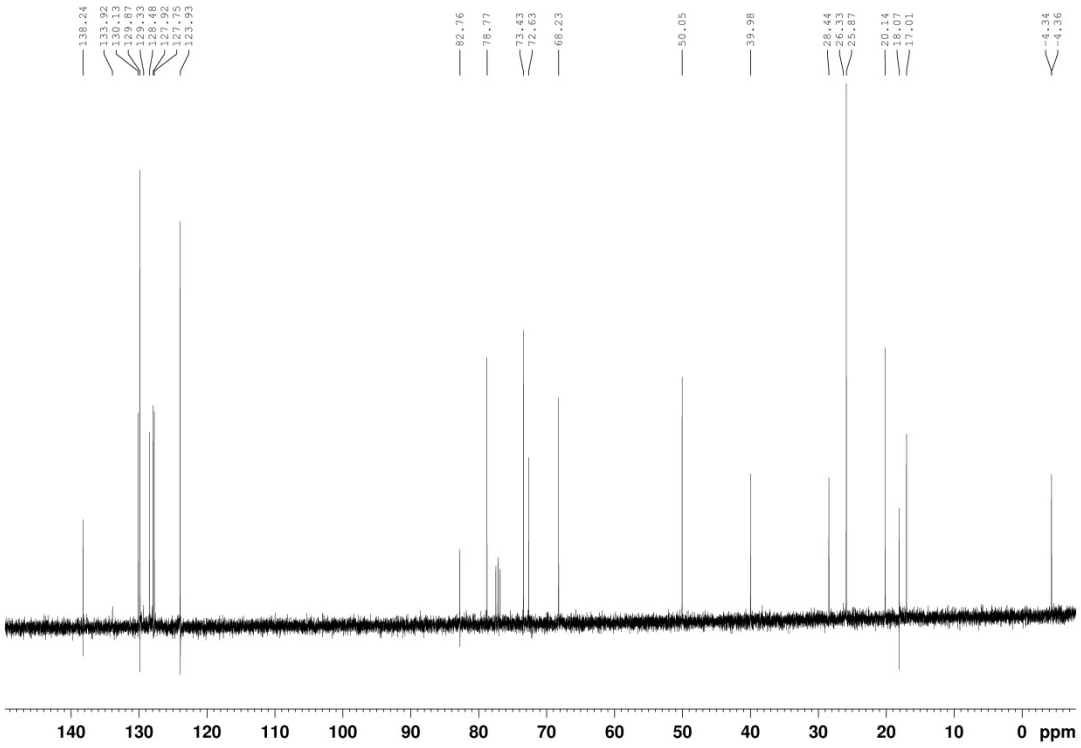
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17.01
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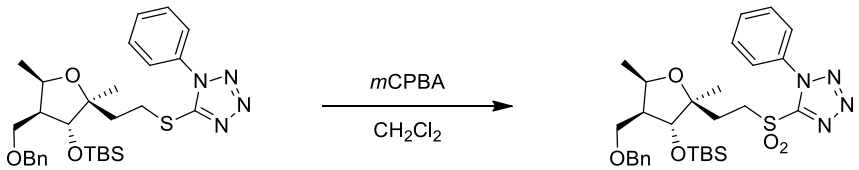
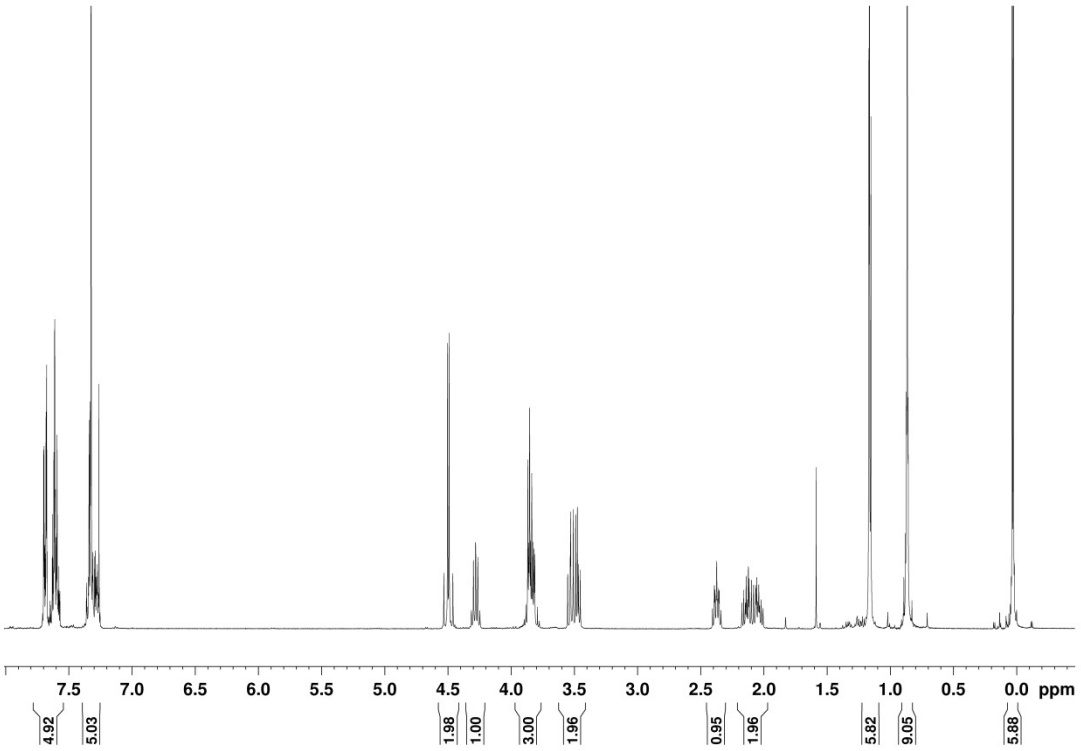



**228** **92**

**Sulfone 92:** To a solution of **228** (0.042 g, 0.0757 mmol, 1.00 equiv.) in 0.76 ml $CH_2Cl_2$, *m*CPBA (0.0457 g, 0.265 mmol, 3.50 equiv.) was added in one portion at rt and the reaction mixture was stirred for 19h. The reaction mixture was diluted with EtOAc, washed with aqu. sat. $Na_2SO_3$ and aqu. sat. $NaHCO_3$. The org. phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:8)) gave 42.7 mg (96 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.65 – 7.56 (m, 3H), 7.38 – 7.24 (m, 5H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.28 (p, *J* = 6.6 Hz, 1H), 3.92 – 3.76 (m, 3H), 3.53 (dd, *J* = 9.3, 8.1 Hz, 1H), 3.47 (dd, *J* = 9.4, 5.6 Hz, 1H), 2.37 (dq, *J* = 7.7, 5.8 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.09 – 1.99 (m, 1H), 1.17 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 153.57, 138.11, 133.20, 131.57, 129.84, 128.53, 127.92, 127.82, 125.26, 81.48, 79.02, 73.48, 72.91, 68.01, 52.32, 50.07, 32.43, 25.84, 20.16, 18.05, 16.96, -4.36, -4.42.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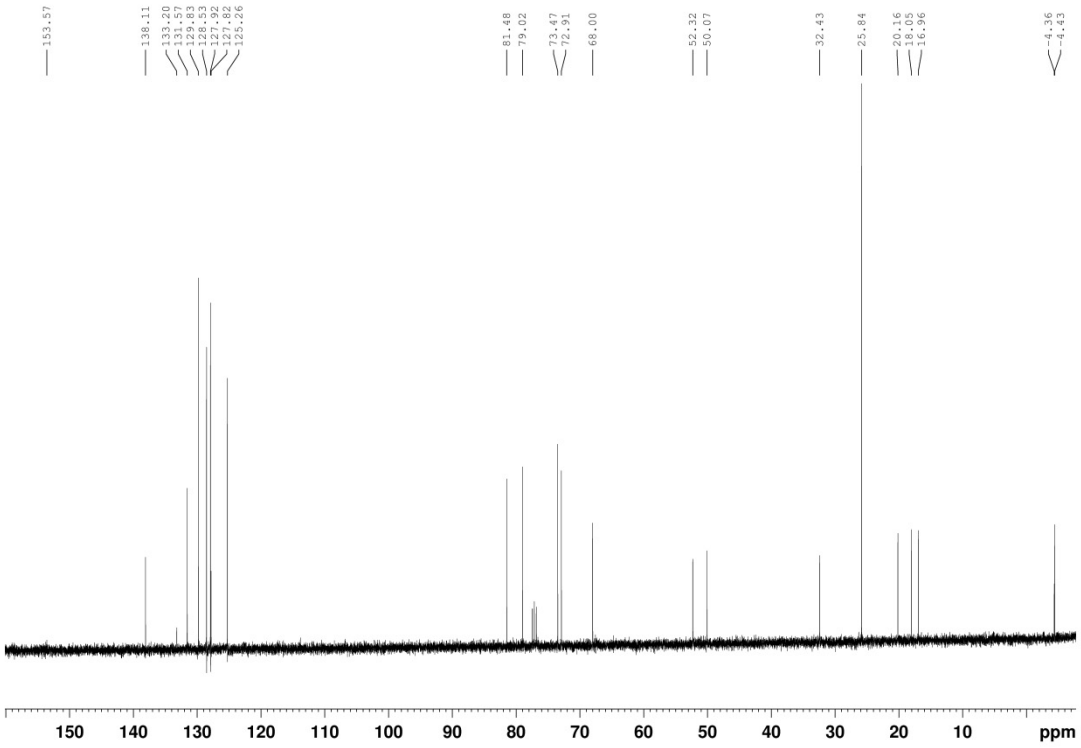
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52.32
50.07
32.43
25.84
20.16
18.05
16.96
-4.36
-4.43
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130
120
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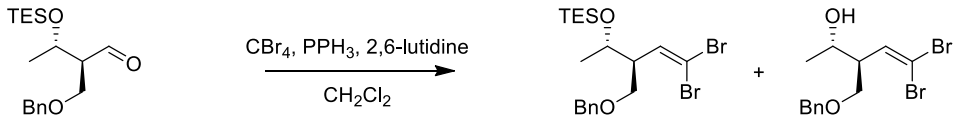
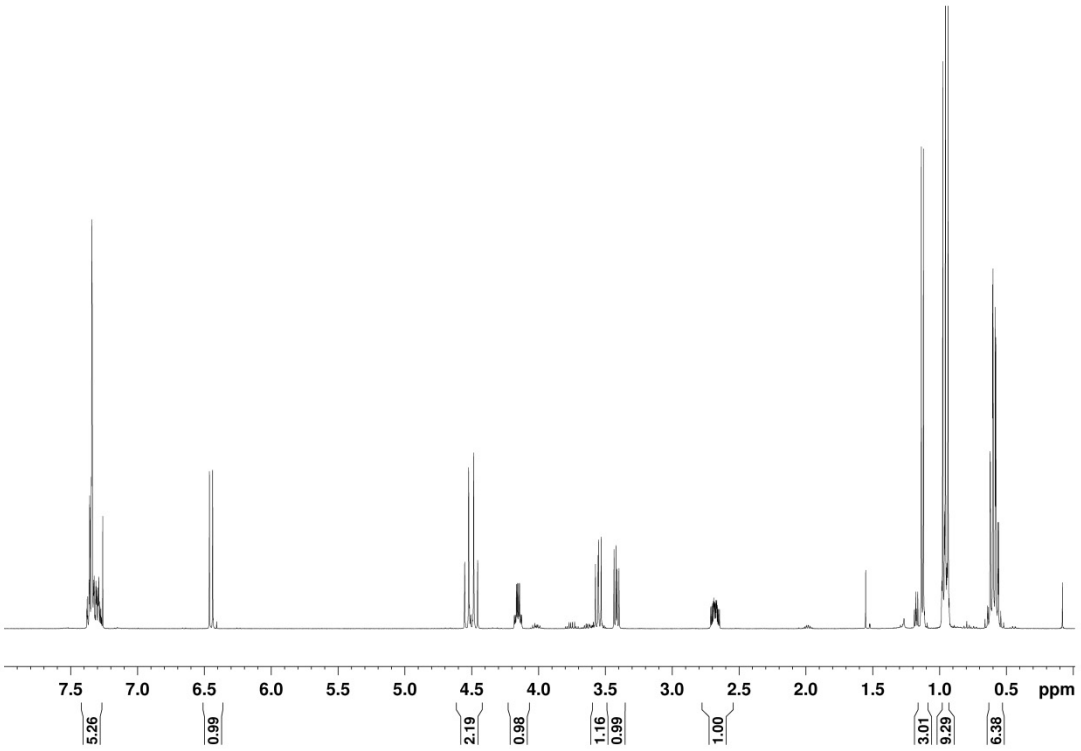
### 5.3.2.3. Approaches Towards the Selective Synthesis of *Z* alkene 76b




**Dibromoolefin 100:** To a solution of $CBr_4$ (0.171 g, 0.515 mmol, 2.00 equiv.) in $CH_2Cl_2$ (5.10 ml), triphenylphosphine (0.270 g, 1.03 mmol, 4.00 equiv.) was added at 0 °C. The yellow reaction mixture was cooled to -78 °C and a solution of **63** (0.083 g, 0.257 mmol, 1.00 equiv.) and 2,6-lutidine (0.060 ml, 0.515 mmol, 2.00 equiv.) in 1.40 ml $CH_2Cl_2$ was added dropwise. After stirring for 1 h at –78°C, the reaction mixture was quenched with aqu. sat. $NH_4Cl$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20 -> 1:4)) gave 54.8 mg (55 %) of the desired product **100** as colorless oil and 35.4 mg (38 %) of the TES deprotected product **102** as colorless oil.

**100 $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 6H), 6.45 (d, *J* = 9.6 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.15 (qd, *J* = 6.3, 3.0 Hz, 1H), 3.55 (dd, *J* = 9.2, 7.8 Hz, 1H), 3.41 (dd, *J* = 9.2, 5.7 Hz, 1H), 2.72 – 2.62 (m, 1H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.64 – 0.54 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.37, 136.81, 128.52, 127.80, 127.75, 90.48, 73.19, 68.99, 66.45, 51.77, 22.27, 7.05, 5.16.

**102 $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.64 (d, *J* = 9.8 Hz, 1H), 4.53 (s, 2H), 4.21 – 4.10 (m, 1H), 3.65 (s, 1H), 3.64 (d, *J* = 0.9 Hz, 1H), 2.71 (d, *J* = 3.0 Hz, 1H), 2.67 – 2.60 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 137.63, 135.67, 128.69, 128.08, 127.80, 91.05, 73.67, 71.26, 68.66, 50.14, 21.13.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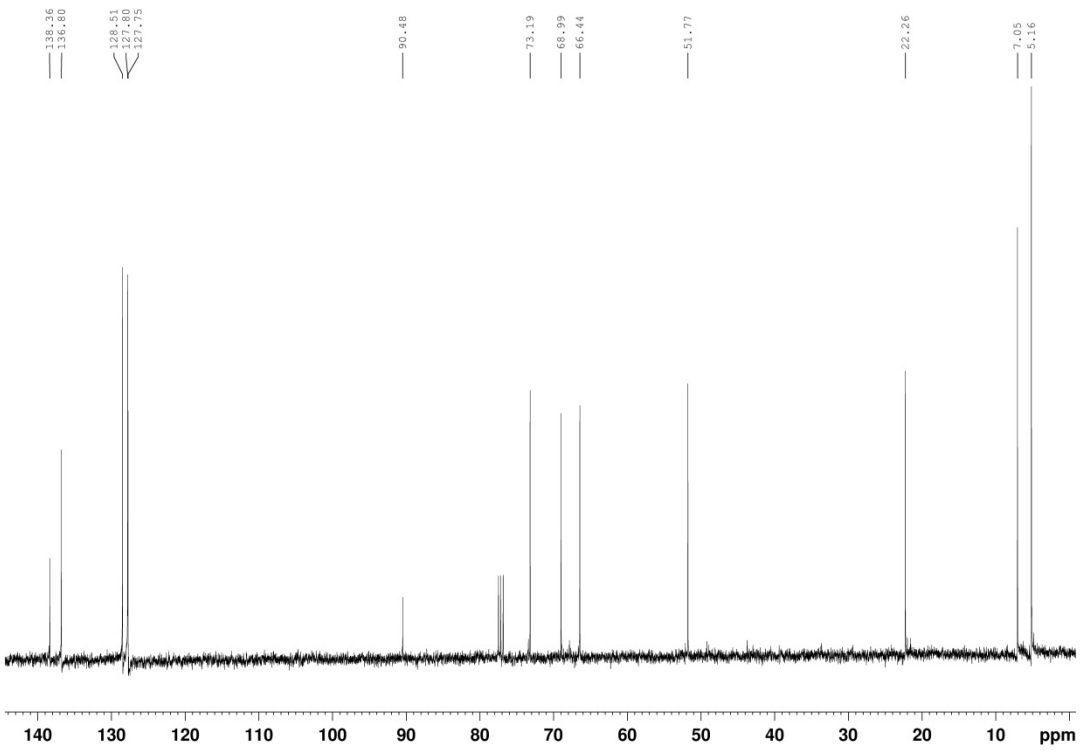
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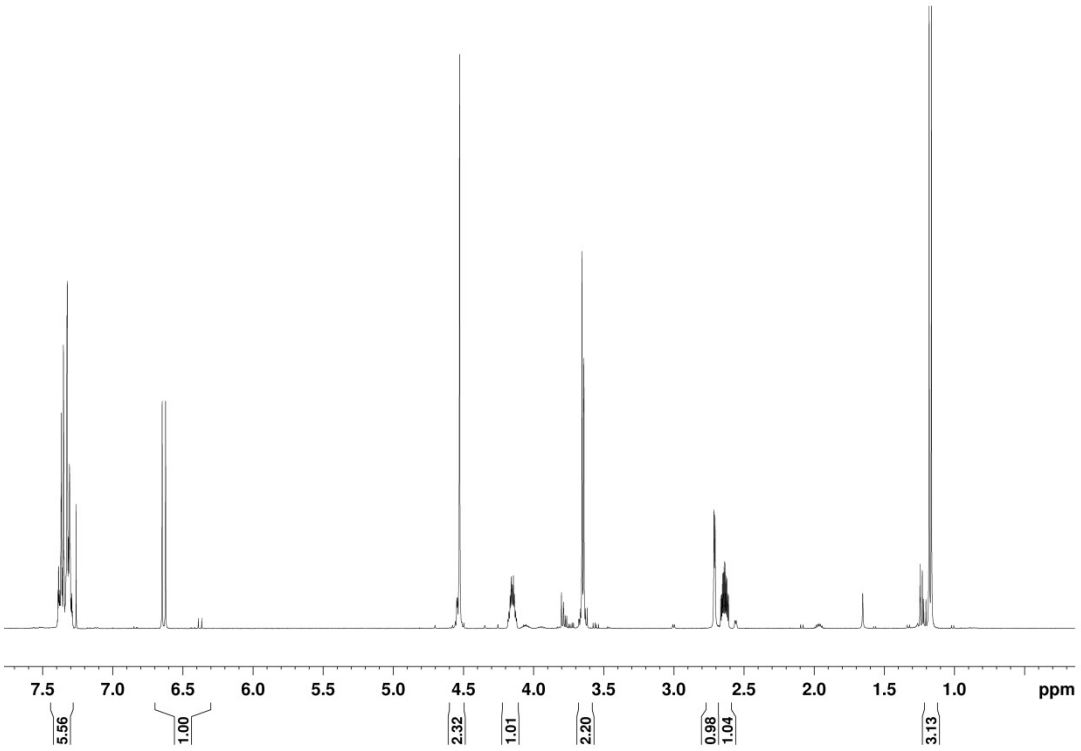
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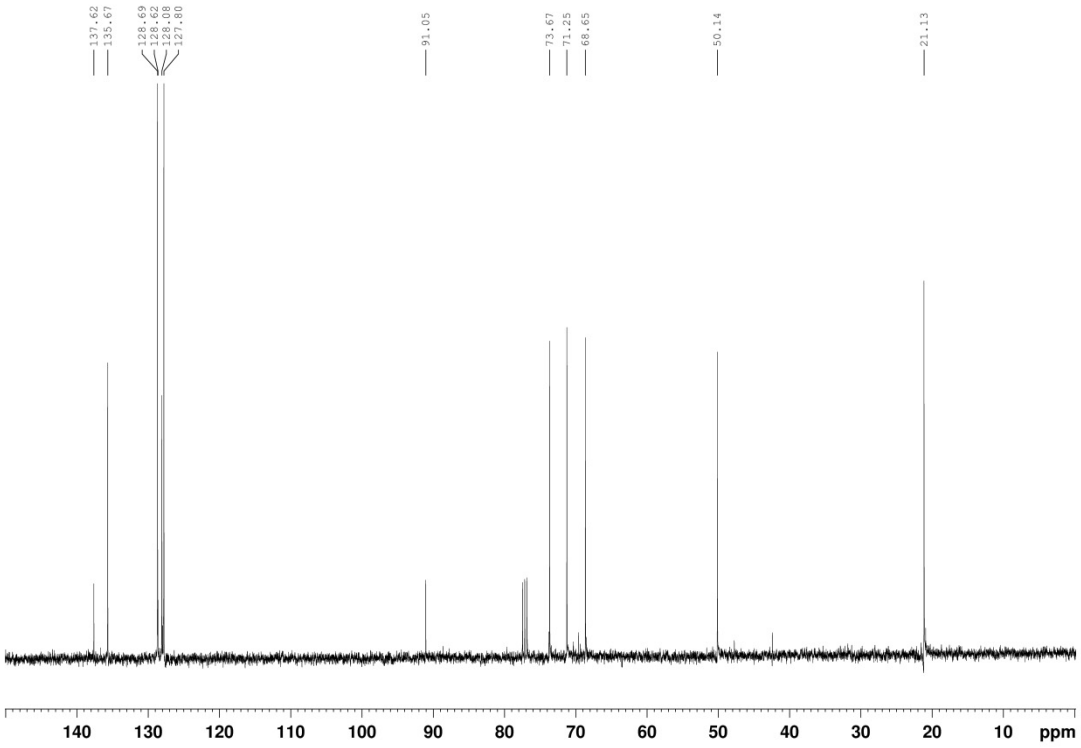
3.13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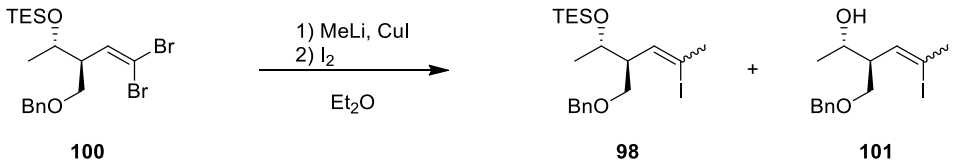
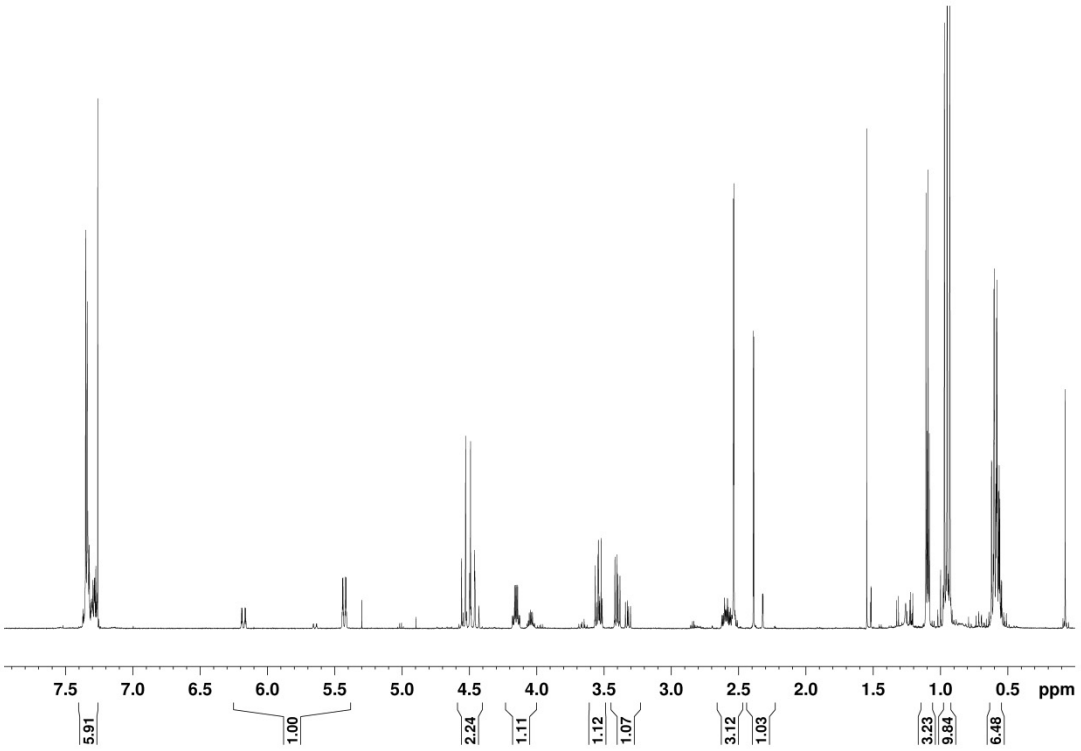



**100** **98** **101**

**Vinyl iodide 98:** To a solution of CuI (0.080 g, 0.420 mmol, 3.00 equiv.) in $Et_2O$ (1.20 ml) at 0 °C, MeLi (0.525 ml, 0.840 mmol, 6.00 equiv., 1.6 M in $Et_2O$) was added over 30 min via syringe pump. (The solution became strongly yellow at first, but afterwards it became nearly colorless). After 5 min the reaction mixture was cooled to -78 °C. A solution of **100** (0.067 g, 0.140 mmol, 1.00 equiv.) in 0.55 ml $Et_2O$ was added via syringe pump over 1 h 17 min (reaction mixture became yellow again after addition). After 30 min at – 78°C, $I_2$ (0.213 g, 0.840 mmol, 6.00 equiv.) in $Et_2O$ (1.50 ml) was added over 20 min. After 10 min the reaction mixture was warmed to 0 °C and afterwards poured into a aqu. sat. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:40 -> 1:4)) gave 19.8 mg (31 %; E/Z = 1/2.6) of the desired product as colorless oil. Also 15.5 mg (32 %; E/Z = 1/6.6) of the TES deprotected product **101** and 10.7 mg (23 %) of an unknown side product with a mass of 344 g/mol (according to MS).

**98 Z-Isomer: $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 5.43 (dd, *J* = 9.0, 1.5 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.15 (qd, *J* = 6.3, 2.8 Hz, 1H), 3.54 (dd, *J* = 9.3, 8.1 Hz, 1H), 3.40 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.54 (d, *J* = 1.5 Hz, 2H), 2.39 (d, *J* = 1.5 Hz, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.67 – 0.52 (m, 6H); **E-Isomer:$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.18 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.04 (qd, *J* = 6.3, 3.4 Hz, 1H), 3.53 (dd, *J* = 9.1, 7.3 Hz, 1H), 3.32 (dd, *J* = 9.1, 6.0 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.54 (d, *J* = 1.5 Hz, 2H), 2.32 (d, *J* = 1.3 Hz, 1H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.67 – 0.52 (m, 6H); **both isomers: $^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 139.07, 138.70, 133.18, 128.50, 128.44, 127.78, 127.71, 127.59, 103.76, 73.31, 73.01, 70.27, 69.67, 67.09, 66.83, 54.50, 49.08, 34.20, 28.40, 22.14, 22.09, 7.08, 5.20.

**101 major isomer: $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.60 (dd, *J* = 9.3, 1.5 Hz, 1H), 4.52 (s, 2H), 4.19 – 4.07 (m, 1H), 3.67 – 3.59 (m, 2H), 2.75 (d, *J* = 2.9 Hz, 1H), 2.56 (d, *J* = 1.5 Hz, 3H), 2.40 (d, *J* = 1.5 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 132.07, 128.65, 127.98, 127.80, 73.64, 72.17, 69.21, 53.18, 34.20, 20.95.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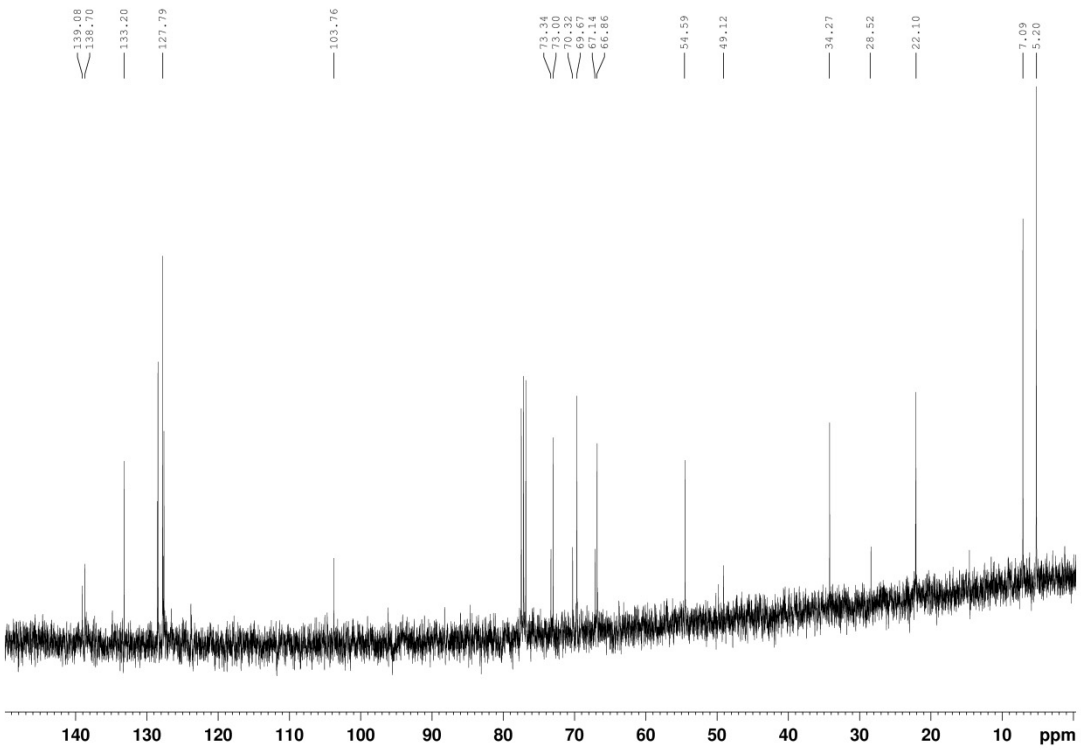
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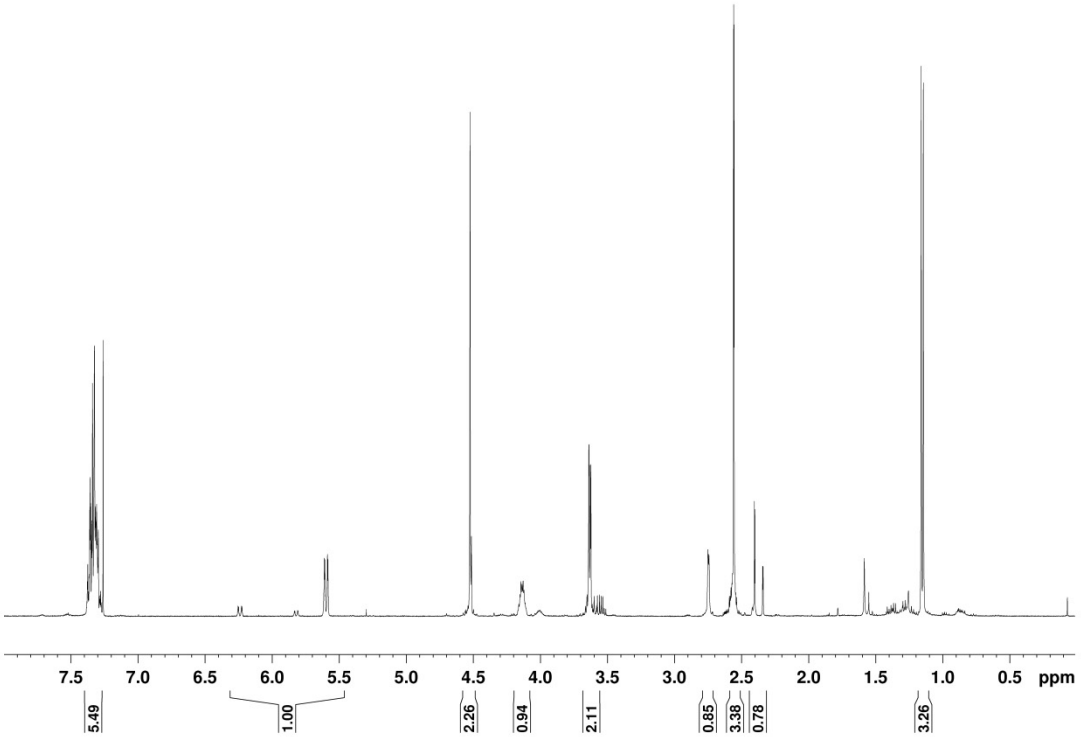
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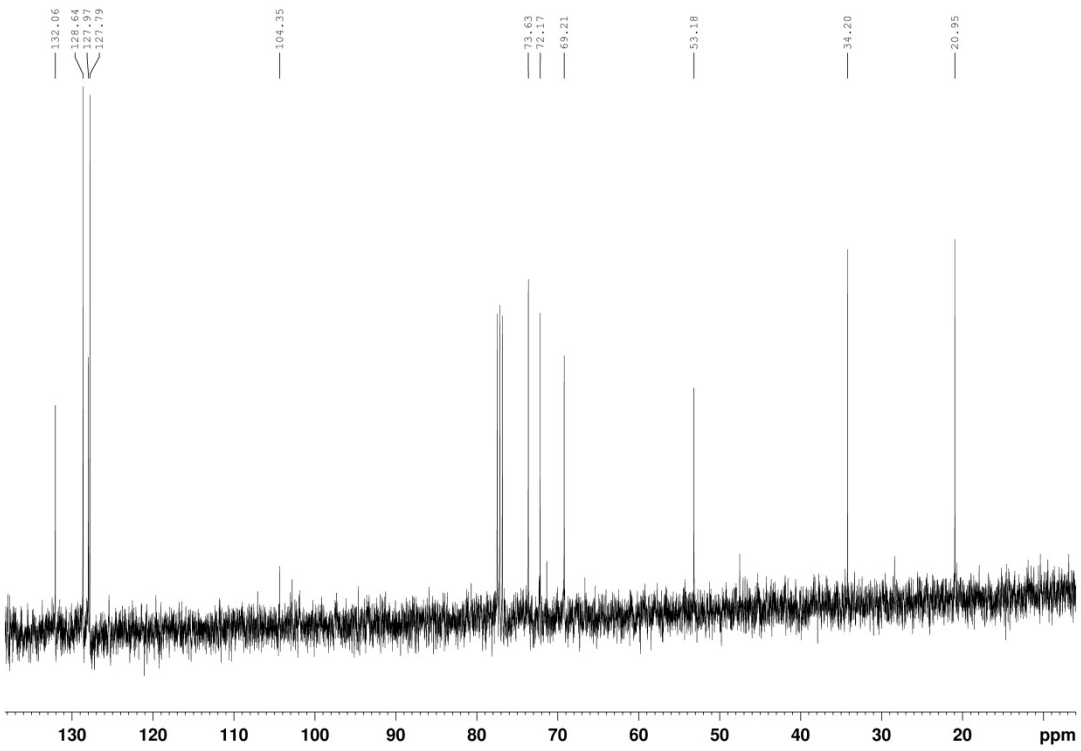
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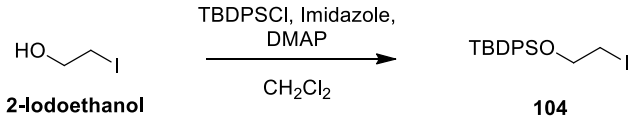
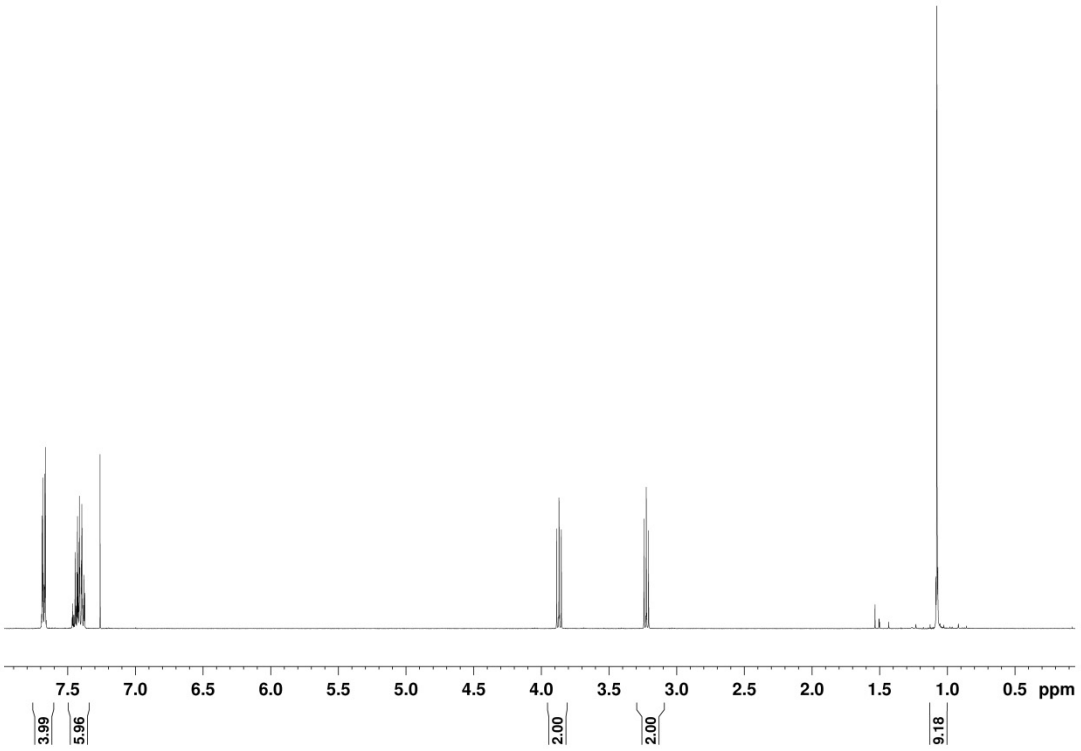



**2-Iodoethanol** **104**

**Silyl ether 104:** A solution of 2-iodoethanol (1.36 ml, 17.44 mmol, 1.00 equiv.), TBDPSCl (5.44 ml, 20.93 mmol, 1.20 equiv.) and imidazole (1.43 g, 20.93 mmol, 1.20 equiv.) in $CH_2Cl_2$ (20 ml) was stirred for 5 h. Water (9 ml) was added and the mixture extracted with $CH_2Cl_2$ (2x10 ml), the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:50)) gave 7.10 g (99 %) of the desired product as colorless oil which became a white solid upon storage in the fridge.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.48 – 7.36 (m, 6H), 3.87 (t, *J* = 6.8 Hz, 2H), 3.22 (t, *J* = 6.8 Hz, 2H), 1.08 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 135.72, 133.45, 129.98, 127.92, 64.78, 26.94, 19.41, 6.89.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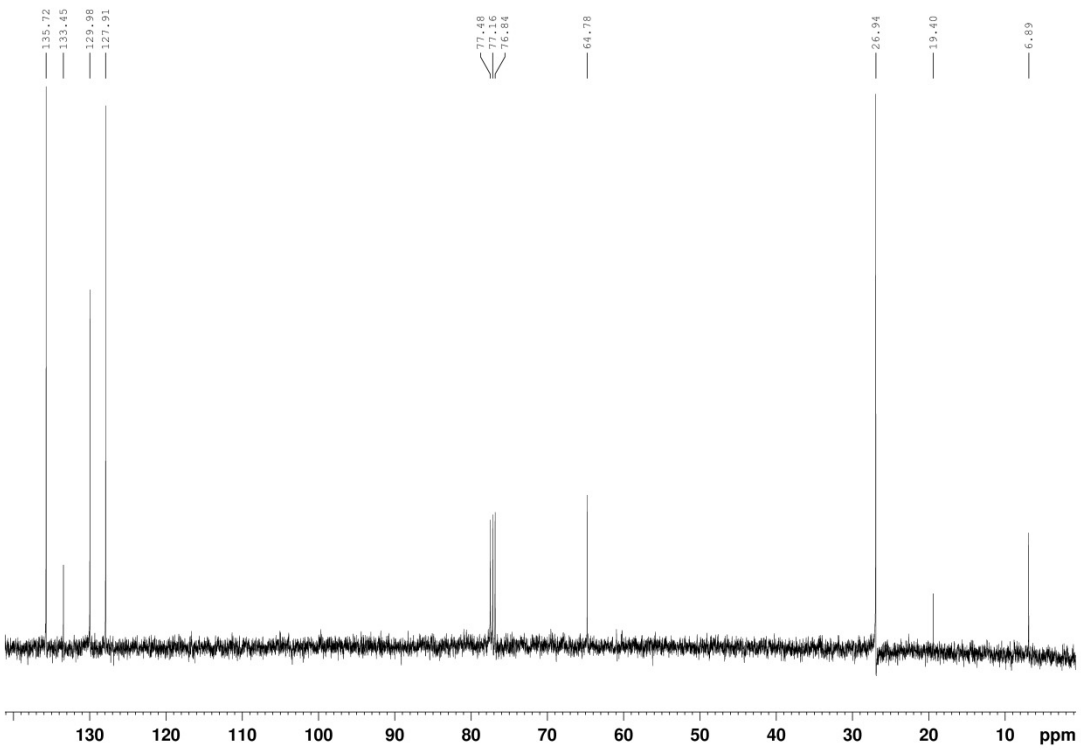
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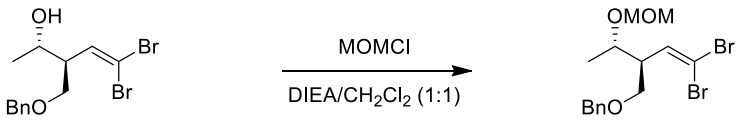
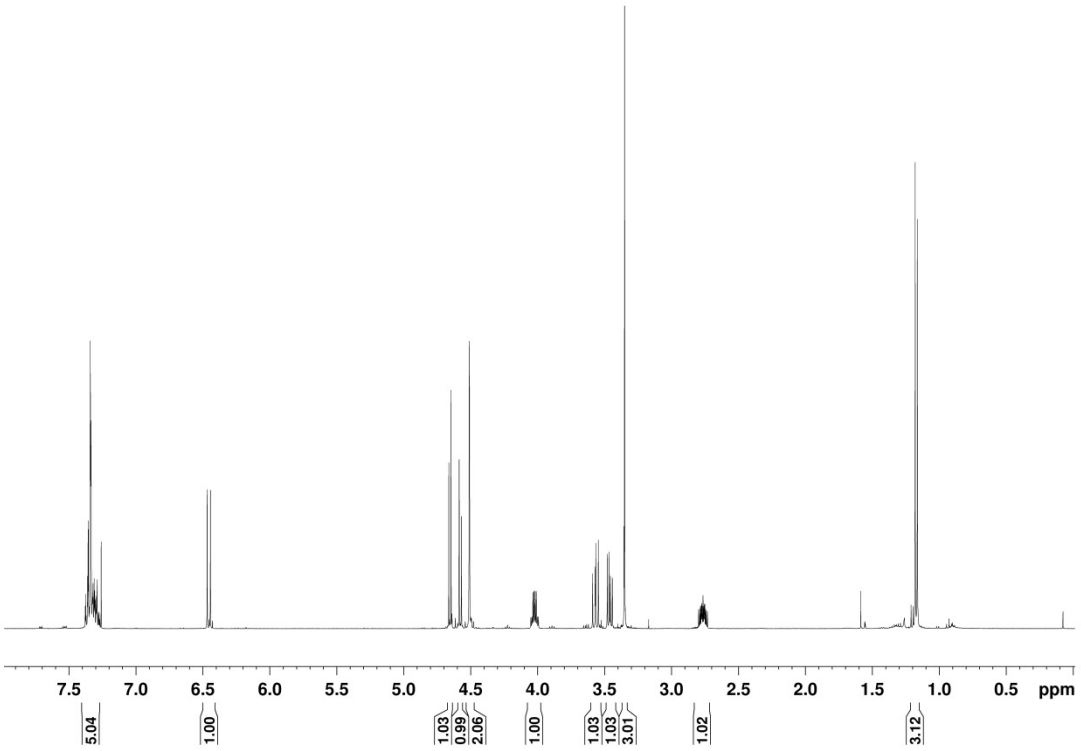



**102** **229**

**Methoxymethyl ether 229:** To a solution of **102** (0.035 g, 0.0961 mmol, 1.00 equiv.) in $CH_2Cl_2$/DIEA (1:1, 1.00 ml), MOMCl (0.073 ml, 0.961 mmol, 10.0 equiv.) was added at 0 °C. The solution was allowed to warm to RT and stirred for 15 h. Afterwards the reaction mixture was quenched with aqu. sat. $NaHCO_3$. Additional $CH_2Cl_2$ was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$. The combined org. phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 37.7 mg (96 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.46 (d, *J* = 9.7 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.51 (s, 2H), 4.02 (qd, *J* = 6.4, 3.4 Hz, 1H), 3.57 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.46 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.35 (s, 3H), 2.81 – 2.73 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.22, 136.45, 128.55, 127.83, 127.81, 95.62, 91.11, 73.22, 71.65, 68.72, 55.67, 50.37, 18.79.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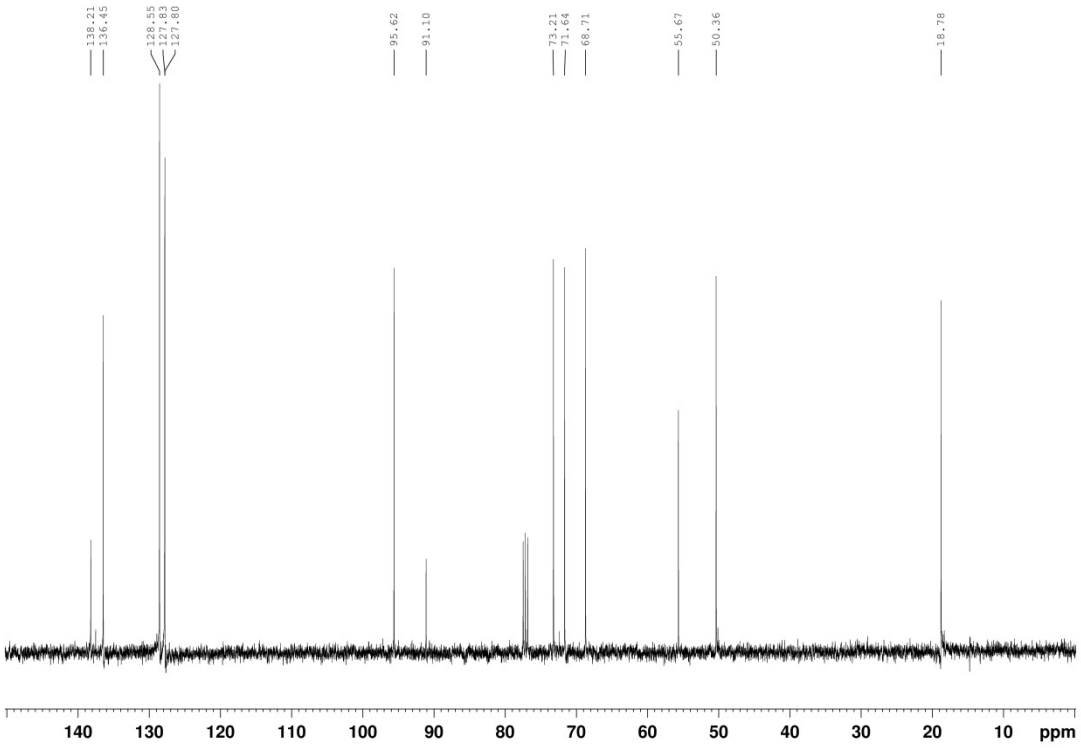
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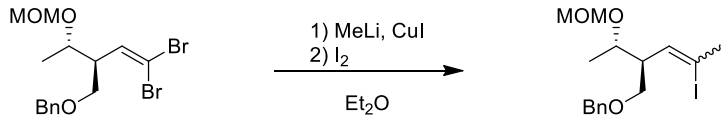
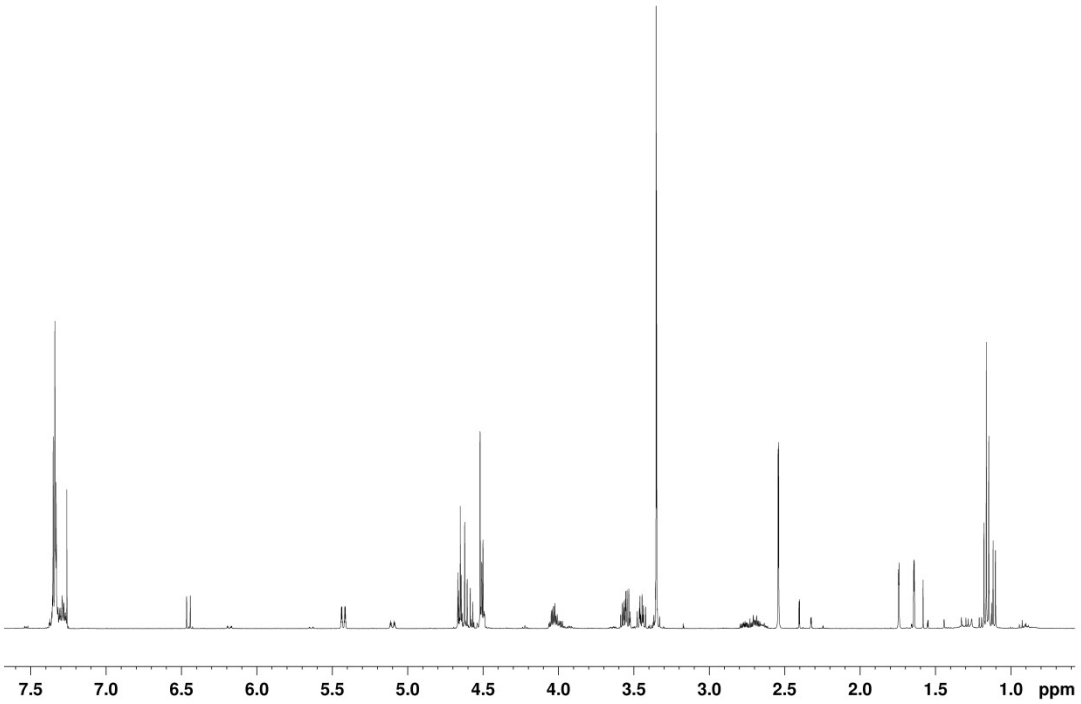



**229** **103**

**Vinyl iodide 103:** To a solution (no complete dissolution of the CuI because of some big CuI particles) of CuI (0.053 g, 0.277 mmol, 3.00 equiv.) in $Et_2O$ (0.80 ml) at 0 °C, MeLi (0.346 ml, 0.554 mmol, 6.00 equiv., 1.6 M in $Et_2O$) was added over 30 min via syringe pump. (The solution became strongly yellow at first, but afterwards it became nearly colorless). After 5 min the reaction mixture was cooled to -78 °C. A solution of **229** (0.037 g, 0.092 mmol, 1.00 equiv.) in 0.40 ml $Et_2O$ was added via syringe pump over 1 h 17 min (reaction mixture became yellow again after addition). After 30 min at – 78°C, $I_2$ (0.140 g, 0.554 mmol, 6.00 equiv.) in $Et_2O$ (1.00 ml) was added over 20 min. After 10 min the reaction mixture was warmed to 0 °C and afterwards poured into a aqu. sat. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:40)) gave 25 mg of a mixture of: desired product/starting material and double methylated side product (2.3:1.2:1). The E/Z ratio of the product is 1:8 in favor of the Z isomer.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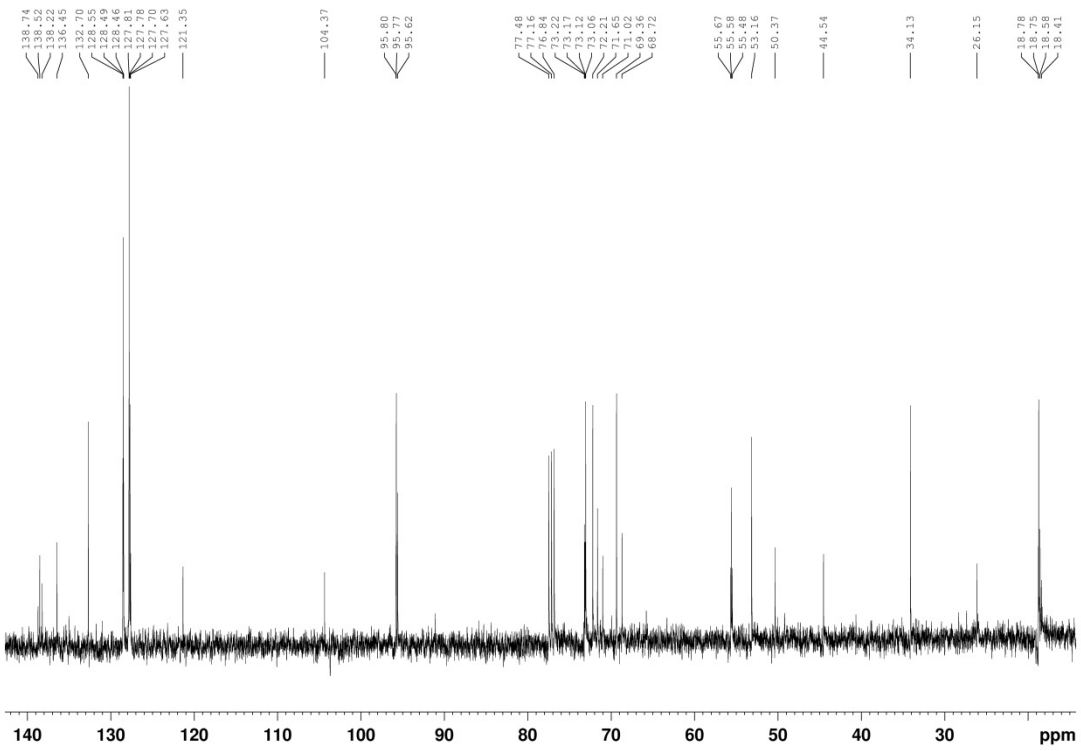
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26.15
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18.58
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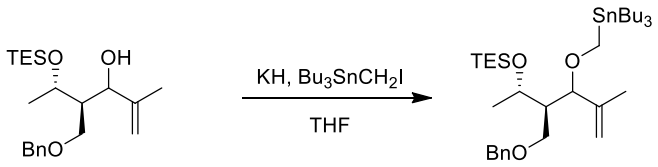
30
ppm

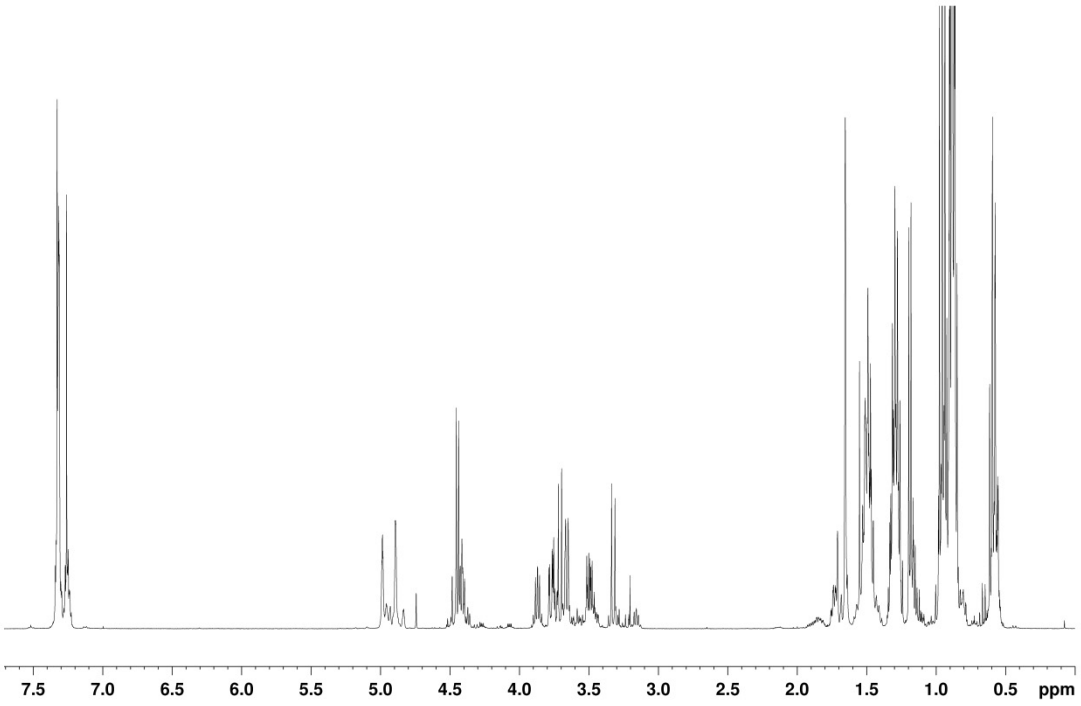
### 5.3.2.4. The *Wittig-Still* Approach




**49** **107**

**Stannane 107:** To a solution of **49** (diastereomeric mixture) (8.21 g, 22.52 mmol, 1.00 equiv.) in THF (101 ml) was added KH (1.98 g, 49.54 mmol, 2.20 equiv.) and dibenzo-18-crown-6 (0.812 g, 2.25 mmol, 0.10 equiv.) at 0 °C. After 3 min a solution of $Bu_3SnCH_2I$ (11.64 g, 27.02 mmol, 1.20 equiv.) in THF (27.0 ml) was added at 0 °C. The brown suspension was then stirred at rt for 3 h. The reaction mixture was quenched with aqu. sat. $NaHCO_3$ and the aqueous layer was extracted with $Et_2O$. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ((Application of yellowish slurry in pure hexane) hexane → EtOAc/hexane (1:60)) gave 14.10 g (93 %) of the desired product **107** as colorless oil (diastereomeric mixture).

**TLC**: $R_f$ = 0.27 (EtOAc/hexane 1:30, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.19 (m, 5H), 5.03 – 4.81 (m, 2H), 4.53 – 4.31 (m, 2H), 3.95 – 3.82 (m, 1H), 3.82 – 3.62 (m, 3H), 3.56 – 3.42 (m, 2H), 3.38 – 3.11 (m, 2H), 1.79 – 1.61 (m, 5H), 1.60 – 1.40 (m, 6H), 1.36 – 1.22 (m, 6H), 1.22 – 1.11 (m, 3H), 1.03 – 0.81 (m, 21H), 0.64 – 0.53 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 143.46, 139.40, 128.28, 127.47, 127.25, 120.13, 113.79, 86.20, 73.04, 68.06, 67.15, 58.98, 48.98, 29.34, 27.52, 27.48, 21.36, 17.74, 13.88, 9.10, 9.00, 7.12, 5.27, 5.07; **IR** (thin film): ν 2954, 2918, 2873, 1464, 1416, 1376, 1237, 1102, 1043, 1007, 901, 776, 729, 696; **HRMS** (ESI): calculated for $C_{34}H_{65}O_3SiSn$ $[M+H]^+$: 669.3726, found 669.3719.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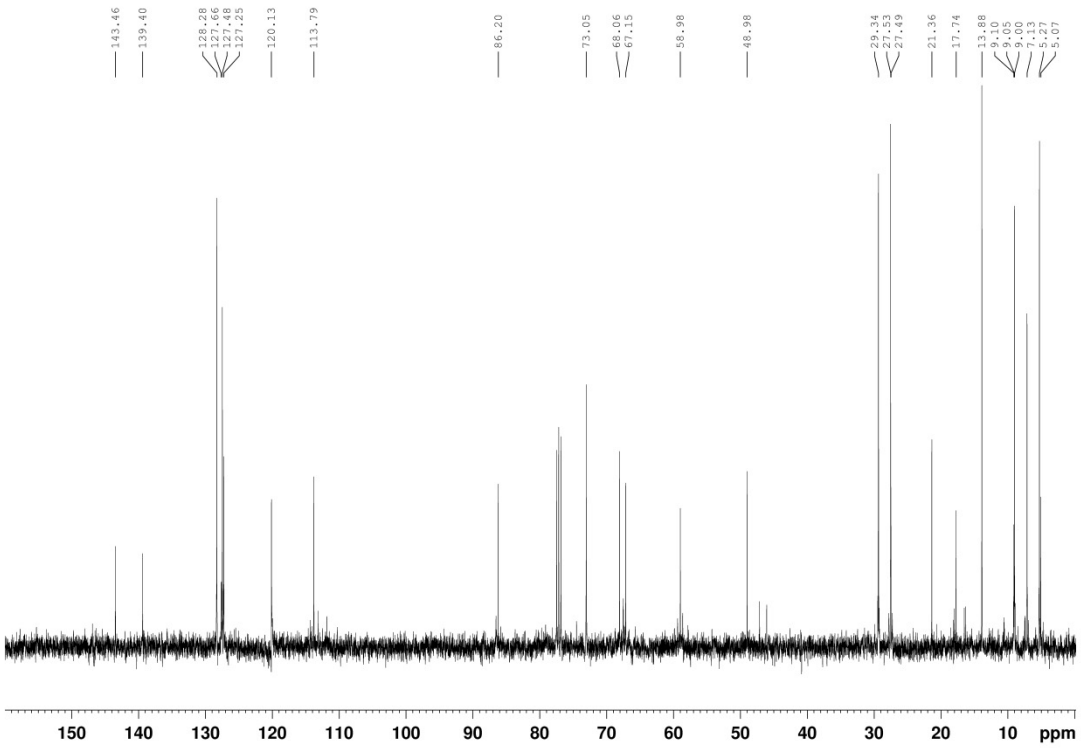
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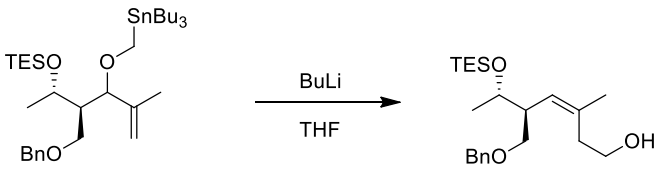
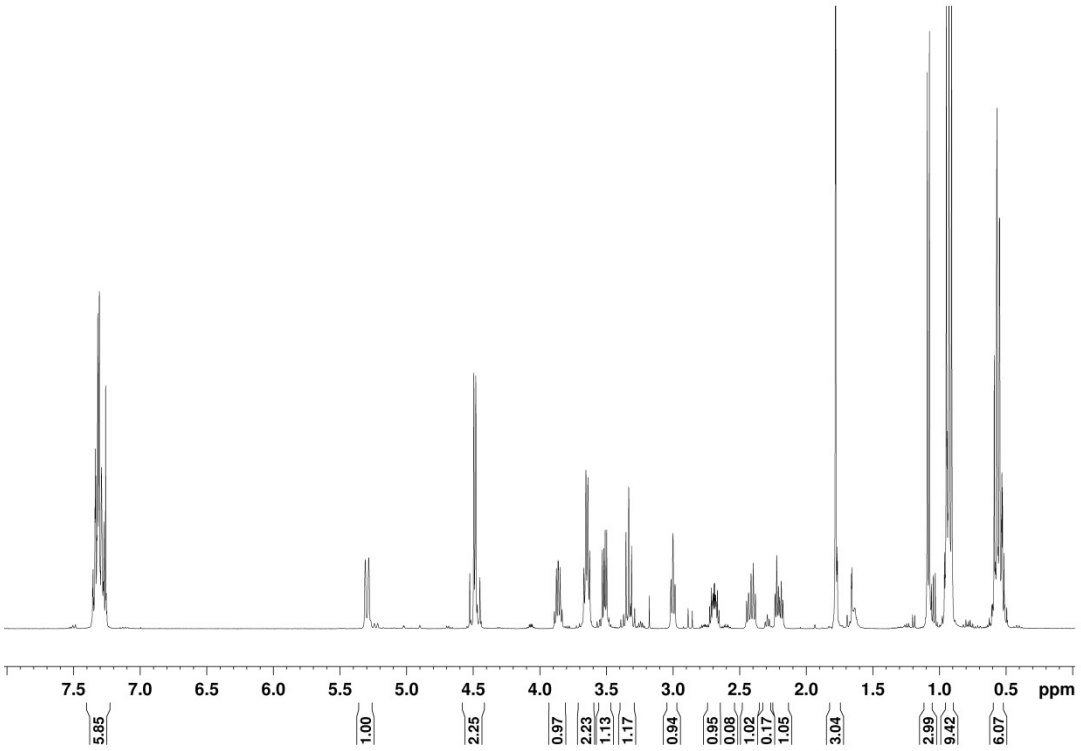



**107** **99**

**Primary alcohol 99:** To a solution of **107** (14.1 g, 21.12 mmol, 1.00 equiv.) in THF (213.0 ml) was added n-BuLi (1.6 M in hexanes, 13.46 ml, 21.54 mmol, 1.02 equiv.) dropwise over 6 min at –78 °C. The reaction mixture was stirred at -78 °C for 10 min and was then transferred to a -20 °C cooling bath (becoming strongly orange during the warm up and finally at the end of the reaction nearly colorless again). After 2.5 h the reaction was quenched with aqu. sat. $NaHCO_3$. The aqueous layer was extracted with $Et_2O$. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (hexane → EtOAc/hexane 1:30 → EtOAc/hexane 1:3)) gave 4.2 g (52 %, Z/E = 15:1) of the desired product **99** as colorless oil and 2.78 g of RSM (not pure). The procedure was repeated with the RSM to give 0.537 g (7 %, Z/E = 18:1) of the desired product. According to LC-MS both products contain 8 % of an unknown impurity.

**TLC**: $R_f$ = 0.18 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 5H), 5.30 (d, *J* = 10.6 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 3.90 – 3.83 (m, 1H), 3.71 – 3.61 (m, 2H), 3.51 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.33 (t, *J* = 8.4 Hz, 1H), 2.98 (s, 1H), 2.74 – 2.64 (m, 1H), 2.47 – 2.36 (m, 1H), 2.20 (dt, *J* = 13.7, 4.9 Hz, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.61 – 0.49 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 138.34, 134.47, 128.46, 127.88, 127.71, 127.04, 73.31, 71.75, 68.90, 60.32, 46.16, 35.65, 23.93, 21.88, 6.99, 5.09; **IR** (thin film): ν 3411, 2956, 2910, 2875, 1453, 1413, 1373, 1238, 1089, 1060, 1005, 900, 871, 730, 696; **HRMS** (ESI): calculated for $C_{22}H_{39}O_3Si$ $[M+H]^+$: 379.2663, found 379.2656; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -3.65° (c = 1.37 in $CHCl_3$).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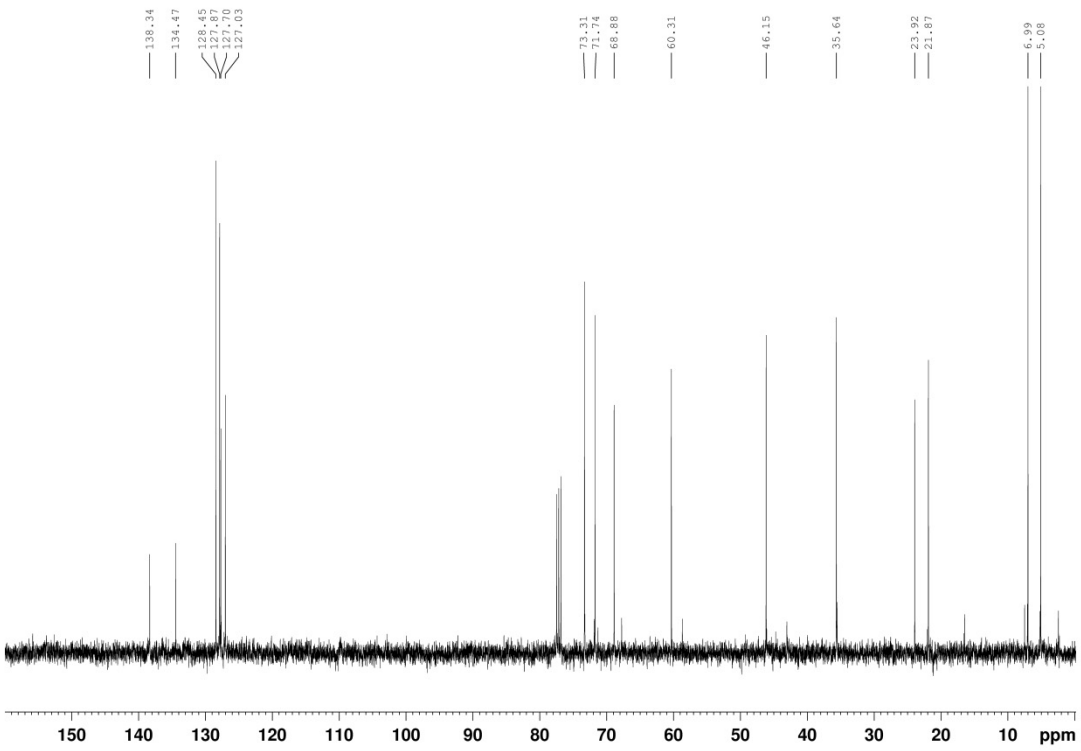
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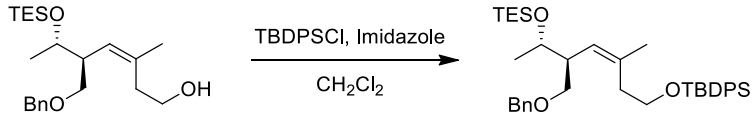
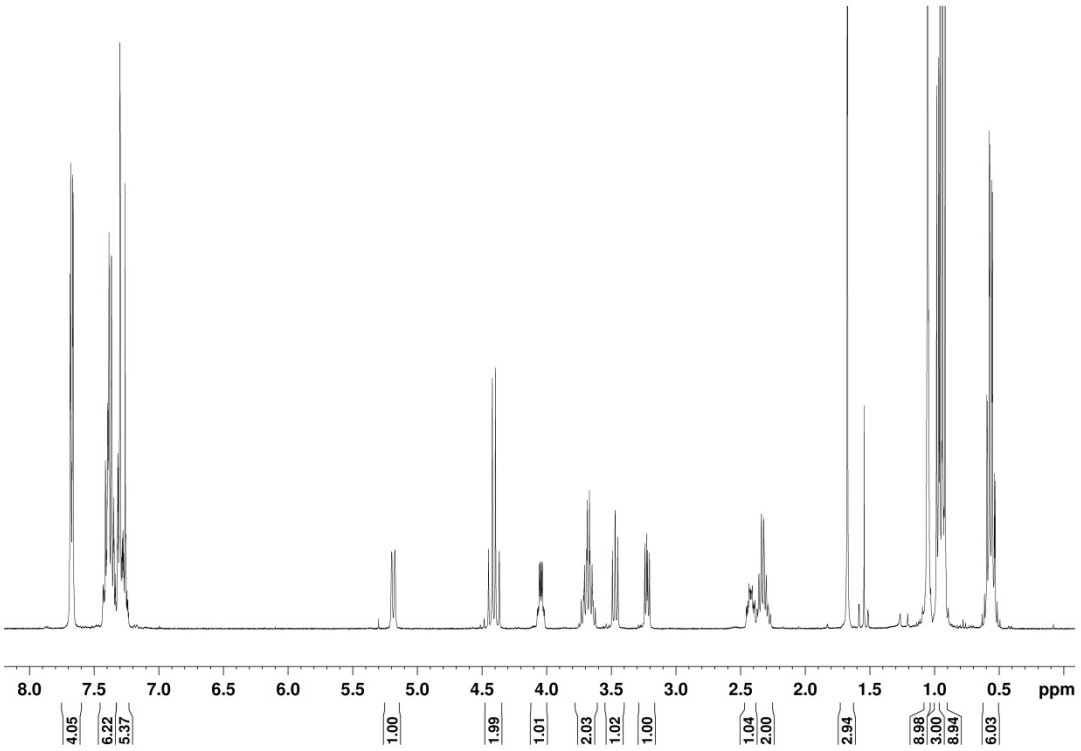



**99** **76b**

**Silyl ether 76b:** To a solution of **99** (4.66 g, 12.31 mmol, 1.00 equiv.) in 24.60 ml $CH_2Cl_2$ at rt, imidazole (1.09 g, 16.00 mmol, 1.30 equiv.) and TBDPSCl (4.16 ml, 16.00 mmol, 1.30 equiv.) were added. The reaction mixture was stirred at rt overnight, then diluted with hexanes and washed with brine. Extraction of the aqu. phase with $Et_2O$. The combined org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (toluene/hexane (1:1)) gave 6.12 g (80 %, Z-Isomer only) of the desired product **76** as colorless oil.

**TLC**: $R_f$ = 0.19 (toluene/hexane 1:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.70 – 7.64 (m, 4H), 7.44 – 7.22 (m, 11H), 5.18 (d, *J* = 9.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 4.04 (qd, *J* = 6.3, 3.0 Hz, 1H), 3.75 – 3.61 (m, 2H), 3.46 (dd, *J* = 8.9, 8.2 Hz, 1H), 3.22 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.38 – 2.25 (m, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.05 (s, 9H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.60 – 0.52 (m, 6H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 138.93, 135.73, 134.87, 134.10, 129.69, 128.38, 127.76, 127.69, 127.47, 123.99, 73.07, 71.45, 67.35, 63.07, 45.65, 35.87, 27.02, 24.41, 22.03, 19.31, 7.10, 5.22.; **IR** (thin film): ν 2956, 2932, 2875, 2857, 1454, 1428, 1372, 1105, 1092, 1007, 952, 917, 823, 736, 700, 613, 506; **HRMS** (ESI): calculated for $C_{38}H_{56}NaO_3Si_2$ $[M+Na]^+$: 639.3660, found 639.3657; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +3.96° (c = 1.01 in $CHCl_3$).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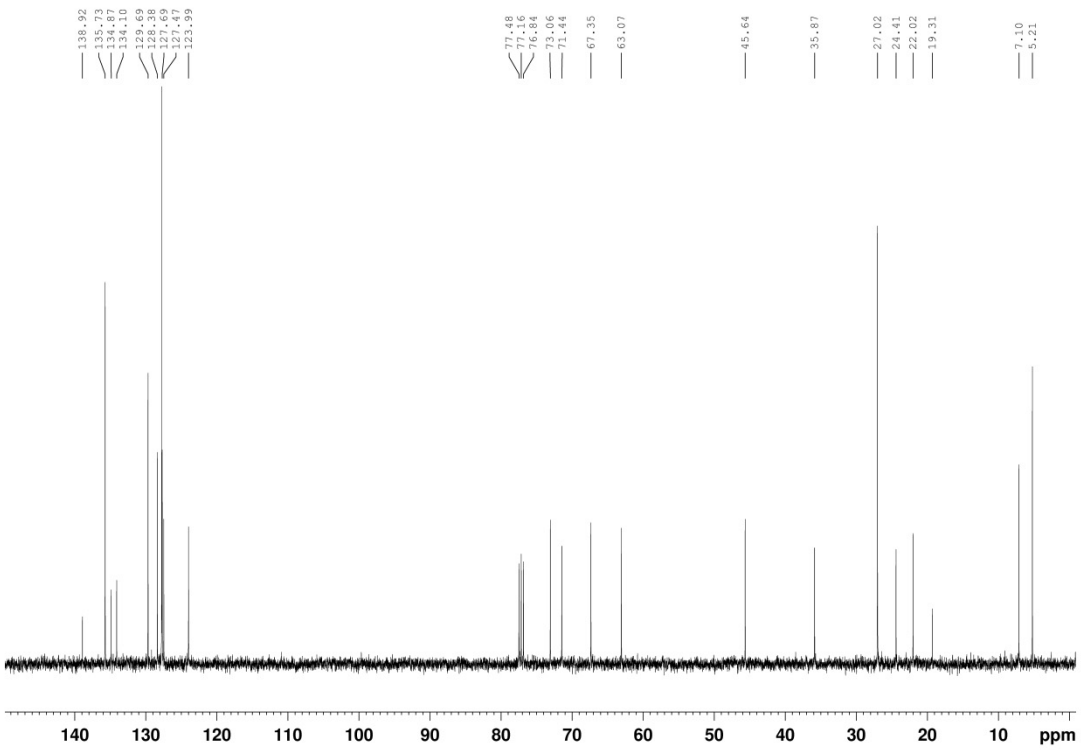
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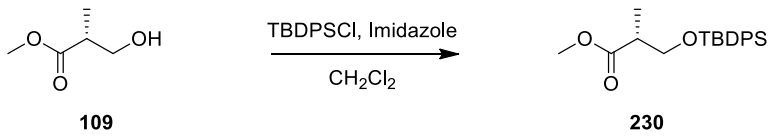
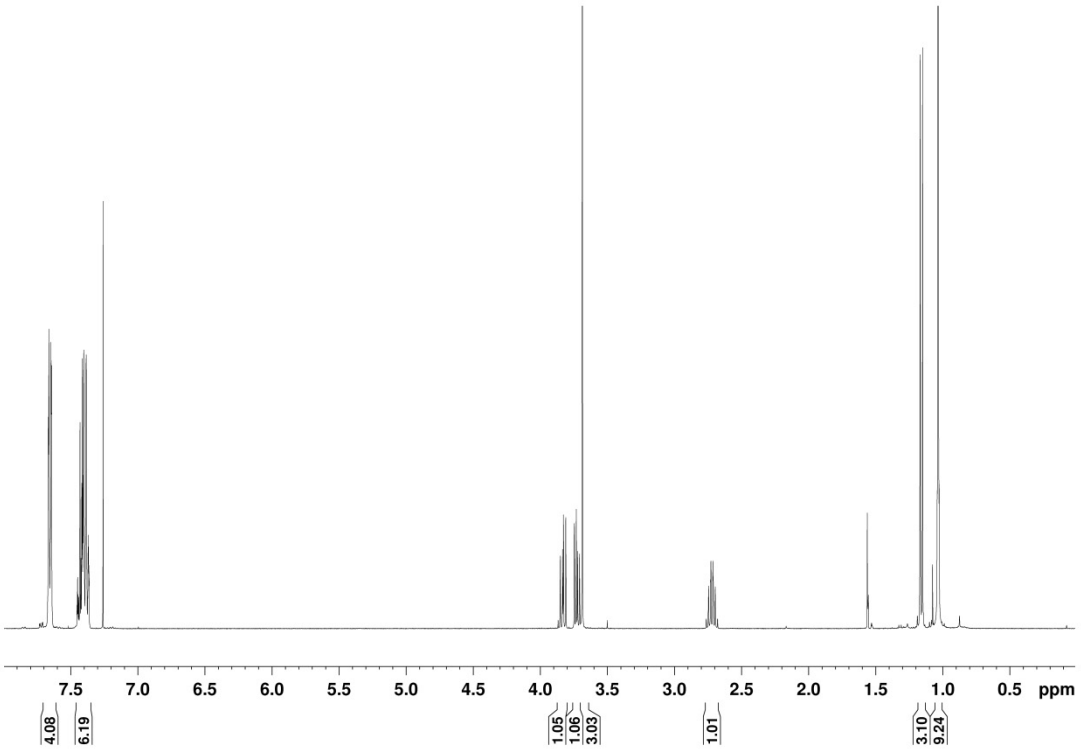
### 5.3.2.5. Synthesis of Aldehyde 74

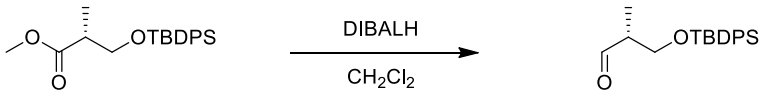



**109** **230**

**Silyl ether 230:** To a solution of (R)-roche ester (**109**) (4.18 g, 35.37 mmol, 1.00 equiv.) in 35 ml THF at rt, imidazole (3.13 g, 45.98 mmol, 1.30 equiv.) and TBDPSCl (11.96 ml, 45.98 mmol, 1.30 equiv.) were added. The reaction mixture was stirred at rt overnight, then quenched with aqu. sat. $NH_4Cl$ and extracted with $Et_2O$. The combined org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:60)) gave 12.04 g (95 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.59 (m, 4H), 7.46 – 7.35 (m, 6H), 3.83 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.73 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.69 (s, 3H), 2.77 – 2.67 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H).

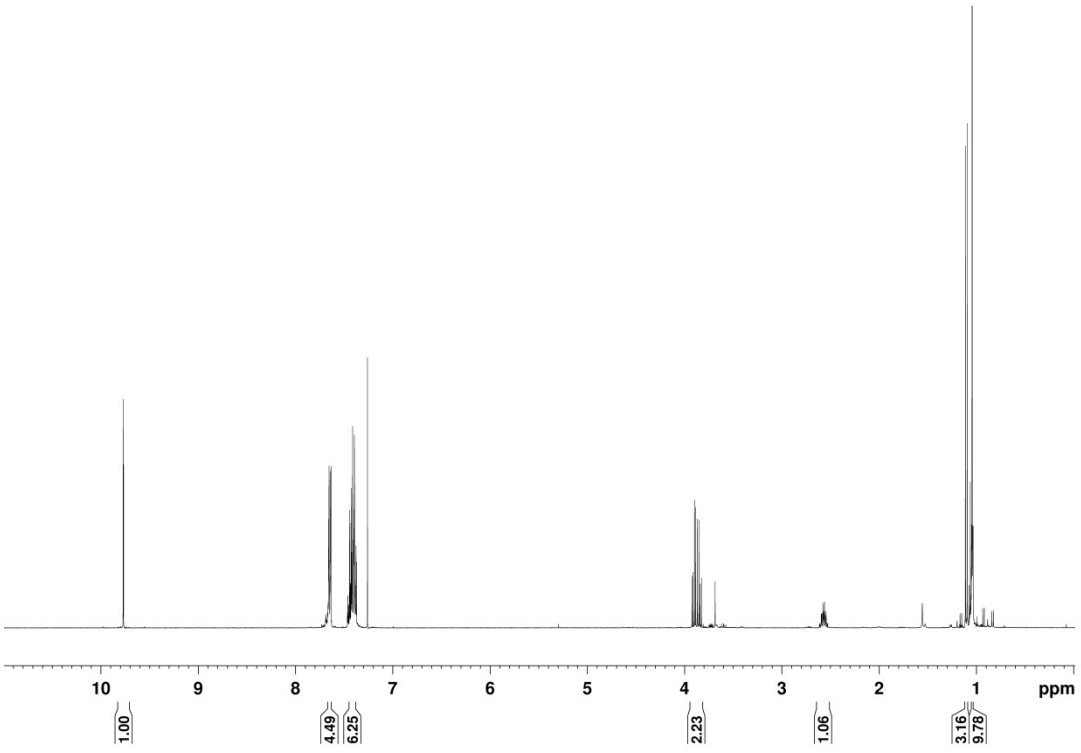


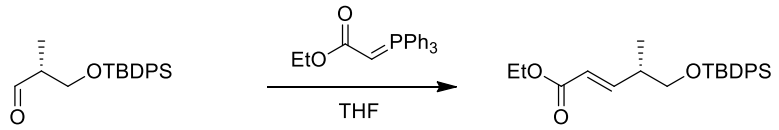



**230** **54**

**Aldehyde 54:** A solution of DIBAL-H in $CH_2Cl_2$ (1 M, 1.54 mL, 1.54 mmol) was added dropwise over 15 min to a solution of ester **230** (0.50 g, 1.40 mmol) in $CH_2Cl_2$ (1.00 mL) at −78°C. After stirring for 2 h at that temperature, the reaction was quenched by aqu. potassium-sodium tartrate solution. The resulting mixture was stirred vigorously at ambient temperature until phase separation occurred. The aqueous phase was repeatedly extracted with $CH_2Cl_2$, the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 0.448 g (97 %) of the desired crude product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.6 Hz, 1H), 7.68 – 7.61 (m, 4H), 7.49 – 7.36 (m, 6H), 3.90 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.85 (dd, *J* = 10.3, 6.3 Hz, 1H), 2.63 – 2.49 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H).

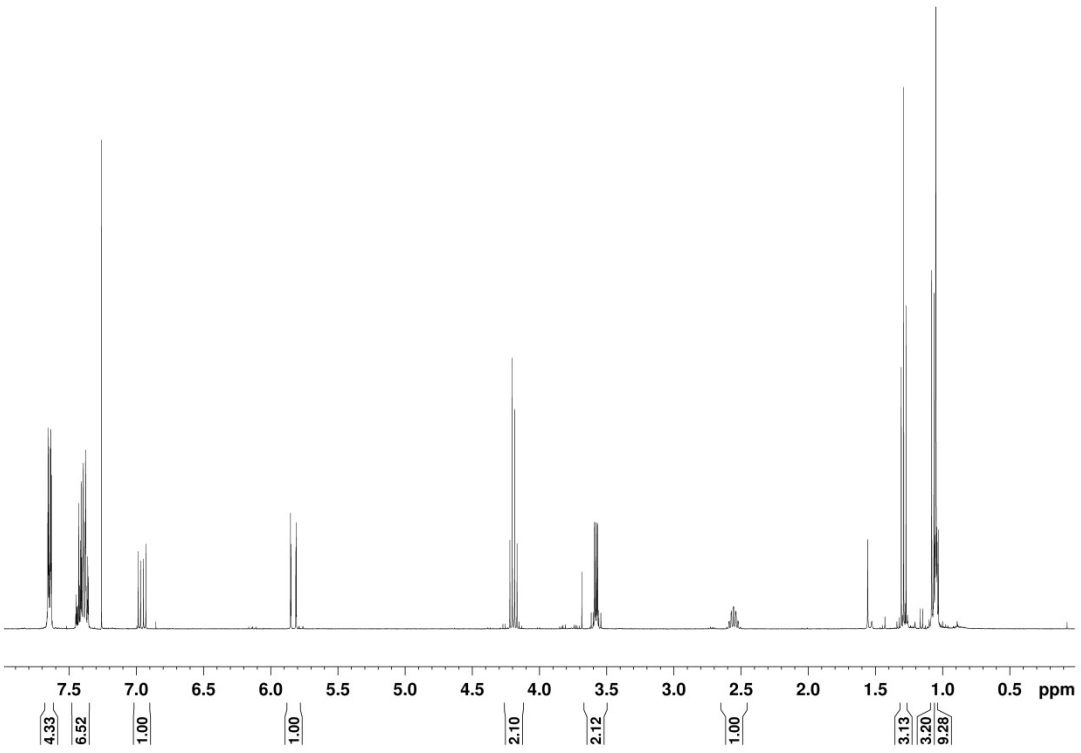


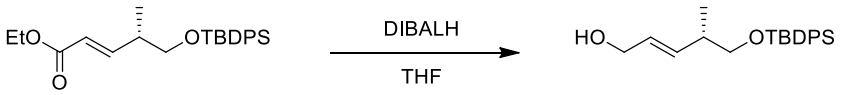



**54** **231**

**Alkene 231:** To a stirring solution of crude **54** (0.448 g, 1.37 mmol, 1.00 equiv.) in 1.40 mL of THF was added carbethoxymethylenetriphenylphosphorane (0.717 g, 2.06 mmol, 1.50 equiv.) and the reaction mixture was subsequentially heated at reflux overnight. The reaction mixture was cooled to room temperature and quenched with $NH_4Cl$ (aq.). The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 0.455 g (84 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 4H), 7.49 – 7.32 (m, 6H), 6.96 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.83 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.48 (m, 2H), 2.62 – 2.48 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H).

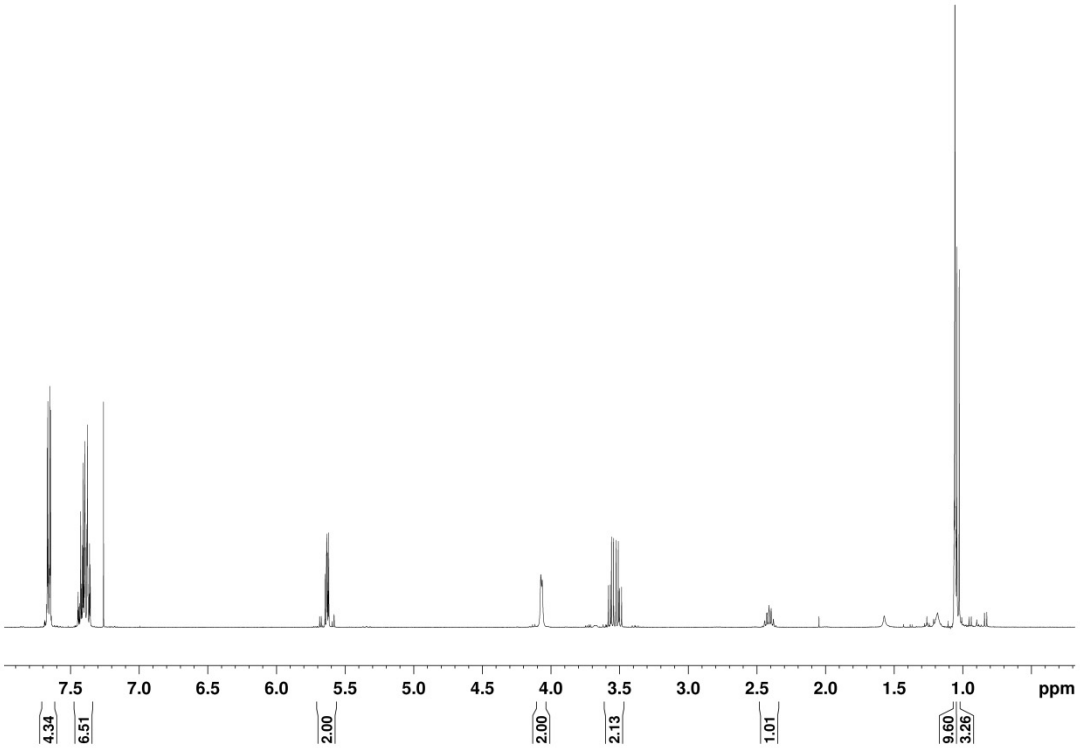


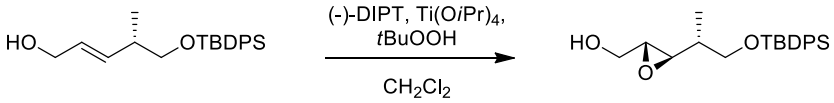



**231** **111**

**Alcohol 111: 231** (0.460 g, 1.15 mmol, 1.00 equiv.) was dissolved in 1.00 mL of $CH_2Cl_2$, cooled to –78 °C and 4.59 mL (4.59 mmol, 1 M in $CH_2Cl_2$) of DIBALH was added drop wise. After 3 h at -78 °C the reaction mixture was quenched by addition of aqu. Rochelle. The phases were separated and the aqueous phase was further extracted with $Et_2O$. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 0.393 g (96 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 4H), 7.50 – 7.30 (m, 6H), 5.70 – 5.57 (m, 2H), 4.07 (d, *J* = 3.9 Hz, 2H), 3.56 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.51 (dd, *J* = 9.8, 6.6 Hz, 1H), 2.49 – 2.34 (m, 1H), 1.06 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H).

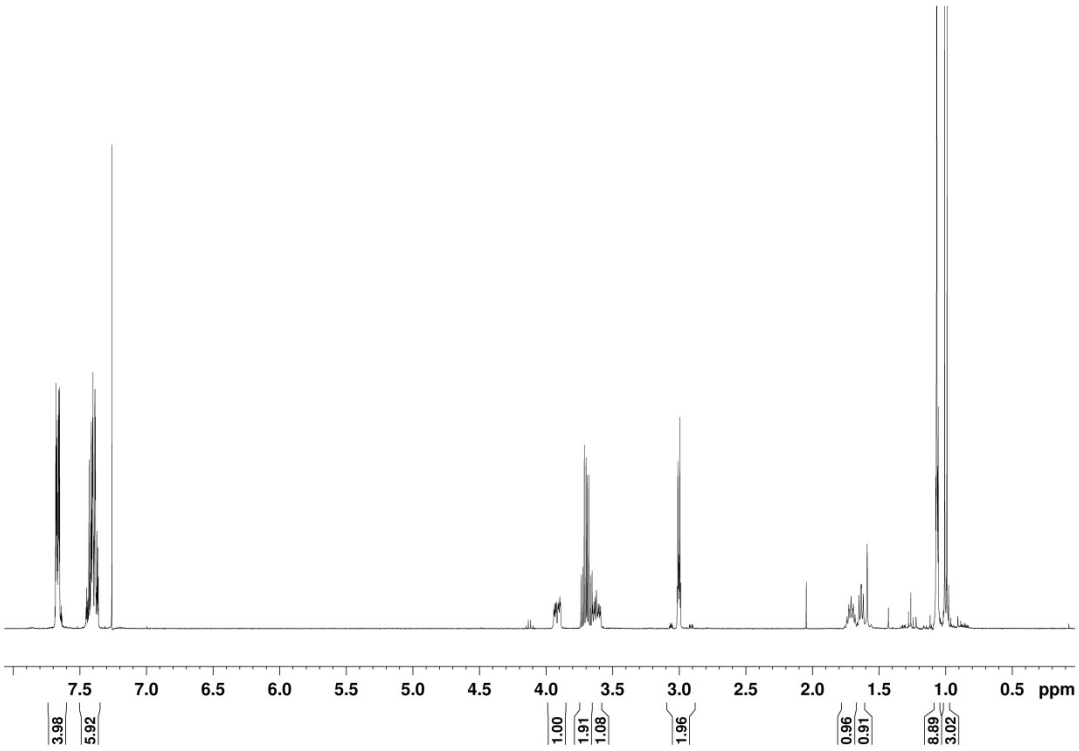





**111** **112**

**Epoxide 112:** To a stirred suspension of diisopropyl-D-tartrate (0.034 g, 0.144 mmol, 0.13 equiv.), Ti($O^iPr$)$_4$ (0.034 ml, 0.111 mmol, 0.10 equiv.) and 4A molecular sieves (72 mg, activated powder) in $CH_2Cl_2$ (2 ml) at -20 °C under argon was added $^t$BuOOH (~5.5 M in nonane, 0.443 ml, 2.22 mmol, 2.00 equiv.) and the whole was stirred for 30 min at -20 °C. Then **111** (0.390 mg, 1.11 mmol, 1.00 equiv.) in $CH_2Cl_2$ (1.00 ml) was added at -20 °C and the mixture was stirred at -20 °C for 26 h. The mixture was poured into a cold mixture of $FeSO_4$*$7H_2O$ (1.84 g, 6.65 mmol, 6.00 equiv.), citric acid monohydrate (1.39 g, 6.65 mmol, 6.00 equiv.) and 13 ml $H_2O$. The mixture was extracted with $Et_2O$ and the extract was washed with 5 % citric acid, aqu. sat. $NaHCO_3$ and brine and dried over $MgSO_4$. Concentrateion under reduced pressure gave an oily residue. To a vigorously stirred solution of the above residue in $Et_2O$ (3.00 ml) at 0 °C was added 4 ml of 30 % NaOH. The mixture was stirred at 0 °C for 1 h and then extracted with $Et_2O$. The extract was washed with $H_2O$, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:5)) gave 347.8 mg (84 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.57 (m, 4H), 7.50 – 7.31 (m, 6H), 3.92 (ddd, *J* = 12.5, 5.4, 2.1 Hz, 1H), 3.72 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.67 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.02 – 2.98 (m, 2H), 1.77 – 1.66 (m, 1H), 1.63 (dd, *J* = 7.0, 5.8 Hz, 1H), 1.07 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H).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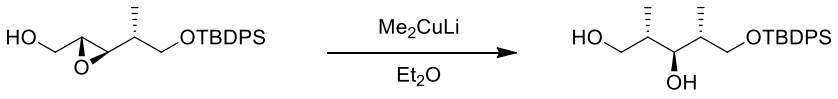
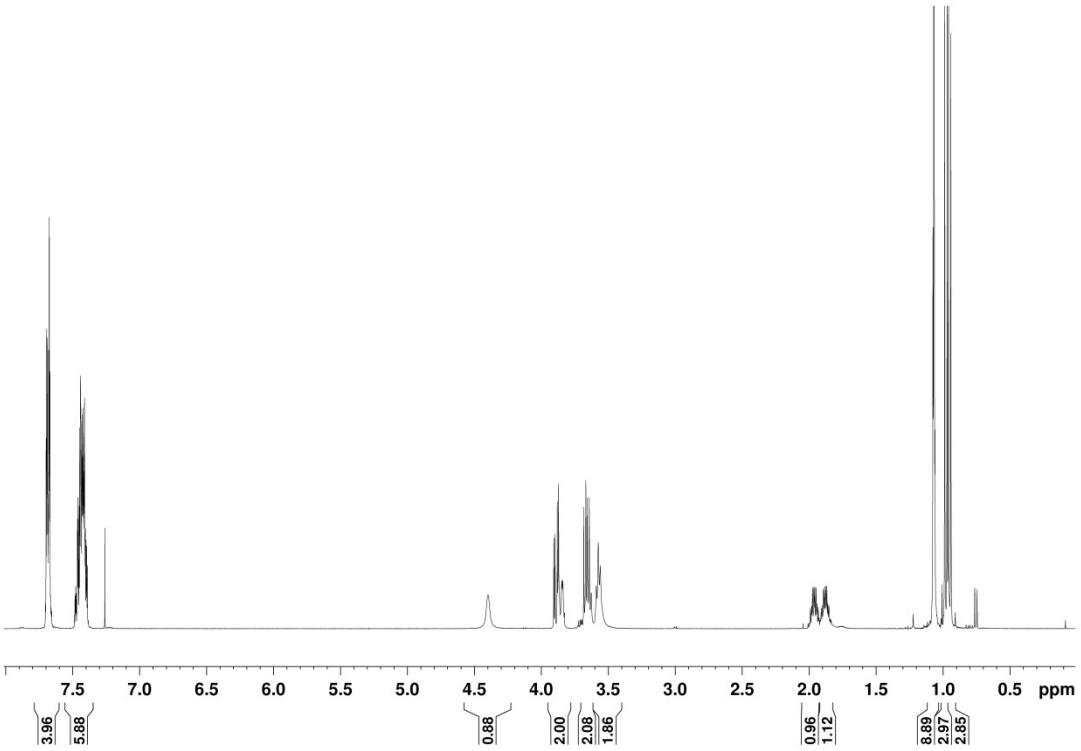



**112** **113**

**Diol 113:** To a suspension of CuI (14.22 g, 74.67 mmol, 10.00 equiv.) in 1.00 ml $Et_2O$ at -18 °C was added dropwise MeLi (1.6 M in $Et_2O$, 93.34 ml, 149.34 mmol, 20.00 equiv.) during 10 min. A solution of **112** in 7.30 ml $Et_2O$ was added dropwise during 5 min at -18 °C. After stirring for 16 h at -15 °C the reaction mixture was quenched with a (2:1) mixture of aqu. sat. $NH_4Cl$ and 25 % aqueous $NH_3$. The layers were separated and the aqu. layer was extracted with $Et_2O$. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 60 % aqueous MeCN (80 ml) followed by slow addition of $NaIO_4$ (3.19 g, 14.93 mmol, 2.00 equiv.) at 0 °C. After stirring for 1 h at room temperature, MeCN was removed under reduced pressure and the aqueous layer was extracted with $CH_2Cl_2$. The comb. org. layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:2) gave 1.98 g (68 %) of the desired product as colorless oil, 0.317 g (11.5 %) of SM.

**TLC**: $R_f$ = 0.18 (EtOAc/hexane 1:2, UV, CPS); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 4H), 7.52 – 7.37 (m, 6H), 3.87 (ddd, *J* = 12.9, 10.6, 3.4 Hz, 2H), 3.64 (dd, *J* = 10.5, 6.2 Hz, 2H), 3.57 (dd, *J* = 6.0 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.92 – 1.82 (m, 1H), 1.06 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 135.75, 135.71, 132.59, 130.13, 130.10, 128.02, 127.97, 83.08, 68.40, 66.92, 37.24, 36.88, 26.94, 14.68, 14.44; **IR** (thin film): ν 3396, 2960, 2930, 2857, 1472, 1428, 1390, 1112, 1073, 985, 822, 740, 700, 614, 506; **HRMS** (ESI): calculated for $C_{23}H_{34}NaO_3Si$ $[M+Na]^+$: 409.2169, found 409.2167; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -12.14° (c = 1.00 in $CHCl_3$).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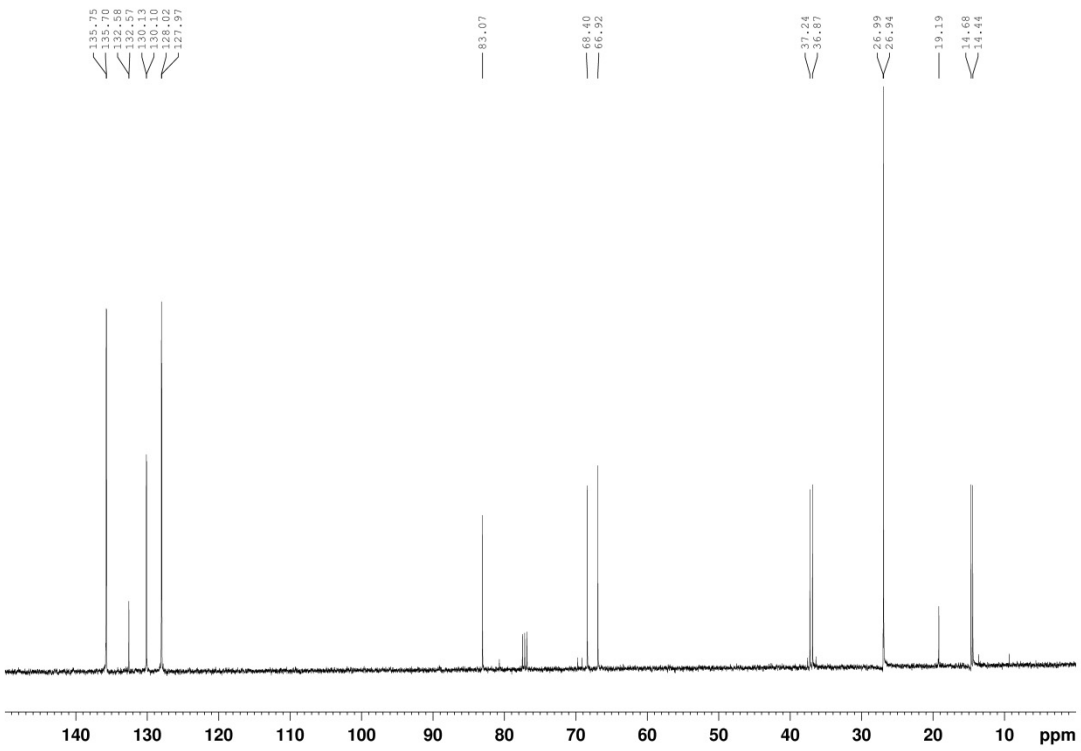
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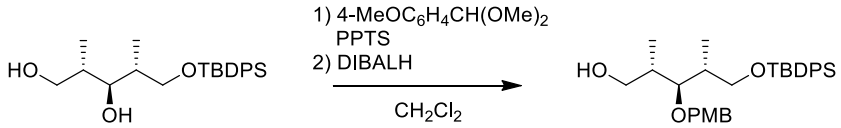
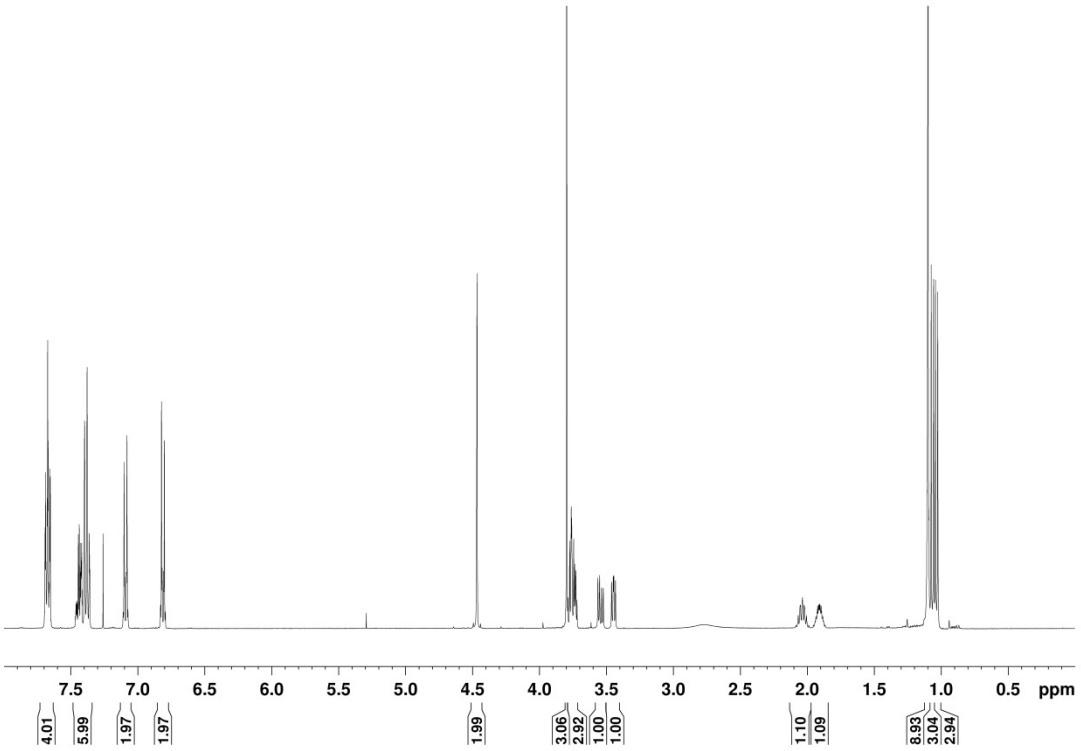



**113** **115**

**PMB ether 115:** To a solution of **113** (0.163 g, 0.422 mmol, 1.00 equiv.) and 10-camphorsulfonic acid (0.0196 g, 0.1.47 mmol, 0.20 equiv.) in anhydrous $CH_2Cl_2$ (1.50 mL) was added *p*-methoxybenzaldehyde dimethyl acetal (0.073 mmol, 0.430 mmol, 1.02 equiv). After stirring for 30 min at RT, the mixture was cooled down to –78 °C whereupon DIBALH (1.0 M in $CH_2Cl_2$, 1.47 mL, 1.47 mmol) was added drop wise. The mixture was stirred at –78 °C for 1 h and then allowed to warm up to RT. After an additional 2 h of stirring at RT, the reaction was diluted with $Et_2O$, quenched by adding a saturated aqueous solution of Rochelle's salt (5 mL) and vigorously stirred for 1 h. The mixture was diluted with ether, washed with a saturated aqueous solution of Rochelle's salt and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:3)) gave the desired product (0.200 g, 94%) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.49 – 7.33 (m, 6H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.84 – 3.69 (m, 3H), 3.53 (dd, *J* = 10.8, 5.0 Hz, 1H), 3.44 (dd, *J* = 6.7, 4.9 Hz, 1H), 2.76 (s, 1H), 2.13 – 1.97 (m, 1H), 1.96 – 1.84 (m, 1H), 1.09 (s, 9H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.37, 135.88, 135.84, 133.91, 133.83, 130.48, 129.77, 129.76, 129.55, 127.81, 127.76, 113.95, 86.33, 74.89, 65.66, 65.64, 55.39, 36.38, 27.12, 19.43, 16.05, 14.70.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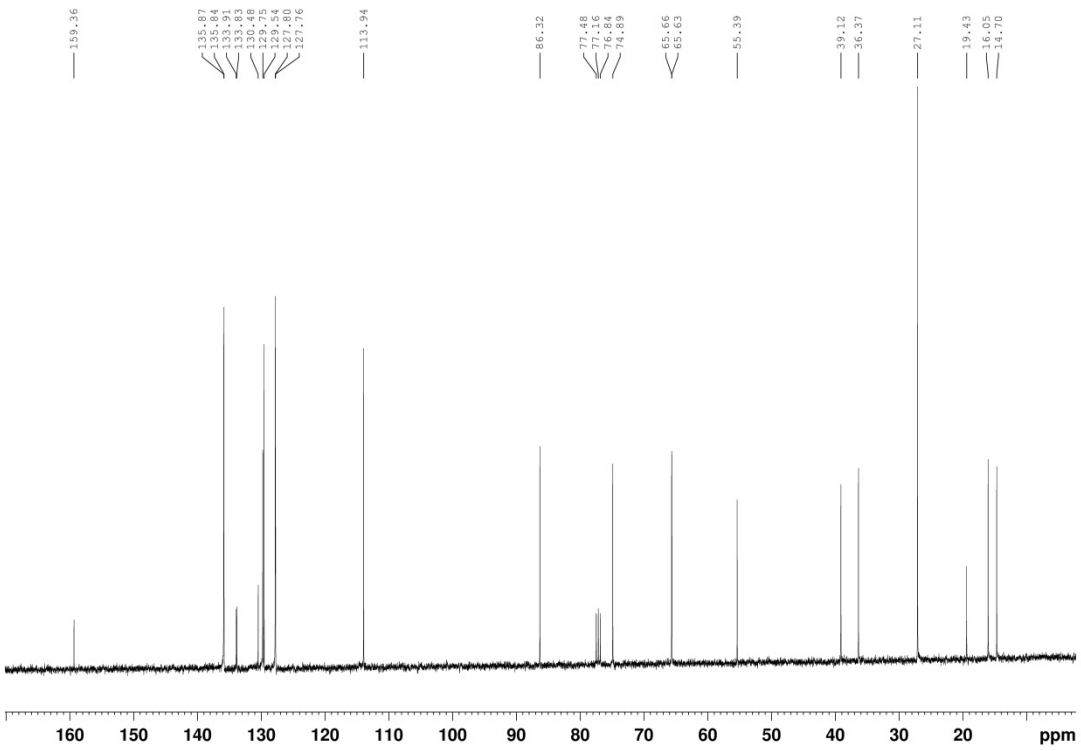
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27.11
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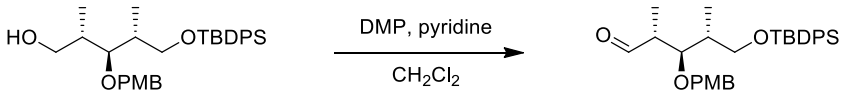
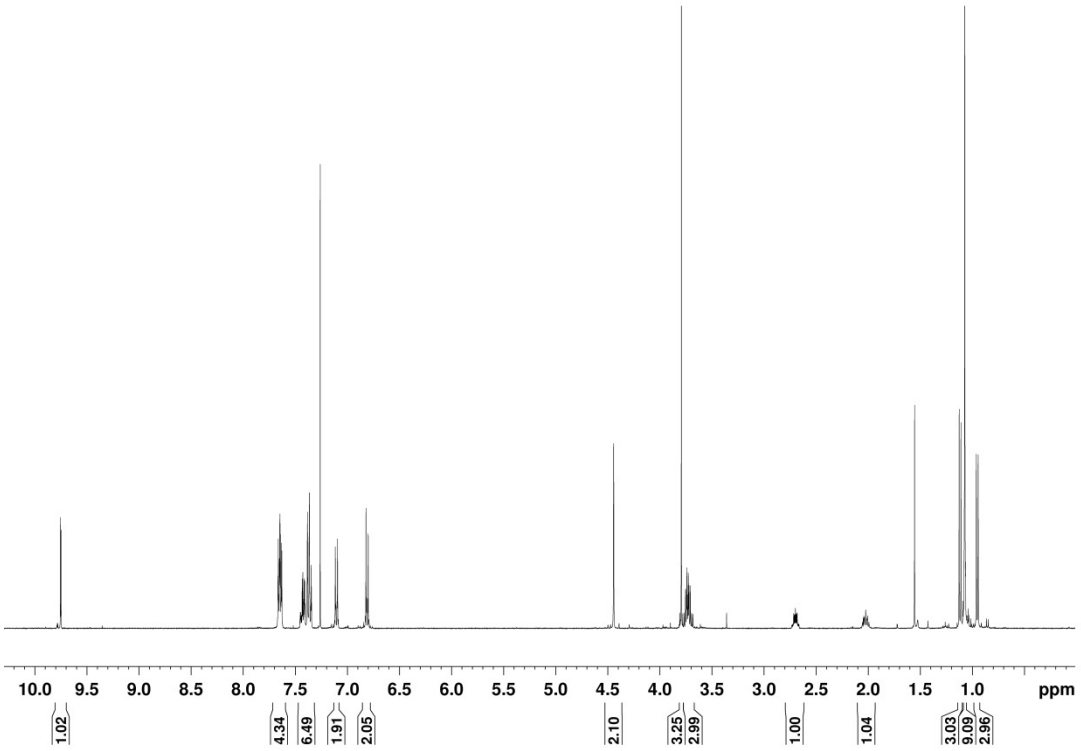



**115** **74**

**Aldehyde 74:** To a solution of **115** (1.37 g, 2.70 mmol, 1.00 equiv.) and pyridine (1.71 mL, 21.1 mmol, 7.80 equiv.) in $CH_2Cl_2$ (26.0 mL) was added Dess–Martin periodinane (1.49 g, 3.52 mmol, 1.30 equiv.). The reaction mixture was stirred for 3 h 20 min at RT before the addition of saturated aqueous $NaHCO_3$ solution (90 mL) and a saturated aqueous sodium thiosulfate solution (25 mL). After stirring for an additional 5 min, the reaction mixture was diluted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:8)) gave the desired product (1.15 g, 84 %) as colourless oil.

**TLC**: $R_f$ = 0.30 (EtOAc/hexane 1:17, UV, CPS); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.2 Hz, 1H), 7.71 – 7.61 (m, 4H), 7.47 – 7.34 (m, 6H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.78 – 3.69 (m, 3H), 2.78 – 2.65 (m, 1H), 2.10 – 1.98 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.09 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 204.77, 159.33, 135.86, 135.82, 133.82, 133.73, 130.50, 129.83, 129.81, 129.42, 127.84, 127.81, 113.91, 81.97, 73.46, 65.55, 55.43, 48.56, 38.63, 27.11, 19.44, 14.16, 11.49; **IR** (thin film): ν 2958, 2931, 2857, 1718, 1612, 1513, 1458, 1302, 1247, 1172, 1111, 1070, 1035, 821, 738, 700, 615, 504, 484; **HRMS** (ESI): calculated for $C_{31}H_{40}NaO_4Si$ $[M+Na]^+$: 527.2588, found 527.2588; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -26.8° (c = 1.00 in $CHCl_3$).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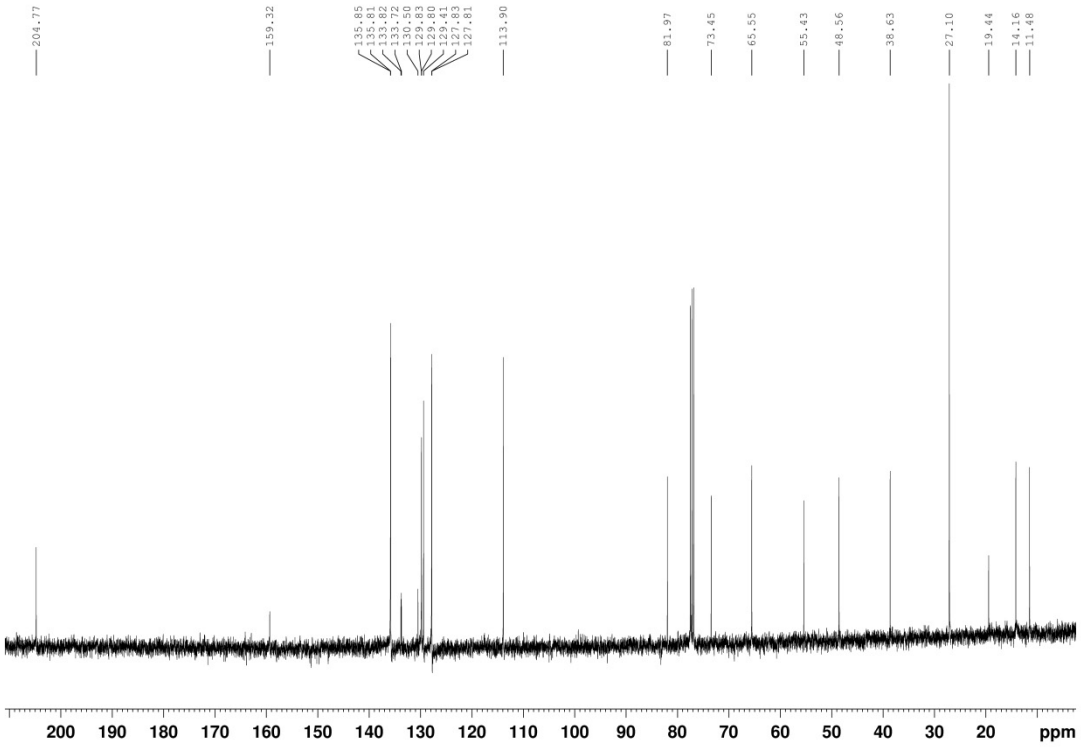
1.00
1.04
3.03
9.09
2.96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38.63
27.10
19.44
14.16
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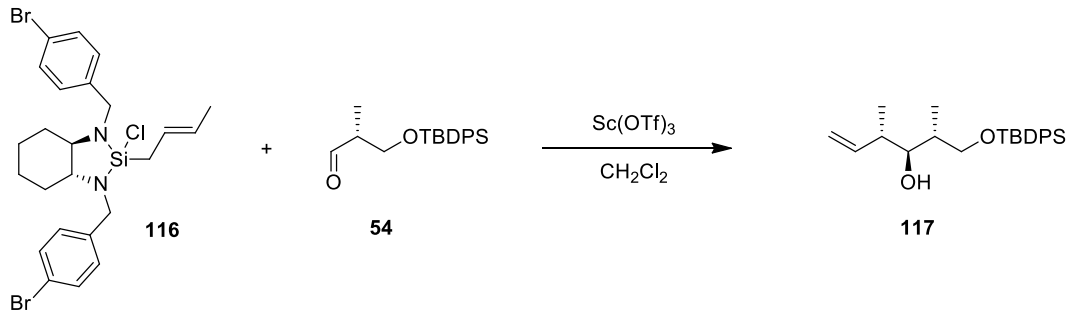
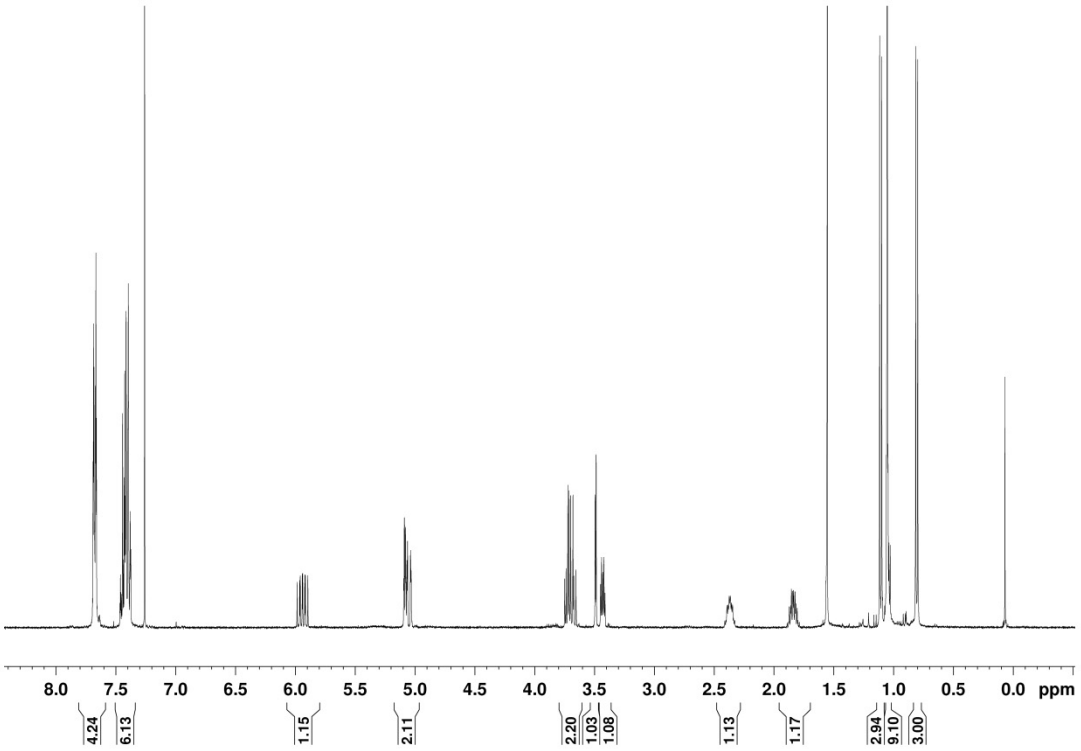
### 5.3.2.6. Alternative Synthesis of Aldehyde 74 via *Leighton* crotylation




**Homoallylic alcohol 117:** To a cooled solution (0 °C) of **54** (90.0 mg, 0.28 mmol, 1.00 equiv.) 2.80 ml dichloromethane were added *Leighton* reagent **116** (235.2 mg, 0.41 mmol, 1.50 equiv.) as well as $Sc(OTf)_3$ (14.9 mg, 0.03 mmol, 0.11 equiv.) and the mixture was stirred for 130 minutes. Afterwards, 1.0 ml HCl (1 M) was added and the mixture was stirred for another 45 minutes at 0 °C. The suspension was filtered, the aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with sat. aqu. $NaHCO_3$. After separation, the aqueous layer was back-extracted two times with dochloromethane. The comb. org. layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:50) gave 61.9 mg (59%, *dr* = 14:1) of the desired product as colorless oil.

**Major isomer: TLC**: $R_f$ = 0.18 (EtOAc/hexane 1:19, UV, CPS); **$^1$H NMR** (400 MHz, CDCl3) δ 7.70-7.66 (m, 4H), 7.47-7.37 (m, 6H), 5.94 (ddd, *J* = 8.35,10.47, 17.12 Hz, 1H), 5.11-5.02 (m, 2H), 3.76-3.65 (m, 2H), 3.48 (d, *J* = 3.24 Hz, 1H), 3.46-3.40 (m, 1H), 2.42-2.31 (m, 1H), 1.90-1.78 (m, 1H), 1.11 (d, *J* = 6.85 Hz, 3H), 1.05 (s, 9H) 0.81 (d, *J* = 6.85 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.03, 135.77, 135.77, 133.09, 133.03, 129.98, 129.97, 127.93, 115.30, 79.90, 69.11, 41.34, 37.98, 26.98, 19.24, 17.92, 13.73; **IR** (thin film): ν 3502, 3071, 2960, 2930, 2858, 2366, 1971, 1638, 1589, 1471,1427, 1105, 1056, 997, 911, 822, 699, 613, 504; **HRMS** (ESI): calculated for $C_{24}H_{34}NaO_2Si$ $[M+Na]^+$: 405.2220, found 405.2218; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -19.9° (c = 1.02 in $CHCl_3$).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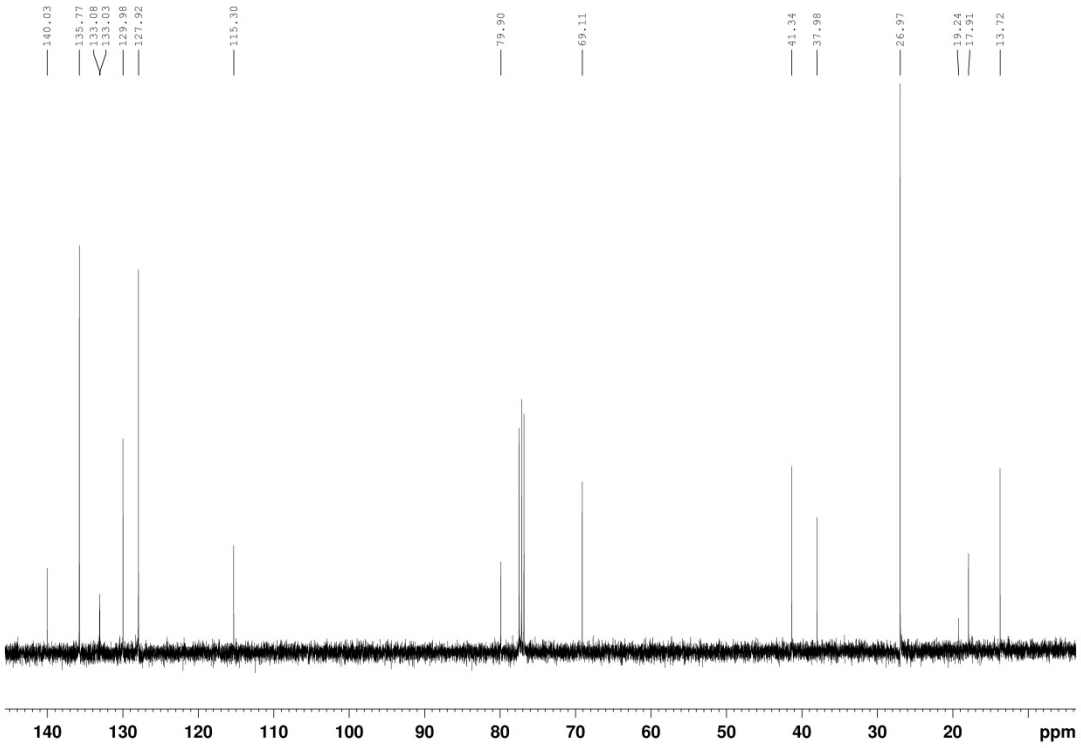
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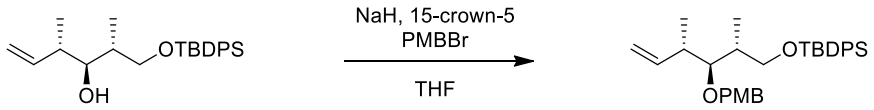
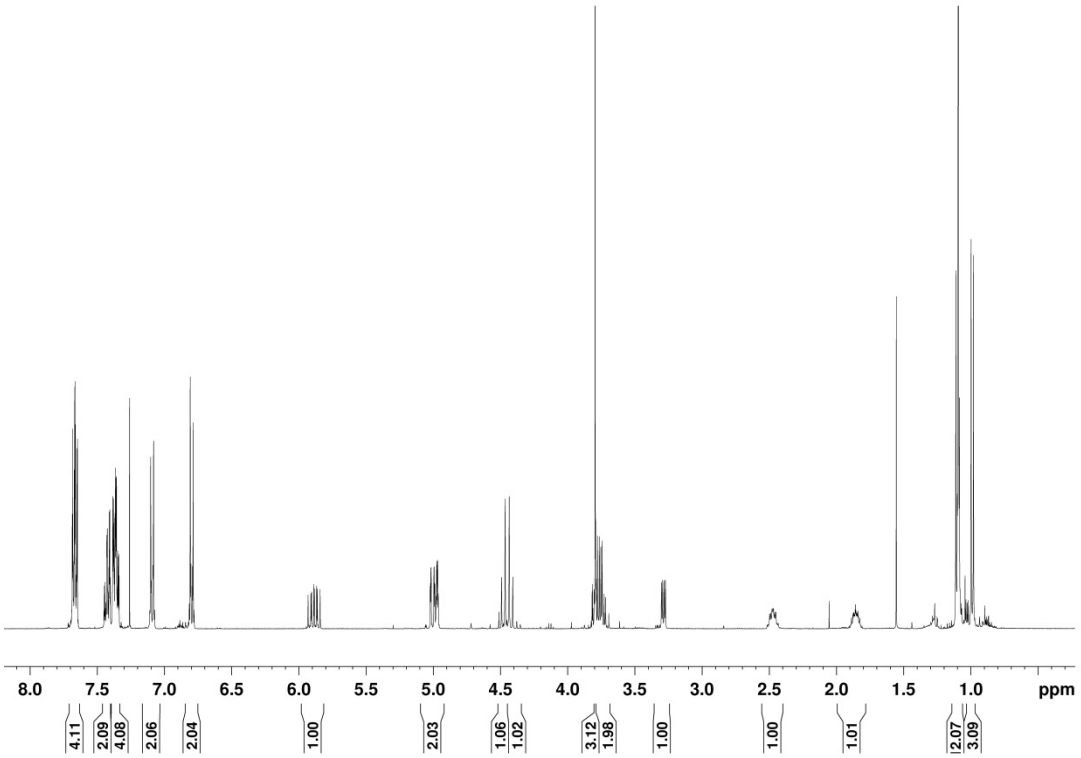



**117** **118**

**PMB ether 118:** To a cooled solution (0 °C) of **117** (120.0 mg, 0.47 mmol, 1.00 equiv.) in 1.5 ml THF were added NaH (16.6 mg, 0.69 mmol, 2.20 equiv.) and 15-crown-5 (6.9 mg, 0.03 mmol, 0.10 equiv.). After stirring for 6 min, *p*-methoxybenzylbromide (94.7 mg, 0.47 mmol, 1.50 equiv.) was added at 0 °C and the white suspension was stirred for 215 minutes at RT. The reaction mixture was quenched by sat. aq. $NaHCO_3$ and the aqueous layer was extracted three times with diethyl ether. The comb. org. layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified over $SiO_2$ (hexane/ethyl acetate: 99:1 up to 49:1) to afford 101.1 mg (64.0%) as colorless oil.

**Major isomer: TLC**: $R_f$ = 0.16 (EtOAc/hexane 1:19, UV, CPS); **$^1$H NMR** (400 MHz, CDCl3) δ 7.71-7.63 (m, 4H), 7.46-7.40 (m, 2H), 7.40-7.33 (m, 4H), 7.14-7.04 (m, 2H), 6.84-6.75 (m, 2H), 5.89 (ddd, *J* = 8.46, 10.41, 17.20 Hz, 1H), 5.09-4.92 (m, 2H), 4.48 (d, *J* = 10.16 Hz, 1H), 4.42 (d, *J* = 10.84 Hz, 1H), 3.79 (s, 3H), 3.79-3.68 (m, 2H), 3.29 (dd, *J* = 3.63, 8.03 Hz, 1H), 2.54-2.40 (m, 1H), 1.95-1.79 (m, 1H), 1.13-1.06 (m, 12H), 0.99 (d, *J* = 6.93 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.08, 140.93, 135.94, 135.89, 134.11, 134.01, 131.34, 129.67, 129.65, 129.33, 127.75, 127.69, 120.11, 114.47, 113.75, 84.54, 74.50, 65.81, 55.40, 40.76, 39.15, 27.14, 19.48, 18.47, 14.63; **IR** (thin film): ν 3071, 2959, 2931, 287, 2359, 2318, 2040, 1988, 1969, 1613, 1513, 1463, 1428, 1301, 1247, 1172, 1112, 912, 739, 690, 614; **HRMS** (ESI): calculated for $C_{32}H_{42}NaO_3Si$ $[M+Na]^+$: 525.2795, found 525.2790; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: 5.70° (c = 1.00 in $CHCl_3$).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1.5
1.0
ppm
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2.09
4.08
2.06
2.04
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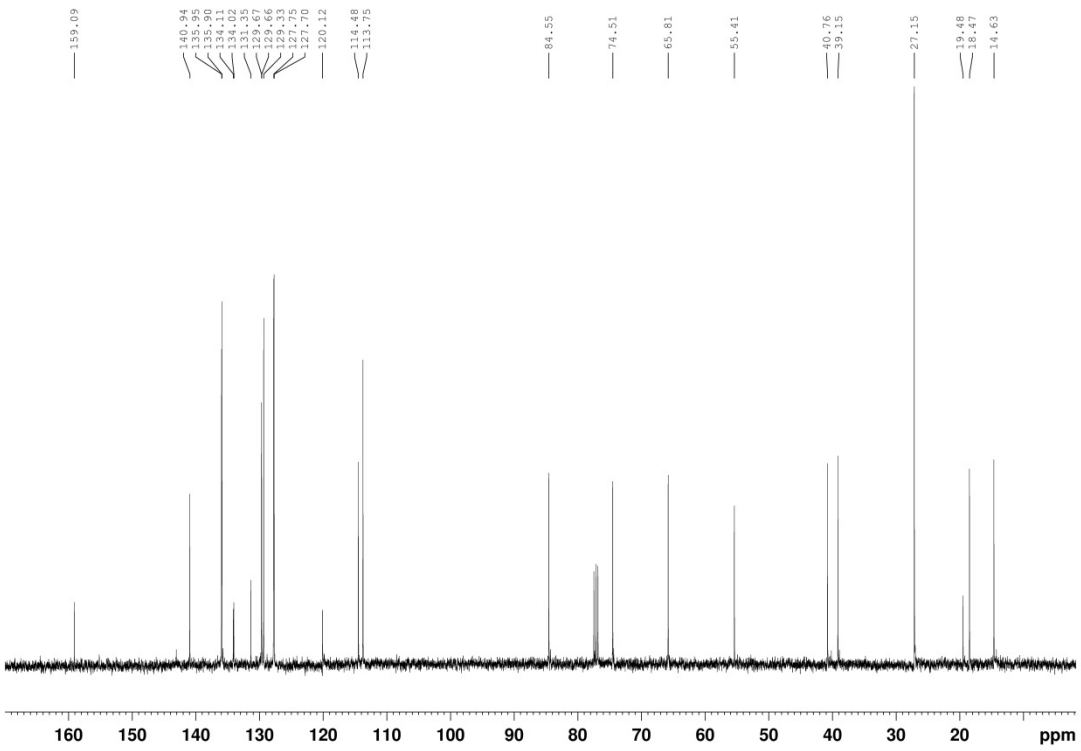
2.03
1.06
1.02
3.12
1.98
1.00
1.00
1.01
2.07
3.09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127.75
127.70
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114.48
113.75
84.55
74.51
65.81
55.41
40.76
39.15
27.15
19.48
18.47
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140
130
120
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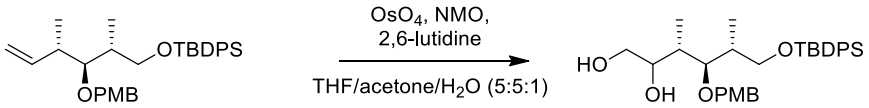
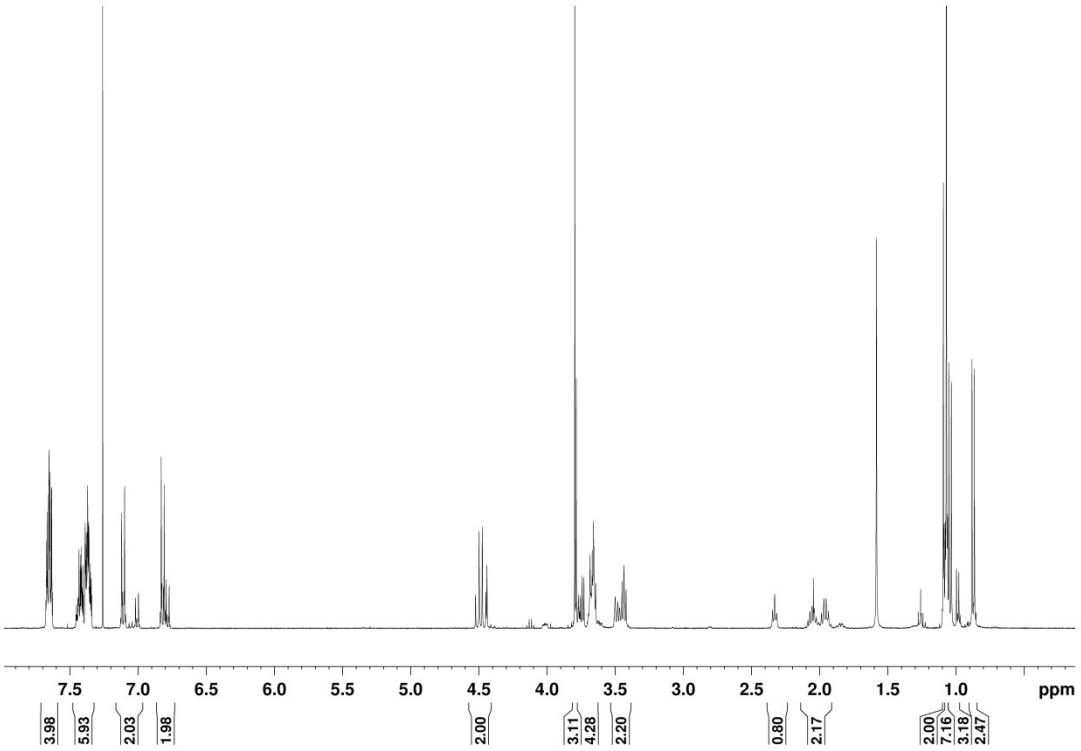
40
30
20
ppm




**118** **232**

**Diol 232:** To a solution of **118** (0.60 g, 1.19 mmol, 1.00 eq.) in 13.5 ml THF/acetone/water (5:5:1) were added NMO (0.21 g, 1.79 mmol, 1.50 eq.), $OsO_4$ (0.22 ml (4% in water), 0.04 mmol, 0.03 equiv.) as well as 2,6-lutidine (0.26 g, 2.39 mmol, 2.00 eq. ) at RT and the mixture was stirred over night. The color of the mixture changed from colourless to yellow while stirring. Afterwards, the reaction was quenched by sat. aq. $Na_2S_2O_3$ solution. After stirring for 25 minutes, ethyl acetate was added and the layers were separated. The dark brown aqueous layer was extracted 3 times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to get a brown liquid. The crude product was purified over $SiO_2$ (hexane/ethyl acetate: 8:2 up to 1:1) to afford 520.6 mg (81.3%, *dr* = 4:1) of a colorless oil.

**Majo isomer: TLC**: $R_f$ = 0.37 (EtOAc/hexane 1:1, UV, CPS); **$^1$H NMR** (400 MHz, CDCl3) δ 7.70-7.61 (m, 4H), 7.47-7.33 (m, 6H), 7.15-6.98 (m, 2H), 6.86-6.75 (m, 2H), 4.50 (d, *J* = 10.50 Hz, 1H), 4.45 (d, *J* = 10.50 Hz, 1H), 3.80 (s, 2H), 3.79-3.72 (m, 2H), 3.71-3.63 (m, 3H), 3.52-3.41 (m, 2H), 2.31 (t, *J* = 6.15 Hz, 1H), 2.12-2.00 (m, 1H), 2.00-1.90 (m, 1H), 1.07 (s, 9H), 1.06-0.72 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.48, 135.93, 135.89, 135.85, 135.82, 133.88, 130.07, 129.80, 129.78, 129.66, 129.56, 127.82, 127.79, 114.01, 86.63, 74.72, 74.55, 65.53, 64.67, 55.41, 39.65, 38.04, 27.15, 27.10, 19.41, 14.96, 14.79; **IR** (thin film): ν 3393brw, 2959m, 2930m, 2857m, 2361m, 2164w, 2064w, 2051w, 2051w, 1990w, 1906w, 1900w, 1612m, 1513s, 1463m, 1427m, 1248s, 1173w, 1111s, 1067s, 1034s, 823m, 742m, 629w, 616m, 504s, 488m; **HRMS** (ESI): calculated for $C_{32}H_{44}NaO_5Si$ $[M+Na]^+$: 559.2850, found 559.2844; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -10.5° (c = 1.00 in $CHCl_3$).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1.5
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ppm
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5.93
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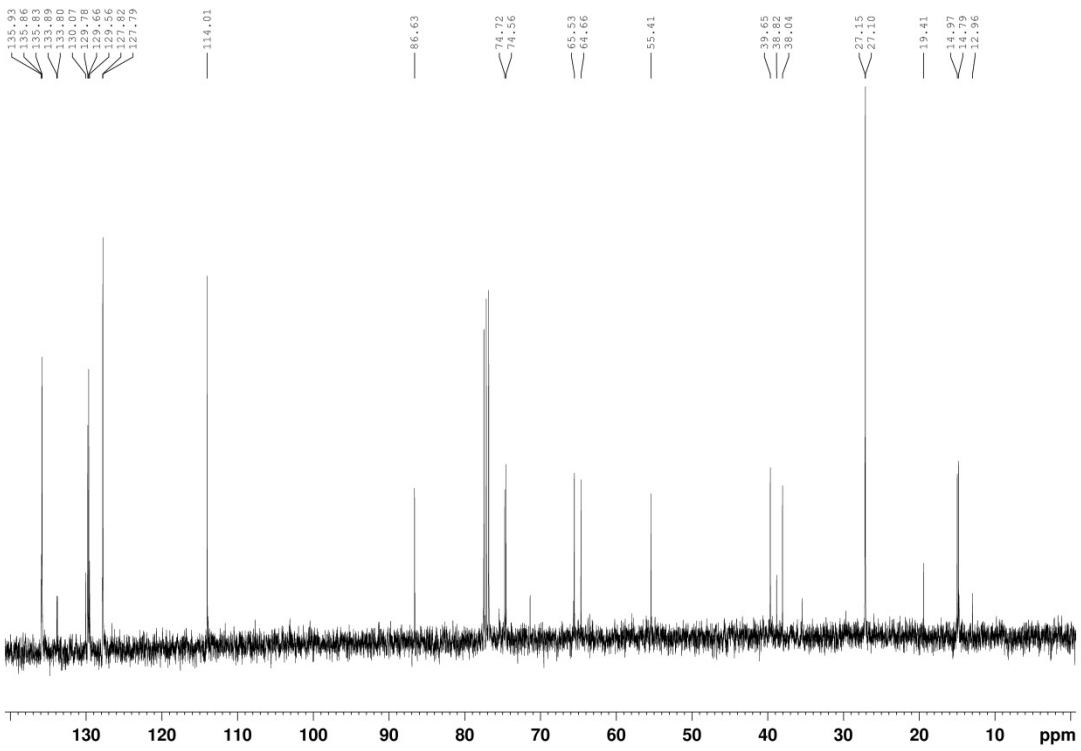
2.00
7.16
3.18
2.47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127.82
127.79
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74.72
74.56
65.53
64.66
55.41
39.65
38.82
38.04
27.15
27.10
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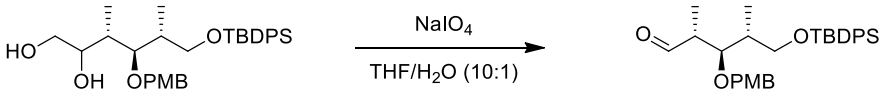
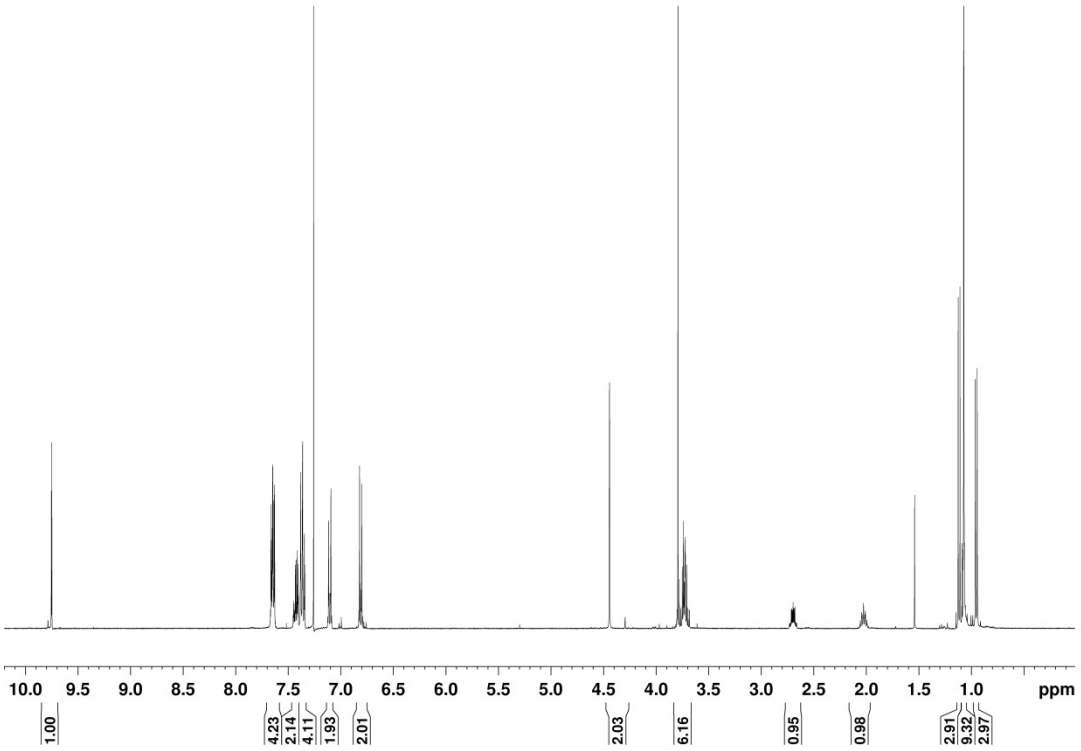
20
10
ppm




**232** **74**

**Aldeyde 74:** To a solution of **232** (13.0 mg, 0.24 mmol, 1.0 eq.) in 0.25 ml THF/water (10:1) was added $NaIO_4$ (15.5 mg, 0.073 mmol, 3.0 eq.) at RT. The reaction mixture was stirred for 25 minutes, diluted with diethyl ether, threated with sat. aq. $Na_2S_2O_3$ solution and the layers were separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified over $SiO_2$ (hexane/ethyl acetate: 17:3) to afford 77.0 mg (96.3%) of a colorless liquid.

**Major isomer: TLC**: $R_f$ = 0.30 (EtOAc/hexane 1:17, UV, CPS); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 2.2 Hz, 1H), 7.71 – 7.61 (m, 4H), 7.47 – 7.34 (m, 6H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.78 – 3.69 (m, 3H), 2.78 – 2.65 (m, 1H), 2.10 – 1.98 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.09 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 204.77, 159.33, 135.86, 135.82, 133.82, 133.73, 130.50, 129.83, 129.81, 129.42, 127.84, 127.81, 113.91, 81.97, 73.46, 65.55, 55.43, 48.56, 38.63, 27.11, 19.44, 14.16, 11.49; **IR** (thin film): ν 2958, 2931, 2857, 1718, 1612, 1513, 1458, 1302, 1247, 1172, 1111, 1070, 1035, 821, 738, 700, 615, 504, 484; **HRMS** (ESI): calculated for $C_{31}H_{40}NaO_4Si$ $[M+Na]^+$: 527.2588, found 527.2588; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -24.97° (c = 0.83 in $CHCl_3$).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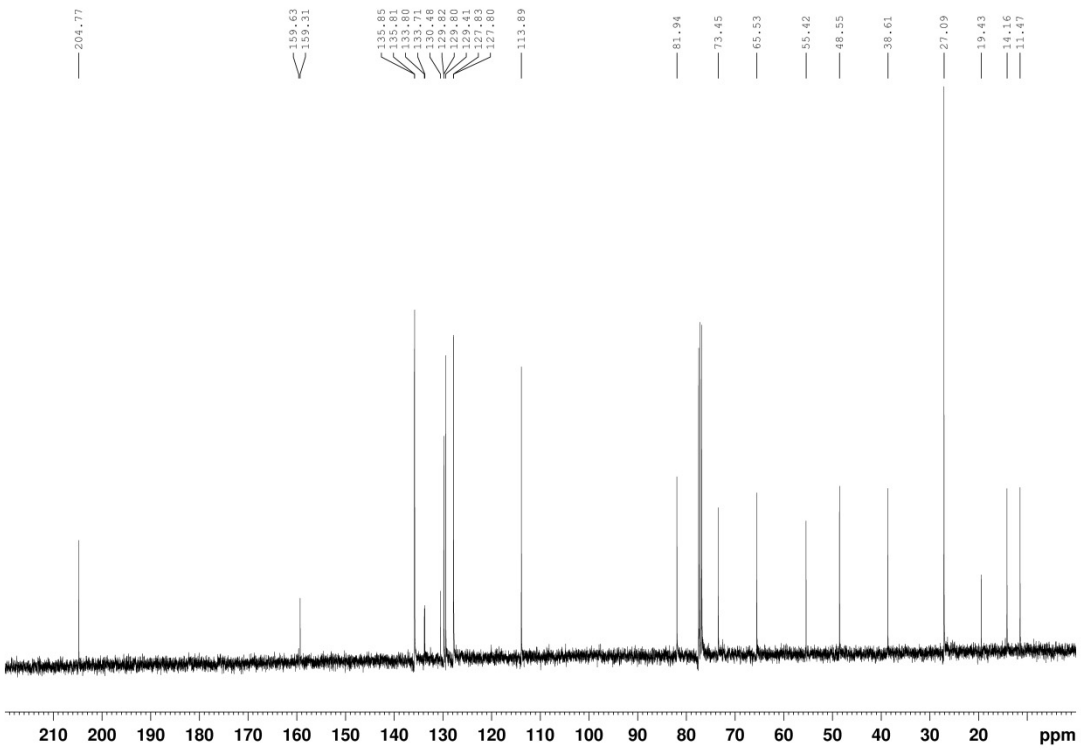
2.91
9.32
2.97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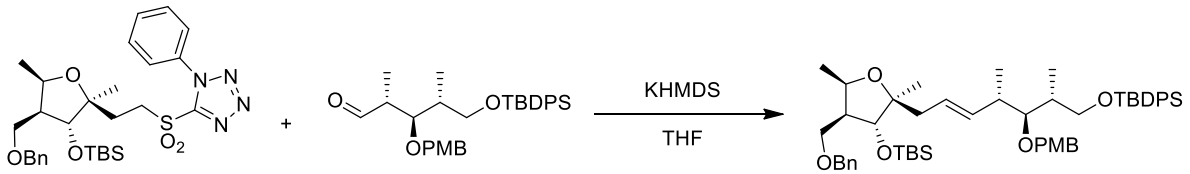
113.89
81.94
73.45
65.53
55.42
48.55
38.61
27.09
19.43
14.16
11.47
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

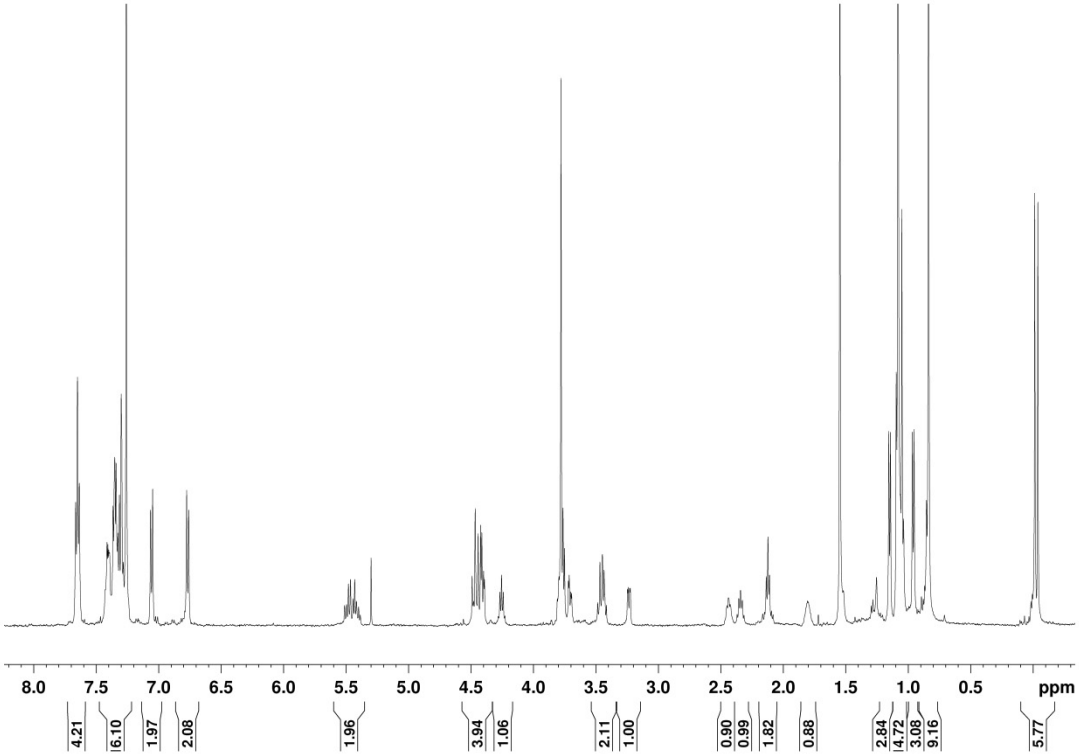
### 5.3.2.7. Fragment Assembly via *Julia* Olefination




**92** **74** **119**

**Alkene 119:** To a solution of **92** (0.0256 g, 0.0436 mmol, 1.00 equiv.) in 0.5 ml THF, KHMDS (0.10 ml, 0.0480 mmol, 1.10 equiv., 0.0096 g in 0.10 ml) was added at -78 °C. After the reaction mixture was stirred at – 78 °C for 30 min, a solution of **74** (0.026 g, 0.0524 mmol, 1.00 equiv.) in 0.40 ml THF was added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. The reaction mixture was then diluted with ether and quenched with water. The phases were separated and the aqu. layer was extracted 3 times with ether. The comb. org. phases were washed with water and brine, were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20)) gave 21 mg (55 %, *E*-isomer only) of the desired product as colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.58 (m, 4H), 7.46 – 7.20 (m, 11H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 5.55 – 5.35 (m, 2H), 4.53 – 4.36 (m, 4H), 4.25 (dd, *J* = 13.5, 6.8 Hz, 1H), 3.82 – 3.74 (m, 3H), 3.78 (s, 2H), 3.71 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.24 (dd, *J* = 8.5, 2.8 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.39 – 2.28 (m, 1H), 2.12 (dd, *J* = 6.4 Hz, 2H), 1.81 (s, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H), 1.12 – 1.01 (m, 6H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H).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1.96
3.94
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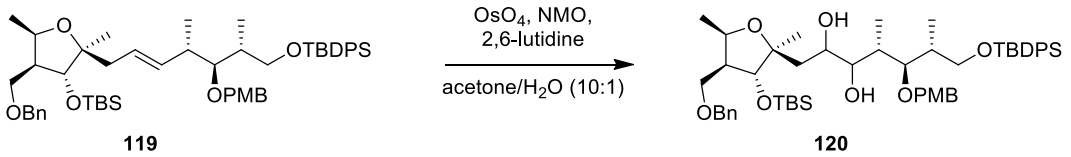
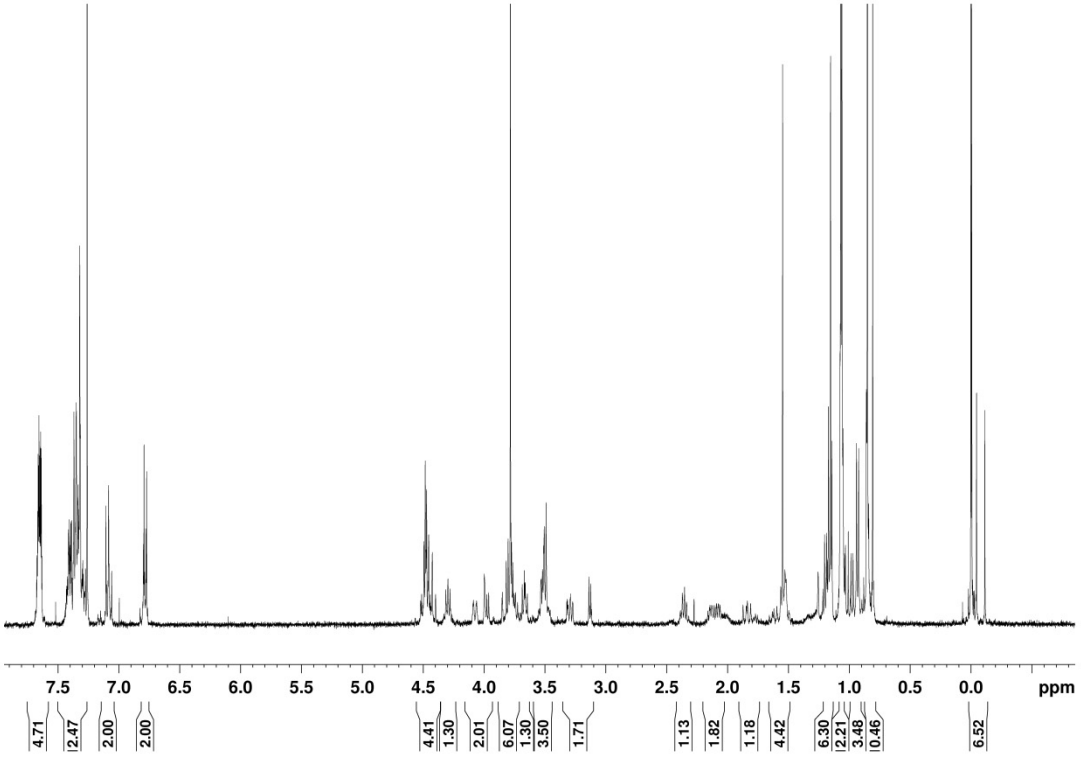
9.16
5.77

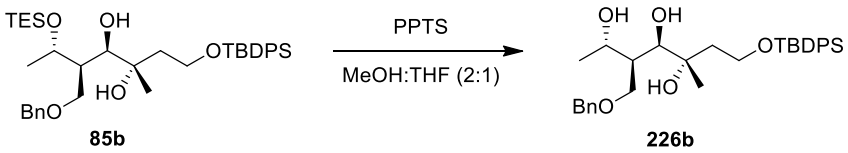



**Diol 120:** To **119** (0.0050 g, 0.0058 mmol, 1.00 equiv.) 0.11 ml of a stock solution containing $OsO_4$ (0.009 ml, 0.001 mmol), NMO (0.010 g, 0.087 mmol) and 2,6-lutidine (0.01 ml, 0.046 mmol) in 1.1 ml acetone/water (10:1) was added at rt. The reaction mixture was stirred at rt for 2 h (TLC and MS showed conversion). Additional 0.11 ml of the stock solution was added and the reaction mixture stirred at rt for 17 h (no full conversion yet). Additional 0.11 ml of the stock solution was added and the reaction mixture was stirred at rt for another 6 h. The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfate solution. The aqueous phase was extracted with EtOAc. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 3.0 mg (57 %) of the desired product as colorless oil (dr ~1:2.5).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H), 7.45 – 7.25 (m, 12H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.51 – 4.36 (m, 4H), 4.34 – 4.24 (m, 1H), 4.12 – 3.92 (m, 2H), 3.78 (s, 3H), 3.88 – 3.71 (m, 3H), 3.72 – 3.61 (m, 1H), 3.51 (dd, *J* = 10.8, 4.9 Hz, 3H), 3.30 (dd, *J* = 14.7, 4.7 Hz, 1H), 3.13 (d, *J* = 6.3 Hz, 1H), 2.44 – 2.28 (m, 1H), 2.22 – 1.94 (m, 1H), 1.91 – 1.77 (m, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.15 (d, *J* = 4.5 Hz, 3H), 1.06 (s, 9H), 0.85 (s, 9H), 0.00 (s, 6H), -0.00 (s, 6H).

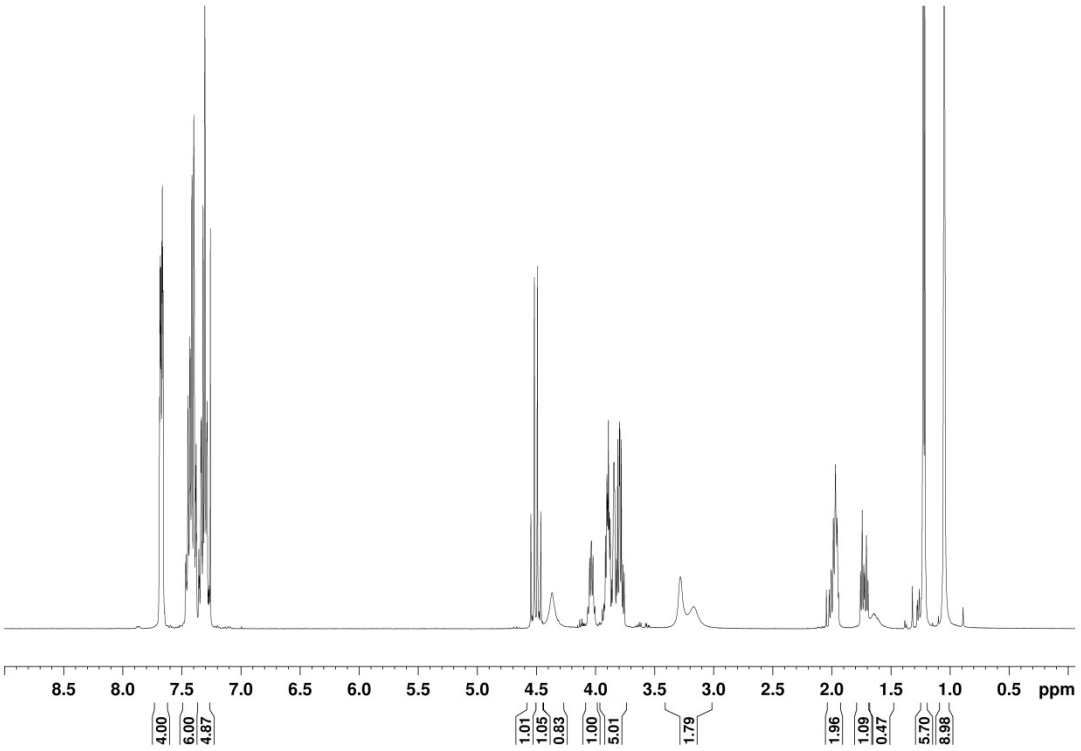


### 5.3.2.8. Synthesis of *Julia* Sulfone 123




**Triol 226b:** To a solution of **85b** (4.48 g, 6.88 mmol, 1.00 equiv.) in MeOH/THF (2:1) (68.0 ml) at rt was added PPTS (1.73 g, 6.88 mmol, 1.00 equiv.) The reaction mixture was stirred at rt for 22 min and was than quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:1) gave 3.54 g (96 %) of **226b** as colorless sticky oil.

**TLC**: $R_f$ = 0.27 (EtOAc/hexane 1:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.71 – 7.64 (m, 4H), 7.49 – 7.37 (m, 6H), 7.37 – 7.26 (m, 5H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.37 (s, 1H), 4.09 – 3.99 (m, 1H), 3.95 – 3.87 (m, 2H), 3.87 – 3.83 (m, 1H), 3.82 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.78 (dd, *J* = 9.7, 4.7 Hz, 1H), 3.28 (s, 1H), 3.17 (s, 1H), 2.08 – 1.91 (m, 2H), 1.73 (dt, *J* = 14.3, 5.5 Hz, 1H), 1.23 (s, 3H), 1.22 (d, *J* = 5.2 Hz, 3H), 1.05 (s, 9H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 137.50, 135.69, 132.99, 132.95, 130.05, 128.68, 128.10, 127.97, 127.94, 75.64, 74.87, 73.77, 69.83, 69.70, 61.50, 44.72, 39.52, 26.94, 22.91, 21.43, 19.15; **IR** (thin film): ν 3413, 3071, 2961, 2930, 2887, 2857, 1463, 1427, 1373, 1105, 1084, 984, 822, 737, 700, 614, 506; **HRMS** (ESI): calculated for $C_{32}H_{44}NaO_5Si$ $[M+Na]^+$: 559.2850, found 559.2841; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +7.93° (c = 1.16 in $CHCl_3$).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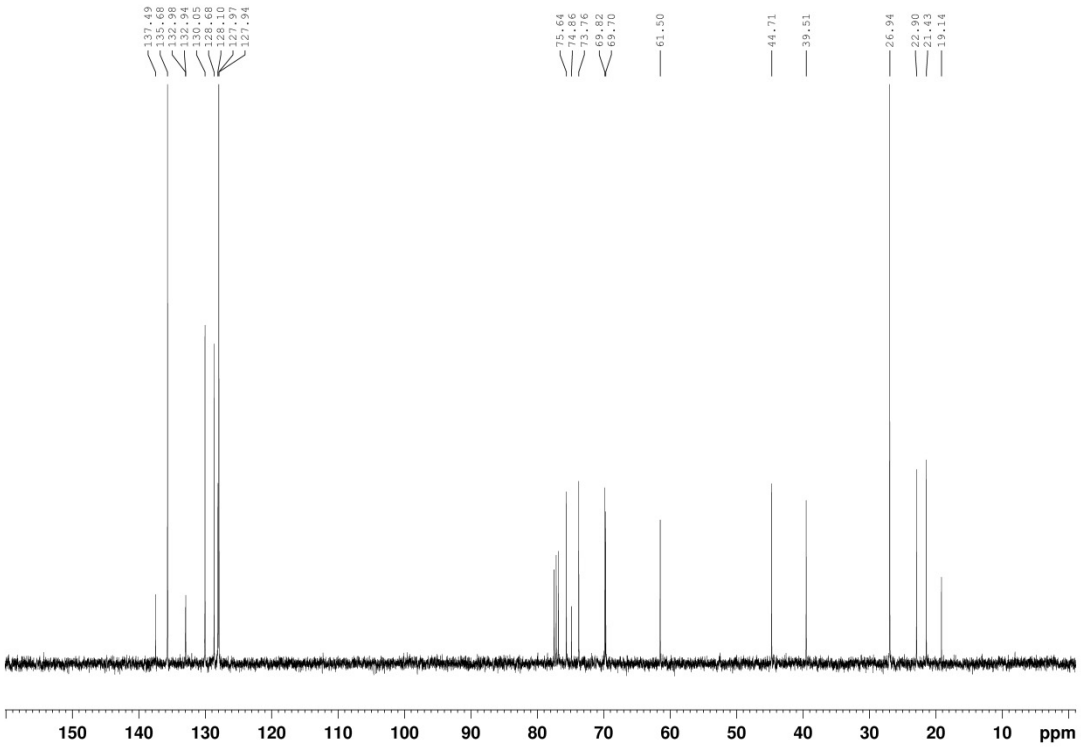
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127.97
127.94
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74.86
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19.14
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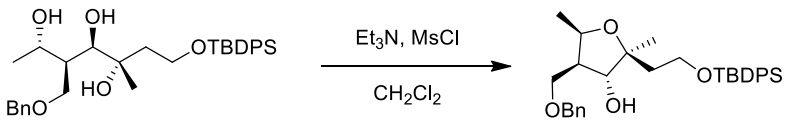
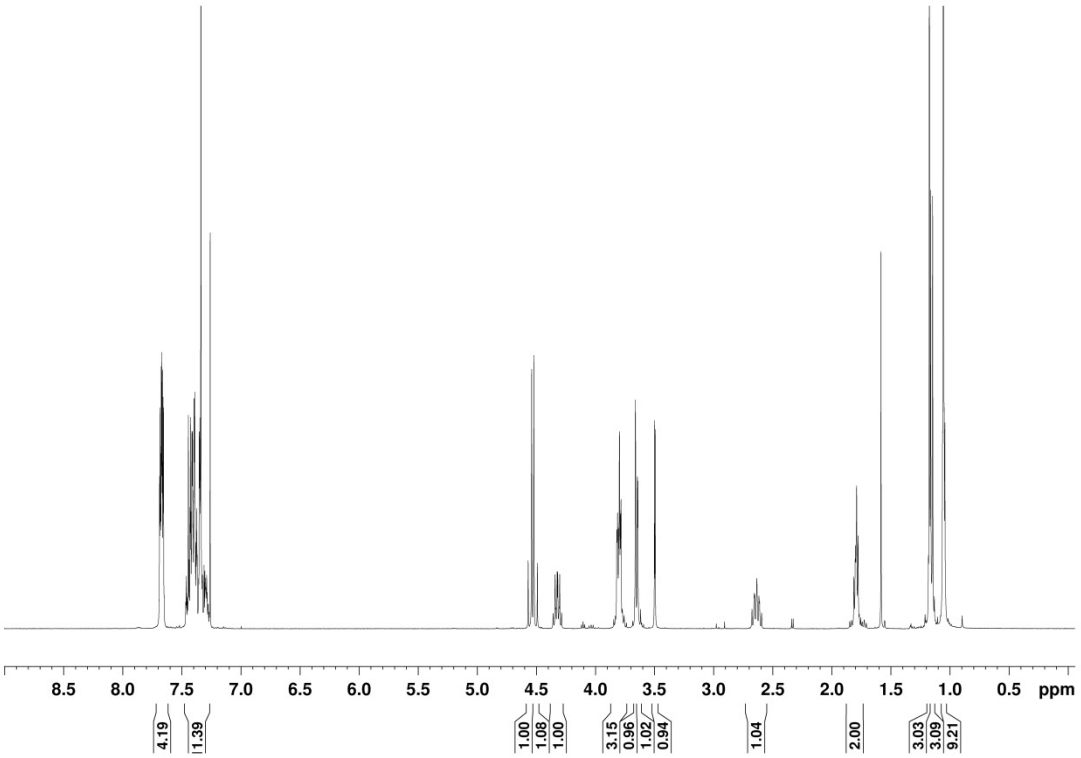



**226b** **121**

**Furan 121:** To a solution of **226b** (3.53 g, 6.57 mmol, 1.00 equiv.) and $NEt_3$ (7.22 ml, 65.76 mmol, 10.0 equiv.) in DCM (105.0 ml) at -40 °C, MsCl (0.561 ml, 7.23 mmol, 1.10 equiv.) was added. The reaction mixture was stirred at -40 °C for 40 min and then quenched by addition of MeOH (24 ml). The reaction mixture was allowed to warm up to rt and then water was added. The layers were separated and the aqu. phase was extracted 3 times with DCM. Thecomb. org. phases were washed with brine, then dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4) gave 3.08 g (90 %, 4% epoxide impurity) of **121** as colorless oil.

**TLC**: $R_f$ = 0.20 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.71 – 7.63 (m, 4H), 7.49 – 7.27 (m, 11H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.32 (dq, *J* = 8.7, 6.6 Hz, 1H), 3.85 – 3.75 (m, 3H), 3.66 (s, 1H), 3.64 (d, *J* = 1.7 Hz, 1H), 3.50 (d, *J* = 2.5 Hz, 1H), 2.71 – 2.58 (m, 1H), 1.86 – 1.71 (m, 2H), 1.17 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ 138.34, 135.71, 135.64, 133.12, 133.00, 130.06, 130.03, 128.56, 127.97, 127.86, 127.81, 81.75, 79.01, 73.60, 72.11, 69.78, 61.54, 46.91, 43.72, 26.96, 19.20, 18.52, 18.02; **IR** (thin film): ν 3457, 3071, 3032, 2959, 2930, 2883, 2857, 1472, 1454, 1428, 1379, 1363, 1309, 1264, 1205, 1107, 1028, 931, 822, 735, 704, 314, 506; **HRMS** (ESI): calculated for $C_{32}H_{43}O_4Si$ $[M+H]^+$: 519.2925, found 519.2928; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +12.27° (c = 0.97 in $CHCl_3$).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1.08
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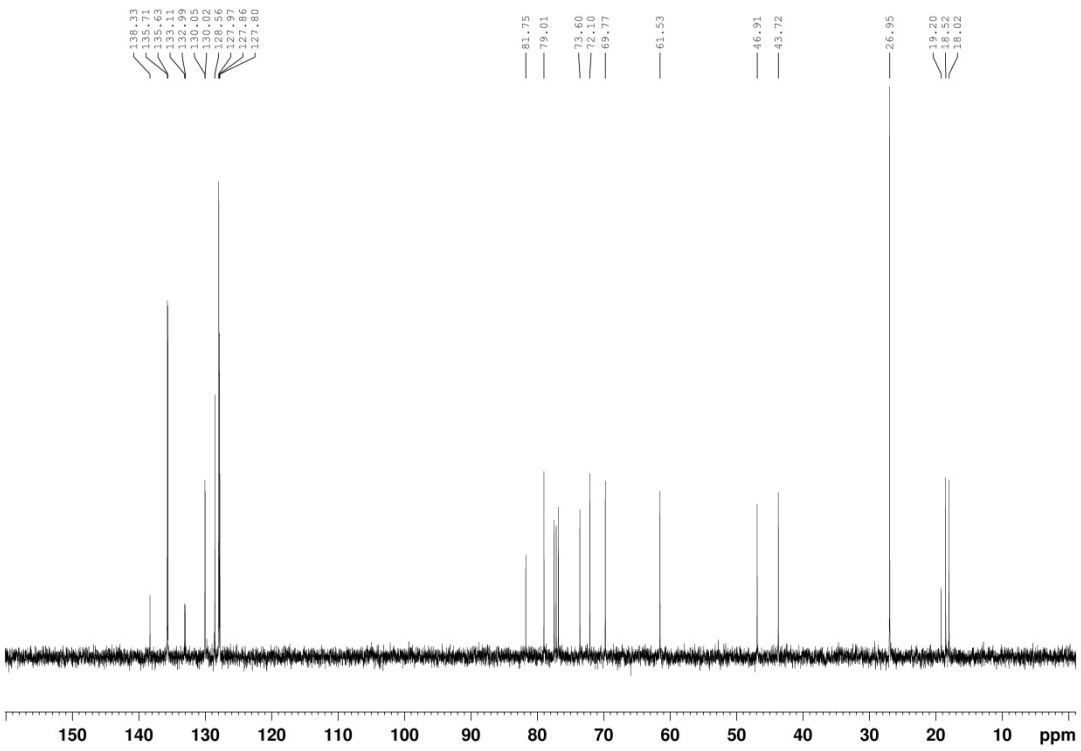
3.03
3.09
9.21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18.52
18.02
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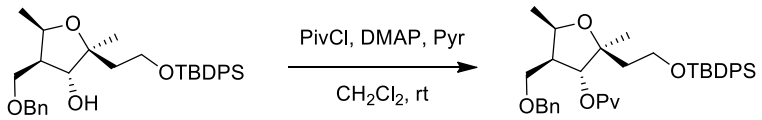
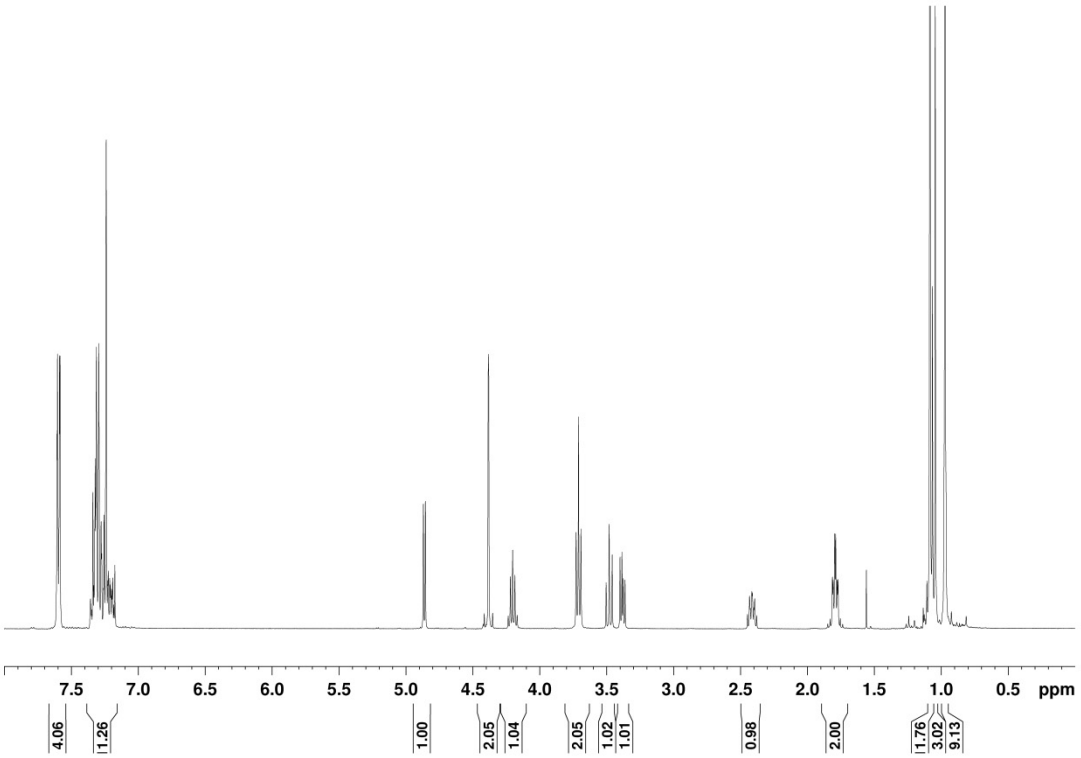



**121** **122**

**Ester 122:** To a solution of **121** (3.08 g, 5.94 mmol, 1.00 equiv.) and DMAP (0.36 g, 2.97 mmol, 0.50 equiv.) in $CH_2Cl_2$ (50.0 ml) at 0 °C was added pyridine (5.28 ml, 65.31 mmol, 11.0 equiv.) and pivaloyl chloride (7.31 ml, 59.37 mmol, 10.00 equiv.). The reaction mixture was allowed to warm up to rt and stirred for 3 d. The reaction mixture was cooled to 0 °C and quenched by addition of 40 ml absolute EtOH. After 10 min aqu. sat. $NaHCO_3$ was added. The phases were separated and the aqu. phase extracted with $CH_2Cl_2$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 3.43 g (96 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.62 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.66 – 7.55 (m, 4H), 7.39 – 7.14 (m, 11H), 4.86 (d, *J* = 6.1 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.20 (p, *J* = 6.6 Hz, 1H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.48 (dd, *J* = 9.1 Hz, 1H), 3.38 (dd, *J* = 9.4, 5.7 Hz, 1H), 2.46 – 2.37 (m, 1H), 1.86 – 1.73 (m, 2H), 1.09 (s, 9H), 1.08 (d, *J* = 7.8 Hz, 3H), 1.05 (s, 3H), 0.97 (s, 9H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 177.64, 138.15, 135.70, 134.04, 134.02, 129.64, 128.48, 127.89, 127.76, 127.73, 81.36, 80.06, 73.41, 72.74, 68.32, 60.34, 48.02, 43.84, 38.84, 27.17, 26.97, 20.53, 19.22, 16.89; **IR** (thin film): ν 3068, 2957, 2931, 2857, 2364, 2335, 1730, 1472, 1455, 1428, 1395, 1362, 1282, 1152, 1111, 1086, 1029, 1006, 822, 737, 613, 501; **HRMS** (ESI): calculated for $C_{37}H_{51}O_5Si$ $[M+H]^+$: 603.3500, found 603.3494; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +9.10° (c = 1.00 in $CHCl_3$).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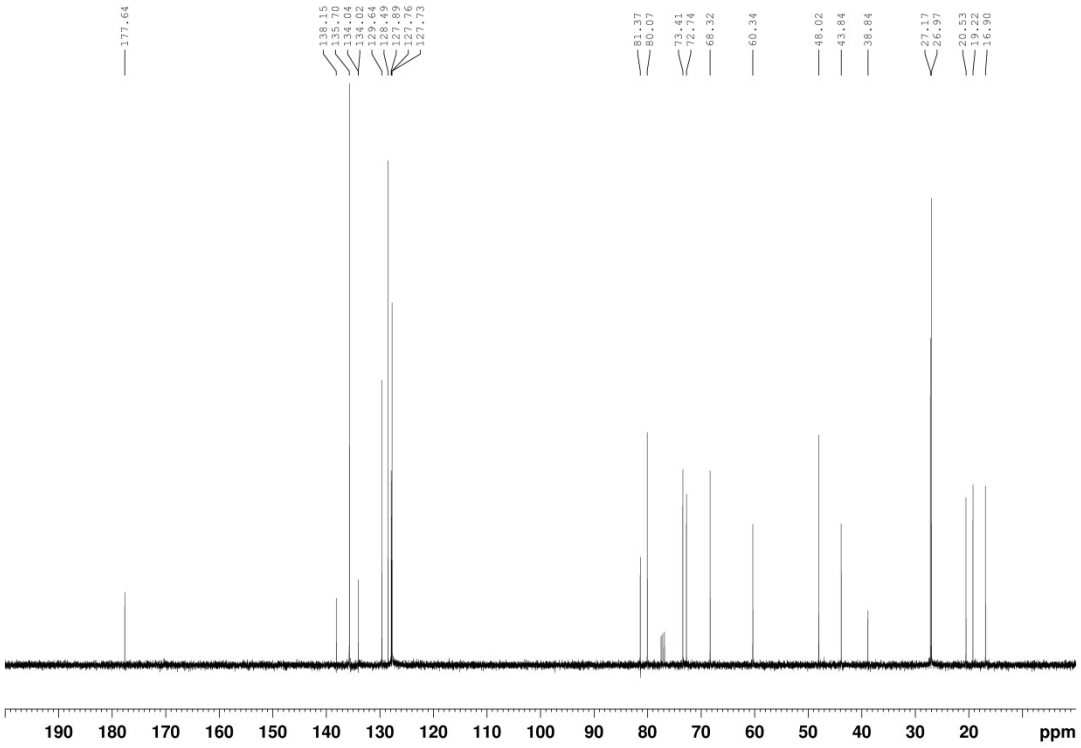
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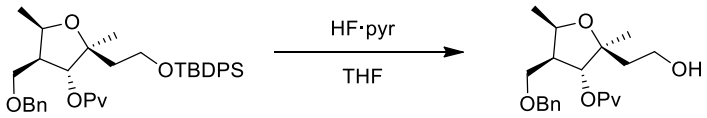
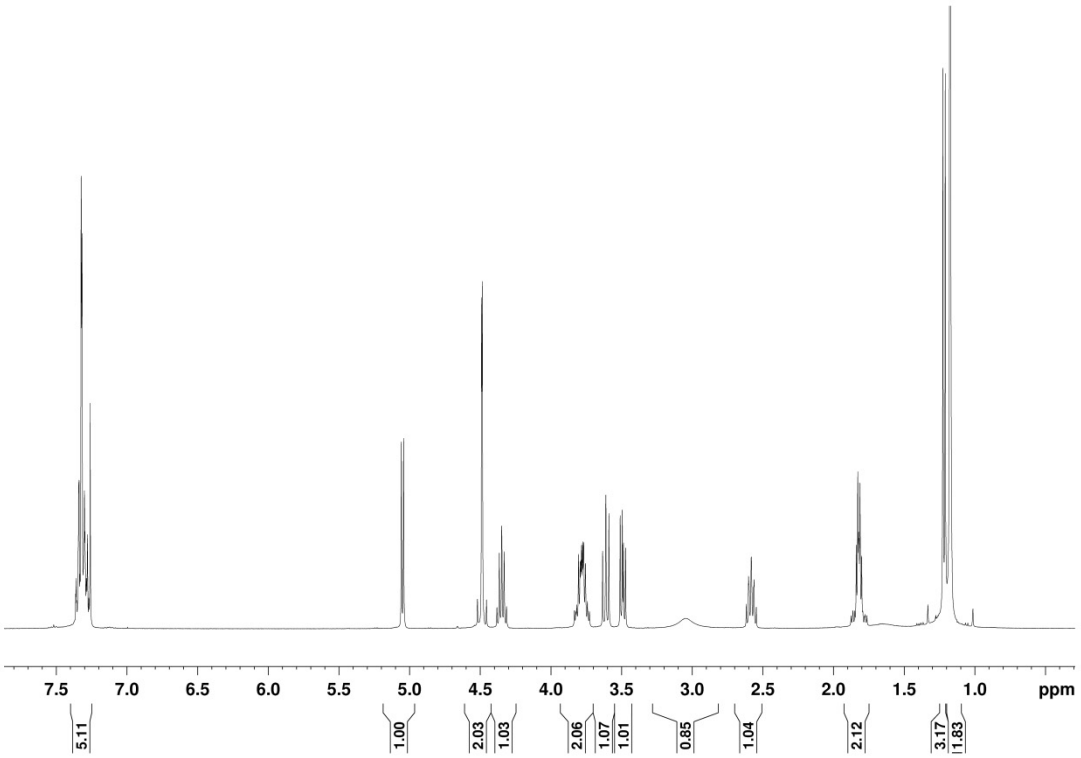



**122** **135**

**Alcohol 135:** To a solution of **122** (3.43 g, 5.69 mmol, 1.00 equiv.) in THF (56.80 ml) at 0 °C was added HF·pyr (6.96 ml, 70 % HF in pyridine). The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm up to rt. The reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled with ice and then quenched by addition of aqu. sat. $KHCO_3$ (210 ml). The phases were separated and the aqueous phase was extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:2)) gave 1.87 g (90 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.39 (EtOAc/hexane 1:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 5.05 (d, *J* = 6.4 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.35 (p, *J* = 6.7 Hz, 1H), 3.86 – 3.71 (m, 2H), 3.61 (dd, *J* = 9.1, 8.5 Hz, 1H), 3.49 (dd, *J* = 9.4, 6.0 Hz, 1H), 3.05 (s, 1H), 2.64 – 2.52 (m, 1H), 1.90 – 1.75 (m, 2H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 12H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 178.11, 137.98, 128.52, 127.93, 127.84, 83.43, 79.53, 73.49, 73.14, 68.11, 59.27, 47.07, 41.54, 38.86, 27.16, 20.24, 16.86; **IR** (thin film): ν 3482, 2975, 2936, 2871, 1729, 1480, 1455, 1397, 1379, 1368, 1283, 1153, 1098, 1068, 1028, 1000, 739, 699, 599; **HRMS** (ESI): calculated for $C_{21}H_{33}O_5$ $[M+H]^+$: 365.2323, found 365.2328; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +31.28° (c = 1.00 in $CHCl_3$).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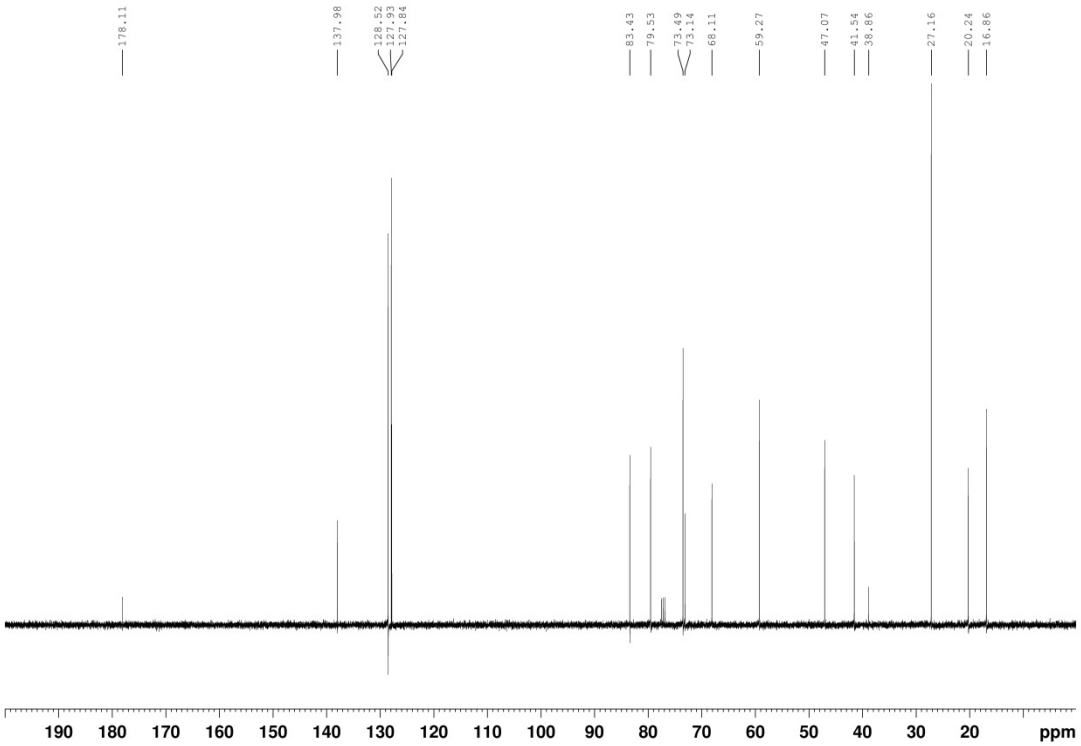
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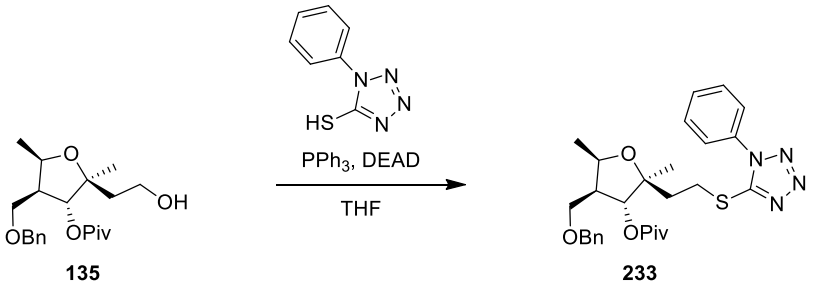
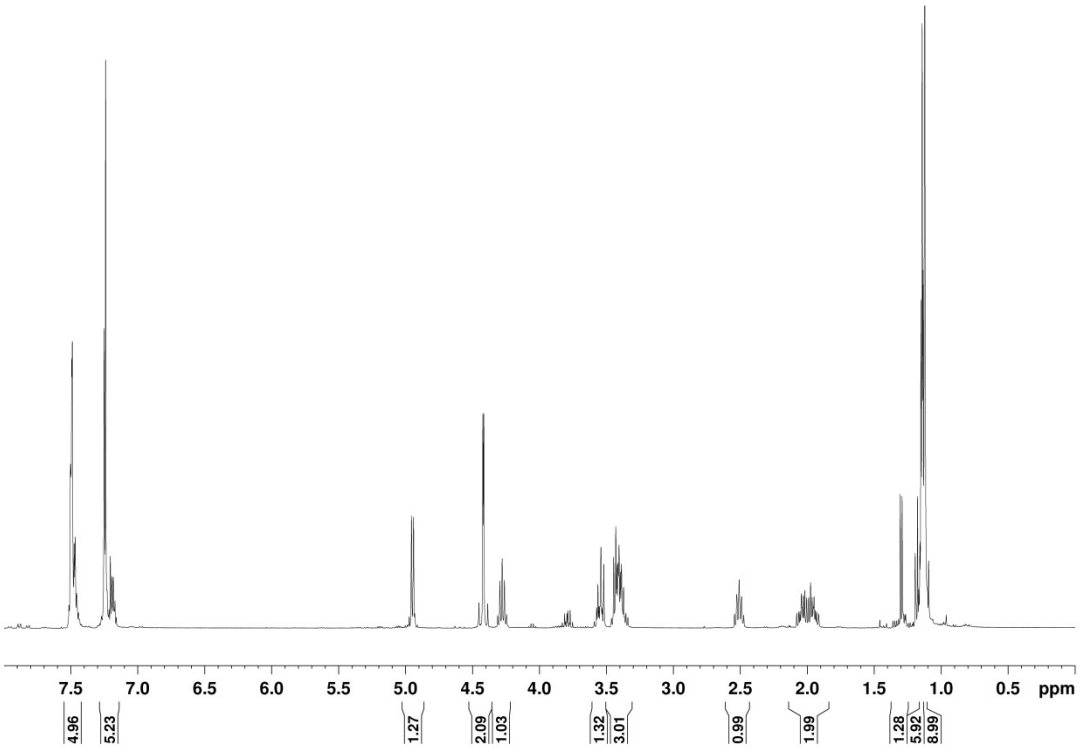
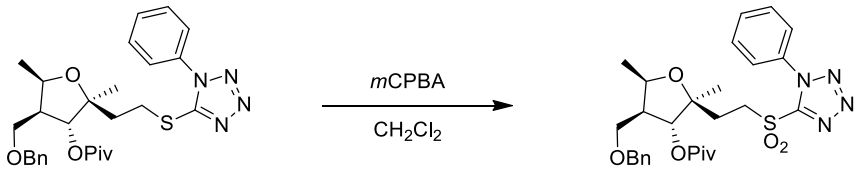
ppm




**Sulfide 233:** To a solution of **135** (0.100 g, 0.274 mmol, 1.00 equiv.) in THF (2.74 ml), 1-phenyl-1H-tetrazole-5-thiol (0.0978 g, 0.549 mmol, 2.00 equiv.) and triphenylphosphine (0.108 g, 0.411 mmol, 1.50 equiv.) were added in one portion at rt. The reaction mixture was then cooled to 0 °C and afterwards DEAD (0.0756 ml, 0.480 mmol, 1.75 equiv.) was added drop wise. The reaction mixture was allowed to warm up to rt and stirred for 140 min. The reaction was then quenched by addition of aqu. sat. $NaHCO_3$. The phases were separated and the aqu. phase extracted 3x with $Et_2O$. The comb. org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 127 mg (88%) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.46 (m, 5H), 7.39 – 7.17 (m, 5H), 5.00 (d, *J* = 6.2 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.33 (qd, *J* = 6.7 Hz, 1H), 3.64 – 3.56 (m, 1H), 3.53 – 3.39 (m, 3H), 2.63 – 2.50 (m, 1H), 2.16 – 1.94 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 9H).

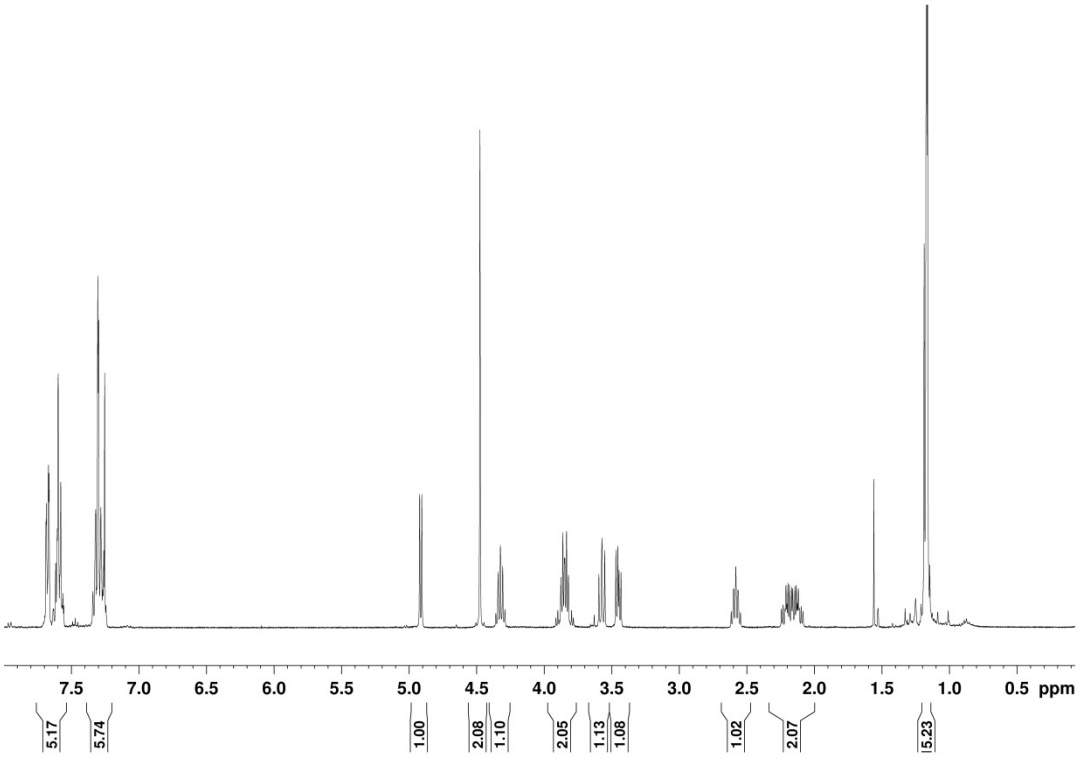




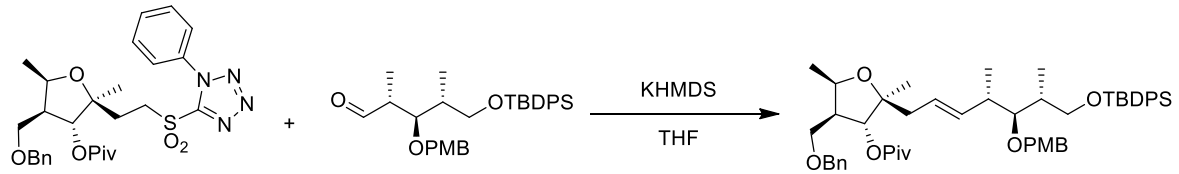

**233** **123**

**Sulfone 123:** To a solution of **233** (0.127 g, 0.242 mmol, 1.00 equiv.) in 2.40 ml $CH_2Cl_2$, *m*CPBA (0.146 g, 0.847 mmol, 3.50 equiv.) was added in one portion at rt and the reaction mixture was stirred over the weekend. The reaction mixture was diluted with EtOAc, washed with aqu. sat. $Na_2SO_3$ and aqu. sat. $NaHCO_3$. The org. phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 107 mg (79 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.64 (m, 2H), 7.65 – 7.55 (m, 3H), 7.36 – 7.24 (m, 5H), 4.92 (d, *J* = 6.4 Hz, 1H), 4.48 (s, 2H), 4.33 (qd, *J* = 6.7 Hz, 1H), 3.94 – 3.75 (m, 2H), 3.58 (dd, *J* = 8.2 Hz, 1H), 3.45 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.27 – 2.07 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 9H), 1.17 (s, 3H).



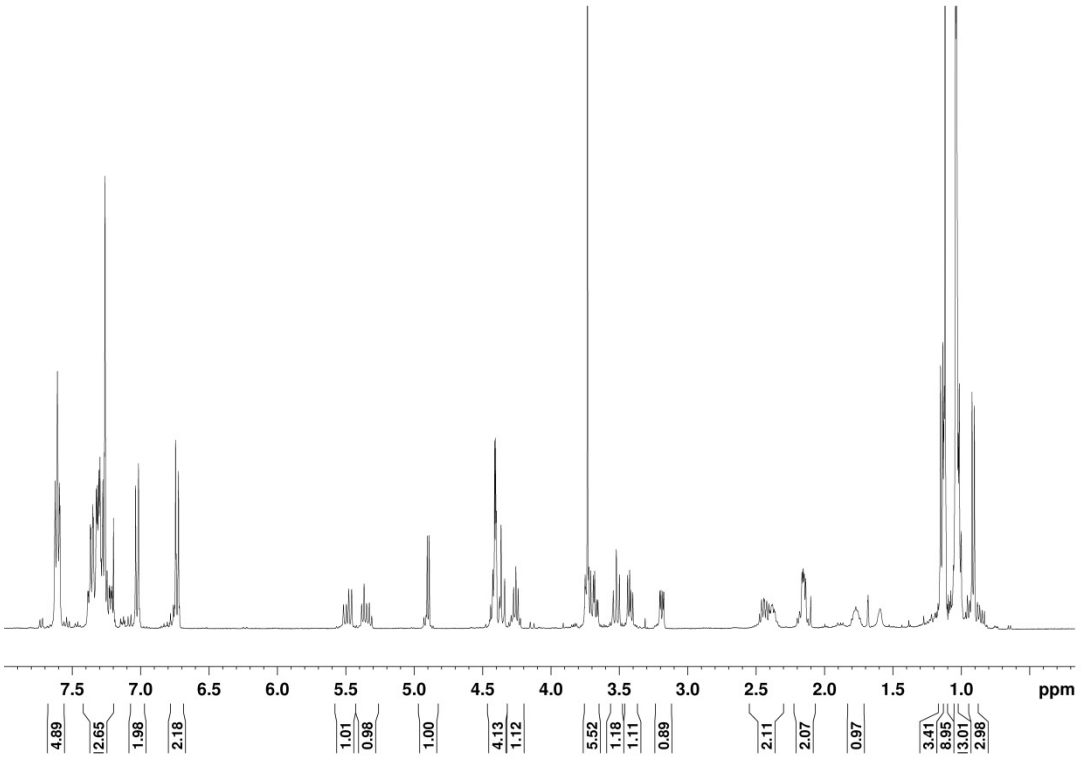
### 5.3.2.9. Second Fragment Assembly via *Julia* Olefination




**123** **74** **124**

**Alkene 124:** To a solution of **123** (0.016 g, 0.0287 mmol, 1.00 equiv.) in 0.20 ml DME, KHMDS (0.1 ml, 0.0316 mmol, 1.10 equiv., 0.063 g in 1.00 ml) was added at -78 °C. After the reaction mixture was stirred at – 78 °C for 30 min, a solution of **74** (0.0174g, 0.0345 mmol, 1.20 equiv.) in 0.20 ml DME was added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature and stirred for 5.5 h. The reaction mixture was quenched by addition of aqu. sat. $NH_4Cl$ and ether was added. The phases were separated and the aqu. layer was extracted 3 times with ether. The comb. org. phases were washed with brine, were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:8)) gave 14.5 mg (60 %, *E/Z* = 11:1) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 5H), 7.47 – 7.25 (m, 10H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.54 (dd, *J* = 15.5, 8.5 Hz, 1H), 5.45 – 5.35 (m, 1H), 4.95 (d, *J* = 5.8 Hz, 1H), 4.53 – 4.36 (m, 4H), 4.31 (qd, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 3.82 – 3.75 (m, 1H), 3.72 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.57 (dd, *J* = 9.0 Hz, 1H), 3.47 (dd, *J* = 9.4, 5.8 Hz, 1H), 3.24 (dd, *J* = 8.3, 3.3 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.47 – 2.39 (m, 1H), 2.27 – 2.16 (m, 2H), 1.87 – 1.77 (m, 1H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.17 (s, 9H), 1.11 – 1.05 (m, 15H), 0.97 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 177.55, 159.05, 138.18, 136.18, 135.93, 135.88, 135.75, 134.14, 134.03, 131.40, 129.64, 129.62, 129.32, 128.49, 127.90, 127.76, 127.73, 127.67, 125.02, 113.73, 84.69, 82.55, 79.30, 74.51, 73.41, 72.81, 68.35, 65.85, 55.38, 48.32, 44.61, 39.87, 39.17, 38.84, 27.22, 27.15, 27.07, 20.53, 19.47, 18.96, 16.88, 14.66.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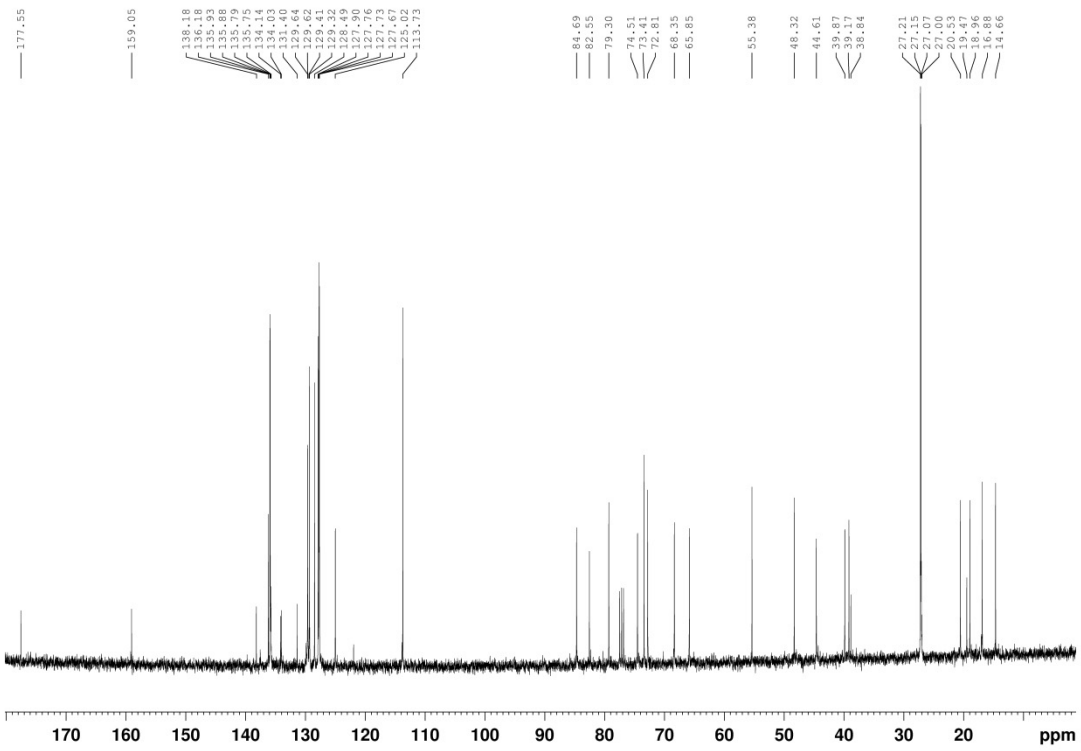
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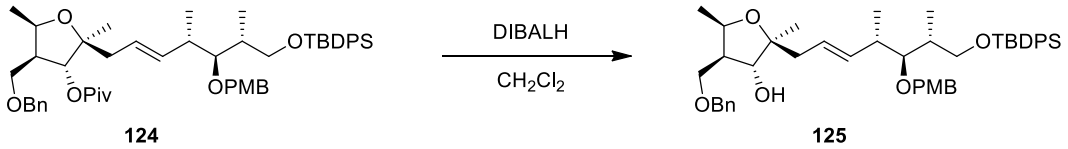
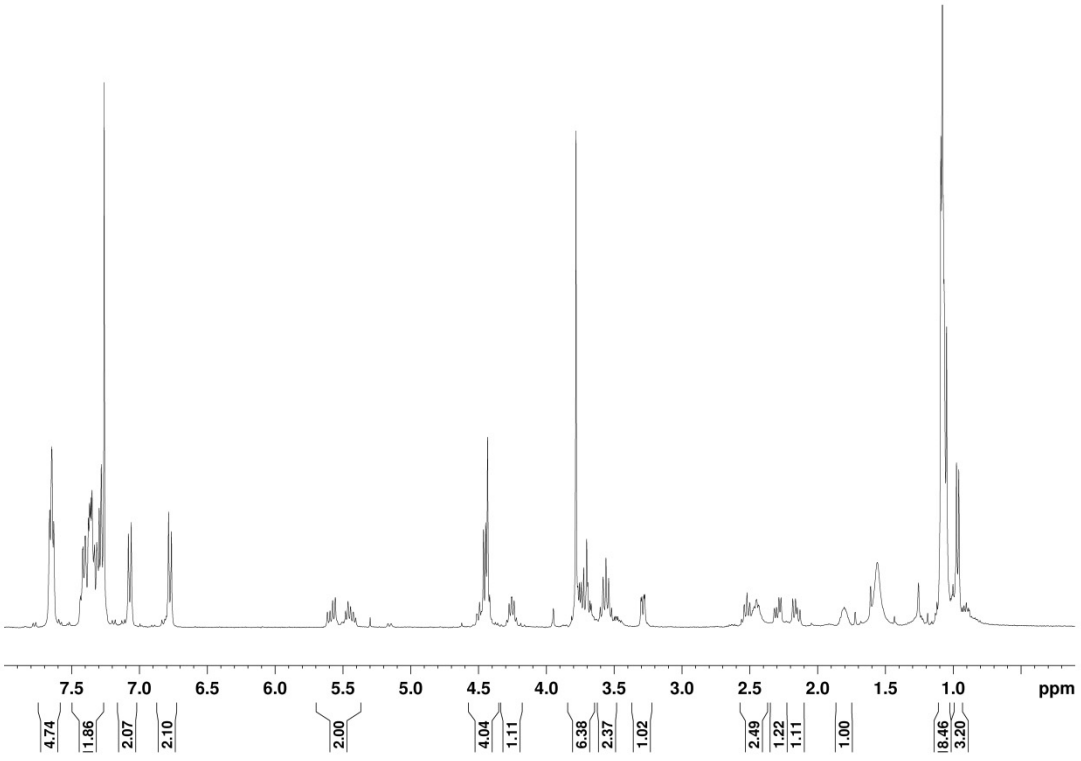
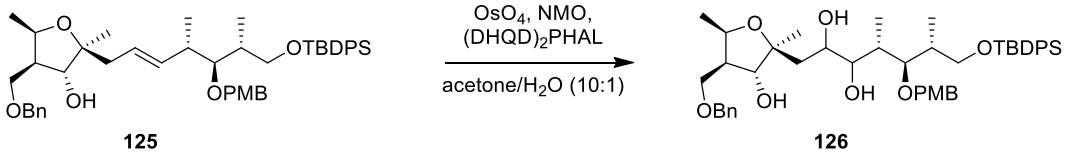



**124** **125**

**Alkohol 125: 124** (0.053g, 0.0635 mmol, 1.00 equiv.) was dissolved in 1.00 mL of $CH_2Cl_2$, cooled to –78 °C and DIBAL (0.063 mL, 0.0762 mmol, 1.20 equiv., 1.2 M in toluene) was added drop wise. After 1.5 h at -78 °C the reaction mixture was quenched by addition of MeOH followed by aqu. Rochelle. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 28.6 mg (60 %) of the desired product as colorless oil and 19.7 mg of a mixture containing mostly the hemiacetal. Hydrolysis of the hemiacetal with HCl to the desired product and a second chromatography gave additional 8.5 mg (17 %) of the desired product.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.57 (m, 5H), 7.49 – 7.22 (m, 10H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.59 (dd, *J* = 15.5, 7.7 Hz, 1H), 5.50 – 5.38 (m, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.43 (s, 2H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.26 (dq, *J* = 13.2, 6.6 Hz, 1H), 3.78 (s, 3H), 3.82 – 3.66 (m, 4H), 3.62 – 3.51 (m, 2H), 3.29 (dd, *J* = 8.6, 2.7 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.49 – 2.41 (m, 1H), 2.29 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.16 (dd, *J* = 13.3, 8.0 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.08 (s, 9H), 1.11 – 1.03 (m, 9H), 0.97 (d, *J* = 6.9 Hz, 3H).





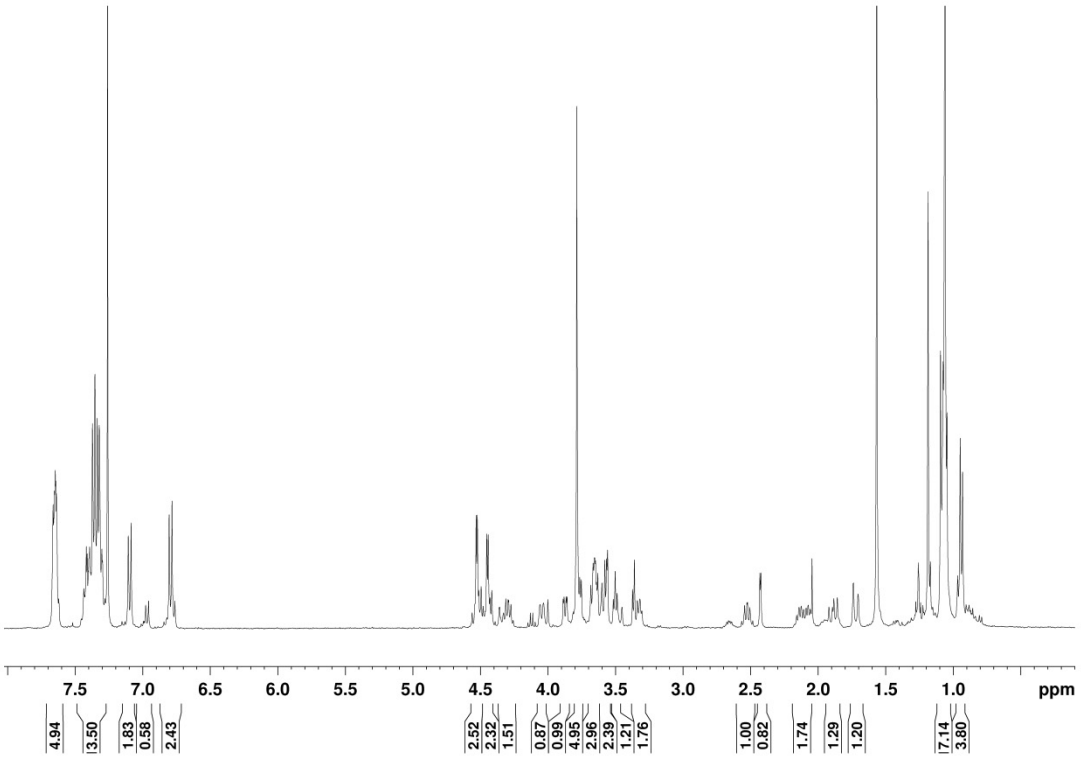

**125** **126**

**Triol 126:** To **125** (0.0050 g, 0.0067 mmol, 1.00 equiv.) at 0°C was added 0.10 ml of a cooled stock solution containing $OsO_4$, NMO and $(DHQD)_2PHAL$. The reaction mixture was at 0 °C for 4 d. The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfate solution. The aqueous phase was extracted with EtOAc. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:1)) gave 4.2 mg (89%) of the desired product as colorless oil (dr ~1:5.4).

Stock solution: 0.04 ml $OsO_4$, 140 mg NMO, 23 mg $(DHQD)_2PHAL$ in 10 ml Aceton/water (5:1)

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 5H), 7.47 – 7.26 (m, 11H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.59 – 4.49 (m, 2H), 4.49 – 4.41 (m, 2H), 4.29 (dq, *J* = 13.3, 6.6 Hz, 1H), 3.87 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.79 (s, 3H), 3.83 – 3.74 (m, 2H), 3.70 – 3.62 (m, 2H), 3.58 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.50 (dd, *J* = 5.7 Hz, 1H), 3.35 (dd, *J* = 15.0, 6.5 Hz, 2H), 2.59 – 2.47 (m, 1H), 2.43 (d, *J* = 3.1 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.89 (dd, *J* = 14.5, 10.3 Hz, 1H), 1.72 (dd, *J* = 14.6, 1.8 Hz, 1H), 1.19 (s, 3H), 1.10 – 1.04 (m, 6H), 1.06 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H).

**Minor Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 5H), 7.47 – 7.26 (m, 11H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.59 – 4.49 (m, 2H), 4.49 – 4.41 (m, 2H), 4.29 (dq, *J* = 13.3, 6.6 Hz, 1H), 3.87 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.79 (s, 3H), 3.83 – 3.74 (m, 2H), 3.70 – 3.62 (m, 2H), 3.58 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.50 (dd, *J* = 5.7 Hz, 1H), 3.35 (dd, *J* = 15.0, 6.5 Hz, 2H), 2.74 – 2.59 (m, 1H), 2.43 (d, *J* = 3.1 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.89 (dd, *J* = 14.5, 10.3 Hz, 1H), 1.72 (dd, *J* = 14.6, 1.8 Hz, 1H), 1.19 (s, 3H), 1.10 – 1.04 (m, 6H), 1.06 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H).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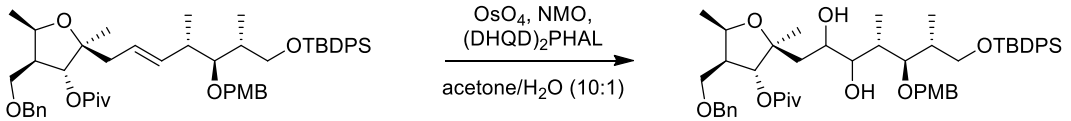
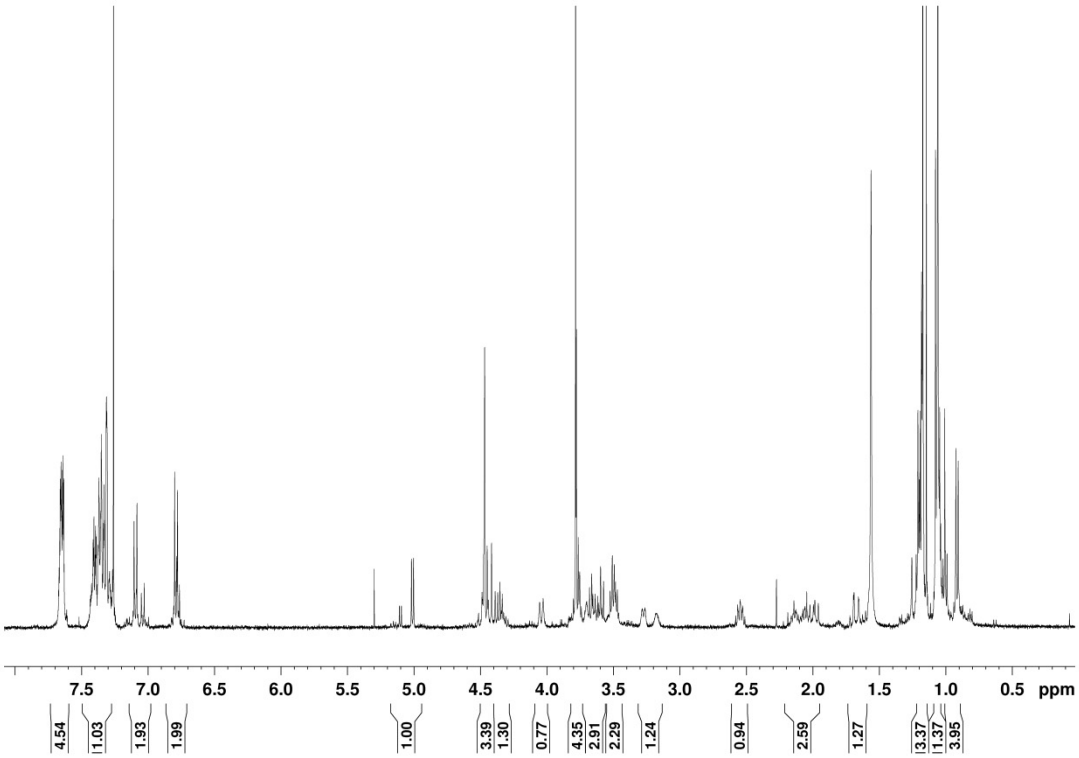



**Diol 127:** To **124** (0.0050 g, 0.006 mmol, 1.00 equiv.) at 0°C was added 0.10 ml of a cooled stock solution containing $OsO_4$, NMO and $(DHQD)_2PHAL$. After warming up to rt, the reaction mixture was stirred at rt for 2 d. The reaction mixture was then quenched by addition of aqu. sat. sodiumthiosulfate solution. The aqueous phase was extracted with EtOAc. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:3)) gave 3.7 mg (71%) of the desired product as colorless oil (dr ~1:3.2).

Stock solution: 0.04 ml $OsO_4$, 140 mg NMO, 23 mg $(DHQD)_2PHAL$ in 10 ml Aceton/water (5:1)

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.58 (m, 5H), 7.49 – 7.20 (m, 10H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.01 (d, *J* = 6.3 Hz, 1H), 4.57 – 4.25 (m, 5H), 4.04 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.81 – 3.75 (m, 2H), 3.72 – 3.57 (m, 3H), 3.54 – 3.46 (m, 2H), 3.27 (d, *J* = 8.1 Hz, 1H), 3.18 (s, 1H), 2.60 – 2.49 (m, 1H), 2.22 – 1.92 (m, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.18 (s, 3H), 1.17 (s, 9H), 1.08 – 1.04 (m, 3H), 1.06 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H).

**Minor Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.58 (m, 5H), 7.49 – 7.20 (m, 10H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.10 (d, *J* = 6.1 Hz, 1H), 4.57 – 4.25 (m, 5H), 4.04 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.81 – 3.75 (m, 2H), 3.72 – 3.57 (m, 3H), 3.54 – 3.46 (m, 2H), 3.27 (d, *J* = 8.1 Hz, 1H), 3.18 (s, 1H), 2.60 – 2.49 (m, 1H), 2.22 – 1.92 (m, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.18 (s, 3H), 1.17 (s, 9H), 1.08 – 1.04 (m, 3H), 1.06 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H).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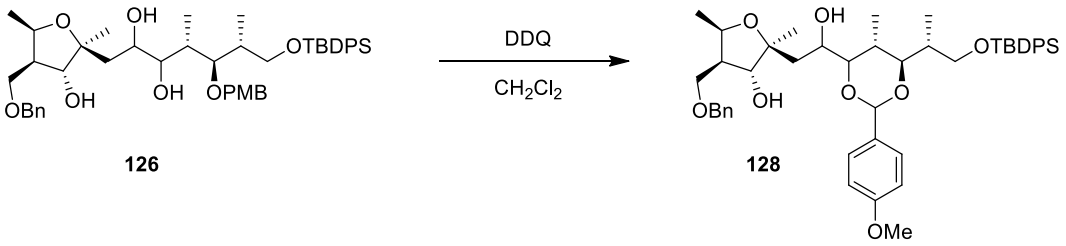
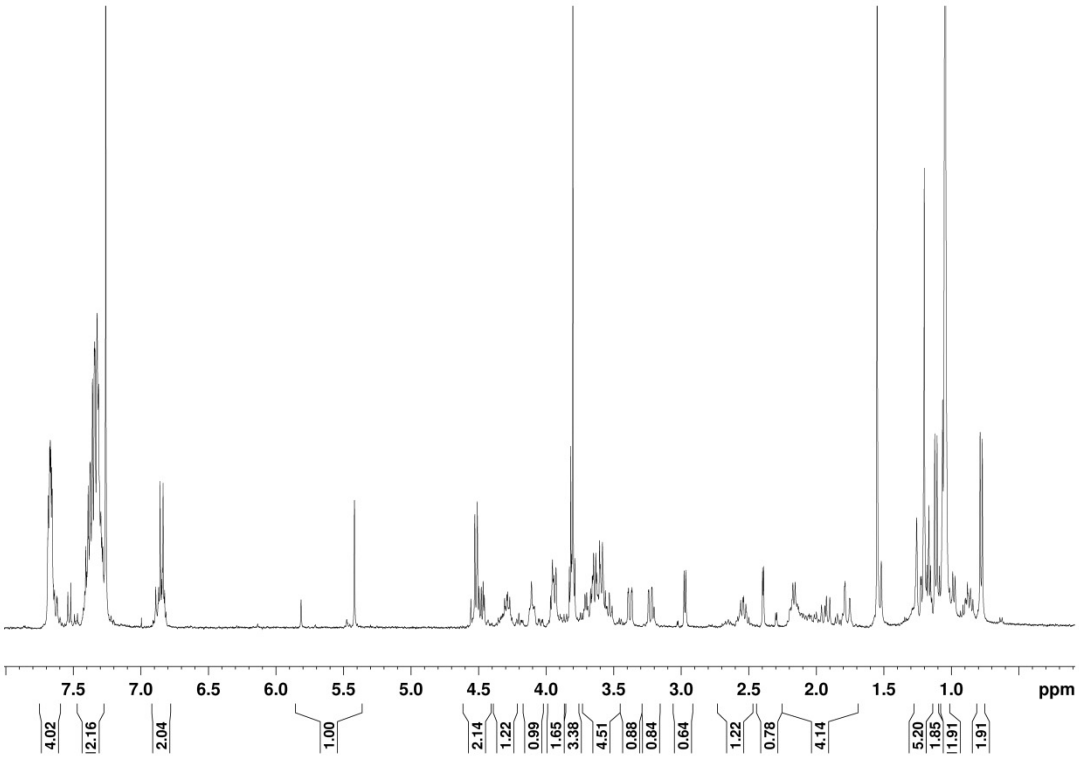



**126** **128**

**Acetal 128:** To a solution of **126** (0.0032 g, 0.0041 mmol, 1.00 equiv.) in 0.20 mL of $CH_2Cl_2$ at 0 °C was added a solution of DDQ (0.0011 g, 0.0049 mmol) in 0.05 mL of $CH_2Cl_2$ (stock solution). After stirring for 1 h at 0 °C TLC and MS showed conversion to the desired product but it was not complete. Therefore additional DDQ was added (multiple times) and the reaction mixture stirred for another 2 h at 0 °C. The reaction mixture was quenched with aqu. sat. $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:2) gave 1.9 mg (59%) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 5H), 7.42 – 7.28 (m, 12H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.42 (s, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.29 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.99 – 3.91 (m, 2H), 3.84 – 3.78 (m, 1H), 3.80 (s, 3H), 3.73 – 3.50 (m, 3H), 3.38 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.23 (dd, *J* = 9.9, 1.3 Hz, 1H), 2.97 (d, *J* = 5.1 Hz, 1H), 2.54 (td, *J* = 15.4, 8.8 Hz, 1H), 2.39 (d, *J* = 3.0 Hz, 1H), 2.26 – 1.88 (m, 2H), 1.77 (d, *J* = 12.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 12H), 0.78 (d, *J* = 6.6 Hz, 3H).

**Minor Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 5H), 7.42 – 7.28 (m, 12H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.81 (s, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.29 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.99 – 3.91 (m, 2H), 3.84 – 3.78 (m, 1H), 3.80 (s, 3H), 3.73 – 3.50 (m, 3H), 3.38 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.23 (dd, *J* = 9.9, 1.3 Hz, 1H), 3.02 (s, 1H), 2.73 – 2.60 (m, 1H), 2.30 (d, *J* = 3.3 Hz, 1H), 2.26 – 1.88 (m, 2H), 1.77 (d, *J* = 12.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 12H), 0.78 (d, *J* = 6.6 Hz, 3H).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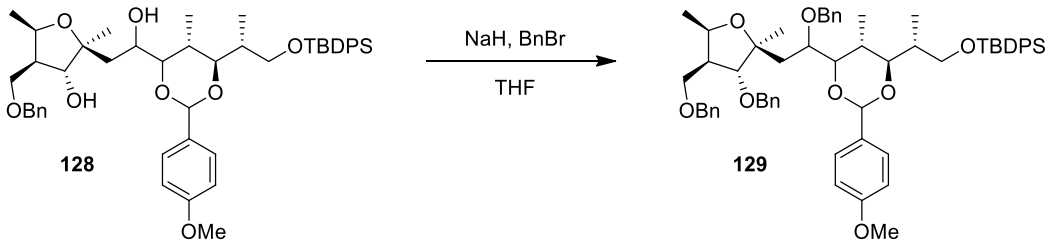
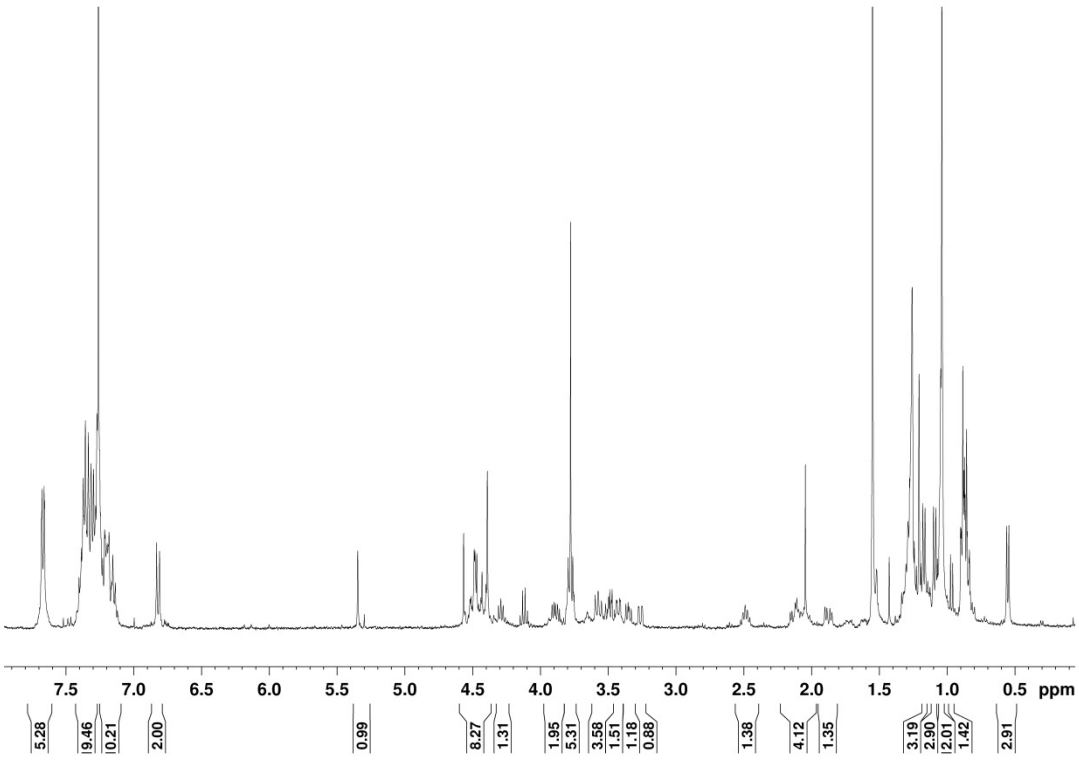
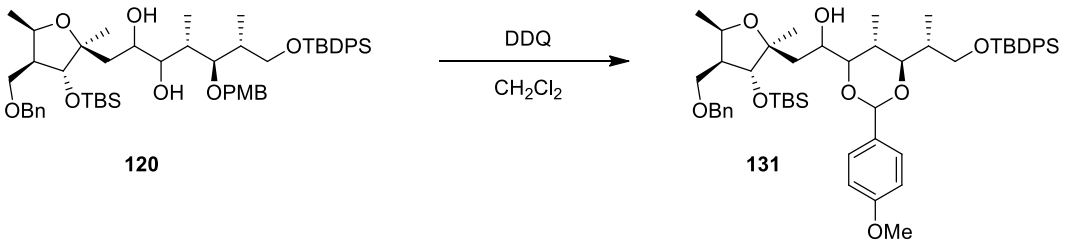



**Bis Benzyl ether 129:** To a solution of **128** (0.004 g, 0.0051 mmol, 1.00 equiv.) in 0.20 mL of THF at 0 °C was added NaH (0.0007 g, 0.0179 mmol, 3.50 equiv. After stirring for 10 min BnBr (0.001 ml, 0.0112 mmol, 2.20 equiv.) was added at 0 °C and then the reaction mixture was allowed to warm up to rt and stirred for 14 h. The reaction mixture was quenched with aqu. sat. $NaHCO_3$. The resulting mixture was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:6) gave 4 mg (81%) of the desired product as colorless oil.

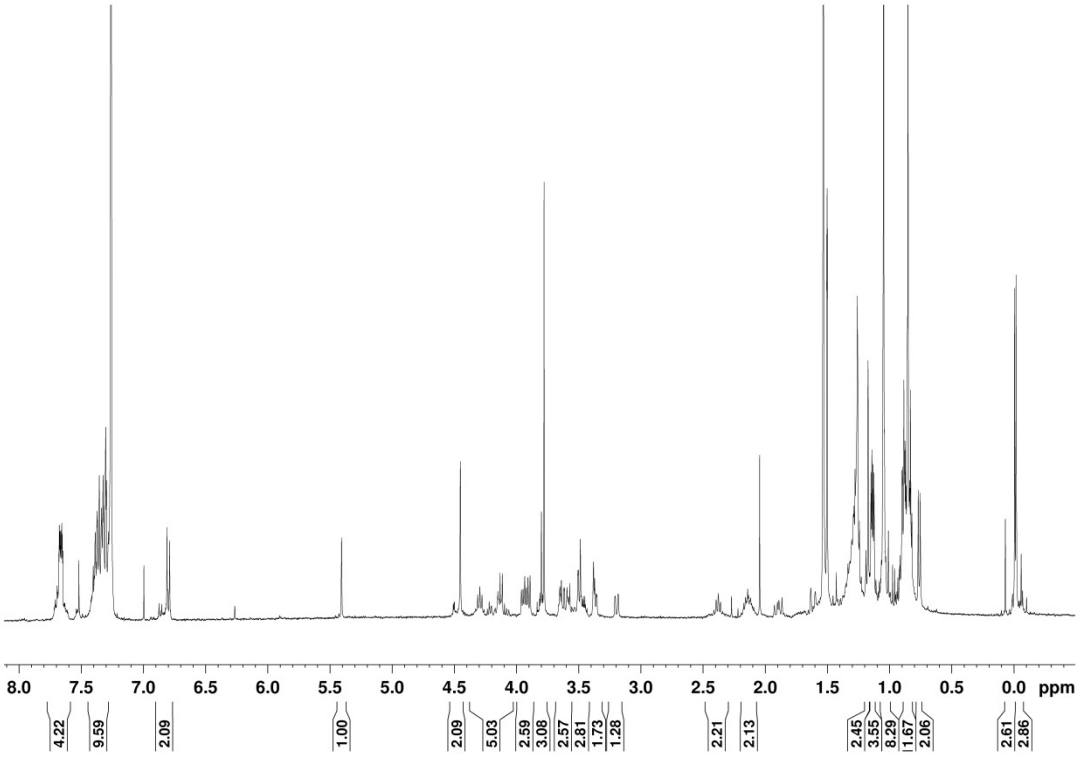
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 5H), 7.43 – 7.10 (m, 22H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 1H), 4.58 – 4.37 (m, 4H), 4.32 – 4.26 (m, 1H), 3.99 – 3.83 (m, 1H), 3.78 (s, 3H), 3.85 – 3.71 (m, 1H), 3.61 – 3.40 (m, 5H), 3.38 – 3.32 (m, 1H), 3.27 (d, *J* = 10.2 Hz, 1H), 2.57 – 2.41 (m, 1H), 2.19 – 1.97 (m, 4H), 1.88 (dd, *J* = 14.7, 5.6 Hz, 1H), 1.21 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H), 0.55 (d, *J* = 6.5 Hz, 3H).

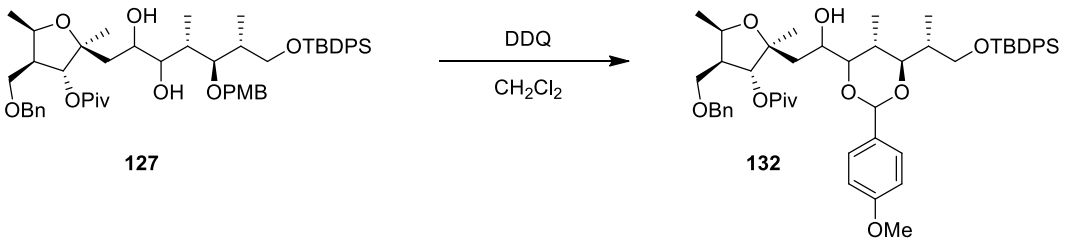





**Acetal 131:** To a solution of **120** (0.001 g, 0.0011 mmol, 1.00 equiv.) in 0.05 mL of $CH_2Cl_2$ at 0 °C was added a solution of DDQ (0.0003 g, 0.0013 mmol) in 0.01 mL of $CH_2Cl_2$. After stirring for 1 h at 0 °C TLC and MS showed conversion to the desired product but it was not complete. Therefore additional DDQ was added and the reaction mixture stirred for another 30 min at 0 °C. The reaction mixture was quenched with aqu. sat. $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:8) gave 0.28 mg (28%) of the desired product as colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.58 (m, 4H), 7.46 – 7.19 (m, 13H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.41 (s, 1H), 4.45 (s, 2H), 4.35 – 4.26 (m, 2H), 4.24 – 4.05 (m, 3H), 3.98 – 3.88 (m, 2H), 3.78 (s, 3H), 3.68 – 3.52 (m, 2H), 3.47 (ddd, *J* = 11.7, 7.5, 3.3 Hz, 3H), 3.40 – 3.33 (m, 1H), 3.19 (d, *J* = 9.6 Hz, 1H), 2.39 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.17 (s, 3H), 1.15 (d, *J* = 2.9 Hz, 3H), 1.13 (d, *J* = 3.3 Hz, 3H), 1.05 (s, 9H), 0.85 (s, 9H), 0.76 (d, *J* = 6.6 Hz, 3H), -0.00 (s, 3H), -0.02 (s, 2H).



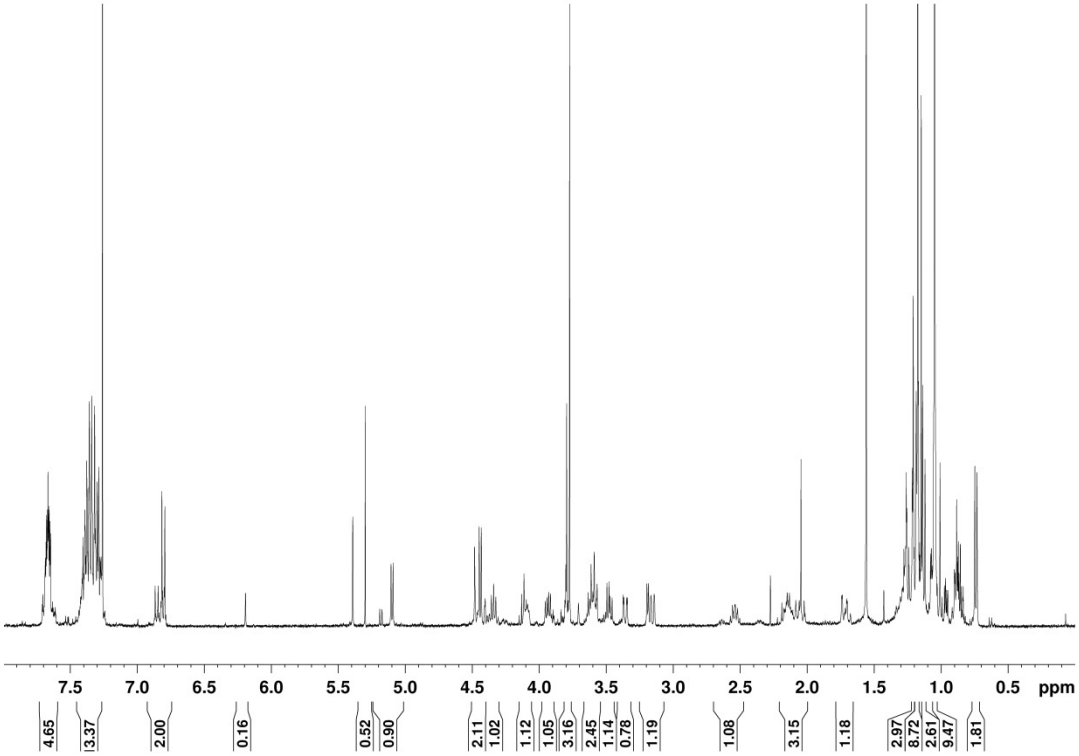



**127** **132**

**Acetal 132:** To a solution of azeotropically dried **127** (0.0071 g, 0.0082 mmol, 1.00 equiv.) with benzene in 0.20 mL of $CH_2Cl_2$ at 0 °C was added 17.4 mg Mol. Sieves and a solution of DDQ (0.0022 g, 0.0098 mmol). After stirring for 30 min at 0 °C. The reaction mixture was quenched with aqu. sat. $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4) gave 5.6 mg (78%) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.57 (m, 5H), 7.46 – 7.20 (m, 12H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.39 (s, 1H), 5.10 (d, *J* = 6.0 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.41 – 4.30 (m, 1H), 4.16 – 4.06 (m, 1H), 3.99 – 3.88 (m, 1H), 3.77 (s, 3H), 3.65 – 3.54 (m, 2H), 3.48 (dd, *J* = 9.4, 6.1 Hz, 1H), 3.36 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.17 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.23 – 2.10 (m, 2H), 2.10 – 2.00 (m, 2H), 1.71 (dd, *J* = 14.1, 10.5 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 9H), 1.20 – 1.15 (m, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 1.05 (s, 9H), 0.74 (d, *J* = 6.6 Hz, 3H).

**Minor Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.57 (m, 5H), 7.46 – 7.20 (m, 12H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.19 (s, 1H), 5.18 (d, *J* = 6.9 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.41 – 4.30 (m, 1H), 4.16 – 4.06 (m, 1H), 3.99 – 3.88 (m, 1H), 3.77 (s, 3H), 3.65 – 3.54 (m, 2H), 3.48 (dd, *J* = 9.4, 6.1 Hz, 1H), 3.36 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.17 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.23 – 2.10 (m, 2H), 2.10 – 2.00 (m, 2H), 1.71 (dd, *J* = 14.1, 10.5 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 9H), 1.20 – 1.15 (m, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 1.05 (s, 9H), 0.74 (d, *J* = 6.6 Hz, 3H).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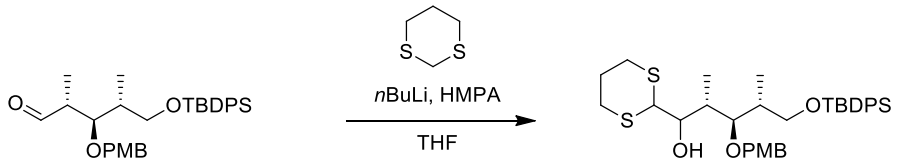
9.47
1.81

## 5.3.3. The Umpolung Approach

### 5.3.3.1. Test Reactions on Aldehyde 74

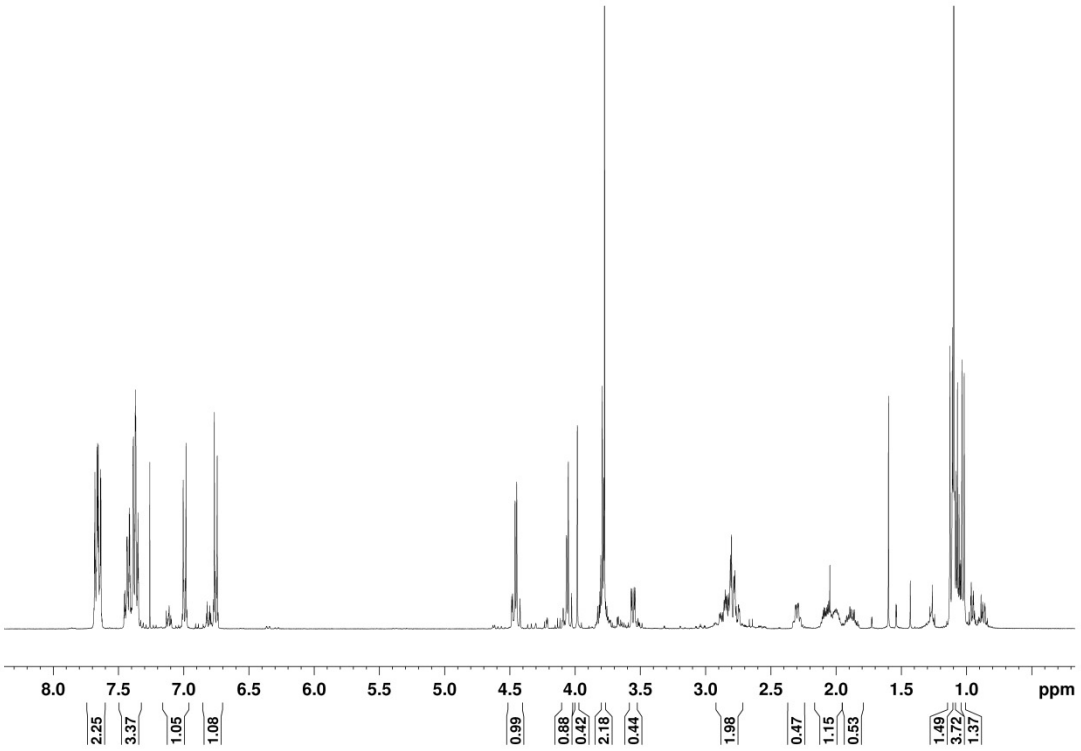



**74** **137**

**Alcohol 137:** To a solution of 1,3-Dithiane (0.0715 g, 0.594 mmol, 3.00 equiv.) and HMPA (0.189 ml, 1.08 mmol, 5.45 equiv.) in 5.00 ml THF at -78 °C was added n-BuLi (0.371 ml, 0.594 mmol, 3.00 equiv., 1.6 M in hexane). The reaction mixture was stirred at -78 °C for 1.5 h. **74** (0.100 g, 0.198 mmol, 1.00 equiv.) in 1.60 ml THF was added dropwise over 10 min and the reaction mixture was stirred at -78 °C for 2 h 40 min (although no full conversion). The reaction mixture was then quenched by addition of MeOH and aqu. sat. $NH_4Cl$. The resulting mixture was diluted with EtOAc and water and the phases were separated. The aqu. phase was extracted 3 times with EtOAc and the combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 93 mg (75 %, *dr* = 4:1) of the desired product as colorless oil.

**Major Isomer:** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.60 (m, 4H), 7.50 – 7.32 (m, 6H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 4.47 (d, *J* = 10.2 Hz, 1H), 4.44 (d, *J* = 10.3 Hz, 1H), 4.10 – 4.02 (m, 2H), 3.98 (s, 1H), 3.83 – 3.76 (m, 2H), 3.77 (s, 3H), 3.56 (dd, *J* = 8.9, 2.9 Hz, 1H), 2.93 – 2.71 (m, 4H), 2.37 – 2.26 (m, 1H), 2.14 – 1.94 (m, 2H), 1.94 – 1.80 (m, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 9H), 1.03 (d, *J* = 6.9 Hz, 3H); $^{13}$**C NMR** (101 MHz, CDCl3) δ 159.39, 135.92, 135.87, 133.87, 133.68, 130.23, 129.79, 129.77, 129.55, 127.83, 127.77, 113.92, 86.48, 75.80, 71.23, 65.55, 55.40, 50.03, 38.76, 34.86, 29.14, 28.68, 27.15, 25.94, 19.45, 14.83, 11.54.

**Minor Isomer:** $^{1}$**H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.60 (m, 4H), 7.50 – 7.32 (m, 6H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.47 (d, *J* = 10.2 Hz, 1H), 4.44 (d, *J* = 10.3 Hz, 1H), 4.10 – 4.02 (m, 2H), 3.98 (s, 1H), 3.83 – 3.76 (m, 2H), 3.77 (s, 3H), 3.56 (dd, *J* = 8.9, 2.9 Hz, 1H), 2.93 – 2.71 (m, 4H), 2.37 – 2.26 (m, 1H), 2.14 – 1.94 (m, 2H), 1.94 – 1.80 (m, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 9H), 1.03 (d, *J* = 6.9 Hz, 3H).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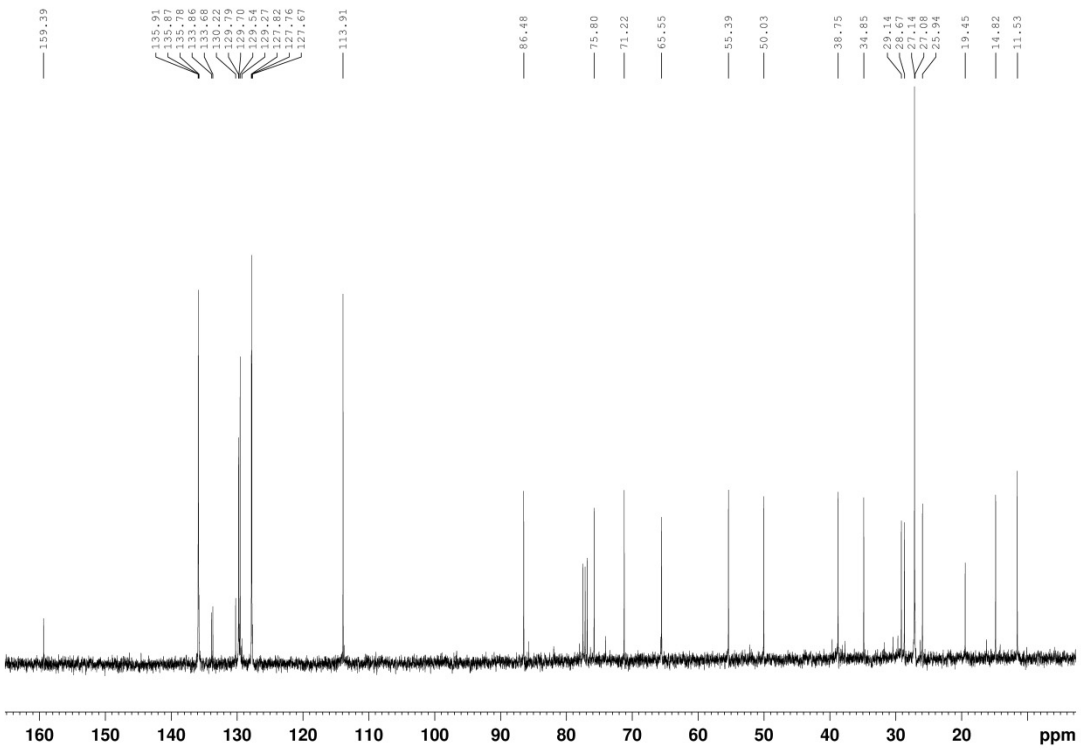
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.25
3.37
1.05
1.08
0.99
0.88
0.42
2.18
0.44
1.98
0.47
1.15
0.53
1.49
3.72
1.37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133.68
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129.54
129.27
127.82
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127.67
113.91
86.48
75.80
71.22
65.55
55.39
50.03
38.75
34.85
29.14
28.67
27.14
27.08
25.94
19.45
14.82
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150
140
130
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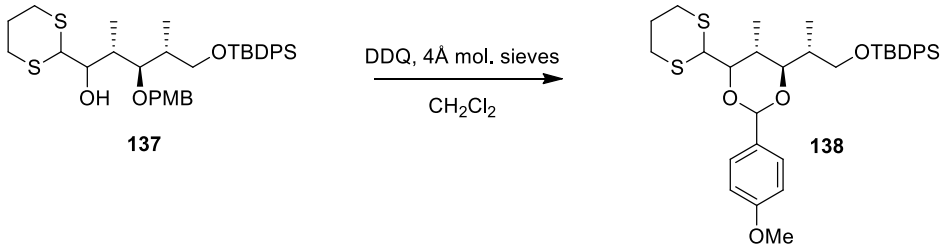
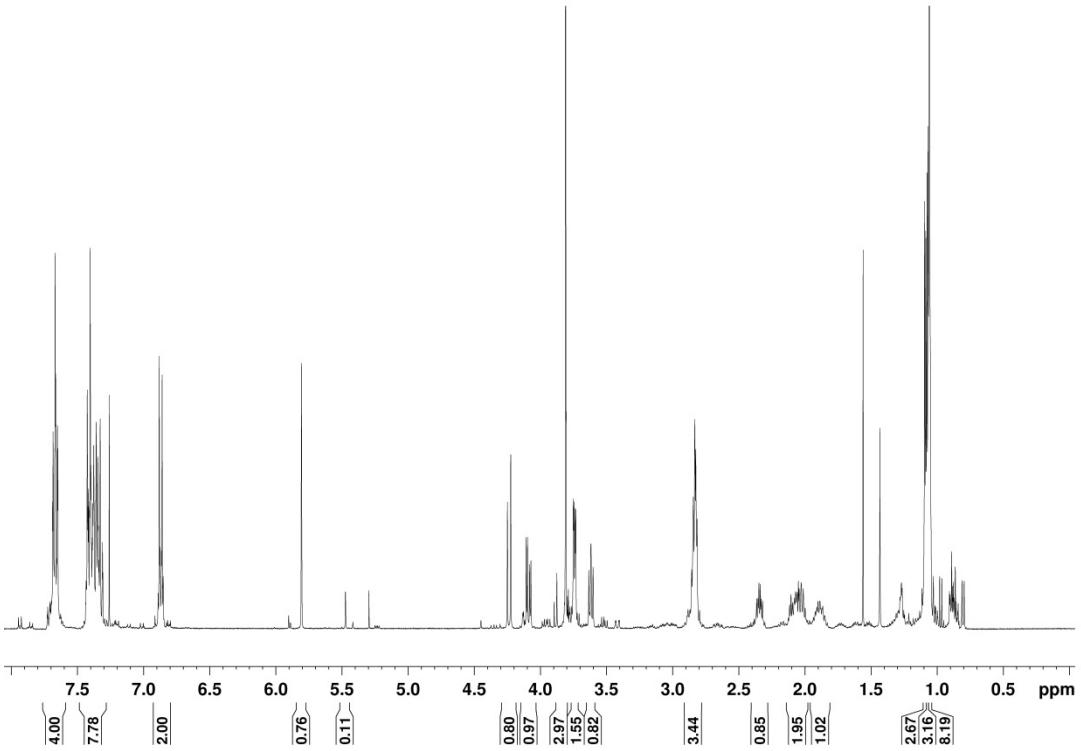
100
90
80
70
60
50
40
30
20
ppm




**Acetal 138:** To a solution of azeotropically dried **137** (0.0341 g, 0.0546 mmol, 1.00 equiv.) in 0.90 mL of $CH_2Cl_2$ at 0 °C was added 83.3 mg Mol. Sieves and DDQ (0.0148 g, 0.0655 mmol, 1.20 equiv.) resulting into a dark blue reaction mixture. After stirring for 30 min at 0 °C. The reaction mixture was quenched with aqu. sat. $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:8) gave 23.8 mg (70%) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.58 (m, 5H), 7.52 – 7.28 (m, 7H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.81 (s, 1H), 4.24 (d, *J* = 10.1 Hz, 1H), 4.09 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 5.4, 1.9 Hz, 2H), 3.66 – 3.59 (m, 1H), 2.90 – 2.72 (m, 4H), 2.43 – 2.26 (m, 1H), 2.20 – 1.96 (m, 2H), 1.95 – 1.79 (m, 1H), 1.09 (d, *J* = 3.3 Hz, 3H), 1.07 (d, *J* = 3.4 Hz, 3H), 1.06 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.83, 135.75, 135.72, 133.91, 133.88, 132.19, 129.70, 129.68, 127.78, 127.76, 127.66, 127.54, 113.59, 113.52, 98.39, 81.70, 71.98, 64.94, 55.41, 47.89, 39.63, 34.98, 29.63, 29.53, 27.08, 27.01, 25.99, 19.44, 13.59, 13.19.

**Minor Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.58 (m, 5H), 7.52 – 7.28 (m, 7H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.47 (s, 1H), 4.24 (d, *J* = 10.1 Hz, 1H), 4.09 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 5.4, 1.9 Hz, 2H), 3.66 – 3.59 (m, 1H), 2.90 – 2.72 (m, 4H), 2.43 – 2.26 (m, 1H), 2.20 – 1.96 (m, 2H), 1.95 – 1.79 (m, 1H), 1.09 (d, *J* = 3.3 Hz, 3H), 1.07 (d, *J* = 3.4 Hz, 3H), 1.06 (s, 9H).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6.0
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1.0
0.5
ppm
4.00
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2.00
0.76
0.11
0.80
0.97
2.97
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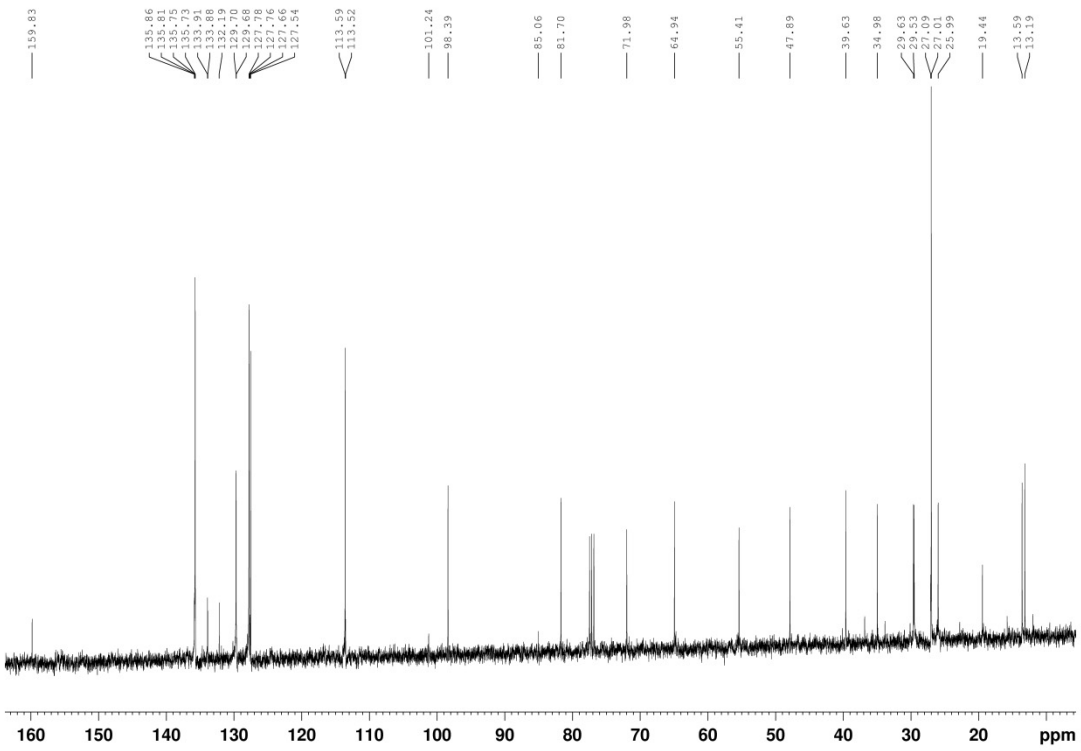
3.44
0.85
1.95
1.02
2.67
3.16
8.19


159.83
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135.81
135.75
135.73
133.91
133.88
132.19
132.00
129.68
127.78
127.76
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127.54
113.59
113.52
101.24
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29.63
29.53
27.09
27.01
25.99
19.44
13.59
13.19
160
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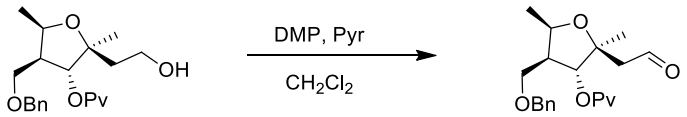
20
ppm

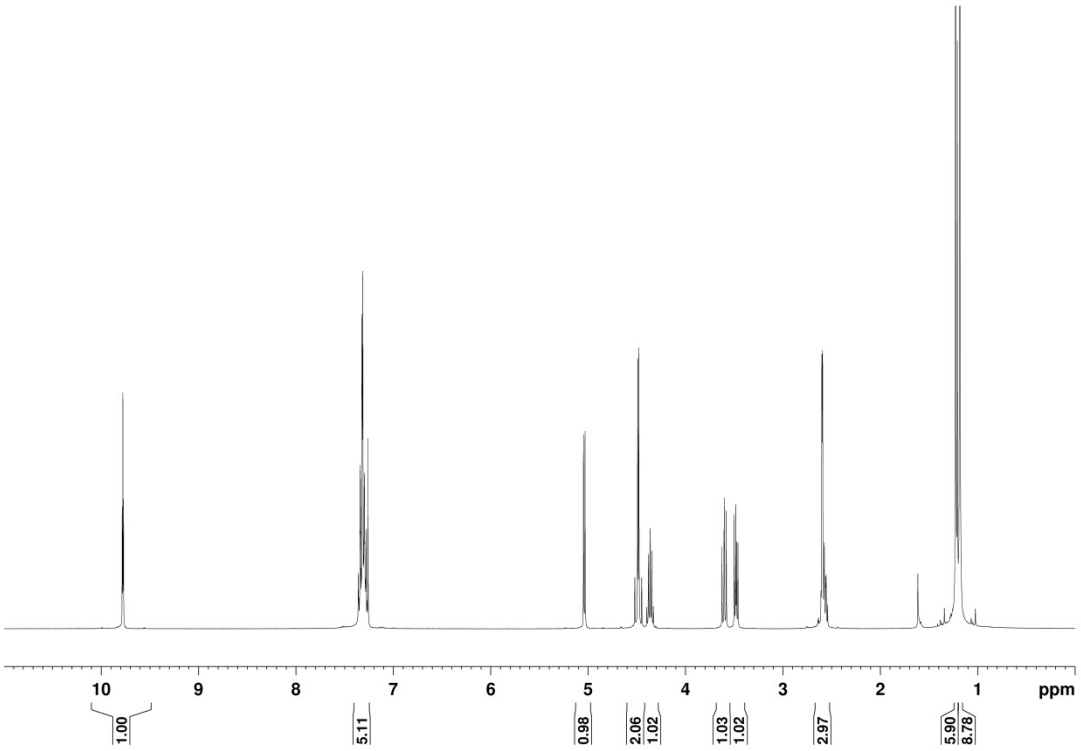
### 5.3.3.2. Synthesis of Dithiane 134




**135** **139**

**Aldehyde 139:** To a solution of **135** (1.86 g, 5.10 mmol, 1.00 equiv.) in 100.0 ml $CH_2Cl_2$, Pyridine (2.72 ml, 33.68 mmol, 6.60 equiv.) and DMP (2.38 g, 5.61 mmol, 1.10 equiv.) were added at rt. The reaction mixture was stirred at rt for 55 min. The reaction mixture was then quenched by addition of aqu. sat. $NaHCO_3$ solution. The aqueous phase was extracted with $CH_2Cl_2$. The comb. org. phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:5)) gave 1.77 g (96 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.25 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.7 Hz, 1H), 7.42 – 7.22 (m, 5H), 5.04 (d, *J* = 6.2 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.36 (p, *J* = 6.6 Hz, 1H), 3.60 (dd, *J* = 9.4, 8.0 Hz, 1H), 3.48 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.65 – 2.53 (m, 3H), 1.23 (s, 3H), 1.22 (d, *J* = 7.7 Hz, 3H), 1.18 (s, 9H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 201.39, 177.96, 137.96, 128.56, 127.97, 80.66, 79.97, 73.53, 73.22, 68.05, 53.77, 47.37, 38.88, 27.18, 20.96, 16.77; **IR** (thin film): ν 2976, 2935, 2905, 2870, 1722, 1480, 1454, 1380, 1282, 1147, 1097, 1029, 1004, 942, 897, 736, 698; **HRMS** (ESI): calculated for $C_{21}H_{31}O_5$ $[M+H]^+$: 363.2166, found 363.2166; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +18.69° (c = 1.07 in $CHCl_3$).


10
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8
7
6
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4
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2.06
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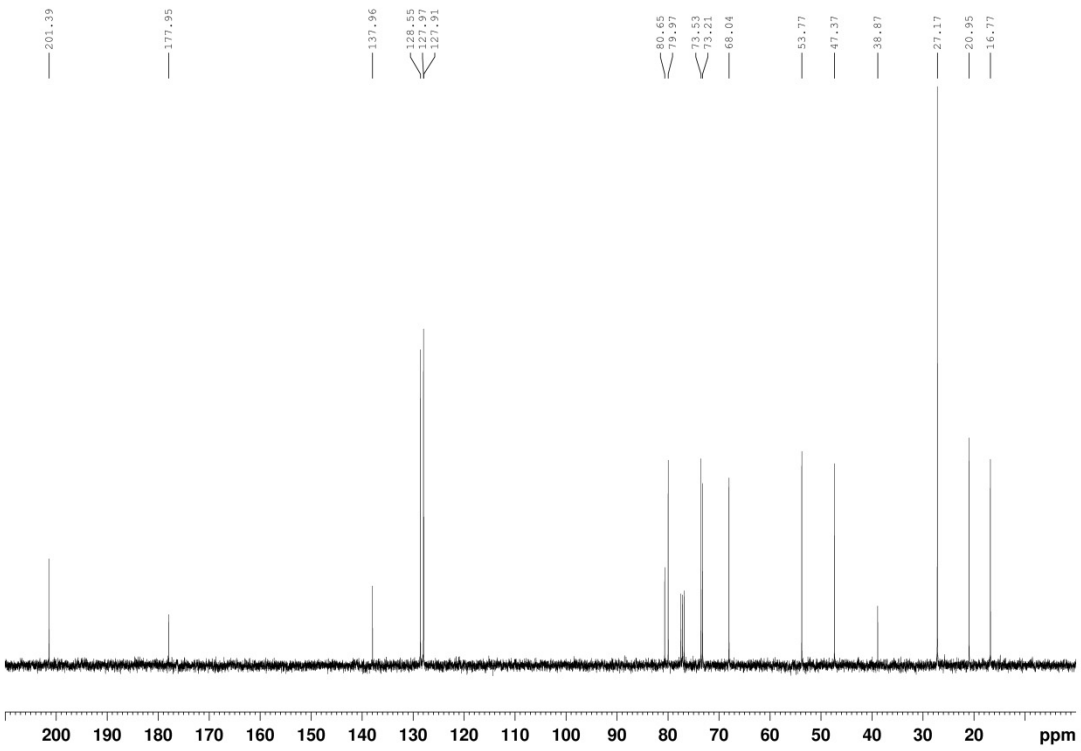
1.03
1.02
2.97
5.90
8.78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127.97
127.91
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73.21
68.04
53.77
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16.77
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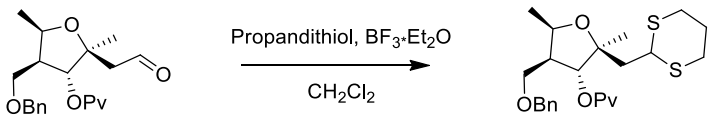
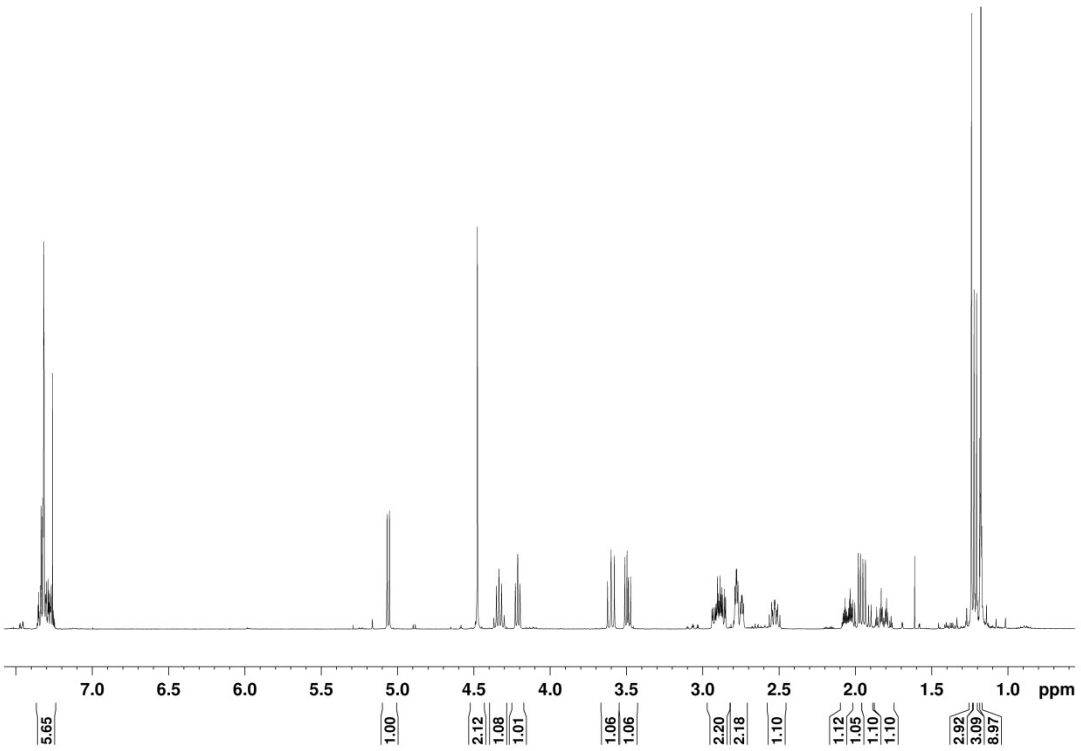
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

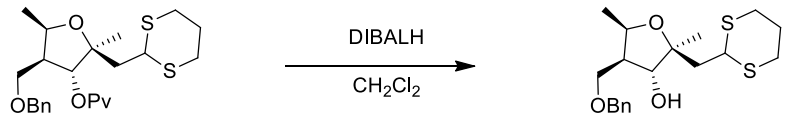



**139** **140**

**Dithiane 140:** To a solution of **139** (0.104 g, 0.287 mmol, 1.00 equiv.) in 3.50 ml $CH_2Cl_2$ at -78 °C were added 1,3-propanedithiol (0.035 ml, 0.350 mmol, 1.22 equiv.) and $BF_3$*$Et_2O$ (0.043 ml, 0.344 mmol, 1.20 equiv.). The reaction mixture was stirred at -78 °C for 50 min. The reaction mixture was then quenched by addition of $NEt_3$ (0.1 ml) and the reaction mixture was diluted with EtOAc. The org. phase was washed with aqu. sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 101 mg (78 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 5.06 (d, *J* = 6.3 Hz, 1H), 4.48 (s, 2H), 4.34 (qd, *J* = 6.7 Hz, 1H), 4.21 (dd, *J* = 6.1 Hz, 1H), 3.60 (dd, *J* = 8.7 Hz, 1H), 3.49 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.96 – 2.84 (m, 2H), 2.78 (dd, *J* = 4.6, 3.2 Hz, 1H), 2.74 (dd, *J* = 4.7, 3.2 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.09 – 2.02 (m, 1H), 1.99 (dd, *J* = 14.9, 5.7 Hz, 1H), 1.92 (dd, *J* = 14.9, 6.6 Hz, 1H), 1.88 – 1.74 (m, 1H), 1.24 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 9H).

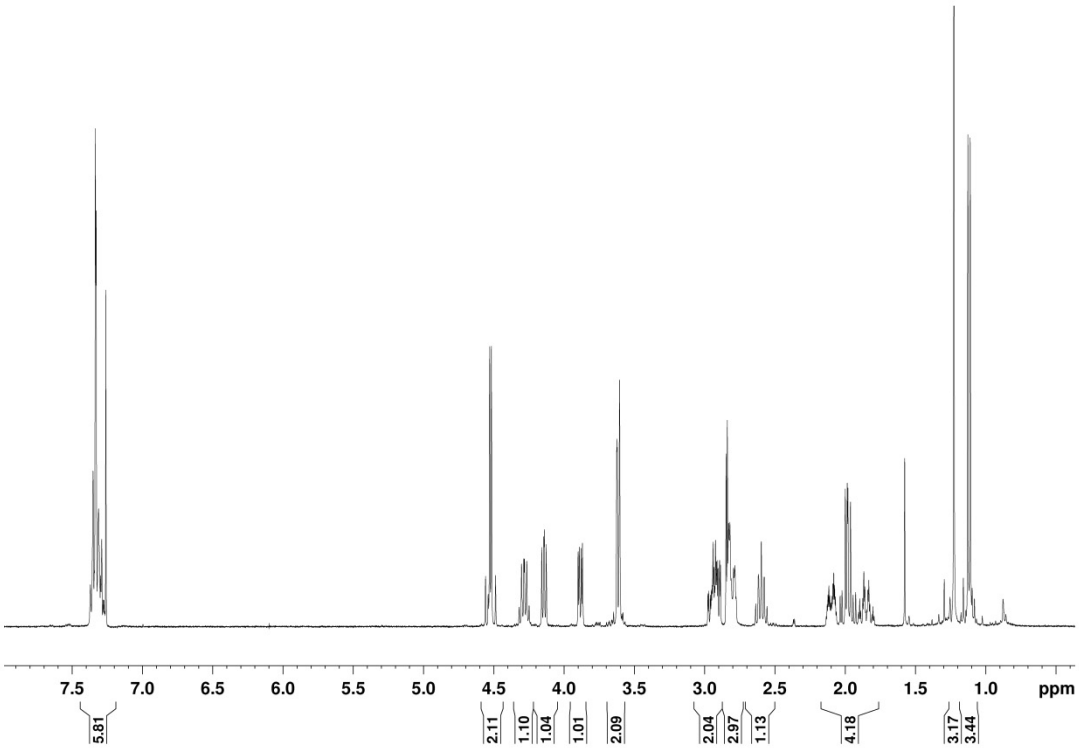


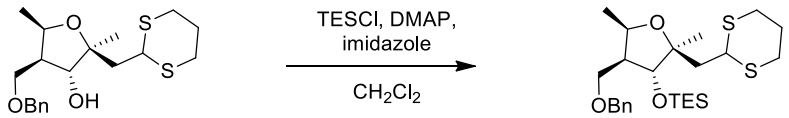



**140** **141**

**Alcohol 141: 140** (0.097 g, 0.214 mmol, 1.00 equiv.) was dissolved in 2.20 mL of $CH_2Cl_2$, cooled to –78 °C and DIBAL (0.393 mL, 0.471 mmol, 2.20 equiv., 1.2 M in toluene) was added drop wise. After 1 h at -78 °C the reaction mixture was quenched by addition of EtOAc. After warming up to rt aqu. Rochelle was added and the mixture was stirred for further 30 min. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 55.1mg (70 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.28 (dq, *J* = 13.3, 6.6 Hz, 1H), 4.14 (dd, *J* = 7.1, 5.6 Hz, 1H), 3.89 (dd, *J* = 9.0, 3.4 Hz, 1H), 3.62 (d, *J* = 7.7 Hz, 2H), 3.01 – 2.87 (m, 2H), 2.86 – 2.77 (m, 3H), 2.66 – 2.54 (m, 1H), 2.16 – 2.05 (m, 1H), 2.01 (dd, *J* = 14.7, 5.5 Hz, 1H), 1.95 (dd, *J* = 14.8, 7.4 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.23 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H).

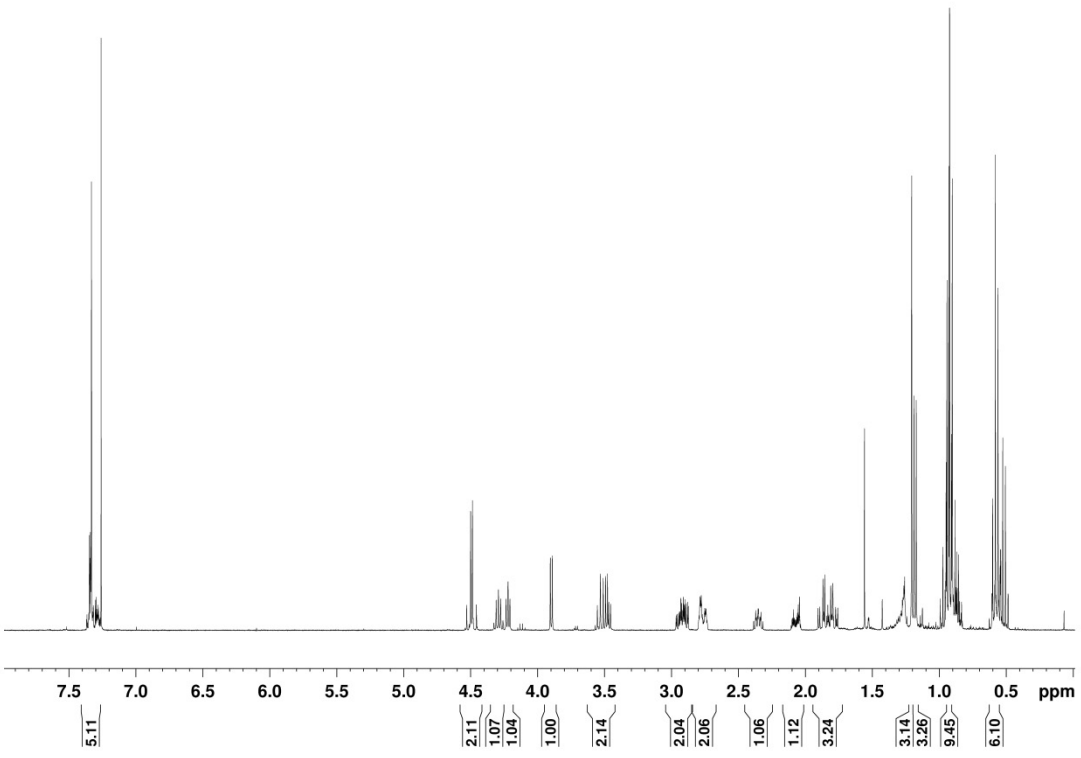





**141** **142**

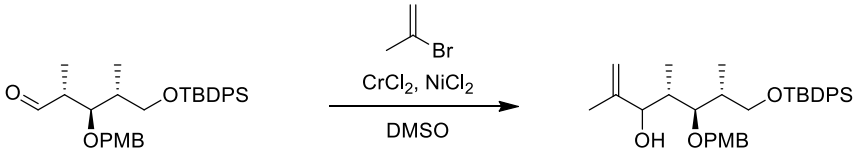
**Silyl ether 142:** To a solution of **141** (25 mg, 0.0678 mmol, 1.00 equiv.) in $CH_2Cl_2$ (0.70 ml) at rt, Imidazole (10.6 mg, 0.156 mmol, 2.30 equiv.) and DMAP (0.8 mg, 0.0068 mmol, 0.10 equiv.) were added. Afterwards TESCl (0.017 ml, 0.102 mmol, 1.50 equiv.) was added neat. (Reaction mixture turned from colorless to a white emulsion within minutes -> sign that the reaction is completed) the reaction mixture was stirred at rt for 4 h. Then the reaction mixture was diluted with hexane, washed with brine, dired over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($Et_2O$/hexane (1:6)) gave 31 mg (95%) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.29 (qd, *J* = 6.7 Hz, 1H), 4.22 (t, *J* = 5.8 Hz, 1H), 3.90 (d, *J* = 6.0 Hz, 1H), 3.53 (dd, *J* = 8.9 Hz, 1H), 3.47 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.81 – 2.72 (m, 2H), 2.35 (dq, *J* = 8.5, 5.9 Hz, 1H), 2.14 – 2.01 (m, 1H), 1.88 (dd, *J* = 14.8, 5.4 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.78 (dd, *J* = 14.7, 6.2 Hz, 1H), 1.21 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 7.7 Hz, 6H).



## 5.3.4. Vinylmetal Addition Approach

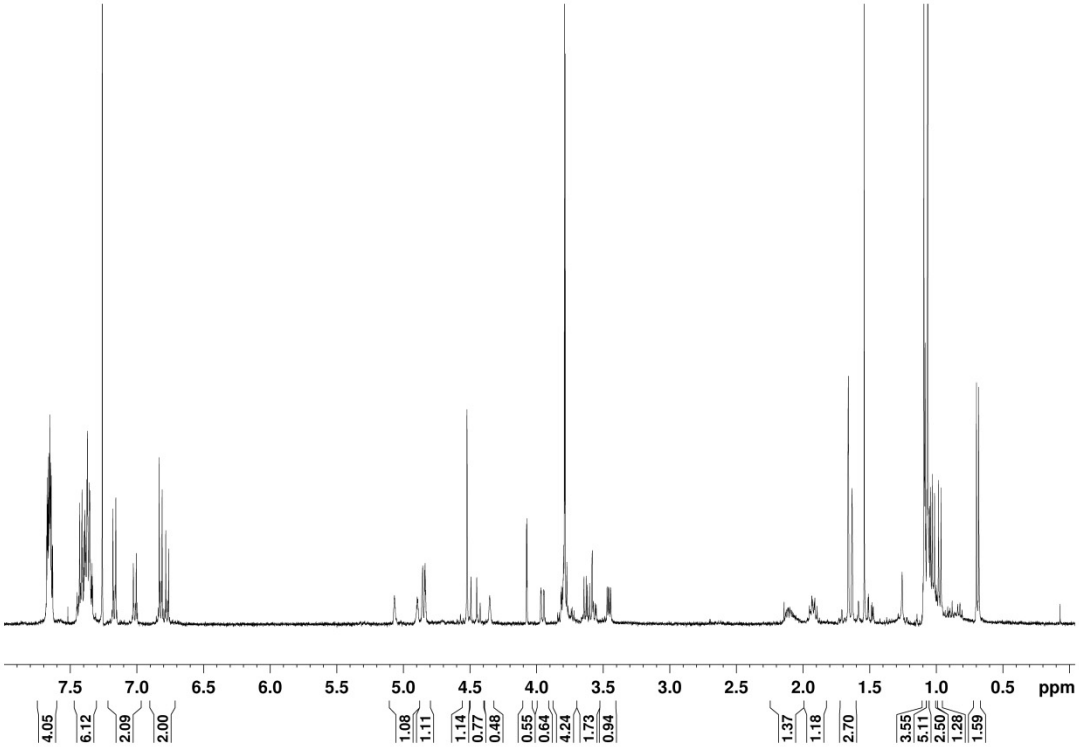
### 5.3.4.1. *NHK* Model Reactions with Aldehyde 74




**74** **150**

**Allylic alcohol 150:** To anhydrous $CrCl_2$ (0.0243 g, 0.198 mmol, 10.00 equiv.) and $NiCl_2$ (0.1 mg, 0.0010 mmol, 0.05 equiv.) was added **74** (5.5 mg, 0.0109 mmol, 1.00 equiv.) in 0.15 ml degassed DMSO. The dark-green solution was stirred at rt for 3d. The reaction was quenched by addition of EDTA solution (0.1 M) and stirred at rt until a purple color persisted. The aqu. mixture was extracted 3 times with EtOAc. The comb. org phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10) gave 2.0 mg (33 %, dr = 1:1.6) of the desired product as colorless oil.

**Major Isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.57 (m, 4H), 7.48 – 7.29 (m, 6H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.85 (s, 1H), 4.84 (s, 1H), 4.52 (s, 2H), 4.07 (d, *J* = 1.5 Hz, 1H), 3.96 (d, *J* = 8.9 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.46 (dd, *J* = 7.3, 4.0 Hz, 1H), 2.15 – 2.03 (m, 1H), 1.97 – 1.88 (m, 1H), 1.66 (s, 3H), 1.06 (s, 9H), 1.05 (d, *J* = 8.1 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H).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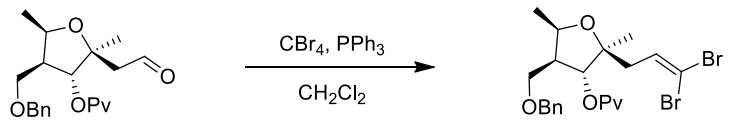
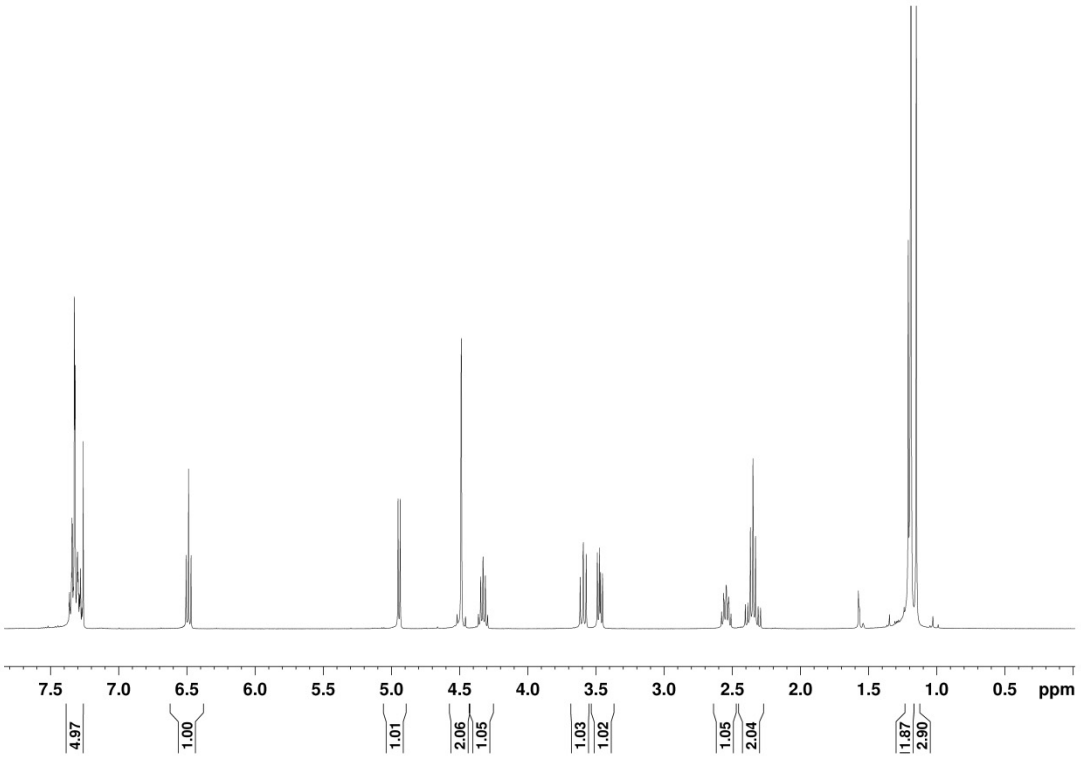
### 5.3.4.2. Synthesis of Vinyl Iodide 149




**139** **156**

**Dibromoolefin 156:** To a solution of $CBr_4$ (3.24 g, 9.77 mmol, 2.00 equiv.) in $CH_2Cl_2$ (39.0 ml), triphenylphosphine (5.12 g, 19.53 mmol, 4.00 equiv.) was added at 0 °C and stirred for 30 min. The yellow reaction mixture was cooled to -78 °C and a solution of **139** (1.77 g, 4.88 mmol, 1.00 equiv.) in 9.80 ml $CH_2Cl_2$ was added dropwise. After stirring for 2 h at –78°C, the reaction mixture was quenched with aqu. sat. $NH_4Cl$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined org. phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 2.43 g (96%) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.29 (EtOAc/hexane 1:5, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 6.49 (t, *J* = 7.3 Hz, 1H), 4.94 (d, *J* = 6.3 Hz, 1H), 4.50 (d, *J* = 12.6 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.33 (p, *J* = 6.6 Hz, 1H), 3.59 (dd, *J* = 9.2, 8.5 Hz, 1H), 3.47 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.38 (dd, *J* = 14.9, 7.5 Hz, 1H), 2.32 (dd, *J* = 15.1, 7.3 Hz, 1H), 1.20 (d, *J* = 7.7 Hz, 3H), 1.19 (s, 9H), 1.15 (s, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 177.83, 138.06, 134.47, 128.55, 127.97, 127.87, 90.99, 81.81, 79.19, 73.54, 73.14, 68.15, 47.80, 44.23, 38.92, 27.23, 20.56, 16.90; **IR** (thin film): ν 2975, 2934, 2870, 1733, 1479, 1455, 1378, 1282, 1151, 1101, 781, 739, 698; **HRMS** (ESI): calculated for $C_{22}H_{31}Br_2O_4$ $[M+H]^+$: 517.0584, found 517.0579; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +18.12° (c = 1.01 in $CHCl_3$).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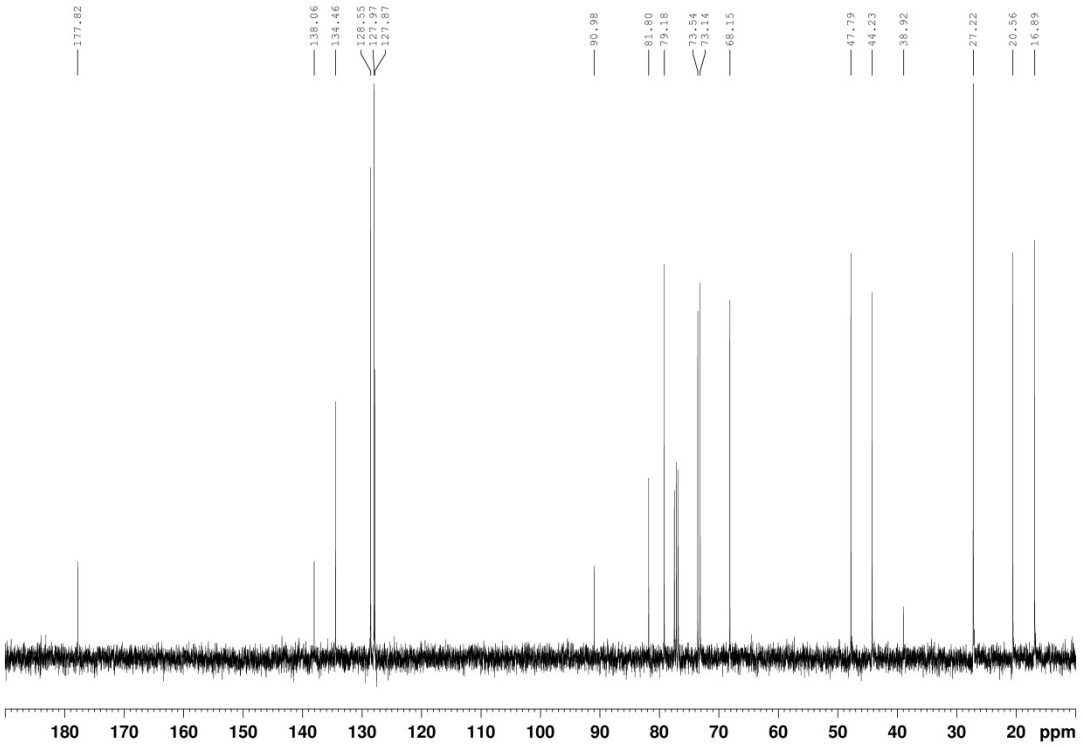
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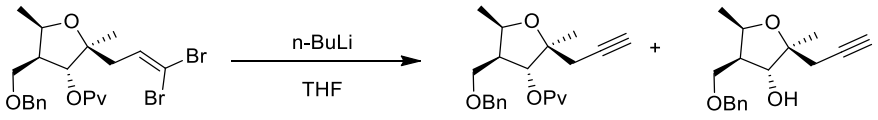
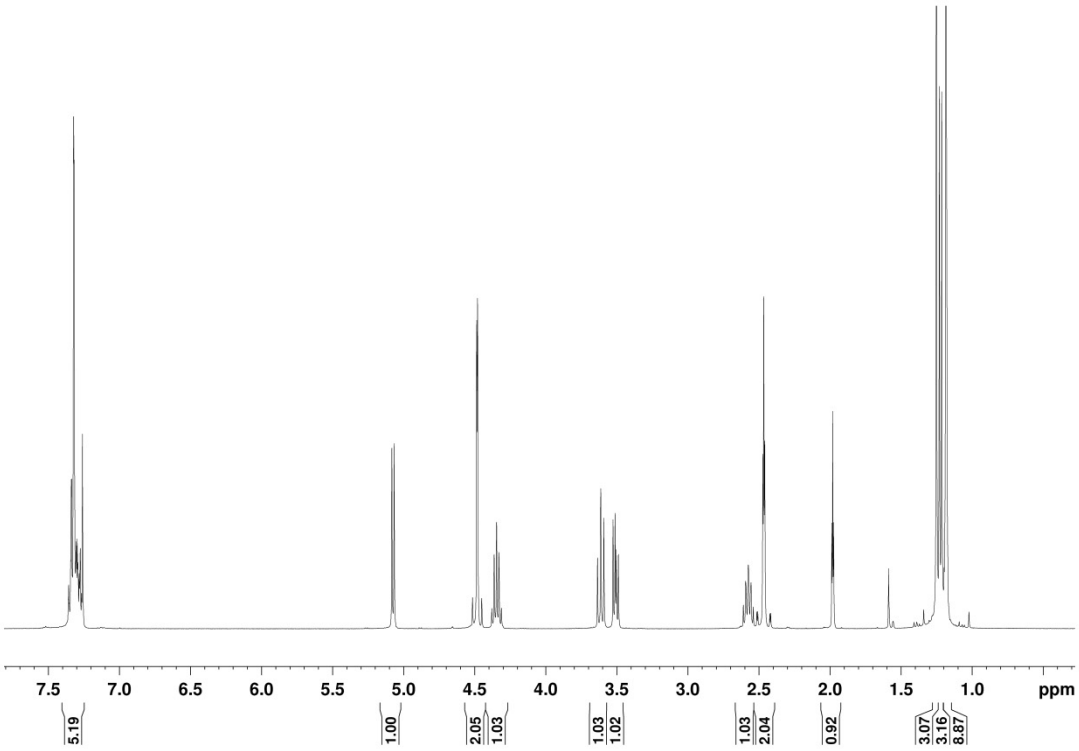



**156** **154** **155**

**Alkyne 154 and 155:** To a solution of **156** (0.255 g, 0.492 mmol, 1.00 equiv.) in THF (5.00 ml) at -78 °C was added n-BuLi (0.615 ml, 0.984 mmol, 2.00 equiv, 1.6 M in hexane) dropwise over 5 min. After completion of the addition, TLC showed almost complete conversion towards **154** and only traces of **155**. After 15 min at -78 °C additional BuLi (1 equiv.) was added dropwise over 1 min. TLC showed that now more **155** was formed, but there was still a lot of **154** and a side product became visible. After 35 min at -78 °C it was decided to stop the reaction by quenching with aqu. sat. $NH_4Cl$. The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:15 -> 1:4)) gave 57.2 mg (42 %) of **155** and 74.8 mg (42 %) of **154**.

**154** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.08 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.39 – 4.30 (m, 1H), 3.61 (dd, *J* = 9.4, 8.7 Hz, 1H), 3.51 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.49 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.44 (dd, *J* = 16.8, 2.7 Hz, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 9H).

**155** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.01 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.66 (dd, *J* = 8.9, 7.0 Hz, 1H), 3.62 (dd, *J* = 8.9, 7.9 Hz, 1H), 2.59 (td, *J* = 15.8, 8.6 Hz, 1H), 2.49 (dd, *J* = 16.7, 2.8 Hz, 1H), 2.44 (dd, *J* = 16.9, 3.0 Hz, 1H), 2.37 (d, *J* = 2.9 Hz, 1H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.26 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H).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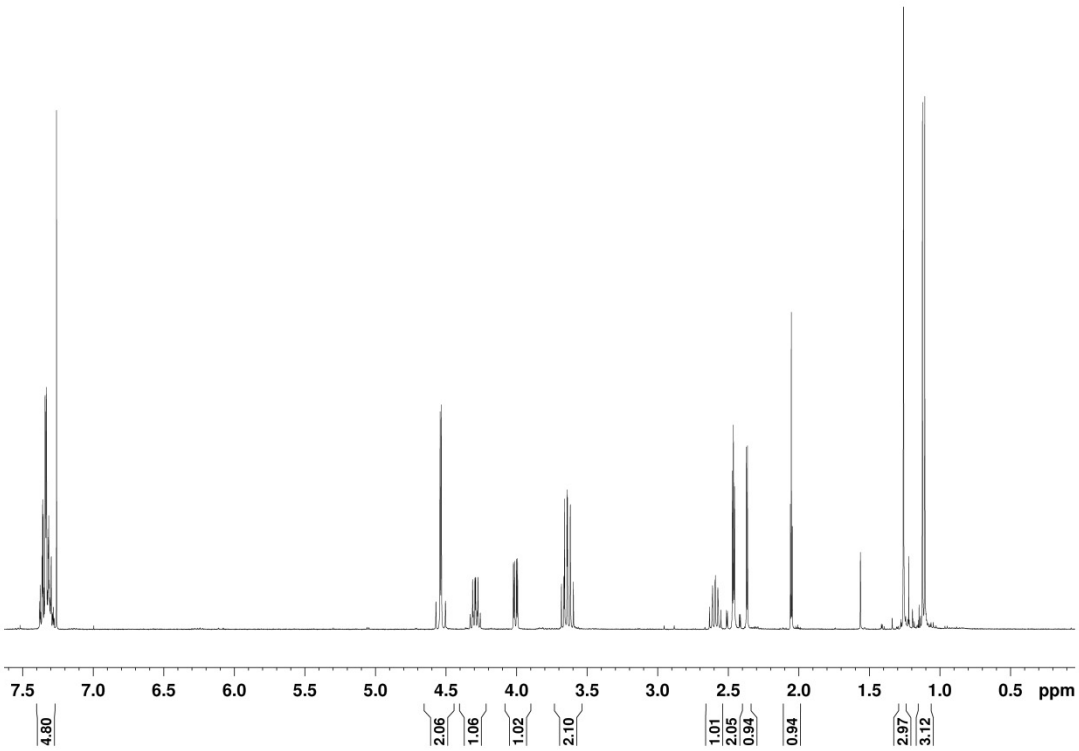
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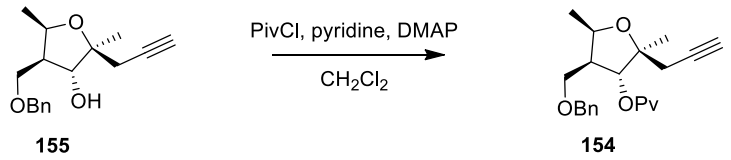
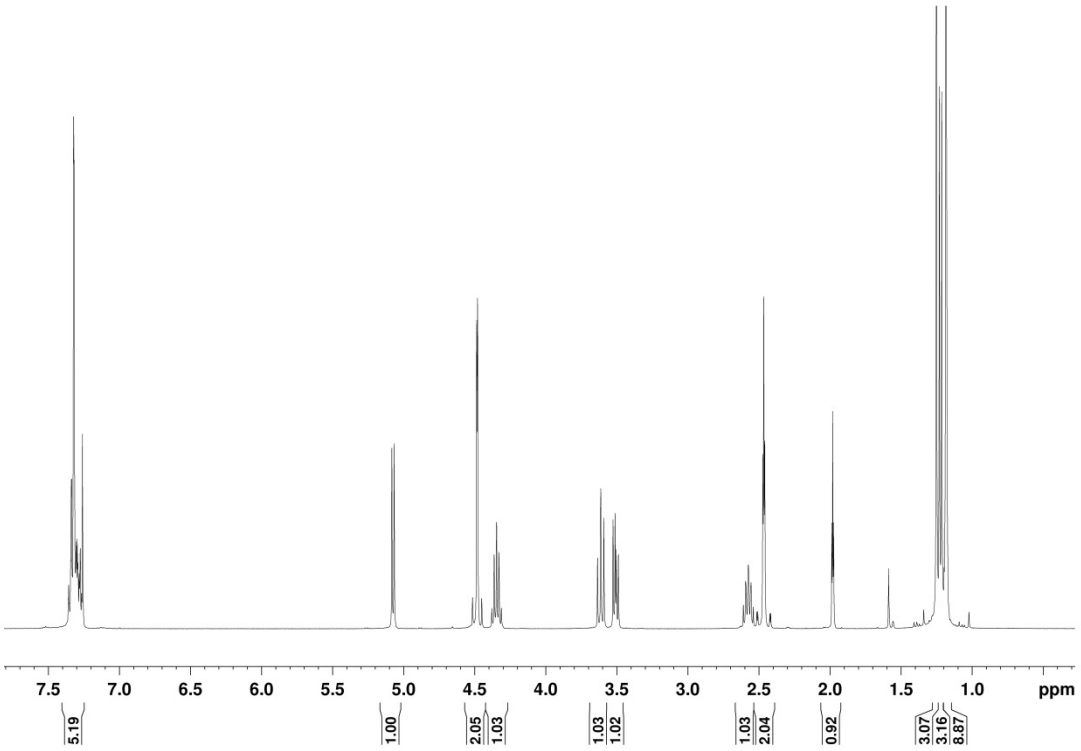
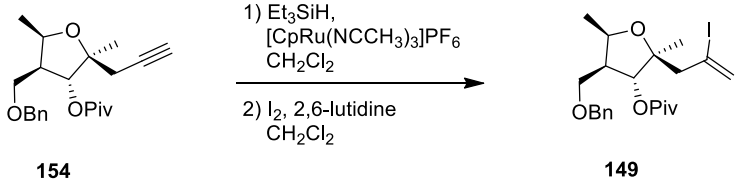



**Ester 154:** To a solution of **155** (156 mg, 0.459 mmol, 1.00 equiv.) and DMAP (0.028 g, 0.229 mmol, 0.50 equiv.) in $CH_2Cl_2$ (2.30 ml) at 0 °C was added pyridine (0.409 ml, 5.05 mmol, 11.0 equiv.) and pivaloyl chloride (0.566 ml, 4.59 mmol, 10.00 equiv.). The reaction mixture was allowed to warm up to rt and stirred for 2 d. The reaction mixture was cooled to 0 °C and quenched by addition of 2 ml absolute EtOH. After 10 min aqu. sat. $NaHCO_3$ was added. The phases were separated and the aqu. phase extracted with $CH_2Cl_2$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 156 mg (95 %) of the desired product as colorless oil.

**154** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.08 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.39 – 4.30 (m, 1H), 3.61 (dd, *J* = 9.4, 8.7 Hz, 1H), 3.51 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.49 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.44 (dd, *J* = 16.8, 2.7 Hz, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 9H).

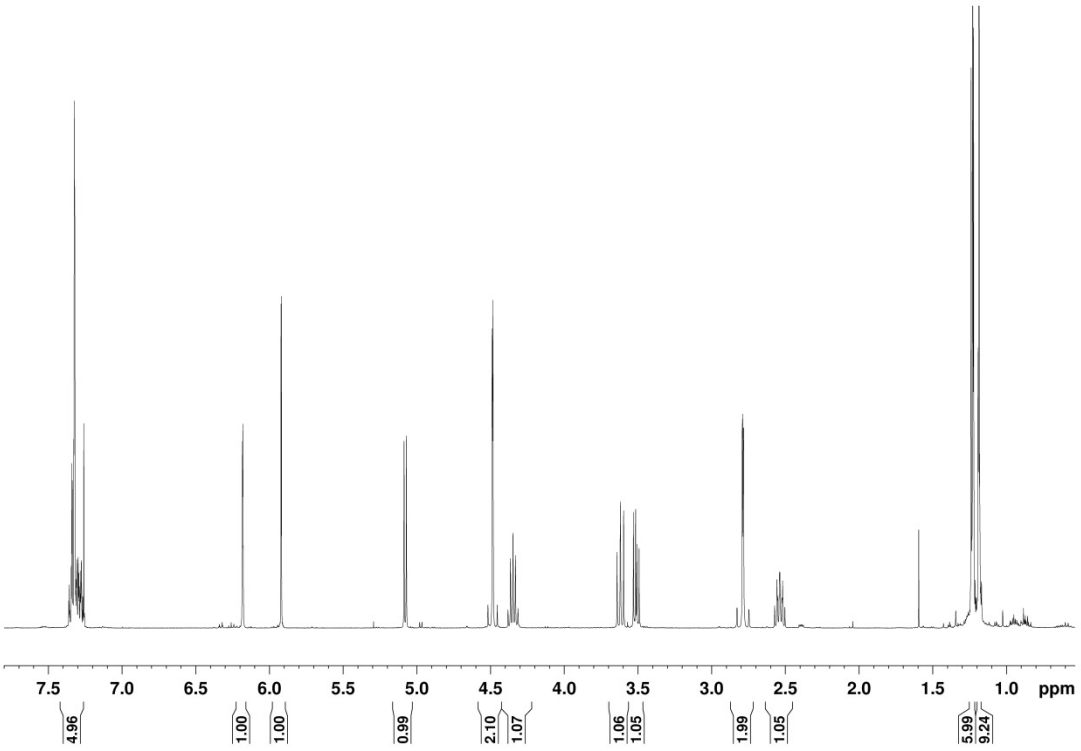


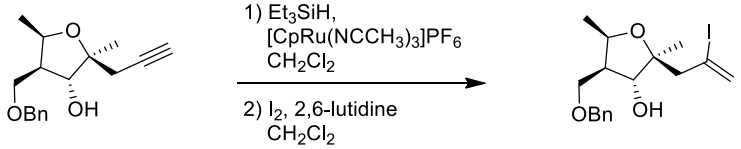



**154** **149**

**Vinyl Iodide 149:** To a solution of alkyne **154** (0.145 g, 0.404 mmol, 1.00 equiv.) and $[CpRu(MeCN)_3]PF_6$ (4.1 mg, 0.0081 mmol, 0.02 equiv.) in $CH_2Cl_2$ (4.00 mL) at 0 °C was added triethylsilane (0.078 mL, 0.485 mmol, 1.20 equiv.). After stirring for 2 h the reaction mixture was concentrated and run through a small silica plug using EtOAc/hexanes (1:10) as the eluent. The filtrate was concentrated and dissolved in $(CF_3)_2CHOH$ (2.00 mL). To the cooled solution (0°C) solution was added $Ag_2CO_3$ (0.0335 g, 0.121 mmol, 0.30 equiv.) and NIS (0.109 g, 0.485 mmol, 1.20 equiv.). After stirring for 20 min the reaction mixture was quenched with a saturated solution of sodium thiosulfate (2 mL). After 20 min the reaction mixture was extracted with $CH_2Cl_2$. The comb. org. phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 138 mg (70 %) of the desired vinyl iodide as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 6.18 (d, *J* = 1.0 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 5.08 (d, *J* = 6.1 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.39 – 4.31 (m, 1H), 3.62 (dd, *J* = 9.4, 8.5 Hz, 1H), 3.51 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.82 (dd, *J* = 14.8, 0.6 Hz, 1H), 2.77 (dd, *J* = 14.8, 0.6 Hz, 1H), 2.54 (dq, *J* = 8.2, 6.1 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.23 (s, 3H), 1.19 (s, 9H).



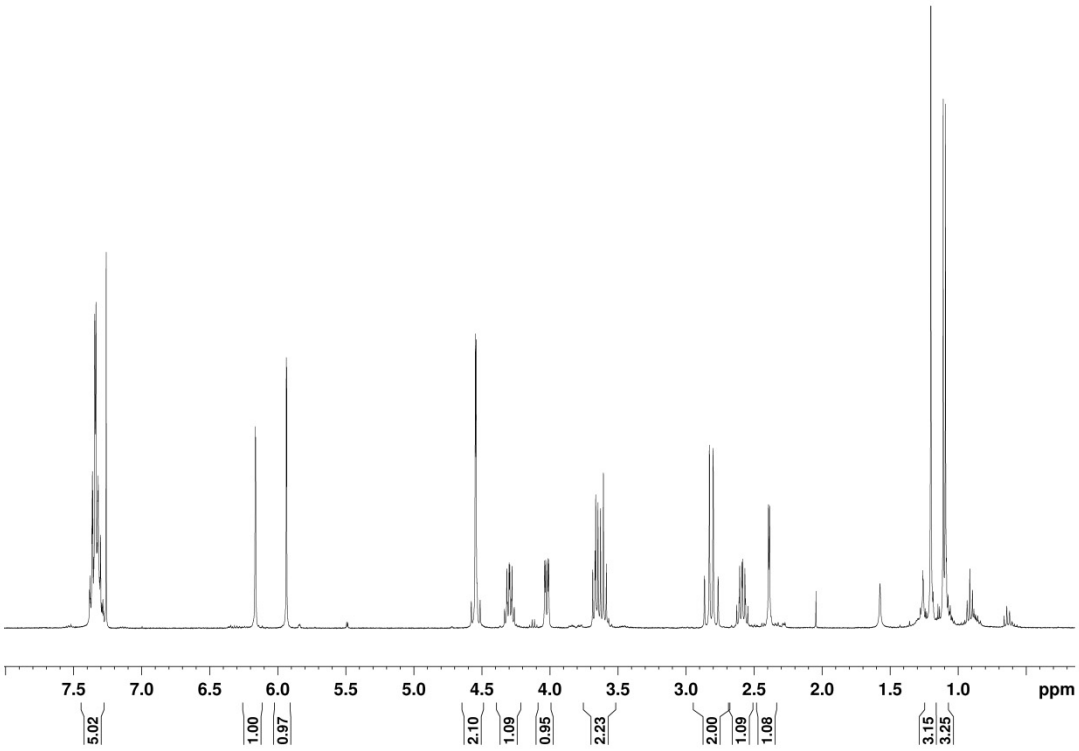



**155** **157**

**Vinyl Iodide 157:** To a solution of alkyne **155** (10.0 mg, 0.0364 mmol, 1.00 equiv.) and $[CpRu(MeCN)_3]PF_6$ (0.4 mg, 0.0007 mmol, 0.02 equiv.) in $CH_2Cl_2$ (0.36 mL) at 0 °C was added triethylsilane (0.007 mL, 0.0437 mmol, 1.20 equiv.). After stirring for 30 min the reaction mixture was run through a small silica plug using EtOAc/hexanes (1:2) as the eluent. The filtrate was concentrated and dissolved in $CH_2Cl_2$ (0.36 mL). To the solution was added 2,6-lutidine (0.005 mL, 0.0437 mmol, 1.20 equiv.) and $I_2$ (0.0278 g, 0.109 mmol, 3.00 equiv.). After stirring for 2 h the reaction did not show complete conversion, therefore additional Iodine (3 equiv.) was added and the reaction mixture was stirred for 1 h at room temperature. Unfortunately still no complete conversion could be observed, therefore additional Iodine (3 equiv.) was added and the reaction mixture was stirred for 1 h at room temperature. Afterwards the reaction mixture was quenched with triethylamine (0.1 mL) and a saturated solution of sodium thiosulfate (1 mL). After 20 min the reaction mixture was extracted with $CH_2Cl_2$, dried over $MgSO_4$, and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 10.6 mg (72 %) of the desired vinyl iodide as brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.16 (d, *J* = 1.0 Hz, 1H), 5.94 (d, *J* = 1.2 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.34 – 4.25 (m, 1H), 4.02 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.67 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.61 (dd, *J* = 8.8 Hz, 1H), 2.85 (d, *J* = 14.8 Hz, 1H), 2.78 (d, *J* = 14.7 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.39 (d, *J* = 3.2 Hz, 1H), 1.20 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H).

For optimized preparation conditions of **157** see page 317.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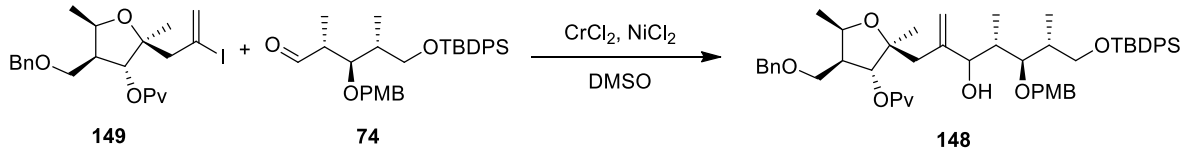
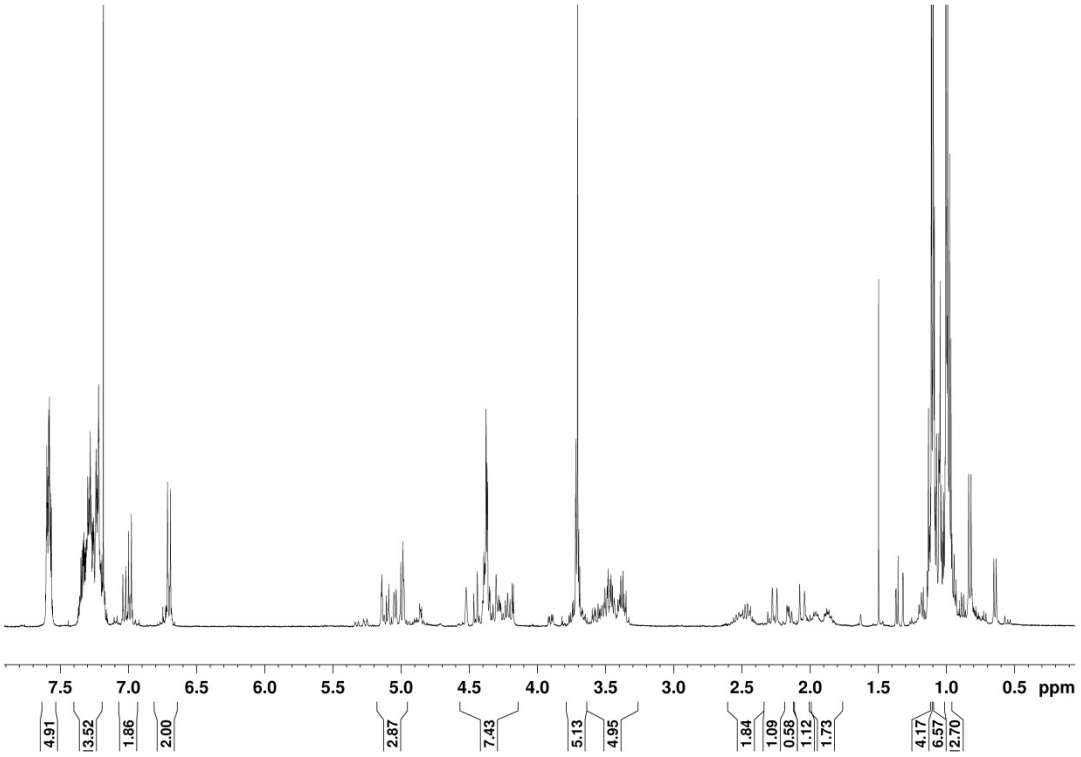


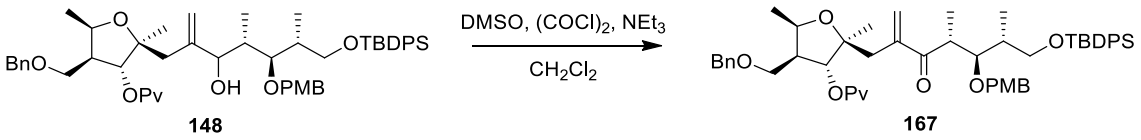

**149** **74** **148**

**Allylic alcohol 148:** To anhydrous $CrCl_2$ (0.0126 g, 0.103 mmol, 10.00 equiv.) and $NiCl_2$ (0.067 mg, 0.0005 mmol, 0.050 equiv.) was added a solution of **74** (7.8 mg, 0.0154 mmol, 1.50 equiv.) and **149** (5.0 mg, 0.0103 mmol, 1.00 equiv.) in 0.14 ml degassed DMSO. The dark-green suspension was stirred at rt for 4 d 17 h. The reaction was quenched by addition of EDTA solution (0.1 M) and stirred at rt until a purple color persisted. The aqu. mixture was extracted 3 times with EtOAc. The comb. org phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10 -> 1:5)) gave 4.8 mg (54 %) of the desired product as diastereomeric mixture of 1:1.5.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.66 – 7.51 (m, 4H), 7.41 – 7.16 (m, 11H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.19 – 4.92 (m, 2H), 4.54 – 4.14 (m, 6H), 3.77 – 3.62 (m, 4H), 3.62 – 3.29 (m, 4H), 2.49 (ddd, *J* = 22.2, 14.8, 6.7 Hz, 1H), 2.26 (d, *J* = 13.4 Hz, 1H), 2.16 (dd, *J* = 8.7, 5.3 Hz, 1H), 2.06 (d, *J* = 14.2 Hz, 1H), 1.14 – 1.06 (m, 15H), 1.06 – 0.95 (m, 15H), 0.83 (d, *J* = 7.1 Hz, 3H).

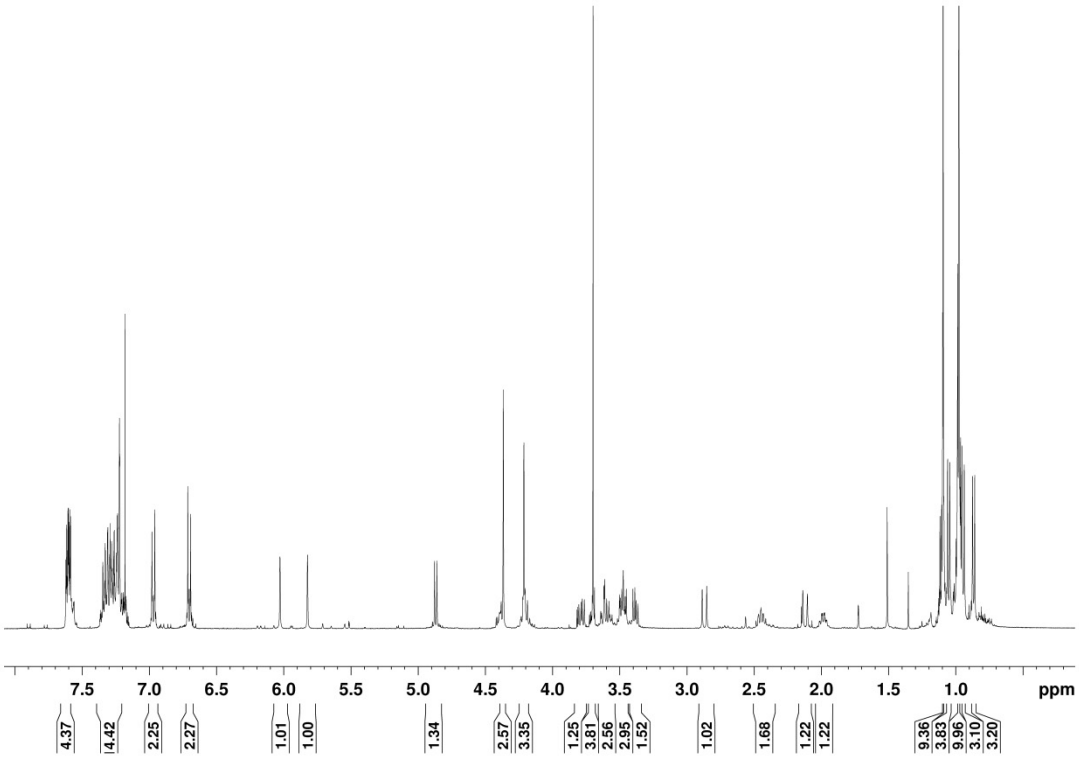


### 5.3.4.3. Towards the Cyclization of the Tricyclic Ketal




**Ketone 167:** To a solution of oxalyl chloride (0.025 ml**,** 0.296 mmol, 8.00 equiv.) in 0.90 mL of anhydrous $CH_2C1_2$ at -78 °C was added DMSO (0.047 ml, 0.666 mmol, 18.00 equiv.) dropwise. The mixture was stirred for 15 min and a solution of **148** (32.0 mg, 0.037 mmol, 1.00 equiv.) in 0.3 mL of anhydrous $CH_2CI_2$ was added dropwise. After 15 min, triethylamine (0.185 ml, 1.33 mmol, 36.00 equiv.) was carefully added, and the reaction was stirred at -78 °C for 10 min. The reaction was allowed to reach room temperature and then diluted with water. The two layers were separated, and the aqueous phase was extracted with $CH_2C1_2$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 20.6 mg (64 %) of the desired product.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.45 – 7.23 (m, 11H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.10 (s, 1H), 5.89 (s, 1H), 4.94 (d, *J* = 7.0 Hz, 1H), 4.44 (s, 2H), 4.28 (s, 3H), 3.85 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.77 (s, 3H), 3.70 (dd, *J* = 9.4, 2.2 Hz, 1H), 3.65 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.58 – 3.52 (m, 2H), 3.45 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.94 (d, *J* = 13.5 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.19 (d, *J* = 13.8 Hz, 1H), 2.06 (dd, *J* = 13.5, 6.4 Hz, 1H), 1.17 (s, 9H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H).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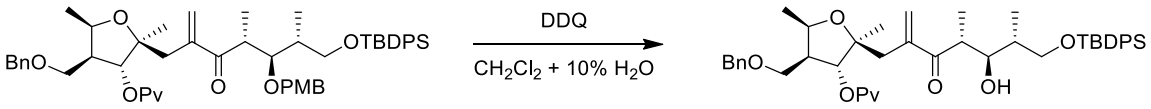
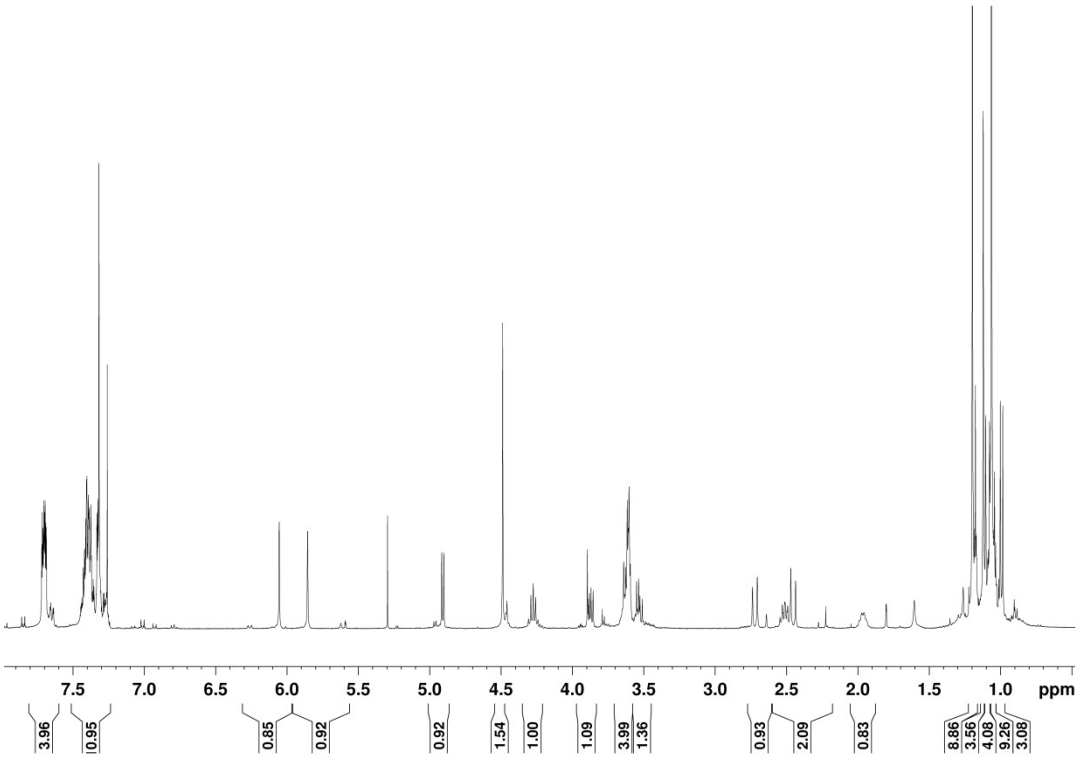



**167** **169**

**Alcohol 169:** To **167** (22.2 mg, 0.0257 mmol, 1.00 equiv.) was added 0.40 ml $CH_2Cl_2$ and 0.04 ml $H_2O$. The mixture was cooled to 0 °C and DDQ (7.0 mg, 0.0309 mmol, 1.20 equiv.) was added (reaction mixture turns brown immediately). The cooling bath was removed and the reaction mixture was stirred at rt for 2h 22 min. The reaction was quenched by addition of aqu. sat $NaHCO_3$ and extracted 3 times with $CH_2Cl_2$. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 16.6 mg of a mixture containing the desired product and PMB-Aldehyde. A second purification over silica gel (DCM/MeOH (200:1)) gave 15 mg (78 %) of the desired product.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 4H), 7.46 – 7.26 (m, 11H), 6.06 (s, 1H), 5.86 (s, 1H), 4.91 (d, *J* = 5.9 Hz, 1H), 4.49 (s, 2H), 4.34 – 4.21 (m, 1H), 3.87 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.65 – 3.59 (m, 5H), 3.53 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.72 (d, *J* = 13.5 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.45 (d, *J* = 13.5 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.20 (s, 9H), 1.12 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 5.6 Hz, 3H), 1.06 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 207.76, 178.05, 144.90, 138.21, 135.78, 133.95, 133.84, 129.71, 128.49, 128.46, 127.92, 127.79, 127.76, 82.54, 78.87, 77.47, 73.43, 73.37, 68.08, 65.18, 47.57, 43.39, 39.43, 38.92, 37.73, 27.22, 27.02, 20.38, 19.36, 16.46, 15.64.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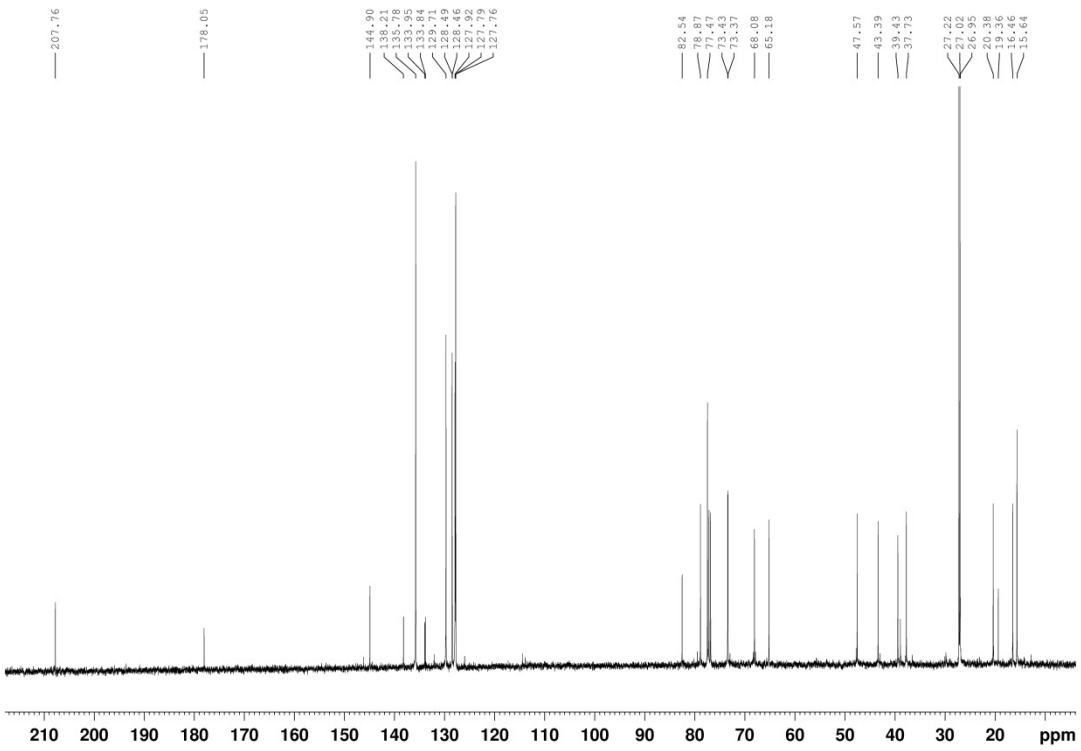
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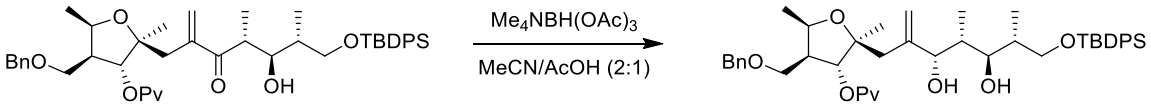
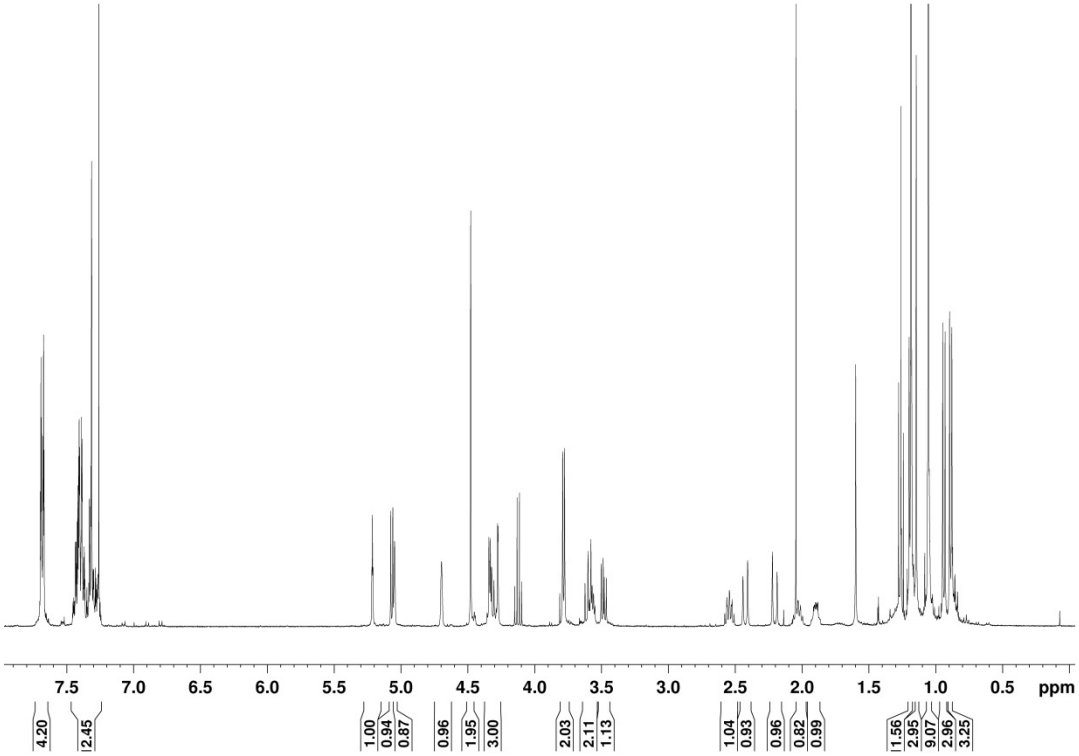



**169** **170**

**Diol 170:** To tetramethylammonium triacetoxyborohydride (20.2 mg, 0.077 mmol, 10.00 equiv.) at room temperature was added AcOH (0.2 ml), and the resulting solution was stirred for 15 min before being cooled to 0 °C. After dilution with MeCN (0.05 ml), the reaction mixture was further cooled to -20 °C. A solution of **169** (15.0 mg, 0.0202 mmol, 1.00 equiv.) in MeCN (0.10 ml) was added dropwise, followed by rinsing with MeCN (2 x 0.1 ml). The reaction mixture was stirred at -20 °C for 24 h and then another 48 h at -10 °C. The reaction mixture was allowed to warm up to 0°C and stirred for another 2 h. The mixture was quenched by addition of aqu. sat. Rochelle solution and was stirred vigorously at rt for 1.5 h and then diluted with ether. After phase separation, the aqu. phase was extracted 3 times with $Et_2O$. The comb. org. layers were washed with aqu. sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane, 1:10) gave 11.3 mg (75 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.47 – 7.23 (m, 11H), 5.21 (t, *J* = 1.5 Hz, 1H), 5.07 (d, *J* = 6.2 Hz, 1H), 5.05 (s, 1H), 4.70 (s, 1H), 4.48 (s, 2H), 4.36 – 4.29 (m, 2H), 4.28 (d, *J* = 1.3 Hz, 1H), 3.78 (d, *J* = 5.7 Hz, 2H), 3.60 (dd, *J* = 9.6, 8.5 Hz, 1H), 3.59 – 3.54 (m, 1H), 3.48 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.20 (d, *J* = 14.1 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.95 – 1.85 (m, 1H), 1.19 (d, *J* = 5.8 Hz, 3H), 1.19 (s, 9H), 1.15 (s, 3H), 1.06 (s, 9H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).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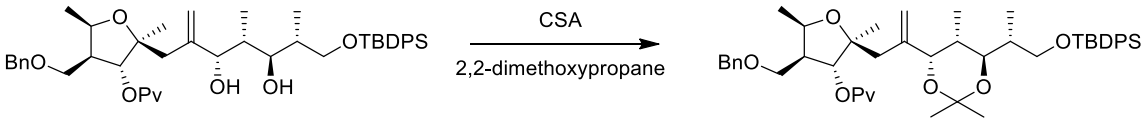
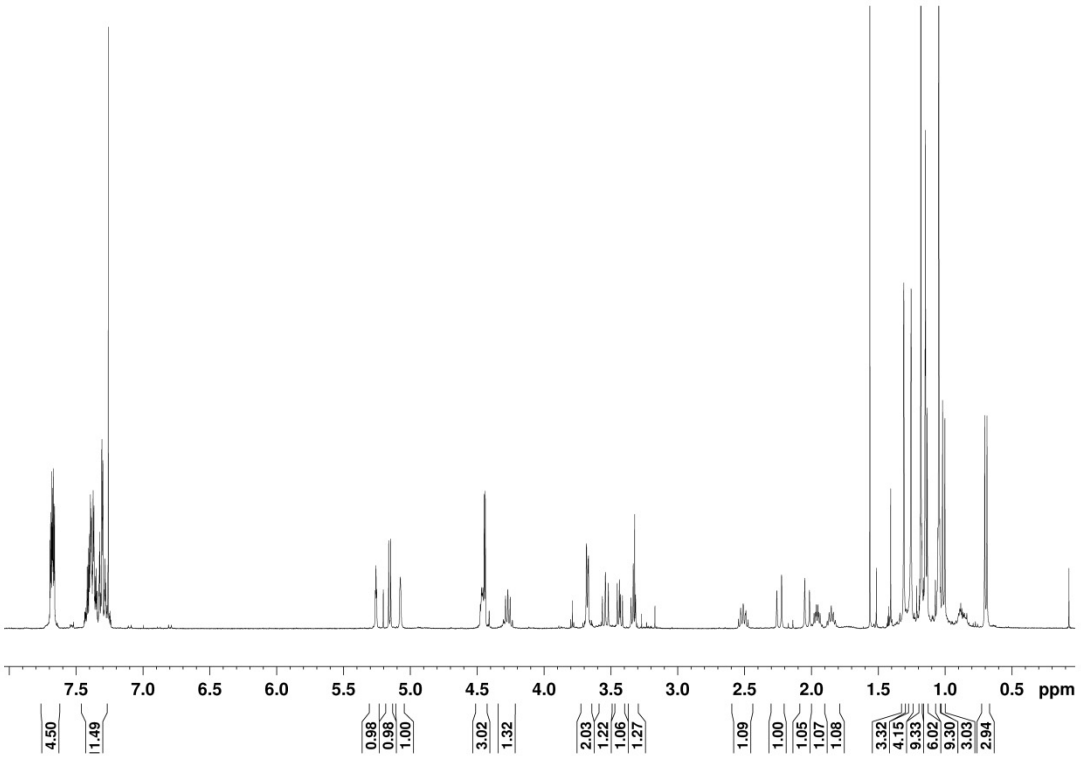



**170** **171**

**Acetonide 171:** To a solution of **170** (0.0011 g, 0.0148 mmol, 1.00 equiv.) in 0.70 ml 2,2-dimethoxypropane at rt, (+)-CSA (0.0003 mg, 0.0013 mmol, 0.09 equiv.) was added. The reaction mixture was stirred at rt for 30 min. (TLC showed full conversion). The reaction mixture was quenched by addition of one drop of $NEt_3$. Direct purification over a short pad of silica gel (EtOAc/hexane 1:20) gave 10.7 mg (92 %) of the **1,3-anti-product** as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.46 – 7.23 (m, 11H), 5.26 (t, *J* = 2.0 Hz, 1H), 5.16 (d, *J* = 6.0 Hz, 1H), 5.08 (s, 1H), 4.48 – 4.45 (m, 1H), 4.44 (d, *J* = 3.1 Hz, 2H), 4.32 – 4.23 (m, 1H), 3.69 – 3.66 (m, 2H), 3.54 (dd, *J* = 9.3, 8.7 Hz, 1H), 3.43 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.33 (t, *J* = 6.7 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.24 (d, *J* = 14.2 Hz, 1H), 2.03 (d, *J* = 14.2 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.89 – 1.81 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.18 (s, 9H), 1.15 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 177.87, 142.29, 138.30, 135.80, 135.78, 134.17, 129.61, 128.49, 127.87, 127.73, 127.69, 120.14, 115.03, 100.37, 82.49, 75.82, 73.40, 72.53, 71.20, 68.39, 65.40, 47.55, 42.12, 40.56, 38.85, 35.06, 29.85, 27.25, 27.02, 26.16, 23.86, 21.98, 19.45, 16.85, 13.85, 13.60, 1.17.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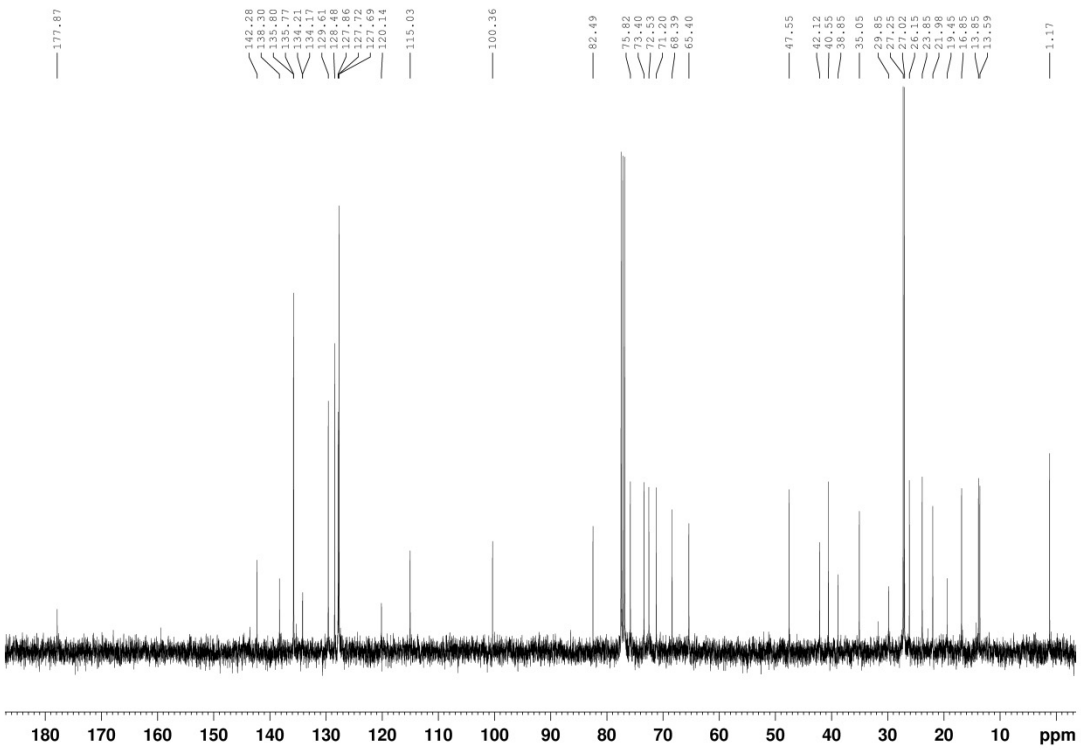
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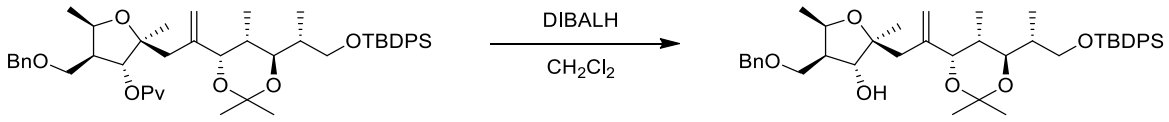
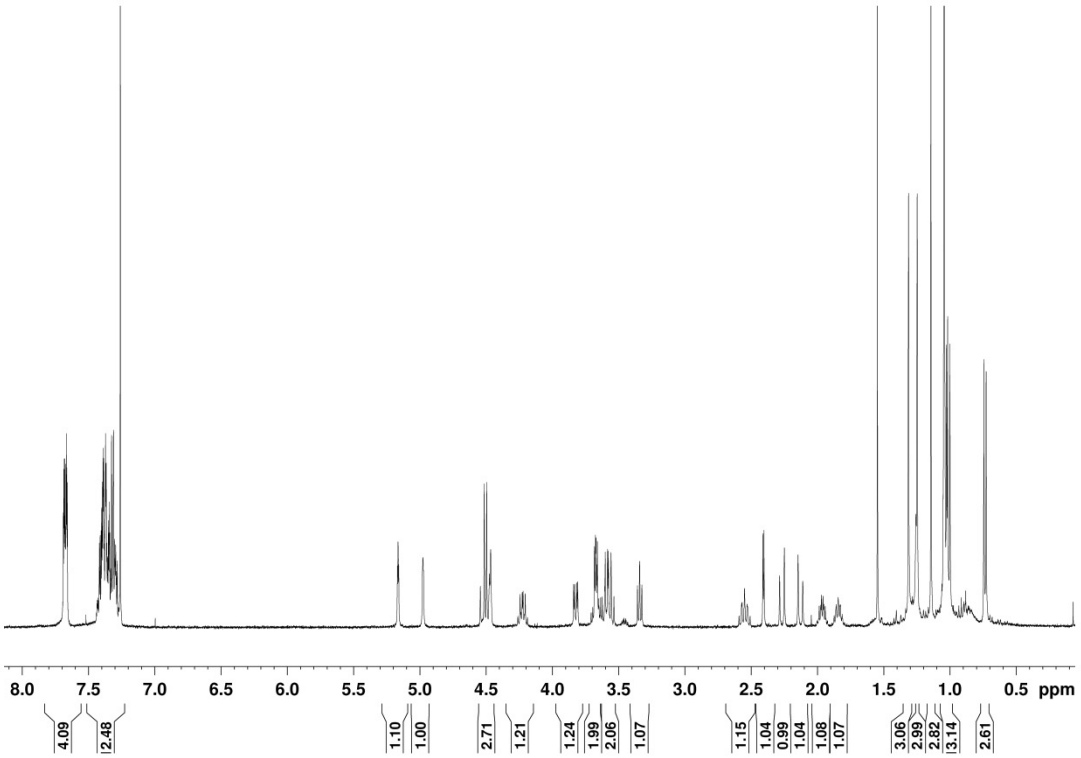



**171** **172**

**Alcohol 172: 171** (0.008 g, 0.0102 mmol, 1.00 equiv.) was dissolved in 0.20 mL of $CH_2Cl_2$, cooled to –78 °C and DIBAL (0.019 mL, 0.0224 mmol, 2.20 equiv., 1.2 M in toluene) was added drop wise. After 0.5 h at -78 °C the reaction mixture was quenched by addition of EtOAc. After warming up to rt aqu. Rochelle was added and the mixture was stirred for further 30 min. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 5.0 mg (70 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 4H), 7.45 – 7.27 (m, 11H), 5.16 (t, *J* = 2.0 Hz, 1H), 4.98 (s, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 8.3 Hz, 1H), 4.47 (s, 1H), 4.28 – 4.18 (m, 1H), 3.82 (dd, *J* = 9.3, 3.1 Hz, 1H), 3.71 – 3.64 (m, 2H), 3.64 – 3.53 (m, 2H), 3.34 (t, *J* = 6.7 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.41 (d, *J* = 3.2 Hz, 1H), 2.27 (d, *J* = 14.3 Hz, 1H), 2.13 (d, *J* = 14.2 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.89 – 1.80 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.05 (s, 9H), 1.04 (d, *J* = 7.6 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.84, 138.11, 135.80, 135.77, 134.18, 129.63, 128.63, 127.91, 127.80, 127.72, 120.14, 114.50, 100.53, 81.99, 76.94, 75.92, 73.66, 71.68, 71.25, 70.35, 65.36, 46.51, 41.59, 40.46, 36.15, 27.02, 25.89, 23.83, 20.85, 19.45, 17.98, 13.77, 13.70.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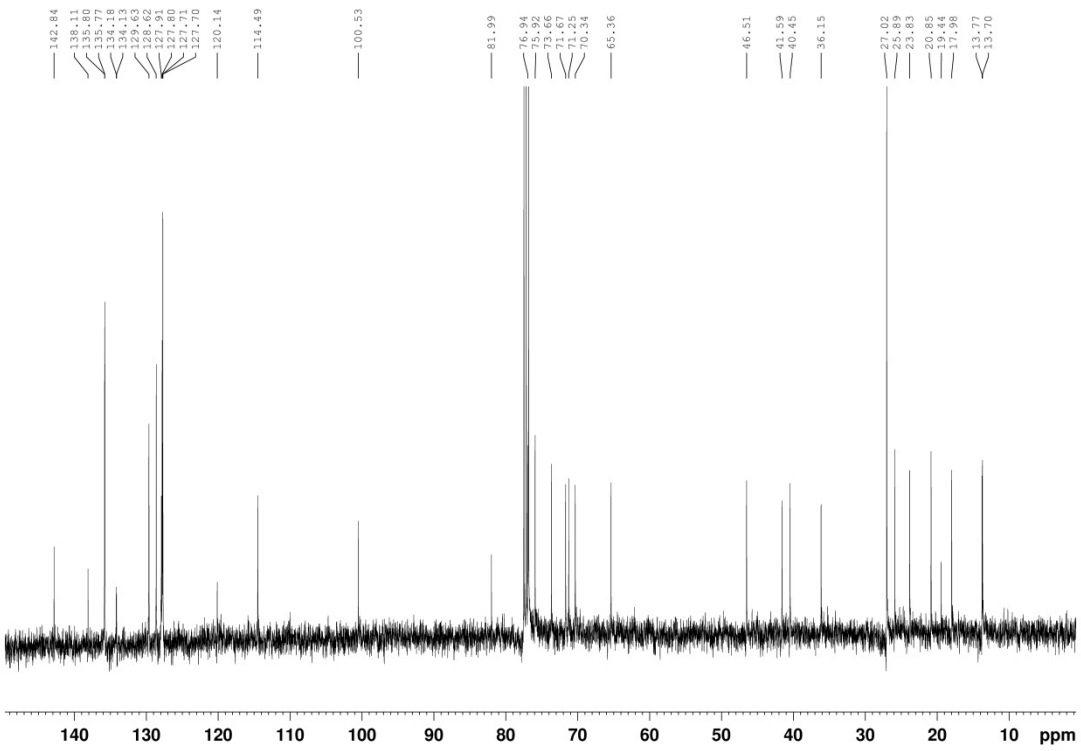
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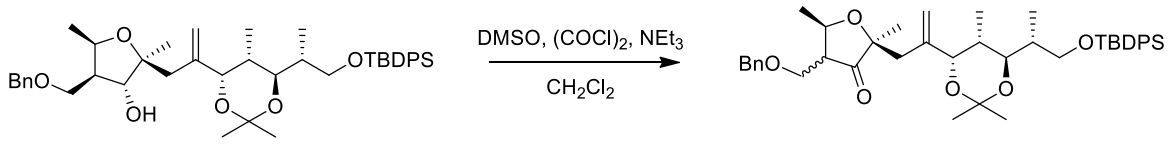
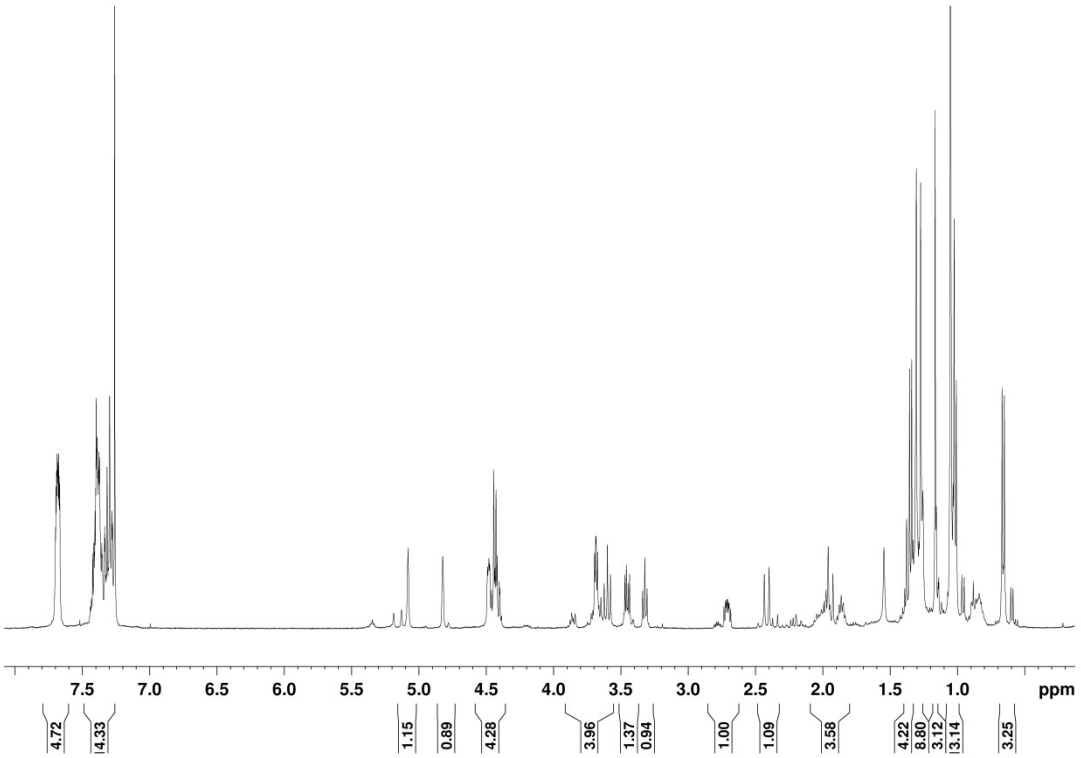



**172** **173**

**Ketone 173:** To a solution of oxalyl chloride (0.048 ml**,** 0.592 mmol, 20.00 equiv.) in 2.00 mL of anhydrous $CH_2C1_2$ at -78 °C was added DMSO (0.090 ml, 1.26 mmol, 45.00 equiv.) dropwise. The mixture was stirred for 15 min and a solution of **172** (19.7 mg, 0.0281 mmol, 1.00 equiv.) in 0.80 mL of anhydrous $CH_2CI_2$ was added dropwise. After 20 min, triethylamine (0.352 ml, 2.53 mmol, 90.00 equiv.) was carefully added, and the reaction was stirred at -78 °C for 10 min. The reaction was allowed to reach room temperature and then diluted with water. The two layers were separated, and the aqueous phase was extracted with $CH_2C1_2$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:15)) gave 19.0 mg (96 %, *dr* = ~1:1.5) of the desired product.

**Major isomer:** $^1$**H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 4H), 7.45 – 7.27 (m, 11H), 5.08 (s, 1H), 4.78 (s, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.25 – 4.15 (m, 1H), 3.73 – 3.64 (m, 3H), 3.61 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.31 (t, *J* = 6.7 Hz, 1H), 2.46 (d, *J* = 14.0 Hz, 1H), 2.08 – 1.94 (m, 2H), 1.91 – 1.81 (m, 1H), 1.78 – 1.64 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.7 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 241.64, 217.88, 142.25, 135.82, 135.79, 134.17, 134.14, 129.64, 128.56, 127.87, 127.71, 114.78, 100.40, 84.49, 75.86, 73.32, 71.38, 66.16, 65.38, 50.54, 40.46, 39.80, 34.94, 27.04, 26.16, 23.79, 21.60, 19.45, 16.63, 13.86, 13.74, 1.17.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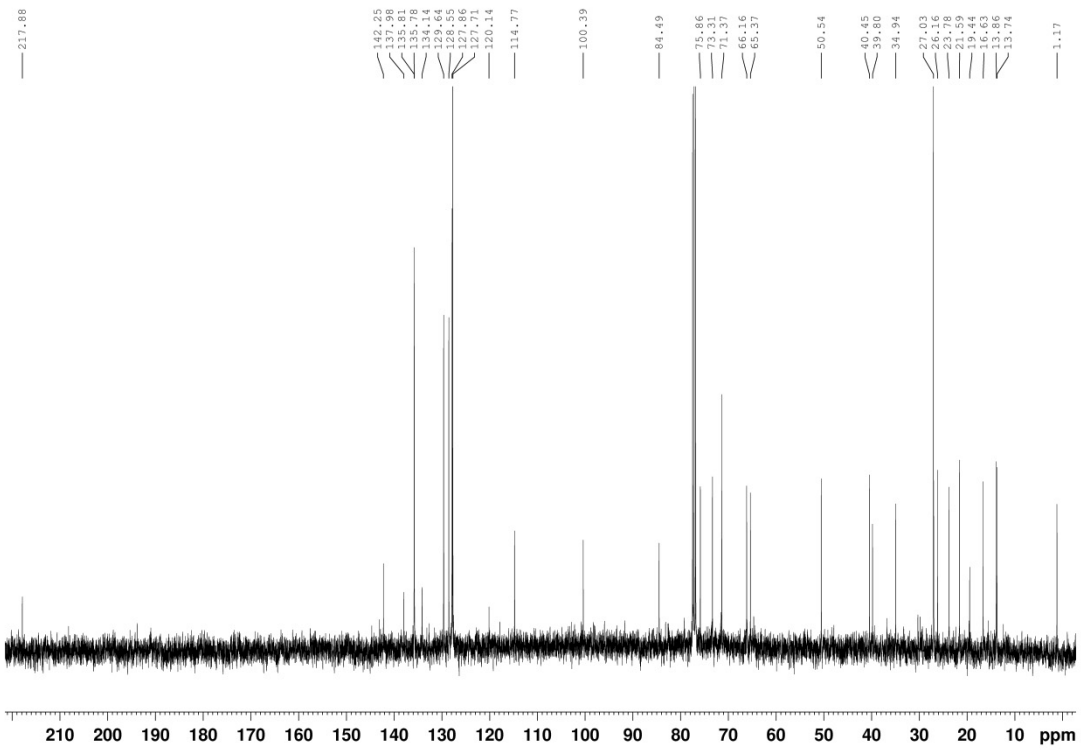
8.80
3.12
3.14
3.25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135.81
135.78
134.14
129.64
128.55
127.86
127.71
120.14
114.77
100.39
84.49
75.86
73.31
71.37
66.16
65.37
50.54
40.45
39.80
34.94
27.03
26.76
25.78
21.59
19.44
16.63
13.86
13.74
1.17
210
200
190
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150
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110
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70
60
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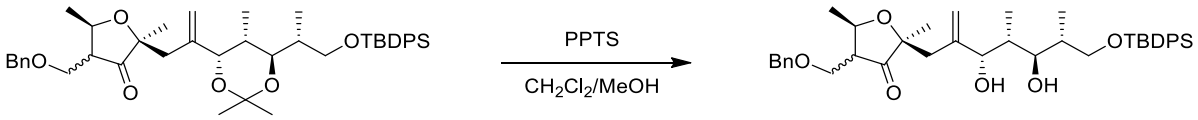
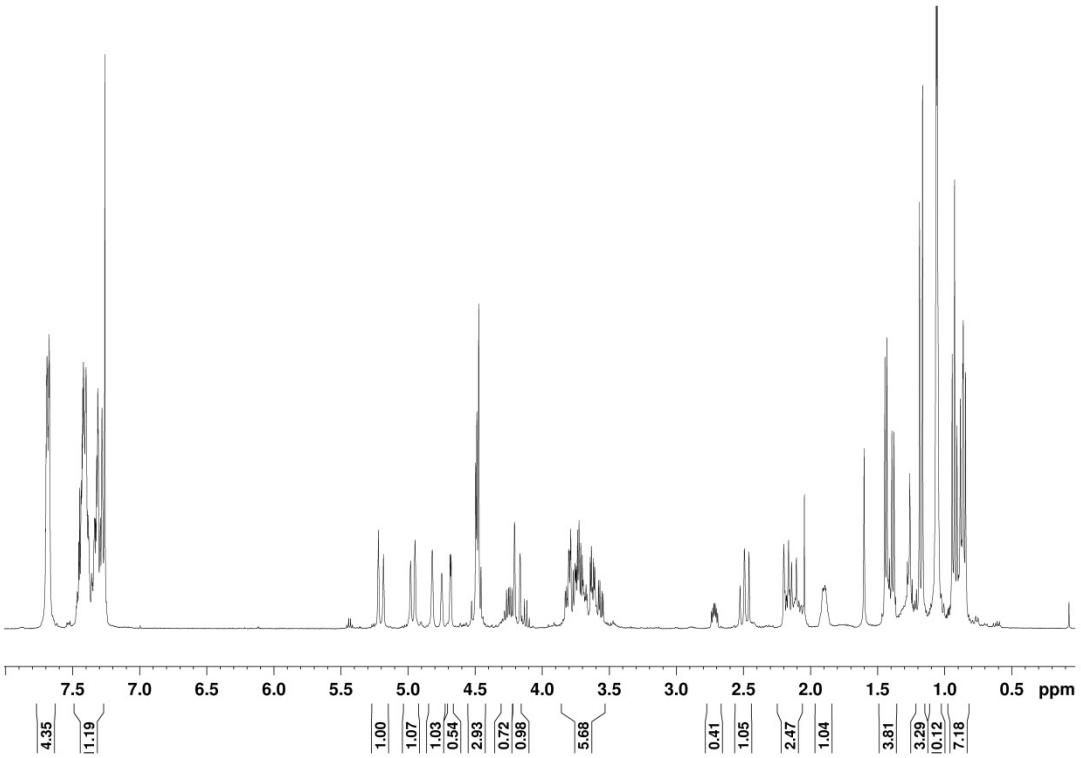
30
20
10
ppm




**173** **174**

**Diol 174:** To a solution of **173** (19.0 mg, 0.0272 mmol, 1.00 equiv.) in MeOH/THF (2:1) (0.27 ml) at rt was added PPTS (13.6 mg, 0.0544 mmol, 2.00 equiv.) The reaction mixture was stirred at rt for 16 h. The reaction mixture was than quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4) gave 9.8 mg (54 %, *dr* ~1:1) of the diol **174**.

**Both isomers $^1$H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 8H), 7.48 – 7.25 (m, 22H), 5.22 (s, 1H), 5.18 (s, 1H), 4.98 (s, 1H), 4.95 (s, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 4.56 – 4.40 (m, 6H), 4.32 – 4.06 (m, 3H), 3.85 – 3.49 (m, 11H), 2.72 (td, *J* = 7.8, 4.0 Hz, 1H), 2.51 (d, *J* = 12.8 Hz, 1H), 2.48 (d, *J* = 13.8 Hz, 1H), 2.22 – 2.02 (m, 5H), 1.96 – 1.85 (m, 2H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.06 (s, 9H), 1.06 (s, 9H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 217.85, 217.03, 145.54, 145.41, 138.17, 137.82, 135.75, 135.73, 135.72, 133.12, 133.00, 132.88, 132.73, 130.11, 130.07, 130.02, 129.98, 128.55, 128.51, 128.00, 127.98, 127.95, 127.93, 127.89, 127.83, 127.76, 127.52, 115.15, 114.69, 84.79, 83.64, 81.99, 81.11, 73.51, 73.45, 72.78, 72.61, 72.31, 71.76, 69.98, 69.33, 66.34, 65.89, 55.55, 50.20, 40.84, 39.96, 38.02, 37.70, 36.86, 36.01, 26.98, 26.94, 21.16, 20.77, 20.34, 19.29, 19.23, 16.36, 13.82, 13.60, 10.83, 10.71.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1.0
0.5
ppm
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2.47
1.04
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3.29
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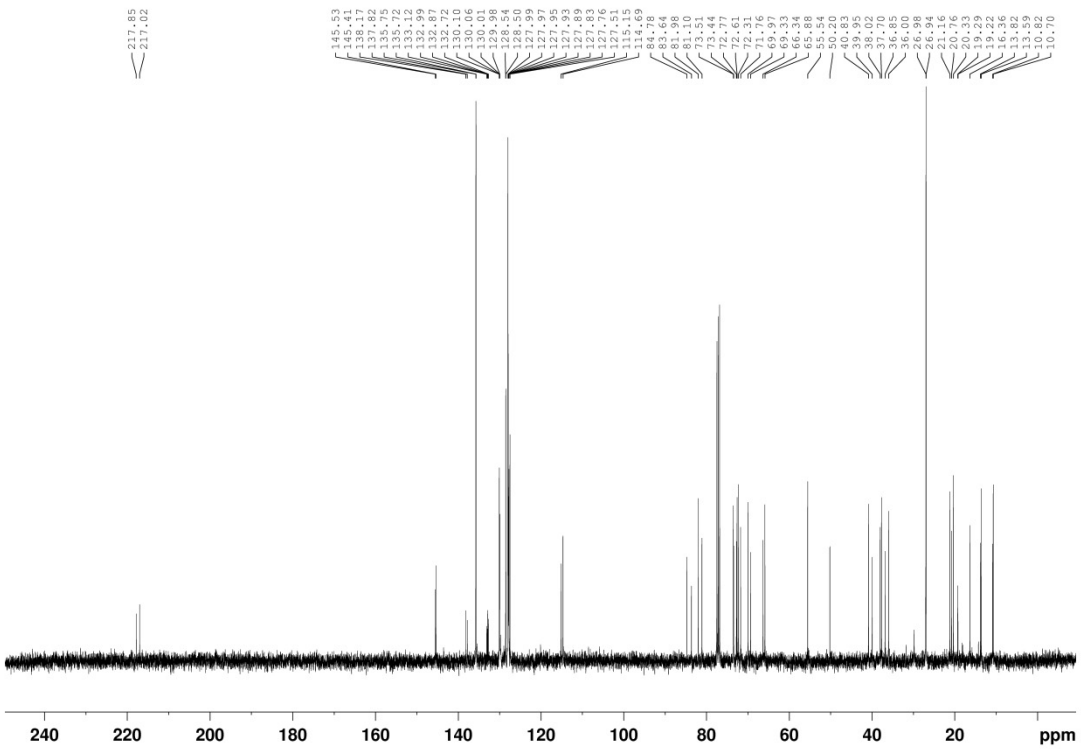
7.18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200
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140
120
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80
60
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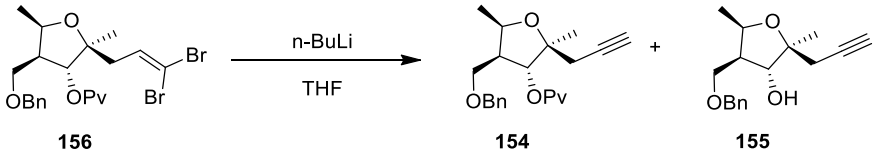
20
ppm

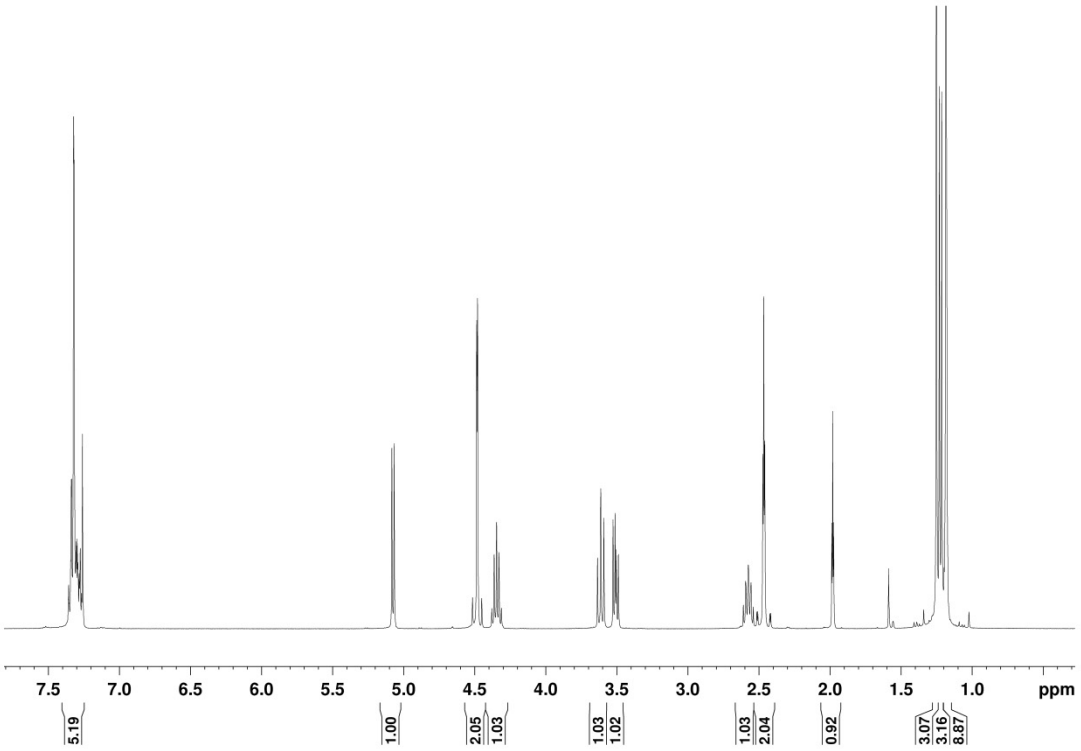
## 5.3.5. Cyclization with Protected Hydroxyl Group

### 5.3.5.1. Synthesis of Vinyl iodide Fragment 149




**Alkyne 154 and 155:** To a solution of **156** (2.43 g, 4.69 mmol, 1.00 equiv.) in THF (47.0 ml) at -78 °C was added *n*-BuLi (5.86 ml, 9.38 mmol, 2.00 equiv, 1.6 M in hexane) dropwise over 18 min. After completion of the addition, TLC showed almost complete conversion towards **154** and only traces of **155**. After 15 min at -78 °C additional *n*-BuLi (0.20 equiv.) was added dropwise over 1 min. TLC still showed traces of the starting material, but to avoid further Piv deprotection it was decided to stop the reaction by quenching with aqu. sat. $NH_4Cl$. The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:15 -> 1:4)) gave 1.44 gg (86 %) of **154** and 131.7 mg (10 %) of **155**.

**TLC**: $R_f$ = 0.46 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 5H), 5.08 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.35 (p, *J* = 6.7 Hz, 1H), 3.61 (dd, *J* = 9.4, 8.9 Hz, 1H), 3.51 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.49 (dd, *J* = 16.8, 2.7 Hz, 1H), 2.44 (dd, *J* = 16.8, 2.7 Hz, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 9H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 177.81, 138.11, 128.53, 127.94, 127.83, 81.41, 80.60, 79.10, 73.49, 73.29, 70.49, 68.16, 47.91, 38.85, 31.25, 27.19, 20.47, 16.92; **IR** (thin film): ν 3290, 2976, 2934, 2872, 1730, 1480, 1454, 1378, 1282, 1153, 1103, 1029, 1002, 771, 735, 698, 628; **HRMS** (ESI): calculated for $C_{22}H_{31}O_4$ $[M+H]^+$: 359.2217, found 359.2215; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +31.25° (c = 1.04 in $CHCl_3$).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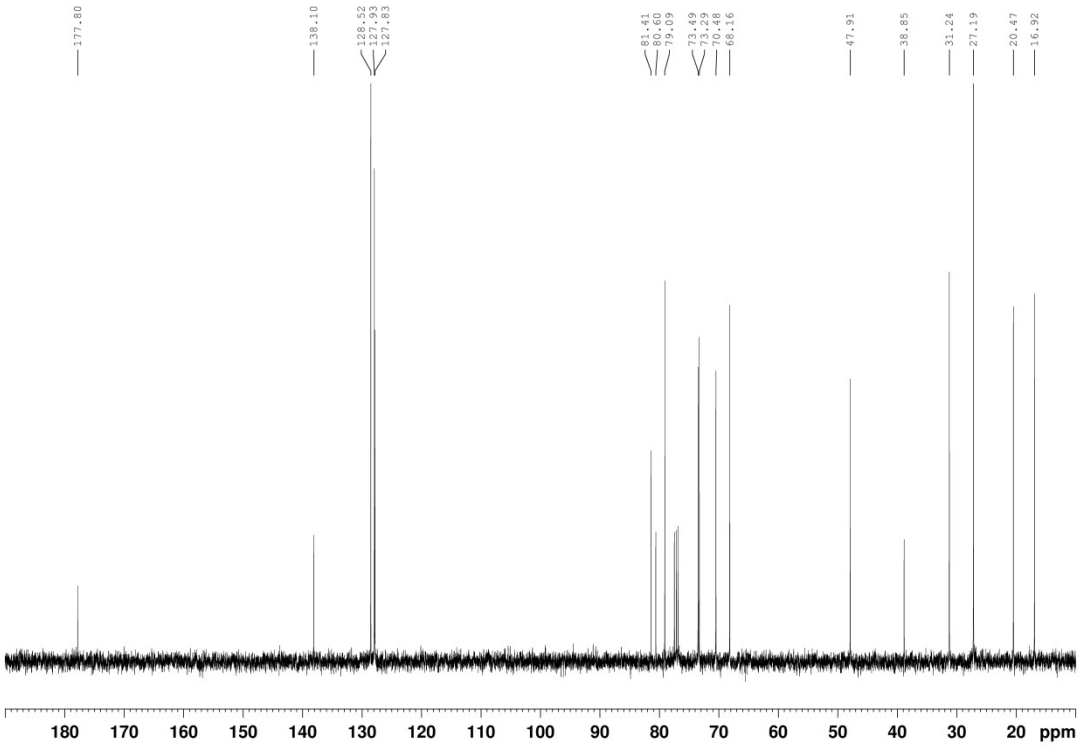
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73.29
70.48
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20.47
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50
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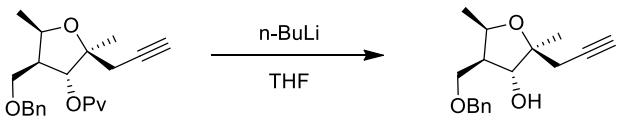
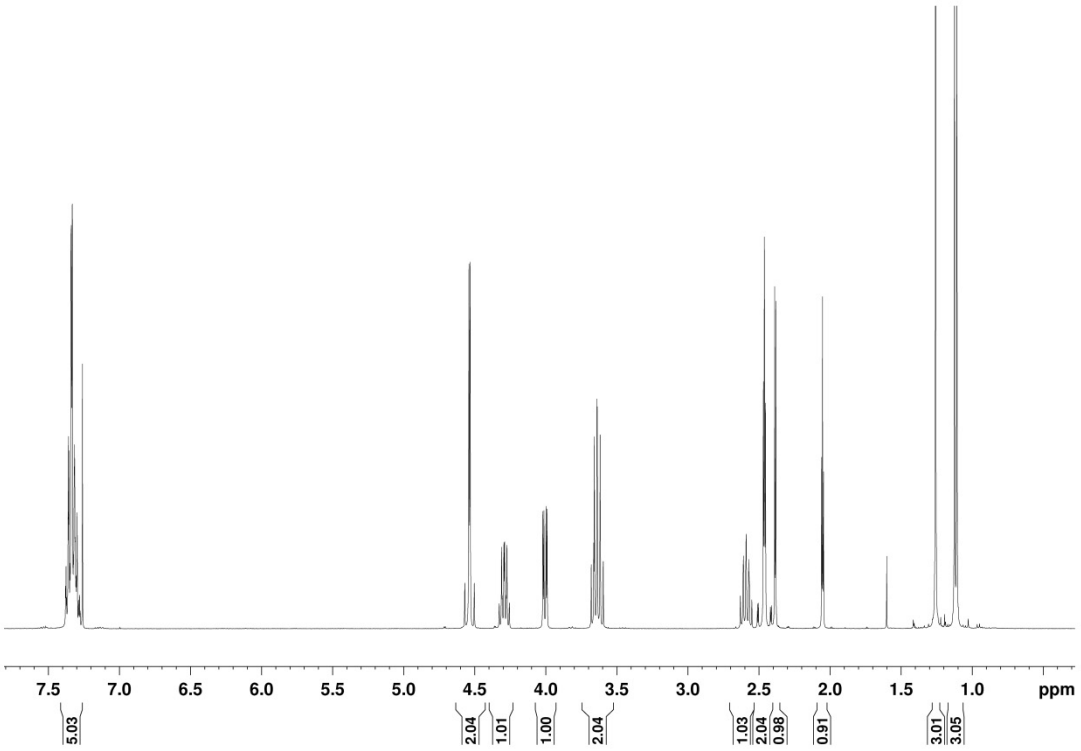
ppm




**154** **155**

**Alkyne 155:** To a solution of **154** (1.30 g, 3.63 mmol, 1.00 equiv.) in THF (36.0 ml) at -78 °C was added *n*-BuLi (7.03 ml, 11.24 mmol, 3.10 equiv, 1.6 M in hexane) dropwise over 5 min. After 1 h at -78 °C the reaction was quenched with aqu. sat. $NH_4Cl$. The layers were separated and the aqueous layer was extracted three times with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 985 mg (99 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.12 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.34 – 4.25 (m, 1H), 4.01 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.66 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.62 (dd, *J* = 8.9, 8.0 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.49 (dd, *J* = 16.5, 2.5 Hz, 1H), 2.44 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.39 (d, *J* = 2.9 Hz, 1H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.26 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 137.98, 128.64, 127.98, 127.87, 81.14, 81.03, 79.57, 73.72, 72.15, 70.66, 69.87, 47.56, 30.98, 19.78, 17.99; **IR** (thin film): ν 3414, 3296, 2975, 2929, 2864, 1496, 1454, 1380, 1308, 1206, 1076, 1027, 738, 698, 637; **HRMS** (ESI): calculated for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1642, found 275.1638; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +24.60° (c = 1.37 in $CHCl_3$).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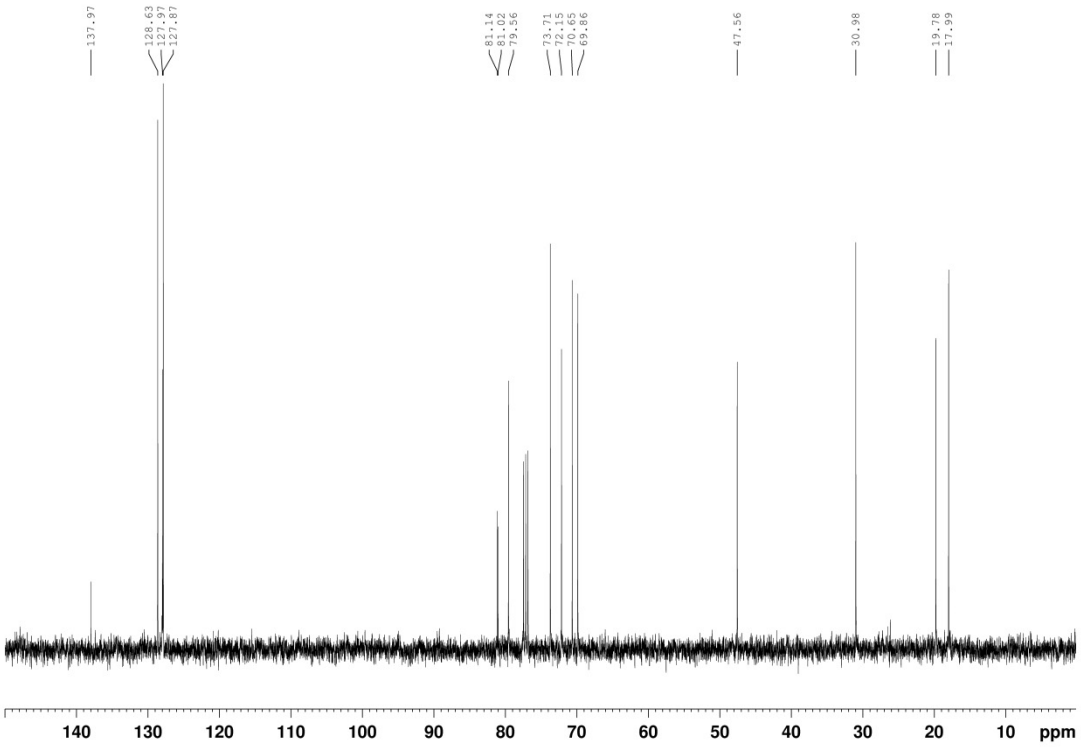
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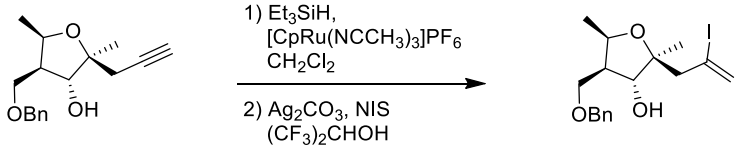
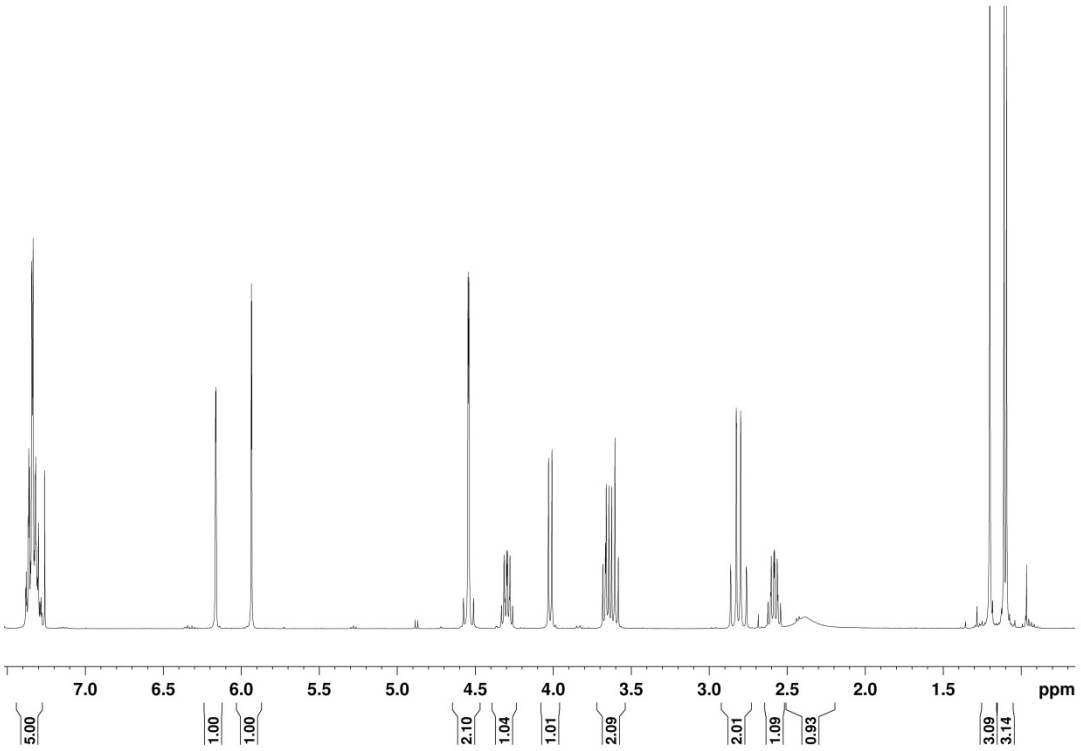
ppm




**155** **157**

**Vinyliodide 157:** To a solution of alkyne **155** (0.985 g, 3.59 mmol, 1.00 equiv.) and $[CpRu(MeCN)_3]PF_6$ (0.109 g, 0.215 mmol, 0.06 equiv.) in $CH_2Cl_2$ (36.0 mL) at 0 °C was added triethylsilane (0.688 mL, 0.501 mmol, 1.20 equiv.) (Reaction turns green). After stirring for 2 h the reaction mixture was concentrated and run through a small silica plug using EtOAc/hexanes (1:4) as the eluent. The filtrate was concentrated and dissolved in $(CF_3)_2CHOH$ (18 mL). To the cooled (0°C) solution was added $Ag_2CO_3$ (0.297 g, 1.07 mmol, 0.30 equiv.) and NIS (0.969 g, 4.31 mmol, 1.20 equiv.). After stirring for 20 min the reaction mixture was quenched with a saturated solution of sodium thiosulfate (40 mL). After 20 min the reaction mixture was extracted with $CH_2Cl_2$. The comb. org. phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:4)) gave 1.153 g (80 %) of the desired vinyl iodide as colorless oil.

**TLC**: $R_f$ = 0.13 (EtOAc/hexane 1:4, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 6.16 (d, *J* = 1.0 Hz, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.34 – 4.25 (m, 1H), 4.02 (d, *J* = 8.8 Hz, 1H), 3.66 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.60 (dd, *J* = 8.8, 8.4 Hz, 1H), 2.84 (dd, *J* = 14.8, 0.8 Hz, 1H), 2.78 (d, *J* = 14.7 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.38 (s, 1H), 1.20 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 137.97, 130.81, 128.65, 127.98, 127.83, 102.38, 82.27, 78.93, 73.70, 71.84, 70.08, 54.45, 47.16, 20.10, 18.04; **IR** (thin film): ν3439, 2973, 2863, 2361, 1611, 1496, 1453, 1378, 1312, 1147, 1099, 1053, 1027, 900, 735, 697; **HRMS** (ESI): calculated for $C_{17}H_{23}INaO_3$ $[M+Na]^+$:425.0584, found 425.0583; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +11.45° (c = 1.24 in $CHCl_3$).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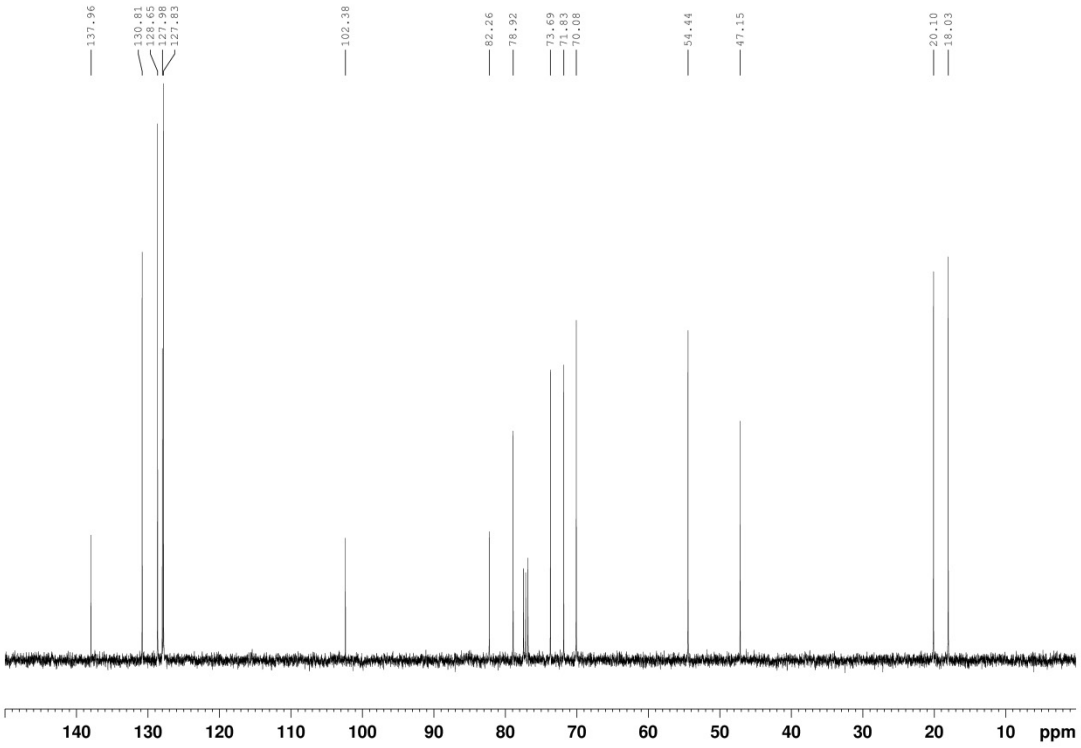
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10
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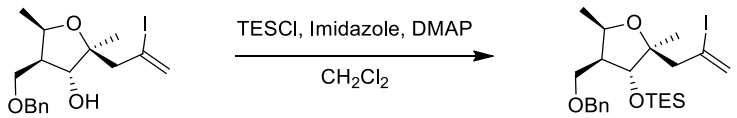
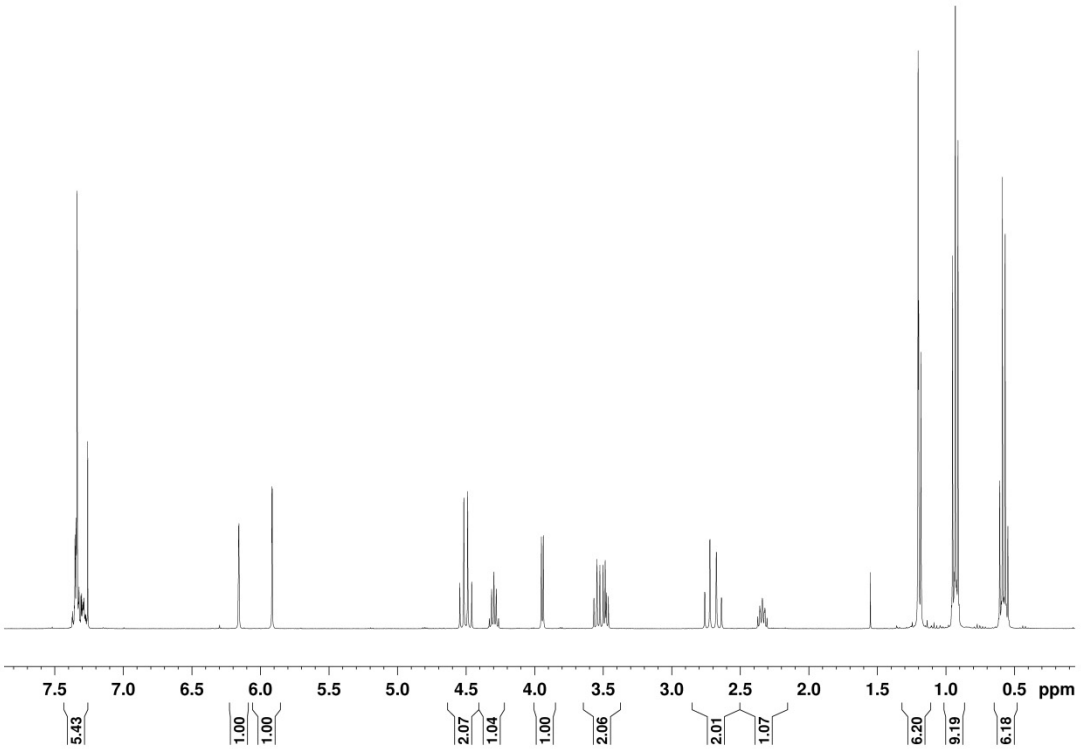



**157** **185**

**Silylether 185:** To a solution of **157** (1.15 g, 2.86 mmol, 1.00 equiv.) in $CH_2Cl_2$ (28.0 ml) at rt, Imidazole (0.448 g, 6.57 mmol, 2.30 equiv.) and DMAP (0.0349 g, 0.286 mmol, 0.10 equiv.) were added. Afterwards TESCl (0.720 ml, 4.29 mmol, 1.50 equiv.) was added neat. (Reaction mixture turned from colorless to a white emulsion within minutes) the reaction mixture was stirred at rt overnight. Then the reaction mixture was diluted with hexane, washed with brine, dired over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (hexane → EtOAc/hexane (1:40) gave 1.44 g (97 %) of the desired product as colorless liquid.

**TLC**: $R_f$ = 0.11 (EtOAc/hexane 1:40, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 6.16 (d, *J* = 1.1 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.30 (p, *J* = 6.6 Hz, 1H), 3.94 (d, *J* = 5.5 Hz, 1H), 3.55 (dd, *J* = 9.2, 8.3 Hz, 1H), 3.48 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.74 (dd, *J* = 14.9, 0.7 Hz, 1H), 2.66 (d, *J* = 14.6 Hz, 1H), 2.40 – 2.28 (m, 1H), 1.20 (s, 2H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 138.30, 130.49, 128.50, 127.96, 127.79, 102.79, 83.76, 79.06, 73.48, 72.62, 68.34, 54.73, 50.18, 20.00, 16.84, 7.04, 5.30; **IR** (thin film): ν 2954, 2874, 1611, 1454, 1381, 1364, 1236, 1115, 1064, 1003, 896, 844, 727, 696; **HRMS** (ESI): calculated for $C_{23}H_{38}IO_3Si$ $[M+H]^+$: 517.1629, found 517.1623; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +8.88° (c = 1.25 in $CHCl_3$).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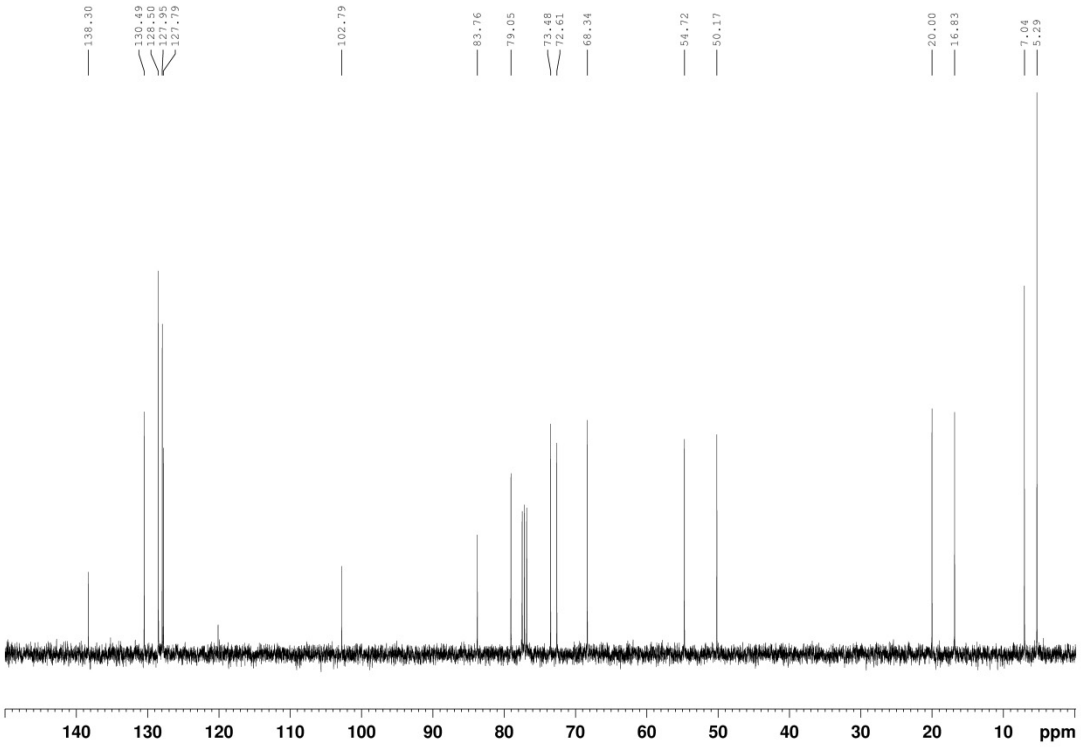
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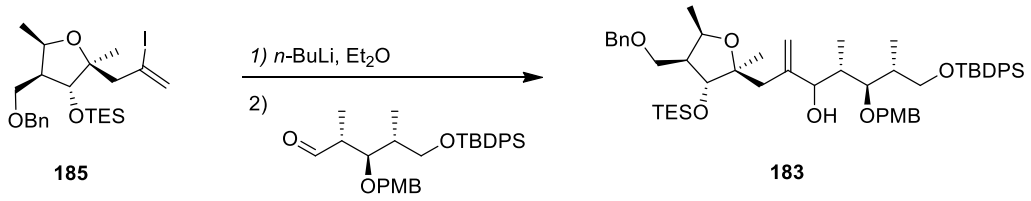
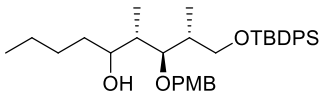
### 5.3.5.2. Fragment Assembly via Vinyllithium Addition

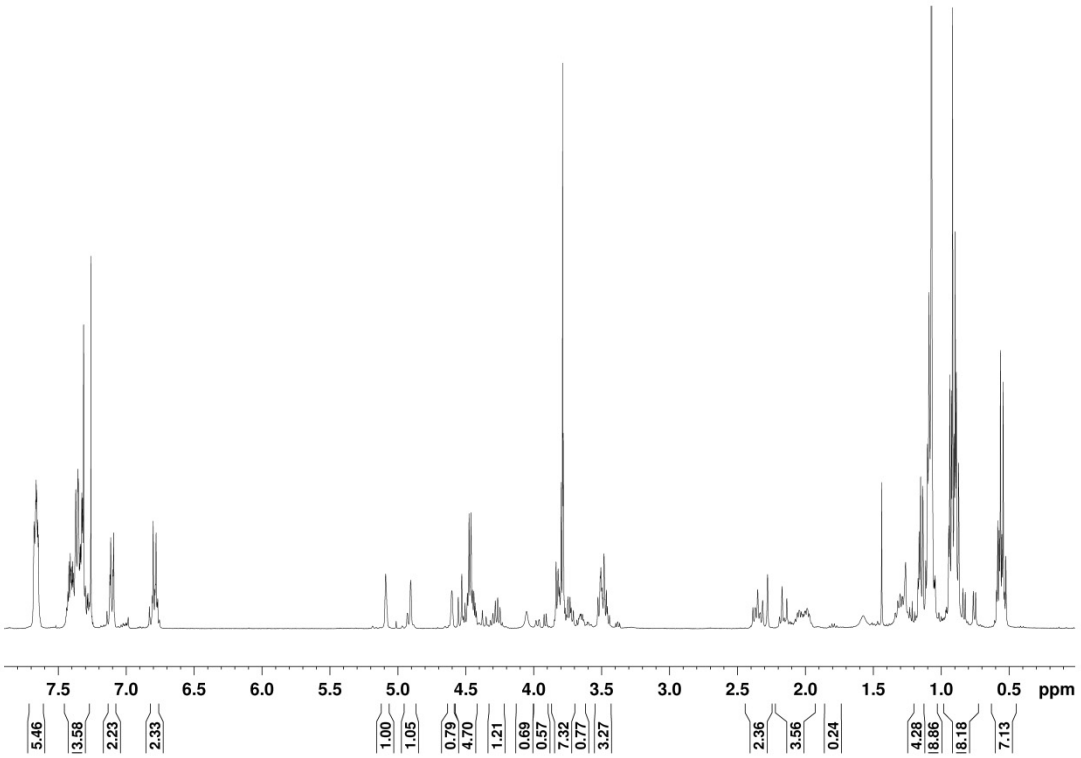



**Allylalcohol 183:** To a cooled solution (-78 °C) of **185** (1.26 g, 2.43 mmol, 2.80 equiv.) in dry ether (22 ml) was added *n*-BuLi (1.52 ml, 2.43 mmol, 2.80 equiv.) and the mixture was stirred at -78°C for 30 min. A solution of **74** (0.439 g, 0.870 mmol, 1.00 equiv.) in 1.5 ml $Et_2O$ was added dropwise over 9 min to the reaction mixture (the flask containing the aldehyde was rinsed twice with 0.5 ml $Et_2O$). After stirring for 2 h the reaction mixture was quenched with aqu. sat. $NH_4Cl$. The phases were separated and the aqu. phase extracted with $Et_2O$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel ($Et_2O$/pentane (1:10 → 1:7 → 1:4)) gave 373 mg (45 %, dr = 1:3.5) of the desired product as colorless oil with 3 % contamination of **188**.

**TLC**: $R_f$ = 0.19 ($Et_2O$/pentane 1:4, UV, CPS); **$^1$H-NMR (major isomer)** (400 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 4H), 7.45 – 7.24 (m, 11H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.09 (s, 1H), 4.91 (s, 1H), 4.60 (s, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.32 – 4.22 (m, 1H), 4.05 (s, 1H), 3.83 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.81 – 3.70 (m, 2H), 3.54 – 3.44 (m, 3H), 2.40 – 2.33 (m, 1H), 2.30 (d, *J* = 14.5 Hz, 1H), 2.15 (d, *J* = 13.9 Hz, 1H), 2.09 – 2.02 (m, 1H), 2.02 – 1.94 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.09 (s, 3H), 1.07 (s, 9H), 0.95 – 0.89 (m, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.60 – 0.52 (m, 6H); **$^{13}$C-NMR (major isomer)** (101 MHz, $CDCl_3$) δ 159.20, 147.00, 138.33, 135.91, 135.87, 134.10, 134.03, 131.08, 129.68, 129.49, 129.29, 128.46, 127.98, 127.76, 127.72, 127.67, 114.29, 113.84, 113.72, 85.10, 83.50, 79.16, 75.32, 73.43, 72.63, 72.16, 68.45, 65.58, 55.42, 49.83, 44.22, 38.46, 38.10, 27.12, 19.74, 16.93, 15.70, 11.08, 7.02, 5.31; **IR** (thin film): ν 3479, 2956, 2931, 2874, 2857, 1612, 1587, 1513, 1455, 1427, 1386, 1361, 1302, 1247, 1172, 1111, 1062, 1036, 1008, 908, 843, 822, 738, 700, 614, 504, 490, 486; **HRMS** (ESI): calculated for $C_{54}H_{79}O_7Si_2$ $[M+H]^+$: 895.5359, found 895.5360; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -2.84° (c = 1.09 in $CHCl_3$).




**188**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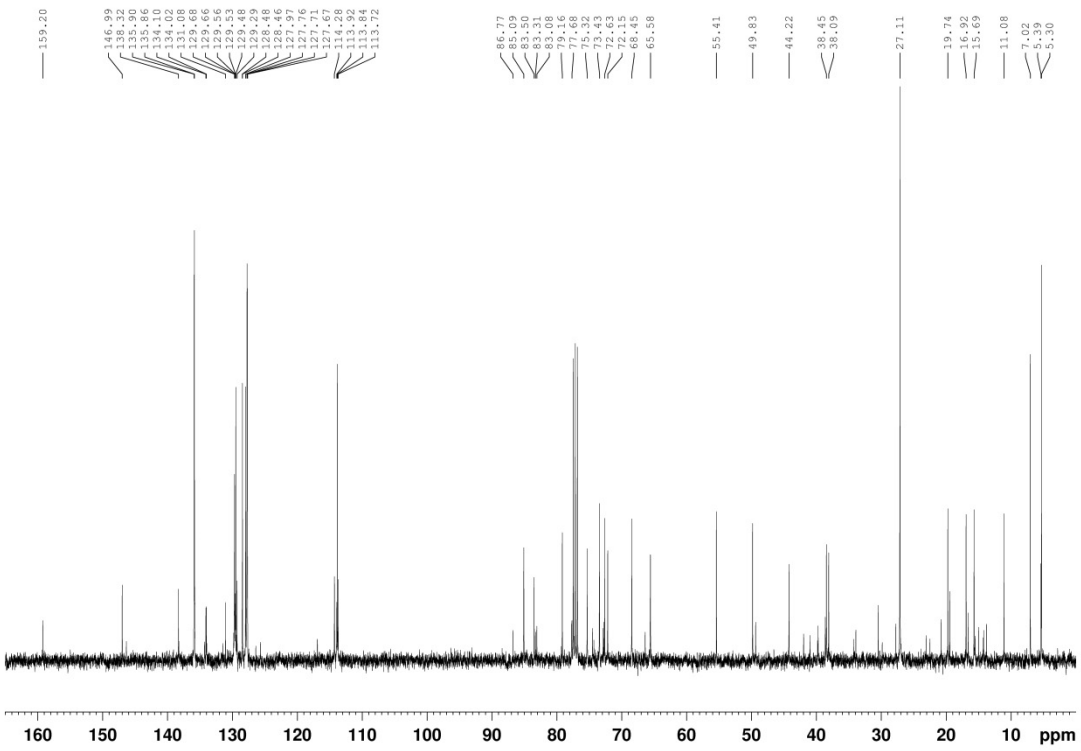
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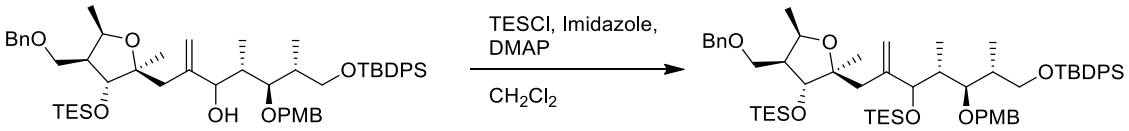
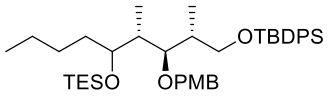


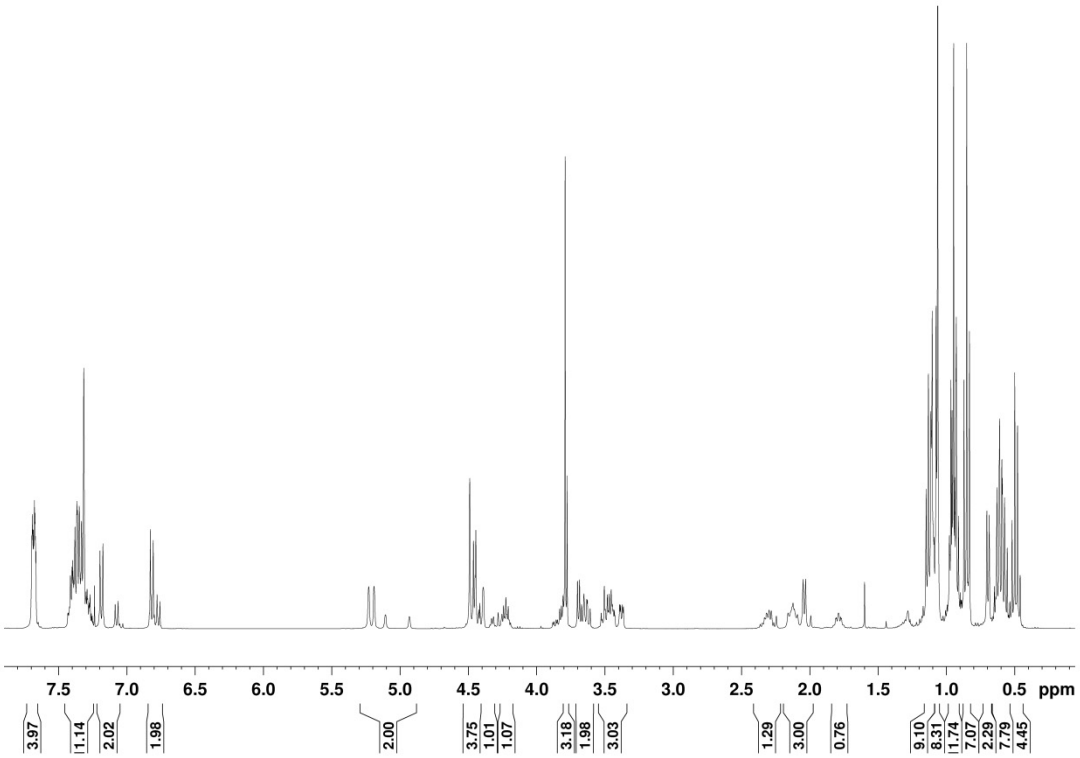

**183** **189**

**Silylether 189:** To a solution of **183** (364 mg, 0.406 mmol, 1.00 equiv.) in $CH_2Cl_2$ (4.06 ml) at rt, Imidazole (0.127 g, 1.87 mmol, 4.60 equiv.) and DMAP (9.9 mg, 0.0813 mmol, 0.20 equiv.) were added. Afterwards TESCl (0.205 ml, 1.22 mmol, 3.00 equiv.) was added neat. (Reaction mixture turned from colorless to a white emulsion within minutes) the reaction mixture was stirred at rt for 24 h. Then the reaction mixture was quenched by addition of aqu. sat. $NaHCO_3$. The aqu. phase was extracted 3 times with $CH_2Cl_2$ , the comb. org. phases were washed with brine, dired over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (hexanes → EtOAc/hexane (1:10) gave 332 mg (81 %) of the isomeric mixture of the desired product as colorless oil and 46 mg (12 %, impure) of the side product **234**.

**TLC**: $R_f$ = 0.48 (EtOAc/hexane 1:10, UV, CPS); **$^1$H-NMR (major isomer)** (400 MHz, $CDCl_3$) δ 7.68 (dd, 4H), 7.45 – 7.25 (m, 11H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.23 (s, 1H), 5.19 (s, 1H), 4.49 (s, 2H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.39 (s, 1H), 4.29 – 4.18 (m, 1H), 3.84 – 3.78 (m, 1H), 3.79 (s, 3H), 3.69 (d, *J* = 6.1 Hz, 1H), 3.63 (dd, *J* = 10.0, 8.2 Hz, 1H), 3.54 – 3.42 (m, 2H), 3.38 (dd, *J* = 8.2, 2.9 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.18 – 2.07 (m, 1H), 2.07 (d, *J* = 16.3 Hz, 1H), 2.01 (d, *J* = 15.4 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 9H), 0.98 – 0.90 (m, 9H), 0.85 (t, *J* = 7.9 Hz, 9H), 0.69 (d, *J* = 6.9 Hz, 3H), 0.66 – 0.54 (m, 6H), 0.49 (q, *J* = 7.8 Hz, 6H); **$^{13}$C-NMR (major isomer)** (101 MHz, $CDCl_3$) δ 158.87, 146.69, 138.37, 135.79, 134.16, 131.84, 129.61, 129.59, 128.68, 128.44, 127.88, 127.71, 113.61, 113.53, 113.43, 83.49, 83.22, 81.72, 80.71, 76.07, 73.39, 73.33, 72.05, 68.83, 65.68, 55.35, 49.56, 42.80, 39.30, 38.45, 27.05, 19.38, 18.90, 17.05, 15.73, 9.38, 7.29, 7.01, 5.58, 5.29; **IR** (thin film): ν 2954, 2875, 1513, 1457, 1428, 1384, 1304, 1246, 1112, 1068, 1009, 822, 740, 700, 612; **HRMS** (ESI): calculated for $C_{60}H_{93}O_7Si_3$ $[M+H]^+$: 1009.6224, found 1009.6221; $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$: -3.84° (c = 1.12 in $CHCl_3$).




**234**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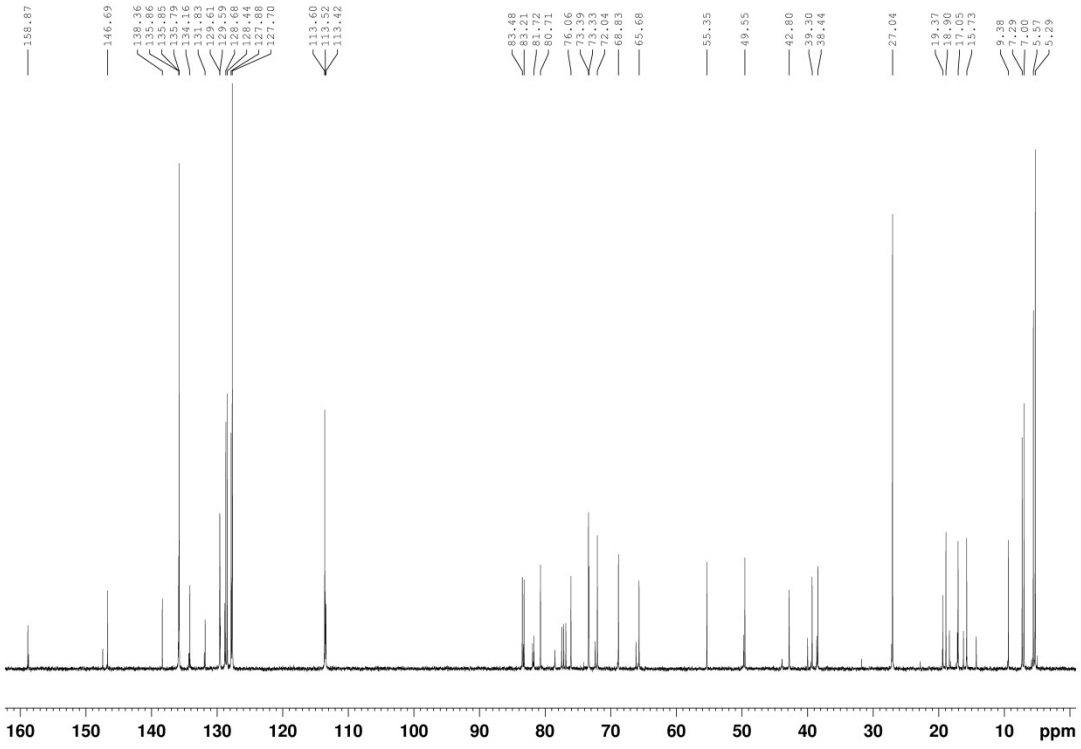
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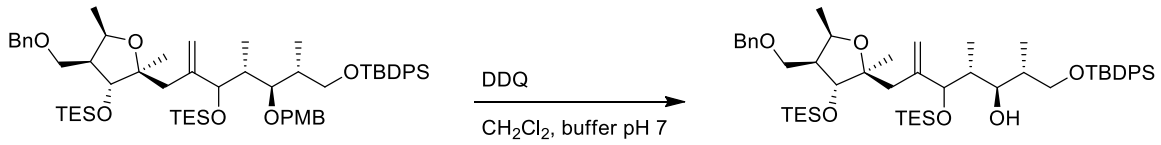
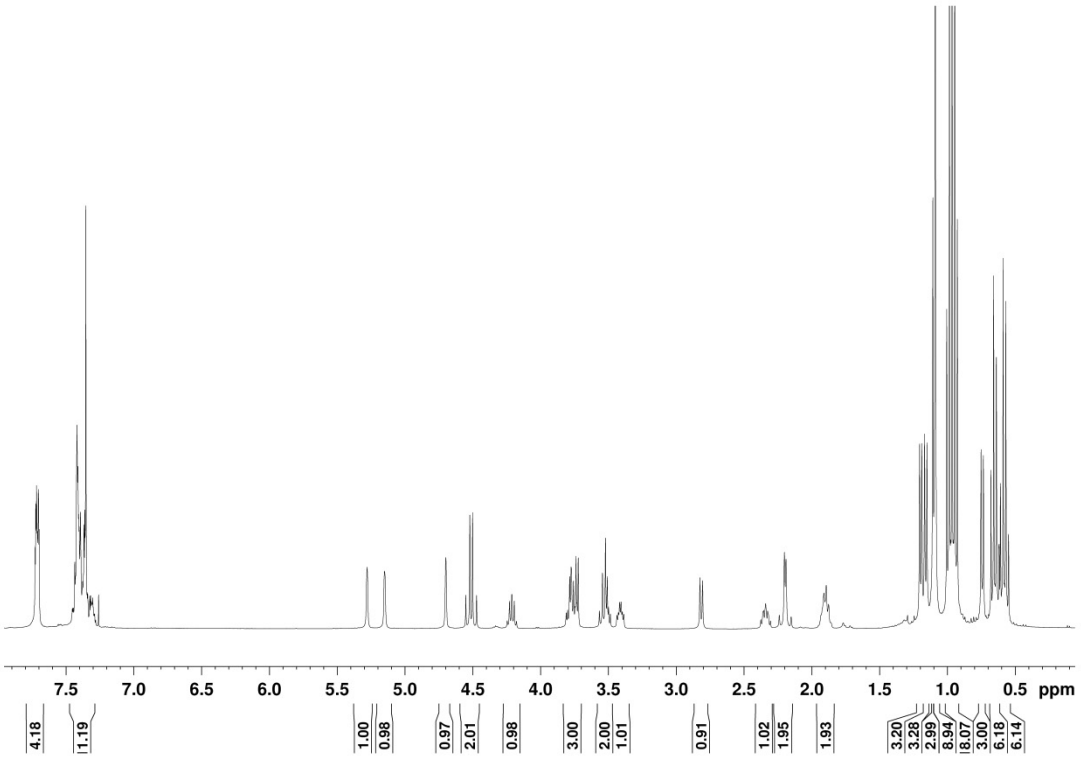



**189** **190**

**Alcohol 190:** To **189** (328 mg, 0.325 mmol, 1.00 equiv.) was added 3.00 ml $CH_2Cl_2$ and 0.30 ml phosphate buffer (pH 7). The mixture was cooled to 0 °C and DDQ (88.5 mg, 0.390 mmol, 1.20 equiv.) was added. The cooling bath was removed and the reaction mixture was stirred at rt for 1 h 50 min. The reaction was quenched by addition of aqu. sat $NaHCO_3$ and extracted 3 times with $CH_2Cl_2$. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:20)) gave 193 mg (66 %), of the desired isomer, of the desired product as colorless oil and 60 mg (20 %) of the undesired isomer.

**TLC**: $R_f$ = 0.41 (EtOAc/hexane 1:10, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.65 (m, 4H), 7.47 – 7.28 (m, 11H), 5.28 (s, 1H), 5.15 (s, 1H), 4.70 (s, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.21 (p, *J* = 6.6 Hz, 1H), 3.82 – 3.73 (m, 2H), 3.73 (d, *J* = 6.5 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.44 – 3.38 (m, 1H), 2.82 (d, *J* = 7.7 Hz, 1H), 2.42 – 2.29 (m, 1H), 2.22 (d, *J* = 15.1 Hz, 1H), 2.17 (d, *J* = 15.2 Hz, 1H), 1.96 – 1.84 (m, 2H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.09 (s, 9H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.95 (d, *J* = 7.8 Hz, 9H), 0.74 (d, *J* = 6.9 Hz, 3H), 0.65 (q, *J* = 7.7 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 146.76, 138.26, 135.79, 135.74, 133.72, 133.66, 129.73, 129.72, 128.47, 127.98, 127.79, 127.76, 114.46, 83.18, 79.35, 77.00, 74.76, 73.47, 72.04, 68.78, 65.59, 49.19, 44.19, 39.25, 37.47, 27.05, 19.35, 19.25, 16.97, 15.91, 9.65, 7.18, 7.04, 5.43, 5.22; **IR** (thin film): ν 3524, 2956, 2932, 2910, 2874, 1455, 1428, 1381, 1237, 1111, 1065, 1005, 906, 822, 737, 699, 614, 503; **HRMS** (ESI): calculated for $C_{52}H_{85}O_6Si_3$ $[M+H]^+$: 889.5648, found 889.5641; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +3.36° (c = 1.16 in $CHCl_3$).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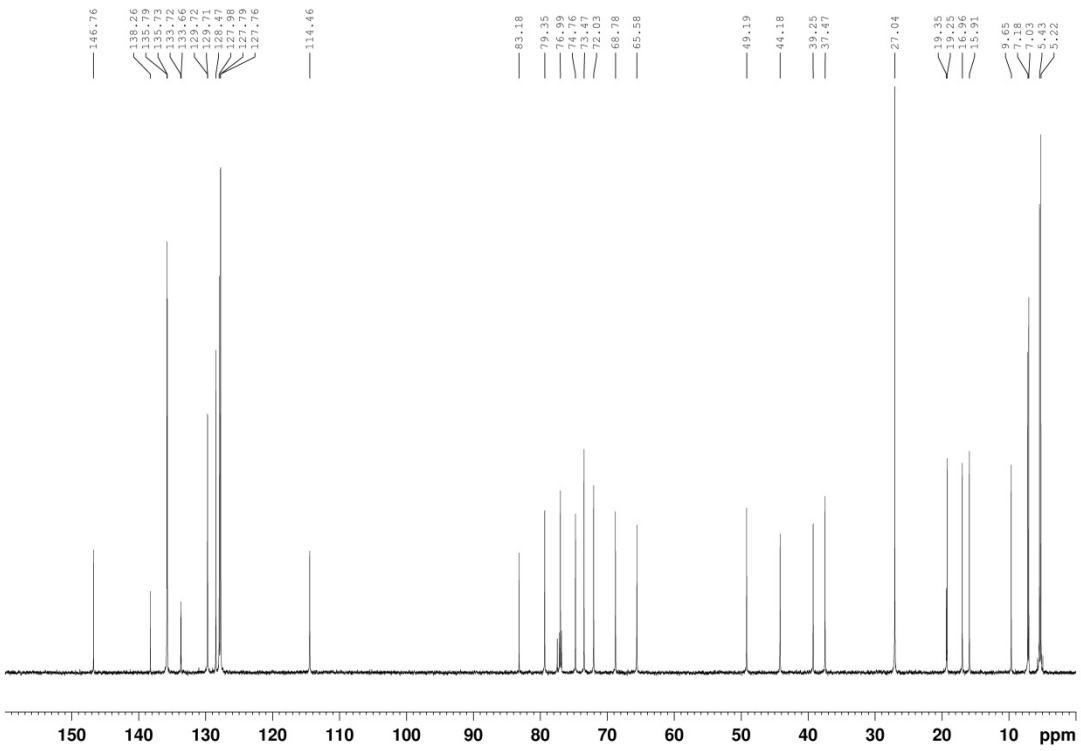
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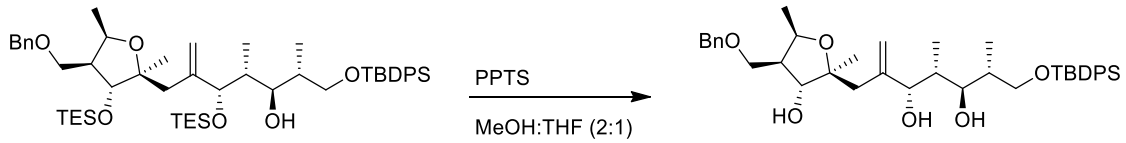
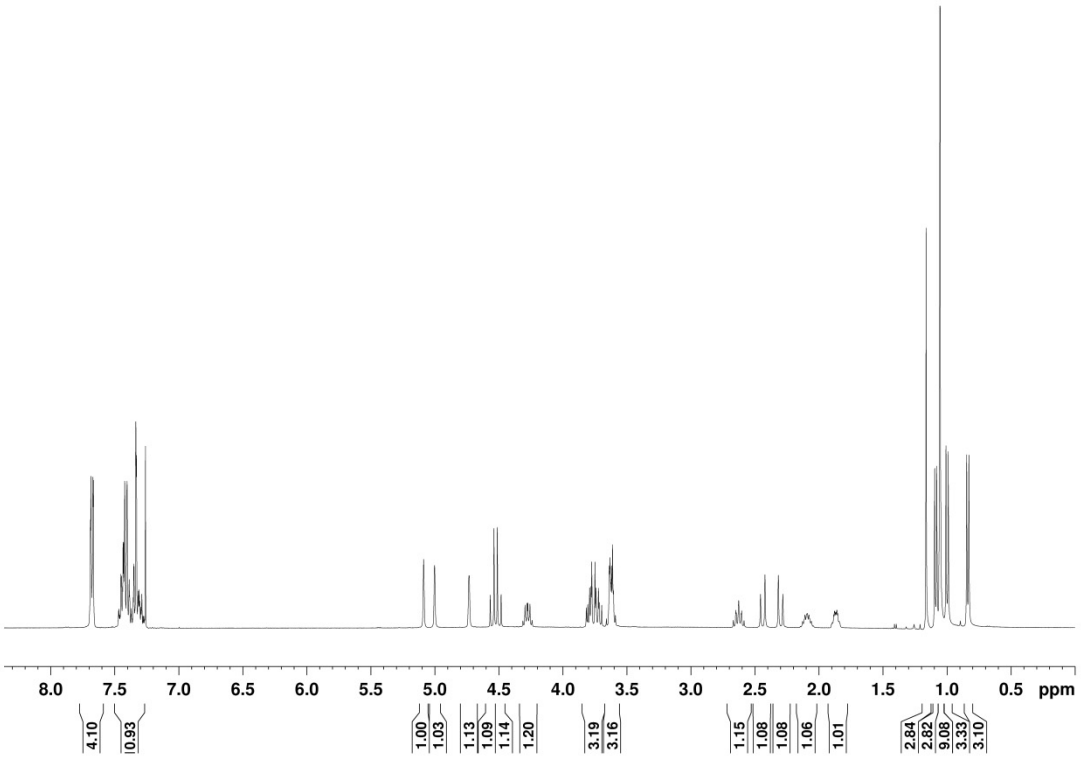



**190** **192**

**Triol 192:** To a solution of **190** (187.0 mg, 0.210 mmol, 1.00 equiv.) in MeOH/THF (2:1) (2.10 ml) at rt was added PPTS (105.6 mg, 0.420 mmol, 2.00 equiv.) The reaction mixture was stirred at rt for 1 h 15 min. The reaction mixture was than quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:2) gave 133.8 mg (96 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.41 (EtOAc/hexane 1:1, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.49 – 7.27 (m, 11H), 5.09 (s, 1H), 5.00 (s, 1H), 4.73 (s, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.80 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.72 (dd, *J* = 10.1, 7.7 Hz, 1H), 3.67 – 3.59 (m, 3H), 2.68 – 2.57 (m, 1H), 2.44 (d, *J* = 14.0 Hz, 1H), 2.30 (d, *J* = 14.0 Hz, 1H), 2.16 – 2.03 (m, 1H), 1.91 – 1.82 (m, 1H), 1.16 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 146.72, 138.14, 135.72, 132.86, 132.77, 130.07, 130.05, 128.59, 127.98, 127.96, 127.89, 113.94, 82.41, 81.92, 76.97, 73.66, 73.64, 71.74, 70.05, 69.72, 46.13, 41.63, 39.20, 37.78, 26.95, 20.48, 19.22, 17.94, 13.61, 11.34; **IR** (thin film): ν 3393, 2965, 2930, 2857, 1454, 1428, 1380, 1311, 1262, 1111, 1081, 1027, 974, 906, 824, 741, 700, 614, 506; **HRMS** (ESI): calculated for $C_{40}H_{57}O_6Si$ $[M+H]^+$: 661.3919, found 661.3912; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -9.28° (c = 0.97 in $CHCl_3$).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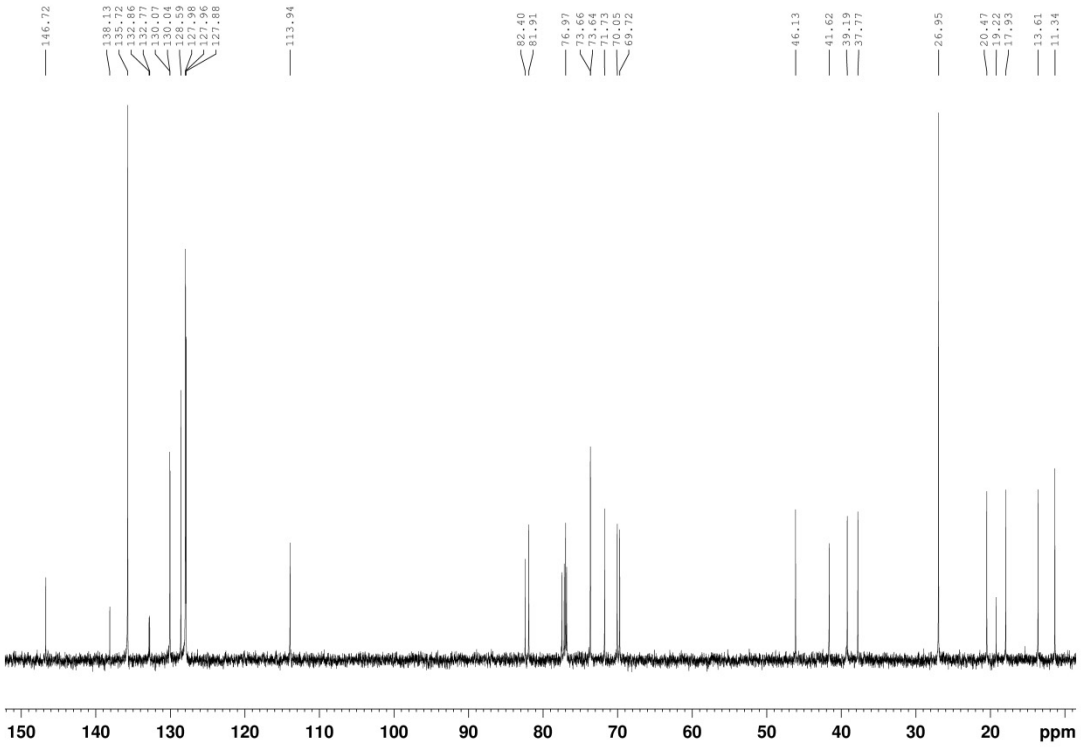
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19.22
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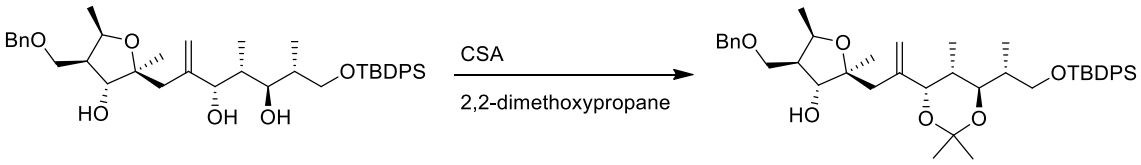
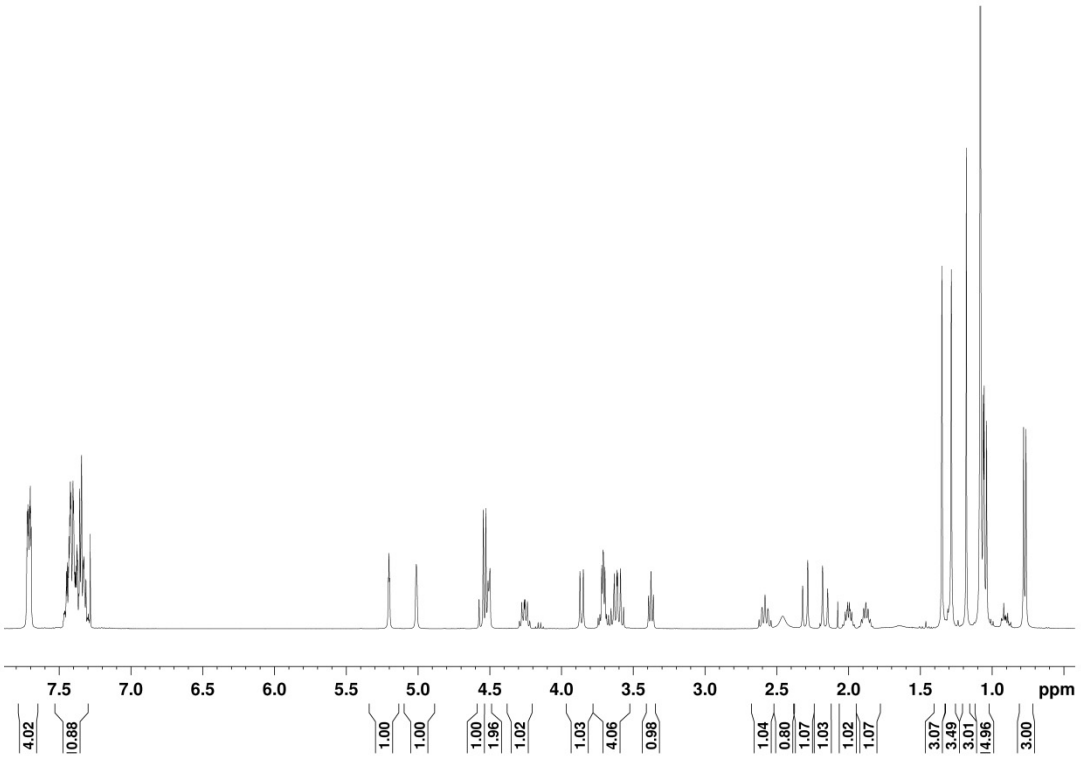



**192** **172**

**Acetonide 172:** To a solution of **192** (0.133 g, 0.201 mmol, 1.00 equiv.) in 4.00 ml 2,2-dimethoxypropane at rt, (+/-)-CSA (3.97 mg, 0.0171 mmol, 0.09 equiv.) was added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4) gave 136 mg (96 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.42 (EtOAc/hexane 1:2, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 4H), 7.45 – 7.27 (m, 11H), 5.19 – 5.17 (m, 1H), 4.99 (s, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.64 – 3.54 (m, 2H), 3.35 (dd, *J* = 6.7 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.43 (s, 1H), 2.28 (d, *J* = 14.2 Hz, 1H), 2.14 (d, *J* = 14.2 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.91 – 1.79 (m, 1H), 1.33 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.06 (s, 9H), 1.05 (d, *J* = 8.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 142.83, 138.08, 135.78, 135.75, 134.15, 134.11, 129.63, 129.61, 128.60, 127.89, 127.79, 127.70, 127.69, 114.48, 100.51, 81.99, 76.87, 75.92, 73.63, 71.64, 71.25, 70.29, 65.35, 46.52, 41.59, 40.44, 36.11, 27.01, 25.88, 23.81, 20.84, 19.42, 17.94, 13.76, 13.70; **IR** (thin film): ν 3425, 2965, 2931, 2857, 1472, 1455, 1428, 1378, 1223, 1177, 1105, 1028, 998, 906, 823, 740, 700, 615, 506, 502; **HRMS** (ESI): calculated for $C_{43}H_{61}O_6Si$ $[M+H]^+$: 701.4232, found 701.4228; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -7.66° (c = 0.94 in $CHCl_3$).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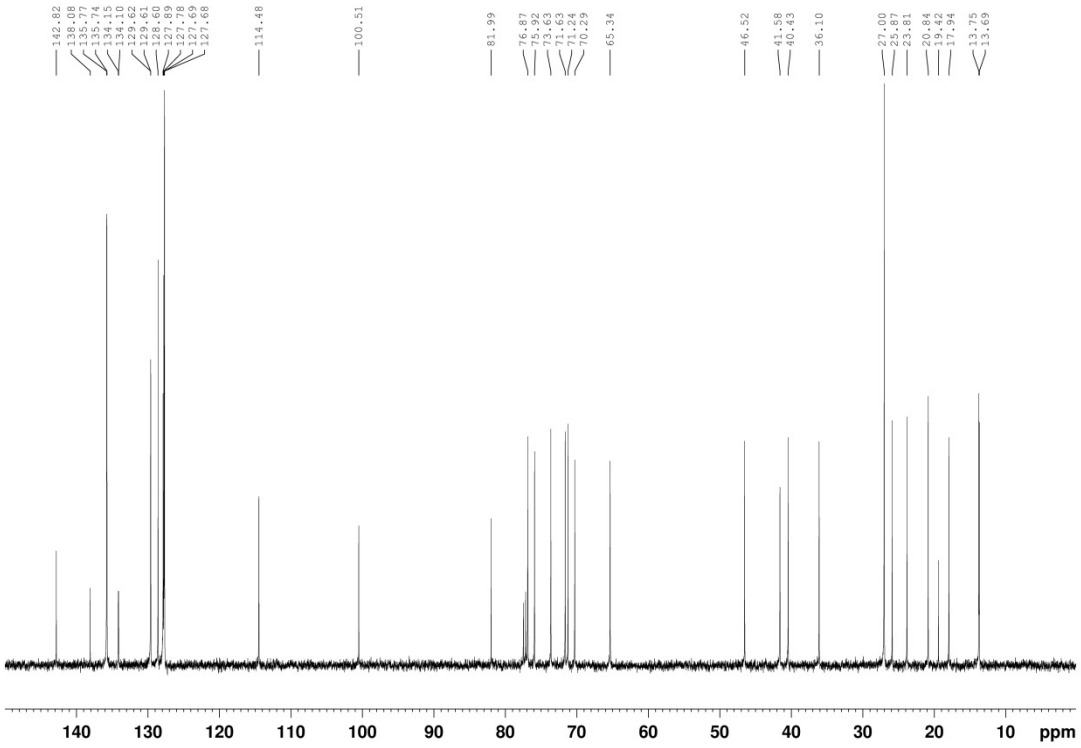
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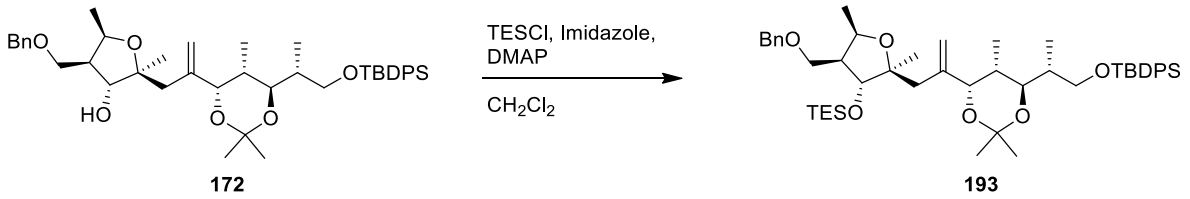
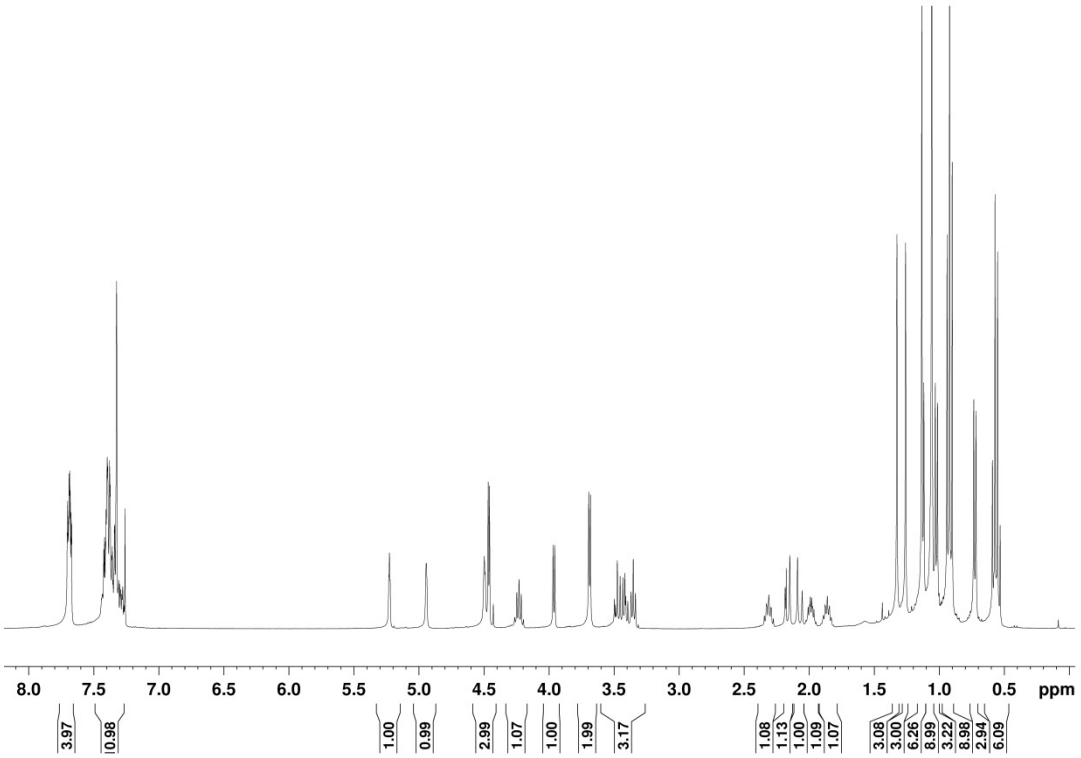
ppm




**172** **193**

**Silylether 193:** To a solution of **172** (130 mg, 0.185 mmol, 1.00 equiv.) in $CH_2Cl_2$ (1.85 ml) at rt, Imidazole (0.029 g, 0.426 mmol, 2.30 equiv.) and DMAP (0.0045 g, 0.0371 mmol, 0.20 equiv.) were added. Afterwards TESCl (0.047 ml, 0.278 mmol, 1.50 equiv.) was added neat. (Reaction mixture turned from colorless to a white emulsion within minutes) the reaction mixture was stirred at rt overnight. Then the reaction mixture was quenched by addition of aqu. sat. $NaHCO_3$. The aqu. phase was extracted 3 times with $CH_2Cl_2$, the comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (hexanes → EtOAc/hexane (1:20) gave 141 mg (93 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.42 (EtOAc/hexane 1:10, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 4H), 7.45 – 7.27 (m, 11H), 5.23 (dd, *J* = 2.0 Hz, 1H), 4.94 (s, 1H), 4.50 (s, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.23 (p, *J* = 6.6 Hz, 1H), 3.96 (d, *J* = 5.5 Hz, 1H), 3.69 (d, *J* = 5.1 Hz, 2H), 3.48 (dd, *J* = 11.5, 6.1 Hz, 1H), 3.41 (dd, *J* = 9.1, 6.3 Hz, 1H), 3.35 (dd, *J* = 6.8 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.17 (d, *J* = 14.3 Hz, 1H), 2.07 (d, *J* = 14.3 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.92 – 1.80 (m, 1H), 1.33 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.56 (q, *J* = 7.9 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 143.26, 138.43, 135.79, 135.77, 134.22, 134.17, 129.61, 128.43, 127.93, 127.69, 127.68, 114.23, 100.35, 83.54, 77.10, 75.81, 73.39, 71.98, 71.12, 68.57, 65.41, 50.26, 42.85, 40.67, 34.98, 27.02, 26.19, 23.89, 21.37, 19.45, 16.88, 13.84, 13.46, 7.04, 5.34; **IR** (thin film): ν 2957, 2932, 2875, 1455, 1428, 1378, 1224, 1178, 1111, 1006, 906, 822, 739, 700, 668, 610; **HRMS** (ESI): calculated for $C_{49}H_{75}O_6Si_2$ $[M+H]^+$: 815.5097, found 815.5090; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -0.37° (c = 1.08 in $CHCl_3$).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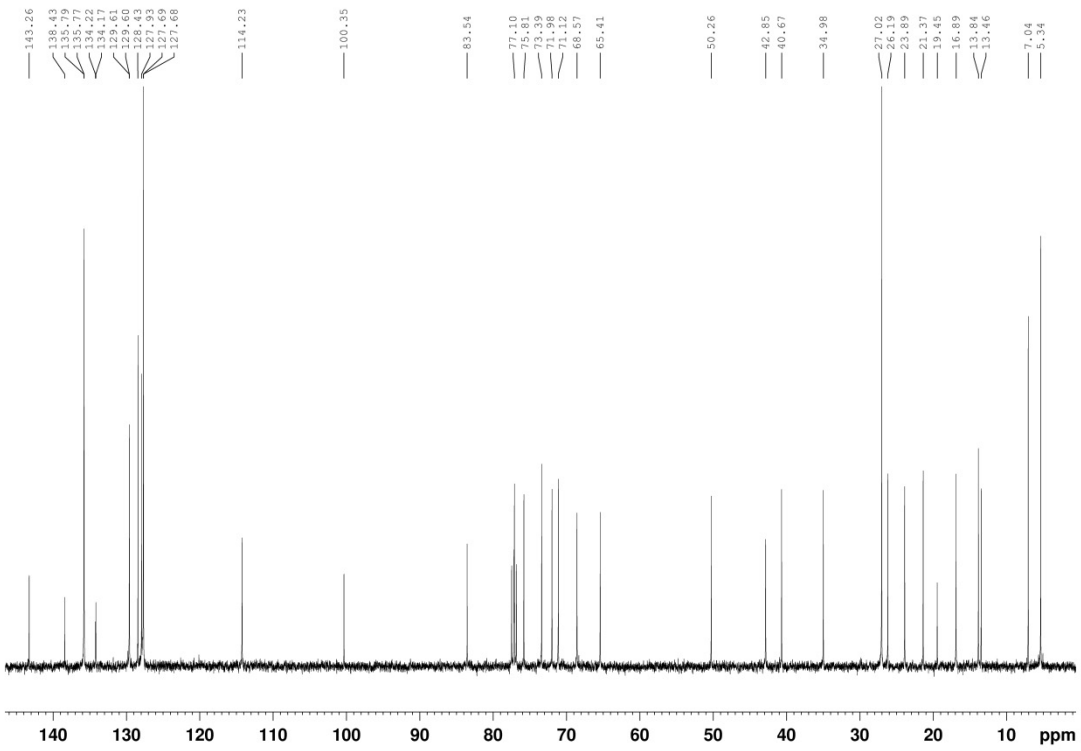
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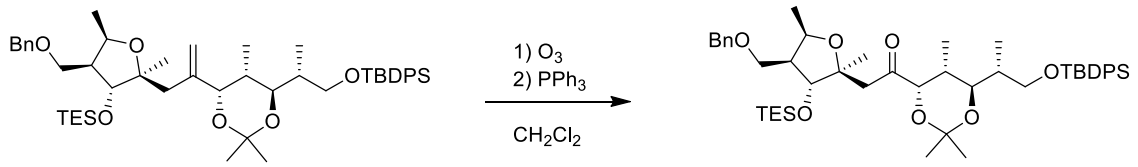
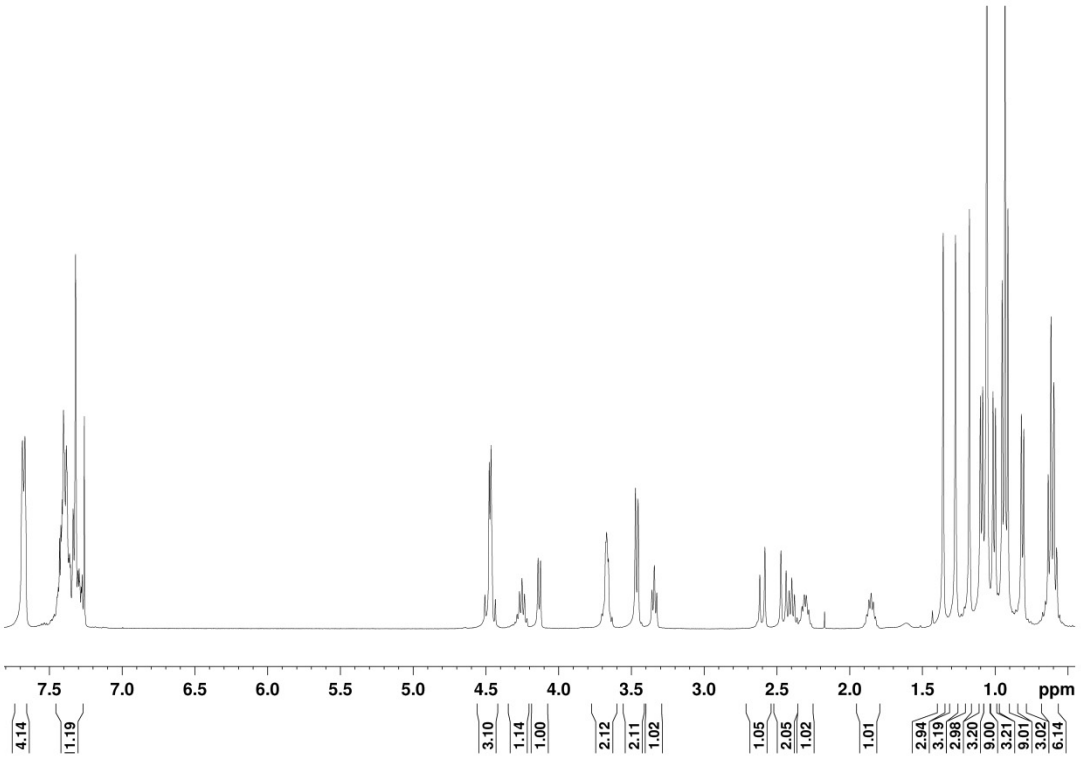



**193** **182**

**Ketone 182:** To a cooled (- 78 °C) solution of **193** (128 mg, 0.157 mmol, 1.00 equiv.) in 15.7 ml DCM, ozone was bubbled through until a light blue color persisted in the solution. The excess of ozone was removed by exchanging with nitrogen gas. Afterwards Triphenylphosphine (0.412 g, 1.57 mmol, 10 equiv.) was added and the reaction mixture was stirred at rt for 1 h. Concentration under reduced pressure followed by purification over silica gel (EtOAc/hexane 1:10) gave 120.4 mg (94 %) of the desired product as a colorless oil.

**TLC**: $R_f$ = 0.25 (EtOAc/hexane 1:8, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.46 – 7.27 (m, 11H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.47 – 4.45 (m, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.31 – 4.21 (m, 1H), 4.13 (d, *J* = 6.7 Hz, 1H), 3.71 – 3.62 (m, 2H), 3.46 (d, *J* = 7.2 Hz, 2H), 3.34 (dd, *J* = 6.6 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.45 (d, *J* = 14.2 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.35 – 2.25 (m, 1H), 1.92 – 1.80 (m, 1H), 1.36 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.61 (q, *J* = 15.3, 7.7 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 207.42, 138.27, 135.79, 135.75, 133.99, 129.71, 128.49, 127.95, 127.76, 101.19, 82.48, 76.85, 76.46, 75.61, 73.47, 72.57, 68.70, 65.14, 49.37, 47.44, 40.01, 36.17, 27.02, 25.61, 23.50, 21.72, 19.42, 17.05, 13.96, 13.72, 7.02, 5.21; **IR** (thin film): ν2957, 2933, 2875, 1717, 1472, 1456, 1428, 1379, 1224, 1177, 1111, 1086, 1022, 1006, 967, 823, 739, 700, 615, 505; **HRMS** (ESI): calculated for $C_{48}H_{73}O_7Si_2$ $[M+H]^+$: 817.4889, found 817.4887; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +11.49° (c = 1.01 in $CHCl_3$).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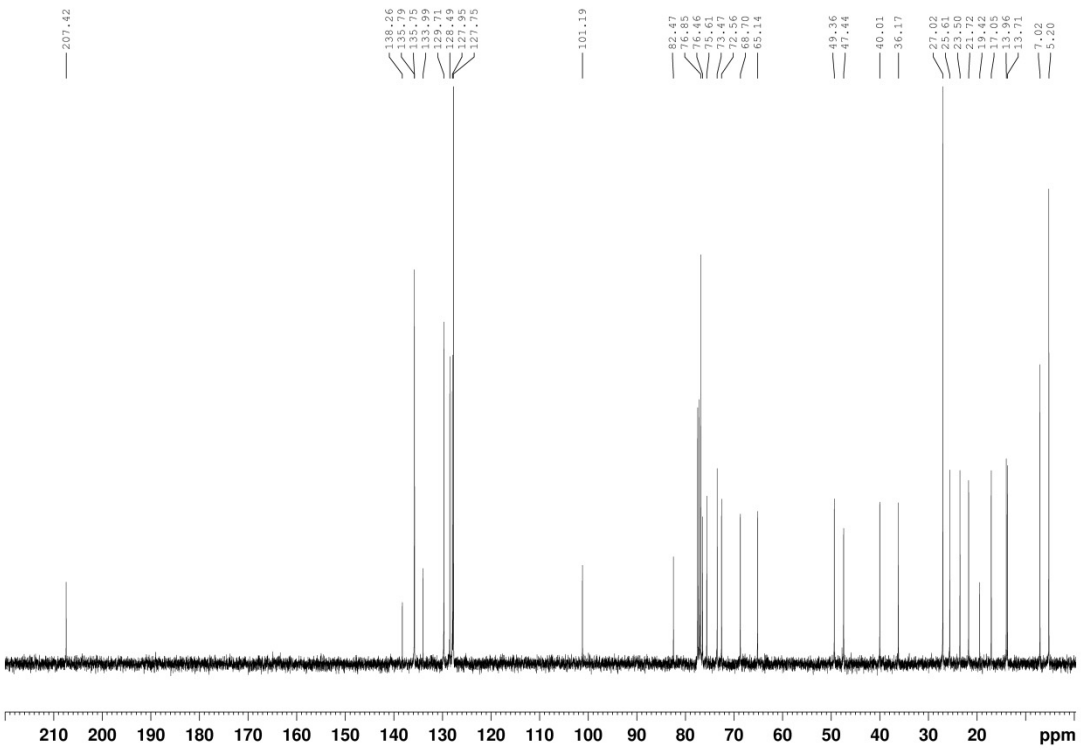
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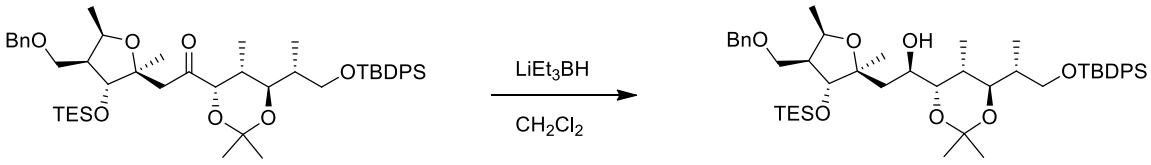
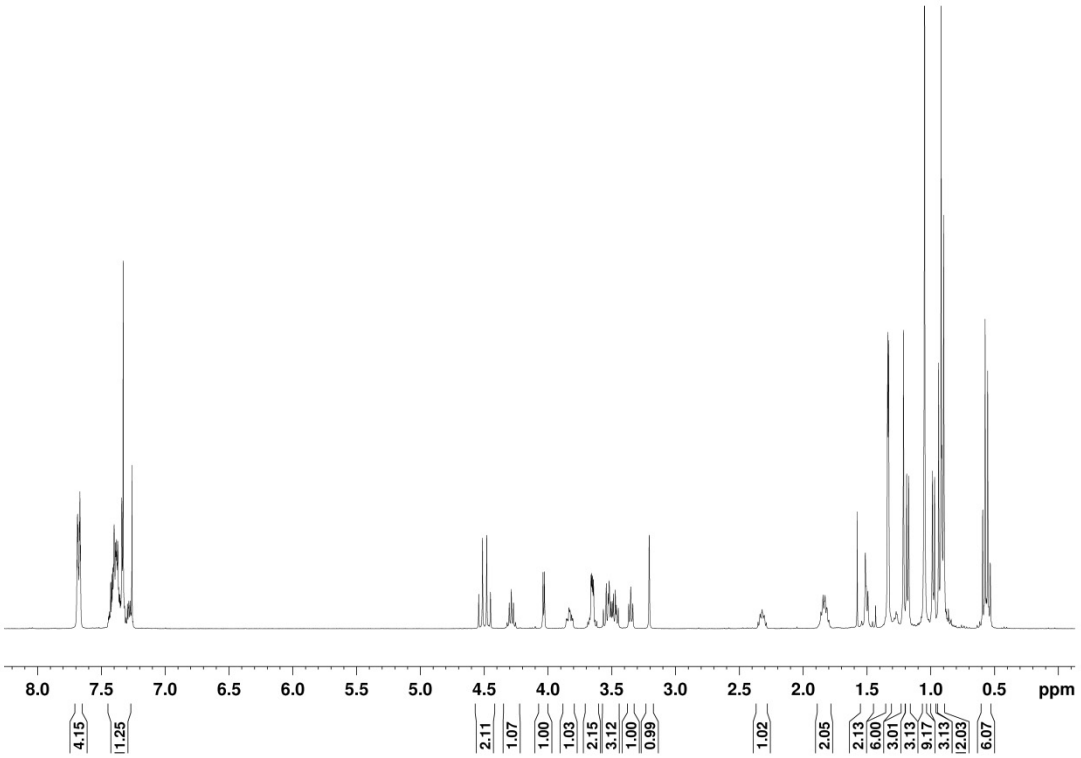



**182** **194**

**Alcohol 194:** To a solution of **182** (20.0 mg, 0.0245 mmol, 1.00 equiv.) in 0.74 ml $CH_2Cl_2$ at -78 °C was added $LiEt_3BH$ (1 M in THF, 0.095 ml, 0.0954 mmol, 3.90 equiv.). The reaction mixture was stirred for 30 min at -78 °C and then quenched by addition of aqu. sat. $NaHCO_3$. The reaction mixture was extracted 3 times with EtOAc (add Rochelle salt for better phase separation). The comb. org phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:10) gave 19.1 mg (91 %) of the desired product as a colorless oil.

**TLC**: $R_f$ = 0.33 (EtOAc/hexane 1:6, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.45 – 7.25 (m, 11H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.29 (p, *J* = 6.6 Hz, 1H), 4.03 (d, *J* = 4.6 Hz, 1H), 3.83 (td, *J* = 8.2, 3.3 Hz, 1H), 3.70 – 3.61 (m, 2H), 3.57 – 3.44 (m, 3H), 3.35 (dd, *J* = 6.4 Hz, 1H), 3.21 (s, 1H), 2.36 – 2.28 (m, 1H), 1.89 – 1.78 (m, 2H), 1.55 – 1.45 (m, 2H), 1.34 (s, 3H), 1.33 (s, 3H), 1.21 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.56 (q, *J* = 7.9 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 138.34, 135.77, 135.75, 134.00, 129.71, 128.49, 127.94, 127.77, 127.73, 100.92, 84.25, 79.31, 75.93, 73.49, 73.46, 72.22, 68.45, 67.43, 65.20, 51.12, 41.63, 40.14, 34.76, 27.01, 25.68, 23.58, 20.90, 19.40, 16.57, 13.73, 12.99, 7.05, 5.22; **IR** (thin film): ν 3513, 2956, 2932, 2875, 2857, 1472, 1455, 1428, 1378, 1223, 1176, 1111, 1072, 1018, 824, 740, 700, 614, 504; **HRMS** (ESI): calculated for $C_{48}H_{75}O_7Si_2$ $[M+H]^+$: 819.5046, found 819.5035; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -15.09° (c = 1.08 in $CHCl_3$).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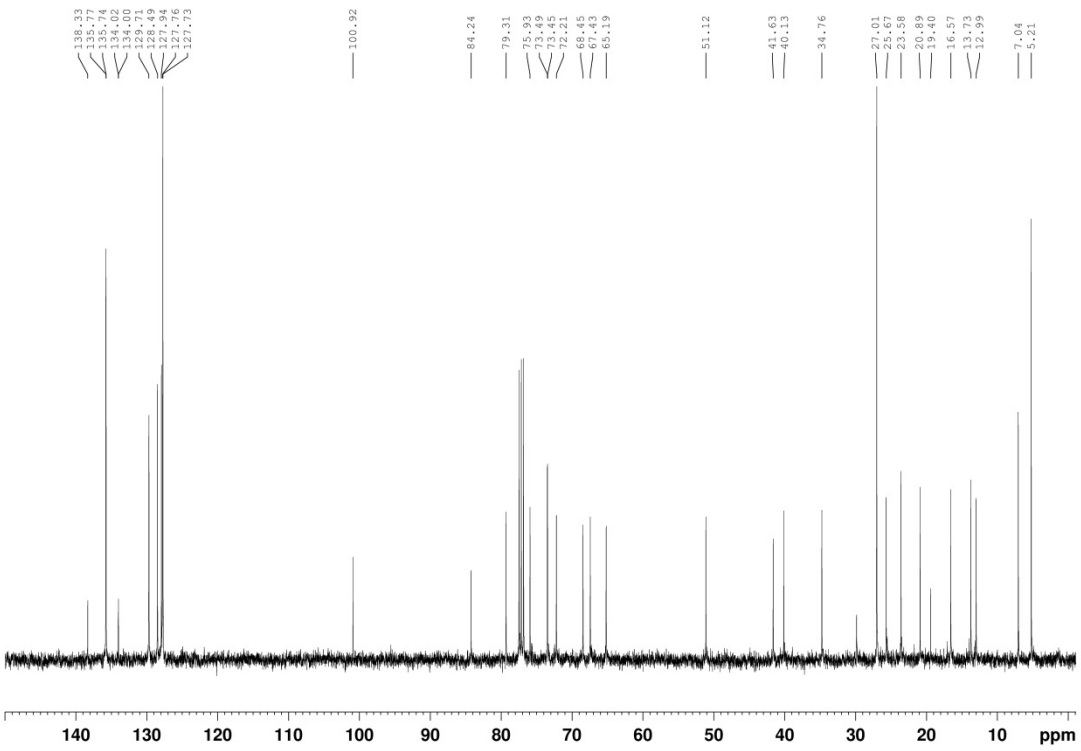
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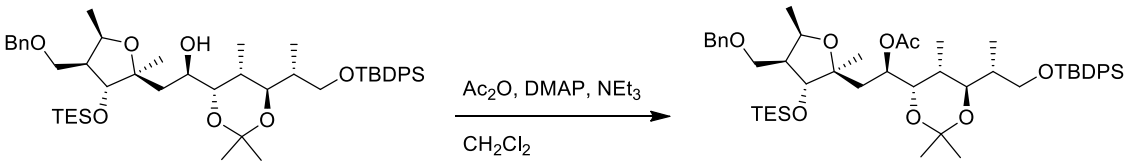
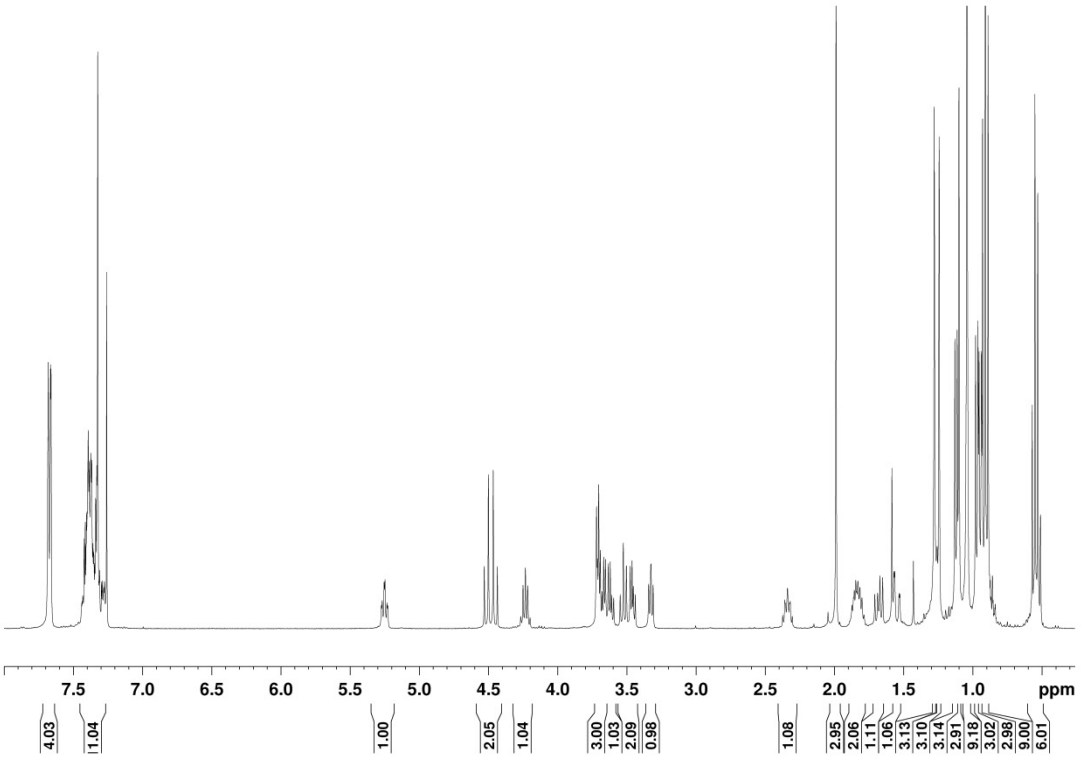



**194** **196**

**Acetate 196:** To a solution of **194** (12.0 mg, 0.0146 mmol, 1.00 equiv.) and DMAP (3.6 mg, 0.0293 mmol, 2.00 equiv.) in $CH_2Cl_2$ (1.50 ml) at 0 °C was added triethylamine (0.054 ml, 0.387 mmol, 26.40 equiv.) and acetic anhydride (0.028 ml, 0.293 mmol, 20.00 equiv.). The reaction mixture was stirred for 20 h and afterwards quenched by addition of aqu. sat. $NaHCO_3$ was added. The phases were separated and the aqu. phase extracted with $CH_2Cl_2$. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 11.8 mg (94 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.32 (EtOAc/hexane 1:6, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 4H), 7.45 – 7.27 (m, 11H), 5.25 (td, *J* = 8.0, 2.4 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.23 (p, *J* = 6.6 Hz, 1H), 3.73 – 3.70 (m, 2H), 3.67 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.62 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.53 (dd, *J* = 9.0 Hz, 1H), 3.46 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.33 (d, *J* = 6.5 Hz, 1H), 2.39 – 2.29 (m, 1H), 1.99 (s, 3H), 1.90 – 1.76 (m, 2H), 1.68 (dd, *J* = 14.7, 8.0 Hz, 1H), 1.55 (dd, *J* = 14.7, 2.3 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.54 (q, *J* = 8.0 Hz, 6H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 170.37, 138.32, 135.77, 135.74, 134.03, 129.68, 128.49, 127.94, 127.78, 127.72, 100.78, 82.25, 80.56, 76.05, 73.44, 72.14, 71.33, 70.12, 68.62, 65.24, 49.84, 40.94, 39.94, 35.82, 27.01, 25.23, 23.59, 21.57, 19.39, 19.14, 16.91, 13.93, 12.68, 7.01, 5.29; **IR** (thin film): ν 2956, 2931, 2875, 2857, 1748, 1472, 1456, 1428, 1378, 1237, 1175, 1112, 1073, 1017, 824, 738, 701, 615; **HRMS** (ESI): calculated for $C_{50}H_{77}O_8Si_2$ $[M+H]^+$: 861.5151, found 861.5141; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -16.06° (c = 0.66 in $CHCl_3$).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1.0
ppm
4.03
1.04
1.00
2.05
1.04
3.00
1.03
2.09
0.98
1.08
2.95
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3.10
3.14
2.91
9.18
3.02
2.98
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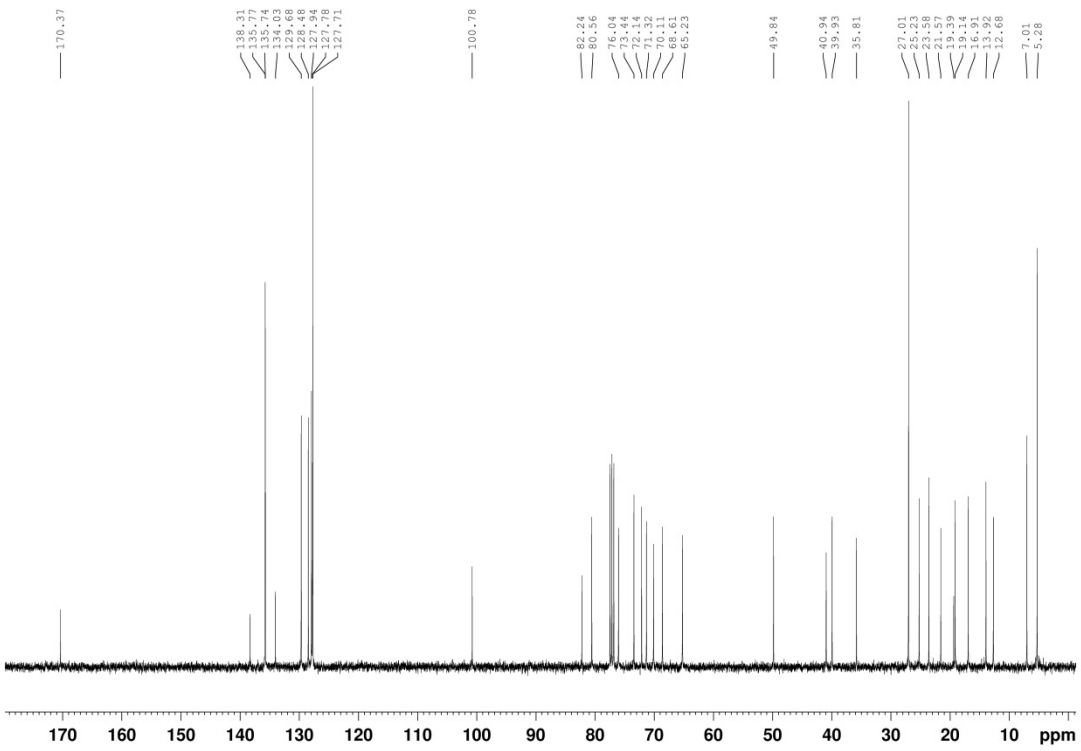
6.01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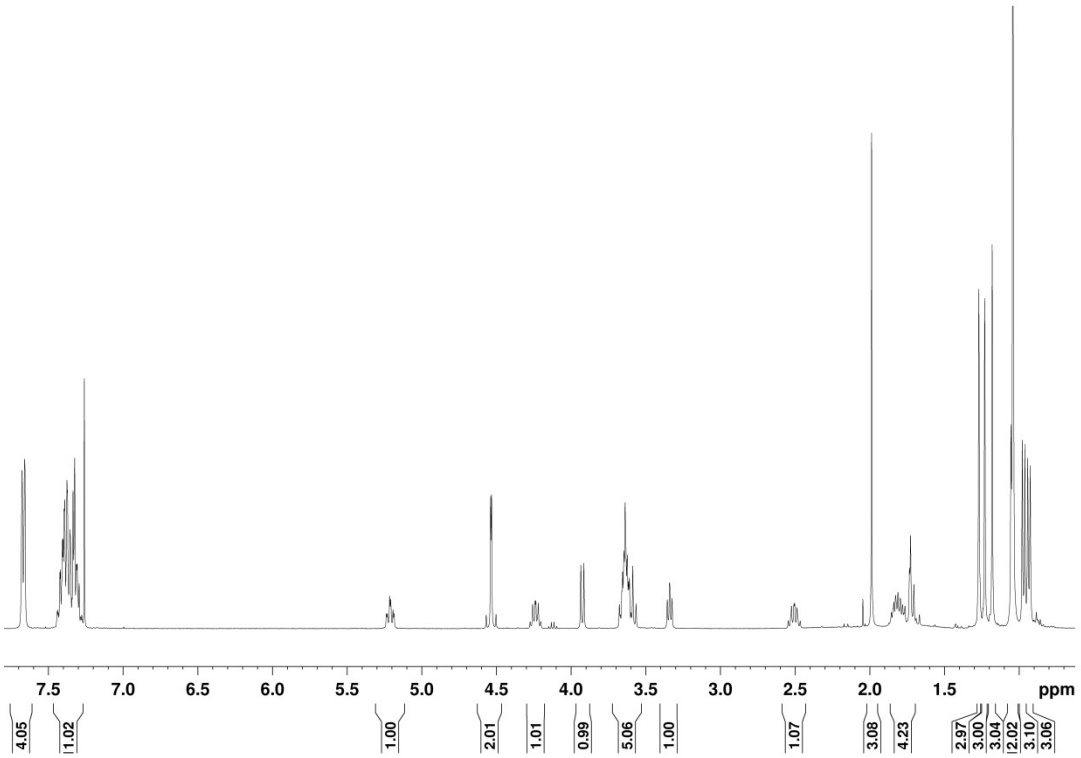
73.44
72.14
71.32
70.11
68.61
65.23
49.84
40.94
39.93
35.81
27.01
25.23
23.58
21.57
19.39
19.14
16.91
13.92
12.68
7.01
5.28
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


**196** **197**

**Alcohol 197:** To a solution of **196** (43.0 mg, 0.0499 mmol, 1.00 equiv.) in MeOH/THF (2:1) (0.90 ml) at rt was added PPTS (37.6 mg, 0.150 mmol, 3.00 equiv.) The reaction mixture was stirred at rt for 3 h. The reaction mixture was than quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:3 → 1:2) gave 25 mg (67 %) of the desired product as colorless oil.

**TLC**: $R_f$ = 0.23 (EtOAc/hexane 1:2, UV, CPS); **$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.0 Hz, 4H), 7.45 – 7.27 (m, 11H), 5.21 (td, *J* = 8.9, 2.8 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.24 (dq, *J* = 13.2, 6.6 Hz, 1H), 3.93 (d, *J* = 8.1 Hz, 1H), 3.69 – 3.55 (m, 5H), 3.34 (dd, *J* = 6.4 Hz, 1H), 2.56 – 2.45 (m, 1H), 1.99 (s, 3H), 1.88 – 1.66 (m, 4H), 1.27 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.05 (d, *J* = 5.1 Hz, 3H), 1.04 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 170.87, 138.06, 135.77, 135.74, 134.04, 134.01, 129.72, 129.69, 128.65, 127.98, 127.81, 127.74, 100.76, 81.65, 80.40, 75.92, 73.71, 71.73, 71.21, 70.46, 69.47, 65.21, 48.05, 40.40, 40.05, 35.38, 27.02, 25.16, 23.49, 21.53, 19.61, 19.40, 17.62, 13.75, 12.50; **IR** (thin film): ν 3456, 2959, 2929, 2857, 1743, 1456, 1428, 1378, 1240, 1179, 1105, 1055, 1019, 822, 736, 700, 612, 504; **HRMS** (ESI): calculated for $C_{44}H_{63}O_8Si$ $[M+H]^+$: 747.4287, found 747.4279; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -30.88° (c = 1.13 in $CHCl_3$).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ppm
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1.00
2.01
1.01
0.99
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1.00
1.07
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4.23
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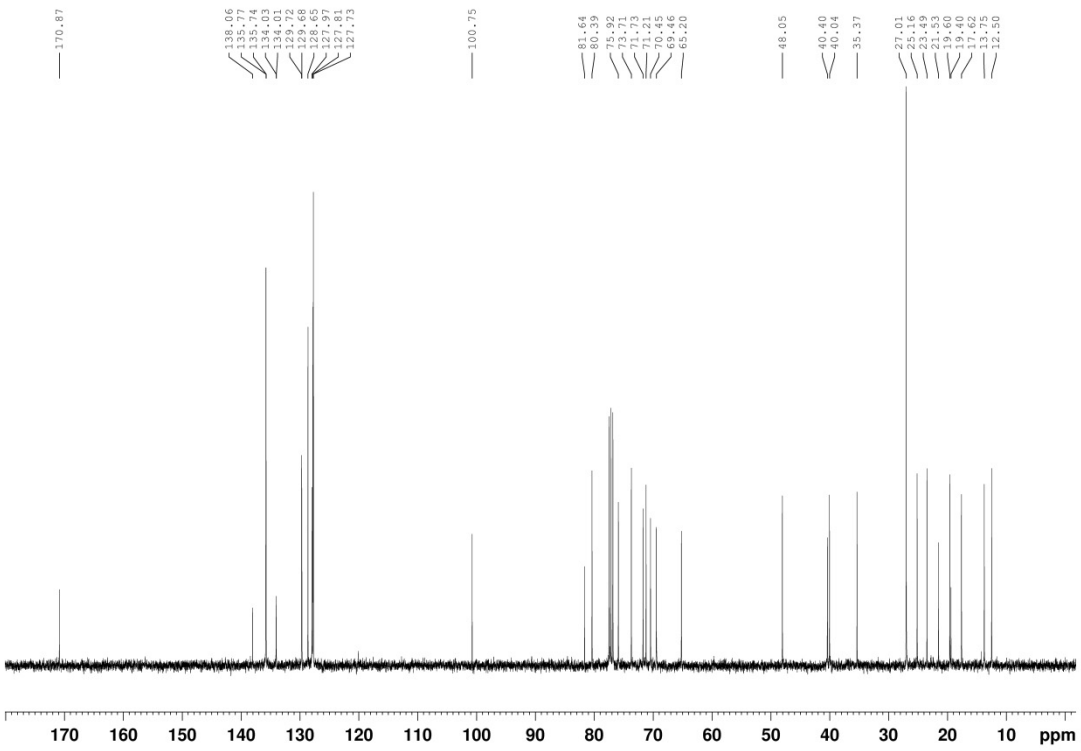
2.02
3.10
3.06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81.64
80.39
75.92
73.71
71.73
71.21
70.45
69.46
65.20
48.05
40.40
40.04
35.37
27.01
25.16
23.49
23.53
19.60
19.40
17.62
13.75
12.50
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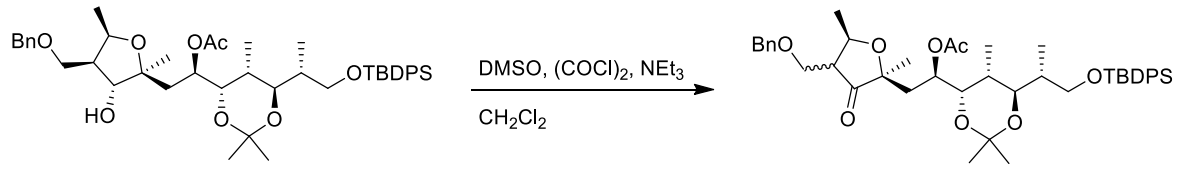
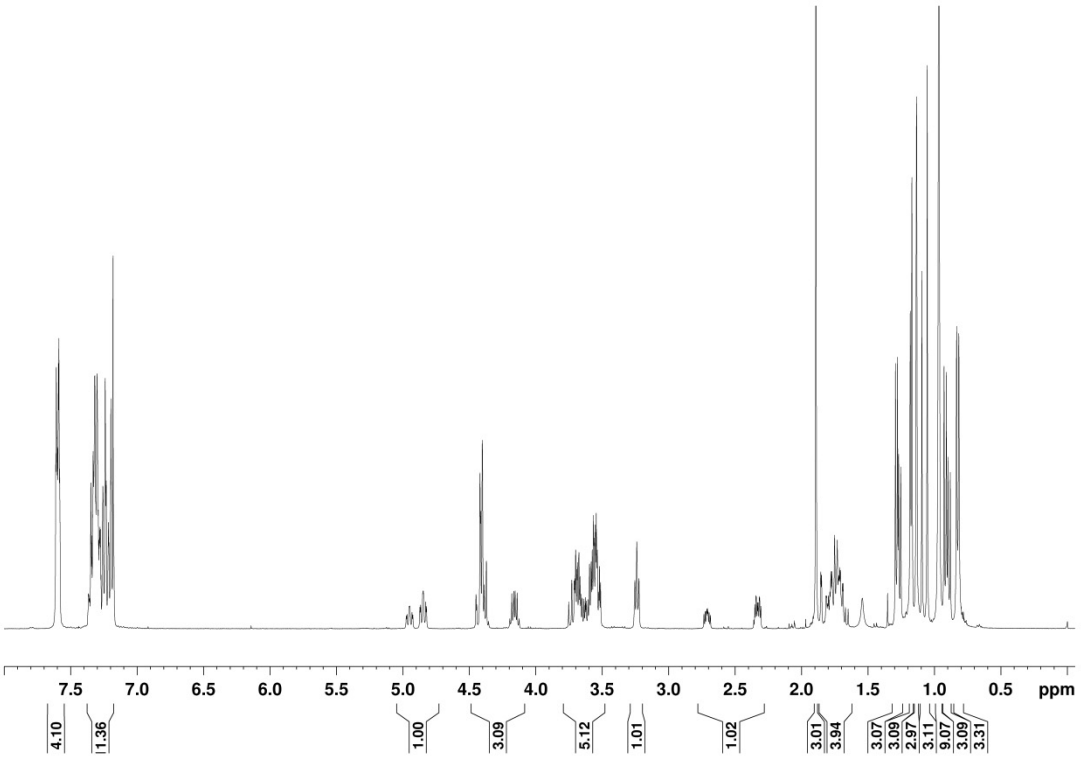
10
ppm




**197** **181**

**Ketone 181:** To a solution of oxalyl chloride (0.046 ml**,** 0.535 mmol, 20.00 equiv.) in 1.80 mL of anhydrous $CH_2C1_2$ at -78 °C was added DMSO (0.085 ml, 1.20 mmol, 45.00 equiv.) dropwise. The mixture was stirred for 15 min and a solution of **172** (20.0 mg, 0.0268 mmol, 1.00 equiv.) in 0.40 mL of anhydrous $CH_2CI_2$ was added dropwise. After 20 min, triethylamine (0.335 ml, 2.41 mmol, 90.00 equiv.) was carefully added, and the reaction was stirred at -78 °C for 10 min. The reaction was allowed to reach room temperature and then diluted with aqu. sat. $NaHCO_3$. The two layers were separated, and the aqueous phase was extracted with $CH_2C1_2$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:6)) gave 18.0 mg (90 %, *dr* = 1:1.6) of the desired product as colorless oil.

**TLC**: $R_f$ (1st isomer) = 0.35 (EtOAc/hexane 1:3, UV, CPS), $R_f$ (2nd isomer) = 0.25 (EtOAc/hexane 1:3, UV, CPS); **$^1$H-NMR (major isomer)** (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 4H), 7.45 – 7.24 (m, 11H), 4.96 – 4.89 (m, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.84 – 3.58 (m, 5H), 3.32 (dd, *J* = 6.2 Hz, 1H), 2.44 – 2.38 (m, 1H), 1.97 (s, 3H), 1.94 – 1.72 (m, 4H), 1.36 (d, *J* = 6.1 Hz, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 1.05 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); **$^{13}$C-NMR (major isomer)** (101 MHz, $CDCl_3$) δ 217.42, 170.49, 138.18, 135.74, 134.05, 129.70, 129.67, 128.50, 127.95, 127.72, 127.48, 100.73, 82.79, 76.25, 73.54, 71.73, 70.97, 69.73, 65.92, 65.23, 54.47, 40.05, 36.72, 35.09, 27.00, 25.22, 23.43, 21.37, 21.25, 19.66, 19.40, 13.83, 12.37; **$^1$H-NMR (minor isomer)** (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.45 – 7.24 (m, 11H), 5.06 – 5.00 (m, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.51 – 4.46 (m, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 3.84 – 3.57 (m, 5H), 3.32 (dd, *J* = 6.2 Hz, 1H), 2.79 (ddd, *J* = 8.7, 7.1, 3.8 Hz, 1H), 1.97 (s, 3H), 1.94 – 1.72 (m, 4H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.04 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); **$^{13}$C-NMR (minor isomer)** (101 MHz, $CDCl_3$) δ 217.23, 170.34, 138.18, 135.78, 134.05, 129.70, 129.67, 128.56, 127.91, 127.72, 127.48, 100.73, 81.50, 76.11, 73.43, 71.24, 71.16, 69.62, 66.64, 49.76, 40.08, 36.17, 35.23, 27.00, 25.27, 23.51, 21.37, 20.99, 16.34, 13.78, 12.42; **IR** (thin film): ν 2960, 2931, 2881, 2857, 1748, 1472, 1456, 1428, 1378, 1242, 1178, 1111, 1018, 909, 884, 823, 741, 707, 615; **HRMS** (ESI): calculated for $C_{44}H_{61}O_8Si$ $[M+H]^+$: 745.4130, found 745.4121; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -39.0° (c = 1.00 in $CHCl_3$).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1.0
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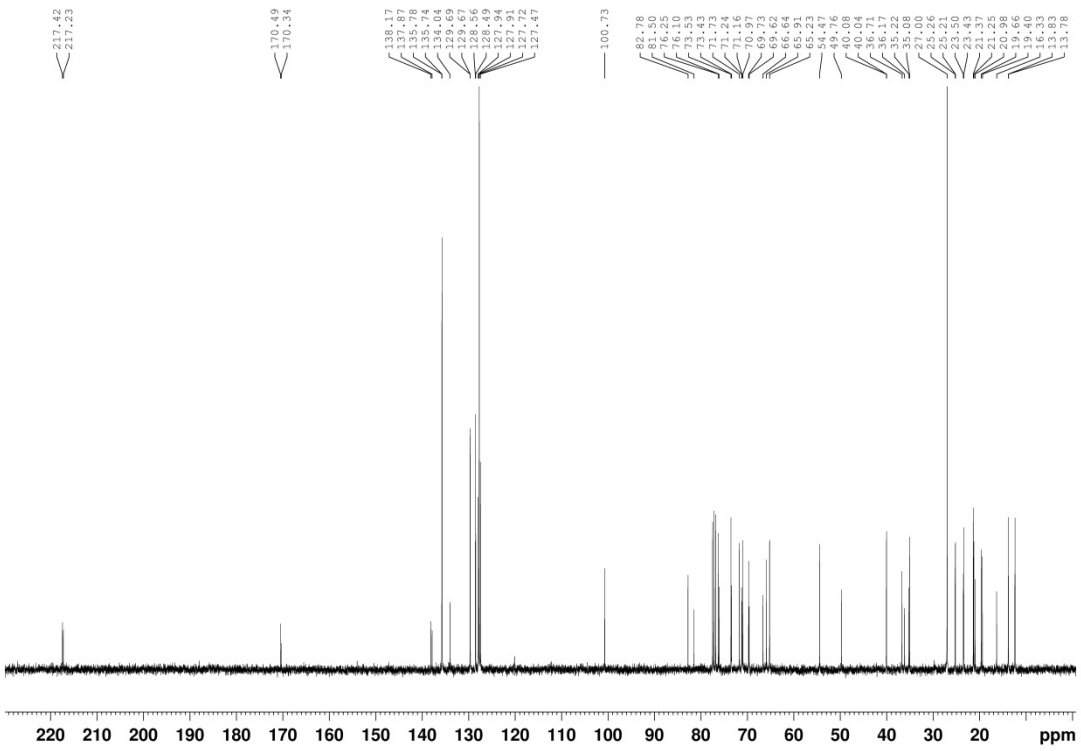
9.07
3.09
3.31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137.87
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129.67
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127.72
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40.08
40.04
36.71
36.17
35.22
35.08
27.00
25.26
25.21
23.50
23.43
21.37
21.25
20.98
19.66
19.40
16.33
13.83
13.78
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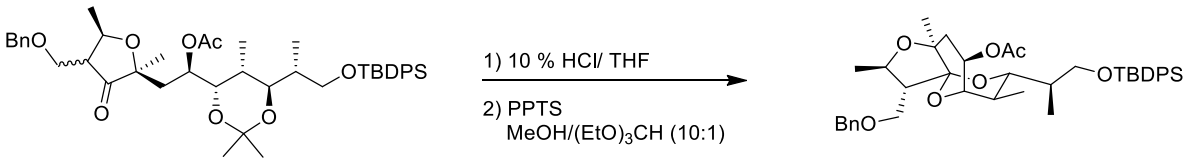
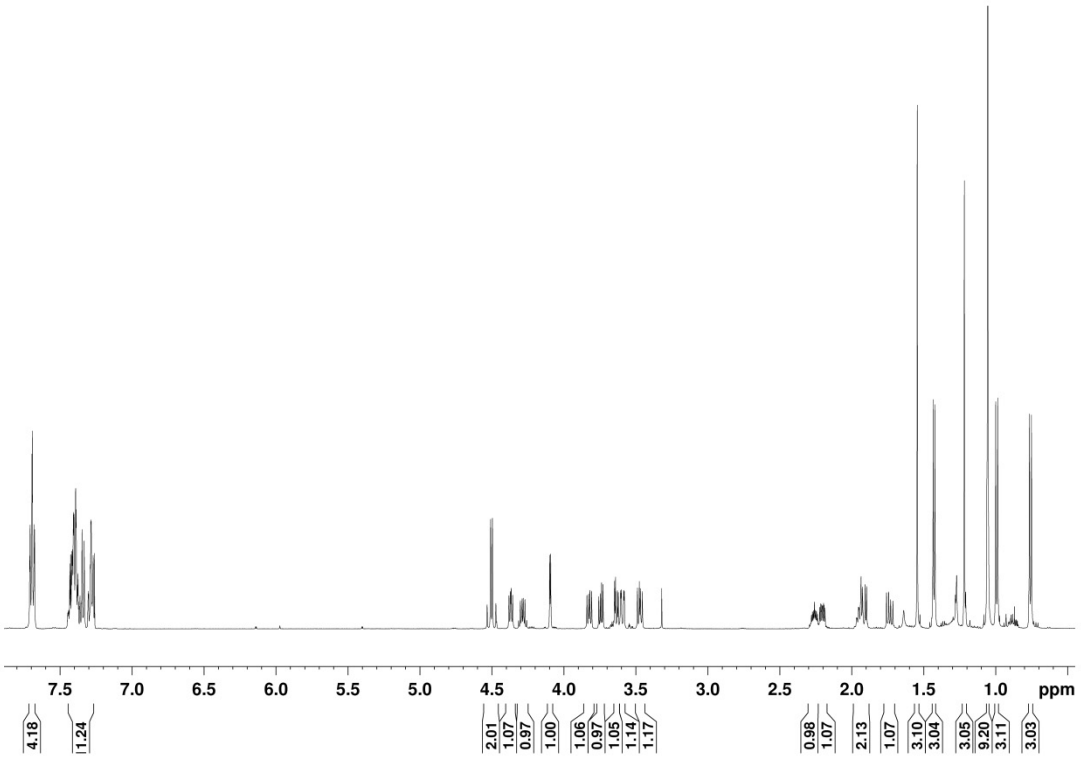
ppm




**181** **180a**

**Ketal 180:** To a solution of **181** (18.0 mg, 0.0242 mmol, 1.00 equiv.) in 1.00 ml THF was added 0.340 ml 10 % HCl (aqu.). The reaction mixture was stirred for 1 h 15 min. Afterwards the reaction was quenched with aqu. sat. $NaHCO_3$. The phases were separated and the aqu. phase was extracted with $Et_2O$. The comb. org. phases were washed with brine dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in methanol (1.00 ml) and 0.10 ml $(EtO)_3CH$ was added. Additionally PPTS (25.5 mg, 0.101 mmol, 4.20 equiv., 0.1 mmol/ml) was added and the reaction mixture was stirred for 19 h. Afterwards the reaction mixture was then heated to 60 °C and stirred for additional 5 h. TLC and mass showed the presence of the desired product only (2 diastereoisomers). Therefore the reaction mixture was then quenched by addition of aqu. sat. $NaHCO_3$. The reaction mixture was extracted with EtOAc and the comb. org phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexanes (1:8)) gave 7.0 mg (42 %) of the undesired product **180a** as colorless oil and 5.4 mg (32 %) of a mixture containing both isomers of the desired product in a 1.9:1 ratio (desired **180b** : undesired **180a**). In order to completely separate the two diastereoisomers the purification was repeated with EtOAc/hexanes (1:12 -> 1:8) which gave 2.6 mg (15 %) of the undesired product **180a** and 2 mg (12 %) of the mixture with ratio 1:1.8 (desired **180b** : undesired **180a**).

**TLC**: $R_f$ = 0.41 (EtOAc/hexane 1:3, UV, CPS); **$^1$H-NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 4H), 7.45 – 7.26 (m, 11H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.37 (dd, *J* = 7.7, 5.2 Hz, 1H), 4.32 – 4.25 (m, 1H), 4.09 (d, *J* = 3.4 Hz, 1H), 3.82 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.74 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.63 (dd, *J* = 9.7, 3.3 Hz, 1H), 3.59 (dd, *J* = 10.6, 2.1 Hz, 1H), 3.47 (dd, *J* = 10.3, 6.7 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.20 (ddd, *J* = 9.7, 5.0, 3.3 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.92 (dd, *J* = 14.3, 5.2 Hz, 1H), 1.74 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.54 (s, 3H), 1.43 (d, *J* = 6.0 Hz, 3H), 1.22 (s, 3H), 1.06 (s, 9H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H); **$^{13}$C-NMR** (126 MHz, $CDCl_3$) δ 217.13, 138.01, 135.77, 135.73, 134.02, 133.96, 129.65, 128.51, 127.81, 127.74, 127.70, 127.51, 118.95, 81.72, 81.68, 77.52, 73.54, 72.28, 72.12, 66.12, 64.87, 54.67, 41.13, 36.81, 32.63, 26.98, 22.51, 20.60, 19.75, 19.27, 15.41, 13.01; **IR** (thin film): ν 2960, 2929, 2857, 1756, 1472, 1455, 1428, 1403, 1388, 1362, 1292, 1267, 1148, 1111, 1089, 1021, 998, 950, 913, 869, 823, 739, 700, 614, 504; **HRMS** (ESI): calculated for $C_{41}H_{55}O_7Si$ $[M+H]^+$: 687.3712, found 687.3706; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: -56.0° (c = 0.70 in $CHCl_3$).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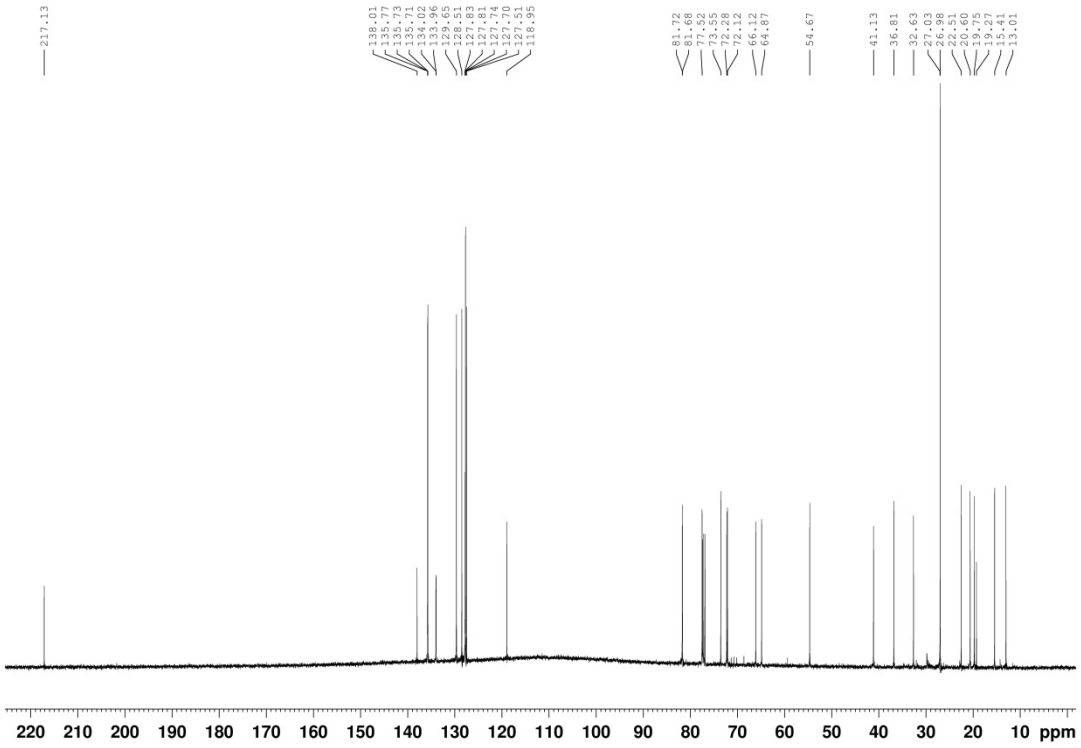
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81.72 81.68 77.52 73.55 72.28 72.12 66.12 64.87
54.67
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220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

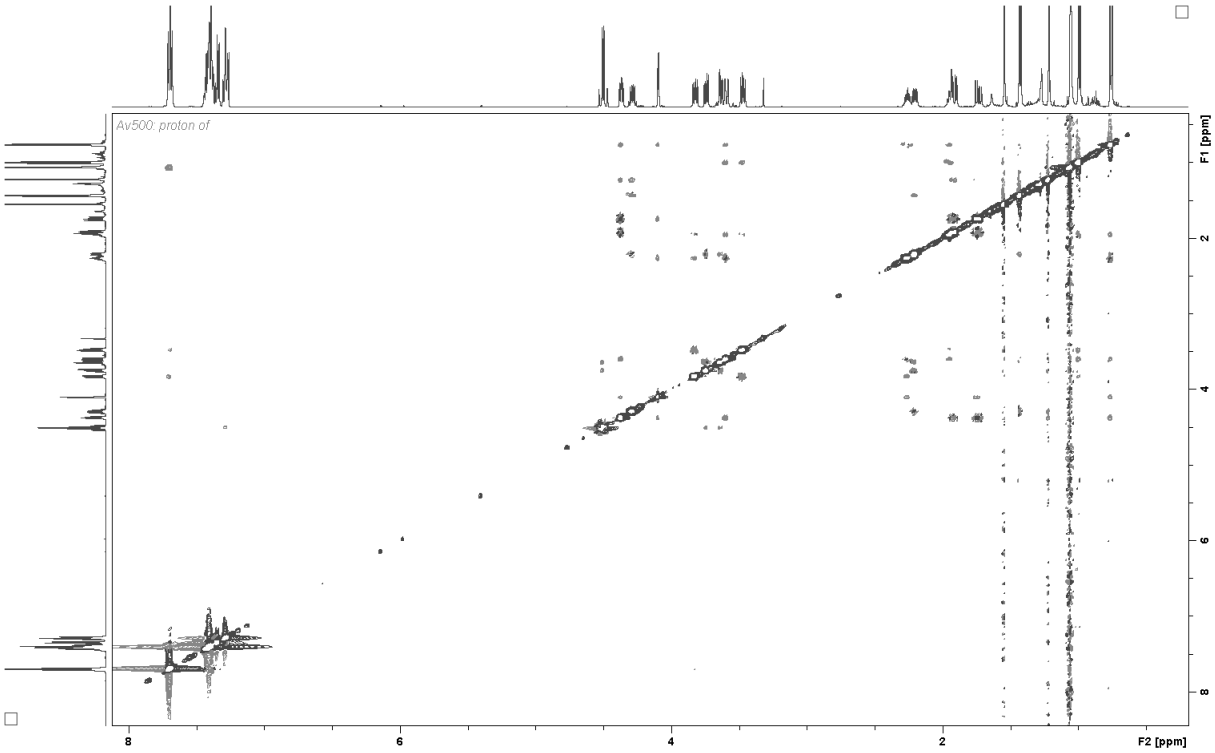
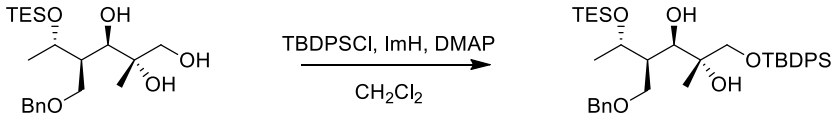



**Figure 31:** NOE spectrum of **180a**.

## 5.3.6. Other Strategies towards the Synthesis of Bu-2313 B

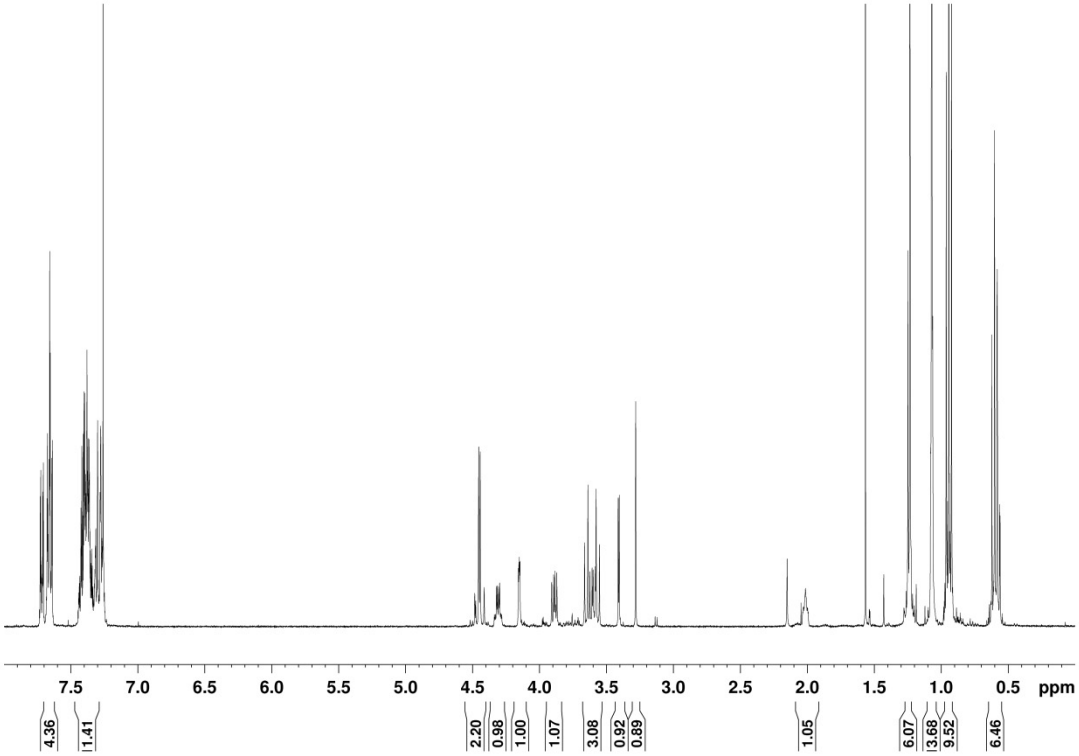
### 5.3.6.1. Iodine Displacement Strategy towards Vinyl Iodide Fragment 185




**64** **235**

**Silyl ether 235:** To a solution of **64** (0.204 g, 0.513 mmol, 1.00 equiv.) in 5.0 ml THF at rt, imidazole (0.045 g, 0.666 mmol, 1.30 equiv.), DMAP (0.006 g, 0.0513 mmol, 0.10 equiv.) and TBDPSCl (0.173 ml, 0.666 mmol, 1.30 equiv.) were added. The reaction mixture was stirred at rt overnight, then quenched by addition of aqu. sat. $NaHCO_3$ and diluted with EtOAc. The phases were separated and the aqu. phase extracted 3 times with EtOAc. The comb. org. phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexanes (1:6)) gave 0.373 g of a mixture of product and TBDPS impurities.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 1H), 7.69 – 7.62 (m, 4H), 7.46 – 7.26 (m, 10H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.31 (qd, *J* = 6.3, 2.fz8 Hz, 1H), 4.15 (dd, *J* = 2.9, 1.6 Hz, 1H), 3.89 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.60 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.57 (d, *J* = 9.9 Hz, 1H), 3.41 (d, *J* = 3.1 Hz, 1H), 3.28 (s, 1H), 2.01 (t, *J* = 5.9 Hz, 1H), 1.24 (d, *J* = 5.6 Hz, 6H), 1.23 (s, 3H), 1.07 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.63 – 0.55 (m, 6H).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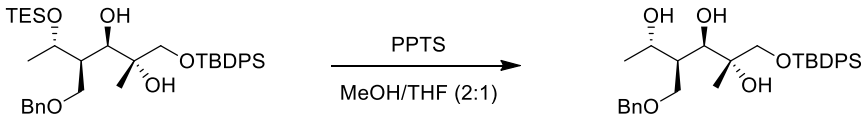
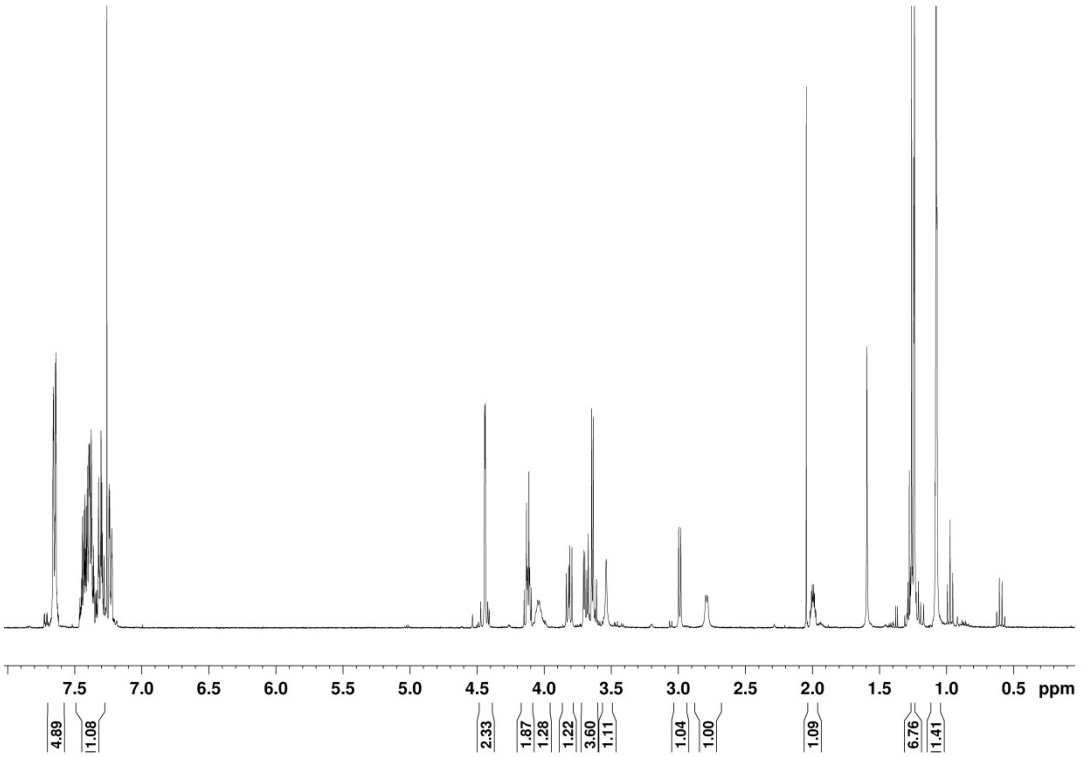
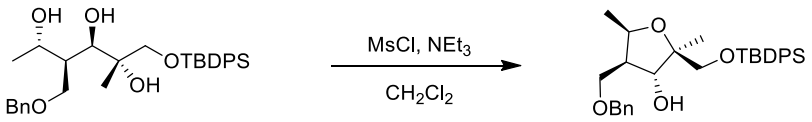



**235** **201**

**Triol 201:** To a solution of **235** (0.327 g, 0.513 mmol, 1.00 equiv.) in MeOH/THF (2:1) (5.00 ml) at rt was added PPTS (0.129 g, 0.513 mmol, 1.00 equiv.) The reaction mixture was stirred at rt for 25 min and was than quenched by addition of aqu. sat. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:2) gave 268 mg (quant.) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H), 7.48 – 7.20 (m, 11H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.12 (dd, *J* = 6.0, 2.3 Hz, 1H), 4.04 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.81 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.69 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.62 (d, *J* = 9.9 Hz, 1H), 3.54 (s, 1H), 2.99 (d, *J* = 6.2 Hz, 1H), 2.79 (d, *J* = 5.3 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.24 (s, 3H), 1.08 (s, 9H).

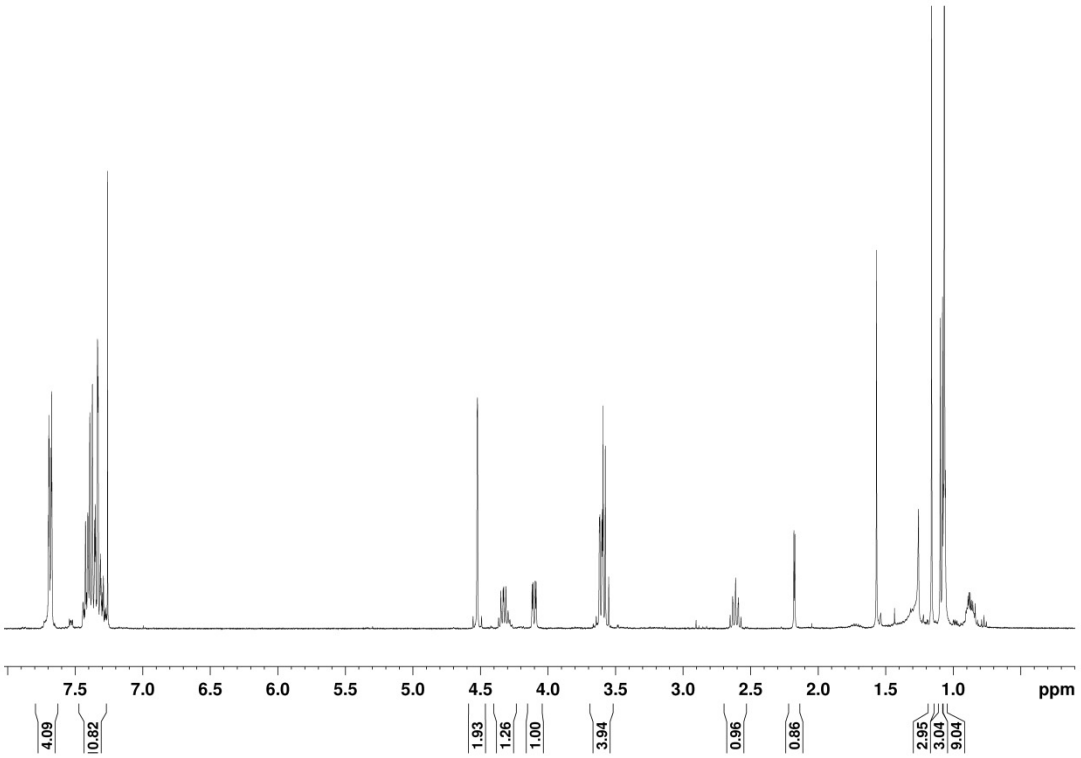





**201** **202**

**Tetrahydrofuran 202:** To a solution of **201** (0.268 g, 0.513 mmol, 1.00 equiv.) and $NEt_3$ (0.519 ml, 5.13 mmol, 10.0 equiv.) in DCM (9.00 ml) at -40 °C, MsCl (0.044 ml, 0.564 mmol, 1.10 equiv.) was added. The reaction mixture was stirred at -40 °C for 40 min and then quenched by addition of MeOH (1.0 ml). The reaction mixture was allowed to warm up to rt and then water was added. The layers were separated and the aqu. phase was extracted with DCM. The comb. org. phases were washed with brine, then dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane 1:4)) gave 213 mg (82 %) of the desired product as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H), 7.45 – 7.27 (m, 11H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.40 – 4.26 (m, 1H), 4.10 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.61 (dd, *J* = 7.7, 1.4 Hz, 1H), 3.61 (d, *J* = 10.0 Hz, 1H), 3.56 (d, *J* = 10.1 Hz, 1H), 2.67 – 2.56 (m, 1H), 1.16 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.07 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.15, 135.85, 135.80, 133.50, 133.40, 129.88, 129.84, 128.61, 127.90, 127.85, 127.83, 82.63, 76.96, 73.63, 72.54, 69.84, 47.48, 29.85, 27.08, 19.44, 18.22, 17.95.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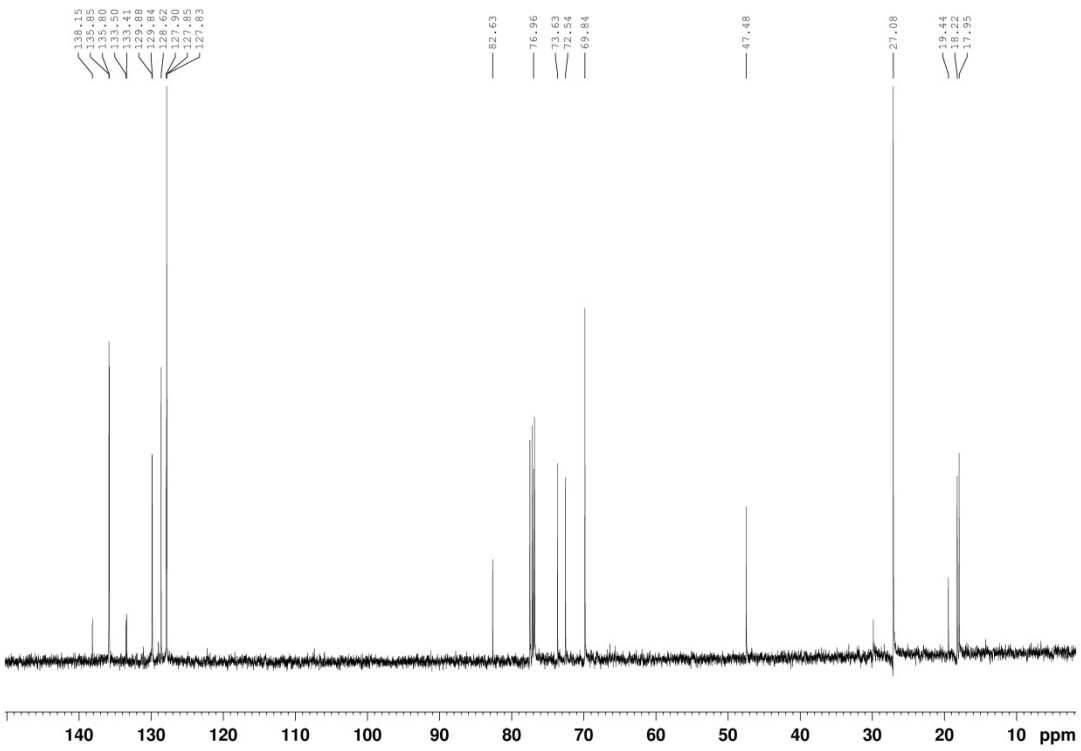
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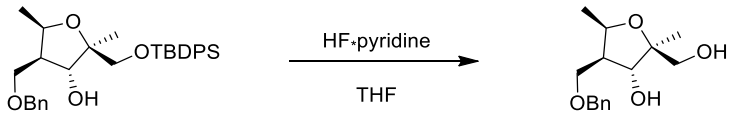
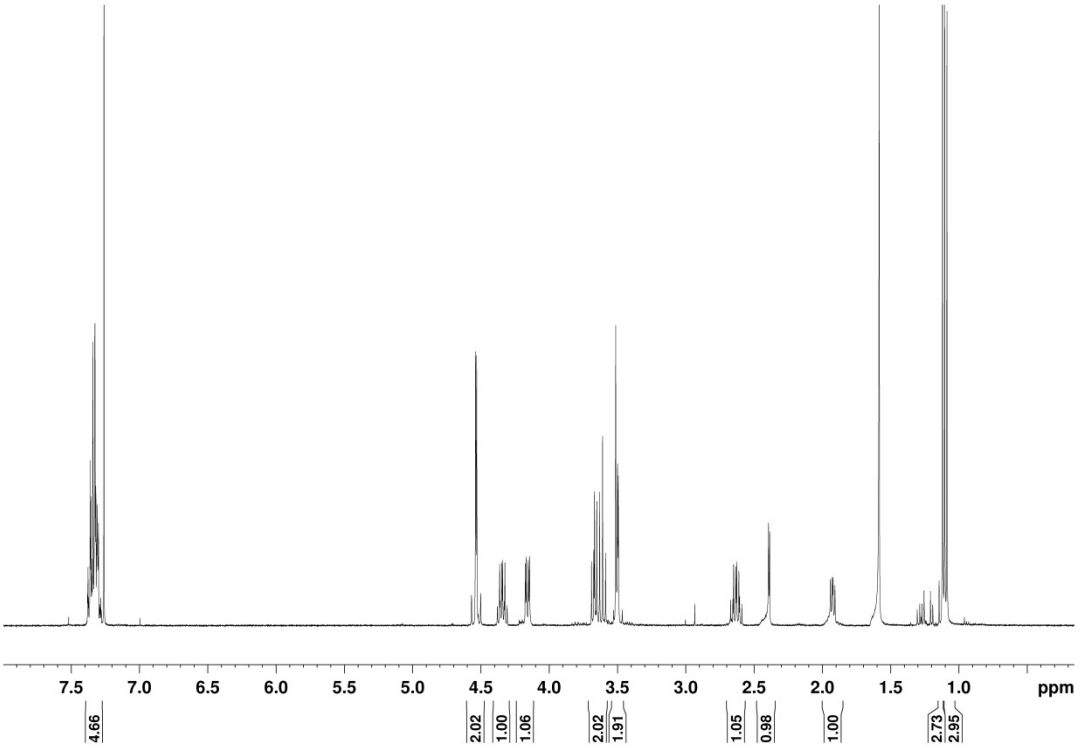
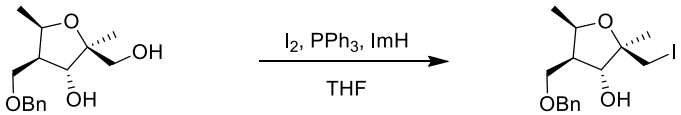



**202** **200**

**Alcohol 200:** To a solution of **202** (0.213 g, 0.353 mmol, 1.00 equiv.) in THF (3.53 ml) at 0 °C was added HF*py (0.432 ml, 70 % HF in pyridine). The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm up to rt. The reaction mixture was stirred at rt for 22 h and then quenched by addition of aqu. sat. $NaHCO_3$. The phases were separated and the aqueous phase was extracted with $Et_2O$. The combined org. phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (2:1)) gave 94 mg (99 %) of the desired product as colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.34 (dq, *J* = 8.8, 6.6 Hz, 1H), 4.16 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.67 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.61 (dd, *J* = 8.7 Hz, 1H), 3.51 (s, 1H), 3.50 (d, *J* = 2.2 Hz, 1H), 2.63 (qd, *J* = 8.8, 6.6 Hz, 1H), 2.39 (d, *J* = 3.3 Hz, 1H), 1.92 (dd, *J* = 7.5, 5.5 Hz, 1H), 1.12 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H).

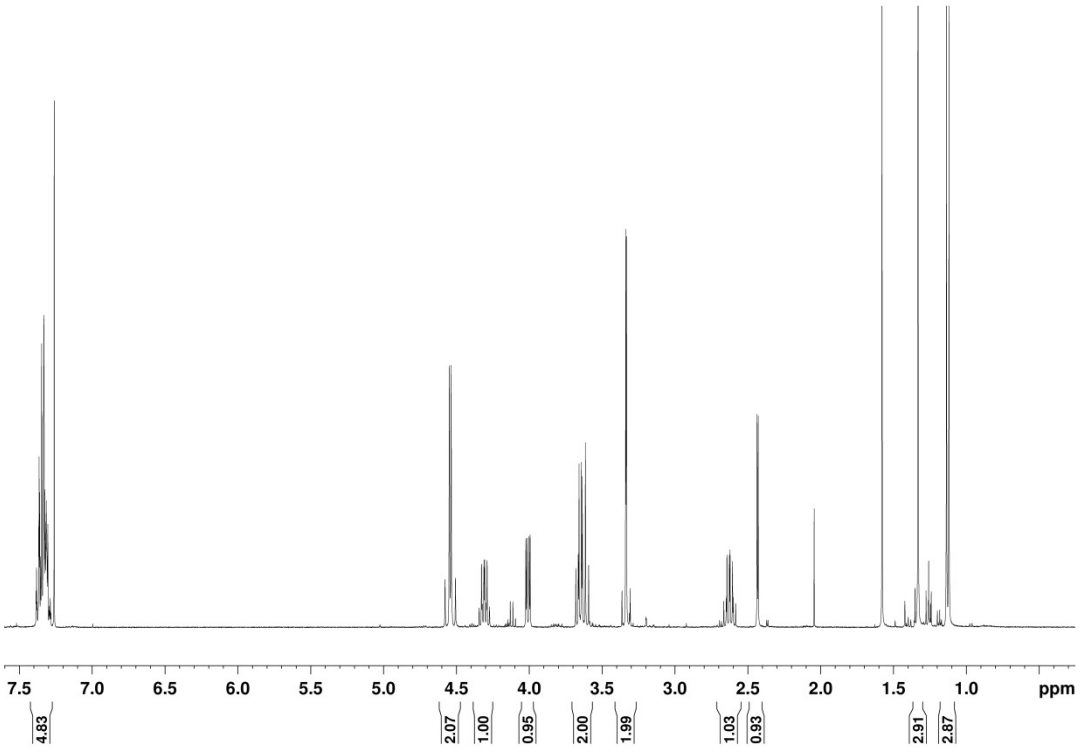


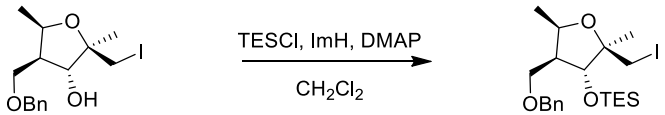



**200** **236**

**Iodide 236:** To a solution of **200** (0.094 g, 0.353 mmol, 1.00 equiv.) in THF (12.0 ml) at rt was added $PPh_3$ (0.111 g, 0.423 mmol, 1.20 equiv.), imidazole (0.048 g, 0.706 mmol, 2.00 equiv.) and iodine (0.107 g, 0.423 mmol, 1.20 equiv.). The brown reaction mixture was immediately heated to reflux (pre-heated oil bath) and stirred at reflux for 30 min. The reaction mixture was diluted with hexanes, filtered and concentrated under reduced pressure. Purification over silica gel ((EtOAc/hexanes (1:1)) gave 132 mg (99 %) of the desired product as yellowish oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.31 (dq, *J* = 8.6, 6.6 Hz, 1H), 4.01 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.68 – 3.58 (m, 2H), 3.35 (d, *J* = 10.4 Hz, 1H), 3.32 (d, *J* = 10.3 Hz, 1H), 2.62 (qd, *J* = 8.6, 6.7 Hz, 1H), 2.43 (d, *J* = 3.0 Hz, 1H), 1.33 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H).

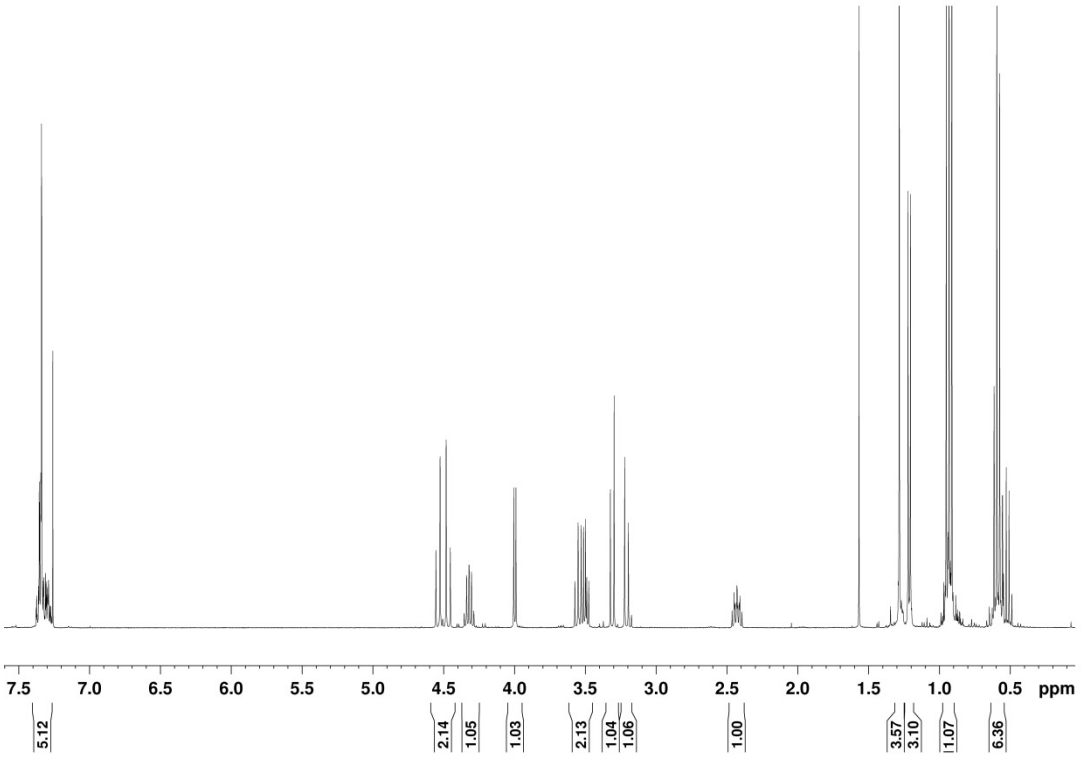




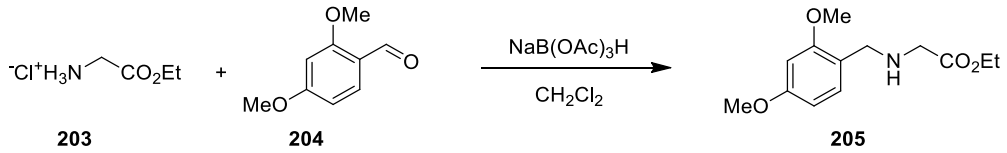

**236** **199**

**Silyl ether 199:** To a solution of **236** (15.0 mg, 0.0399 mmol, 1.00 equiv.) in $CH_2Cl_2$ (0.40 ml) at rt, Imidazole (6.2 mg, 0.0917 mmol, 2.30 equiv.) and DMAP (0.5 mg, 0.004 mmol, 0.10 equiv.) were added. Afterwards TESCl (0.010 ml, 0.0598 mmol, 1.50 equiv.) was added neat. the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with hexane, washed with brine, dired over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (EtOAc/hexane (1:10)) gave 14 mg (73 %) of the desired product as colorless oil contaminated with some TESCl.

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.37 – 4.27 (m, 2H), 4.00 (d, *J* = 6.2 Hz, 1H), 3.59 – 3.47 (m, 2H), 3.31 (d, *J* = 10.5 Hz, 1H), 3.21 (d, *J* = 10.5 Hz, 1H), 2.48 – 2.37 (m, 1H), 1.28 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.8 Hz, 6H).



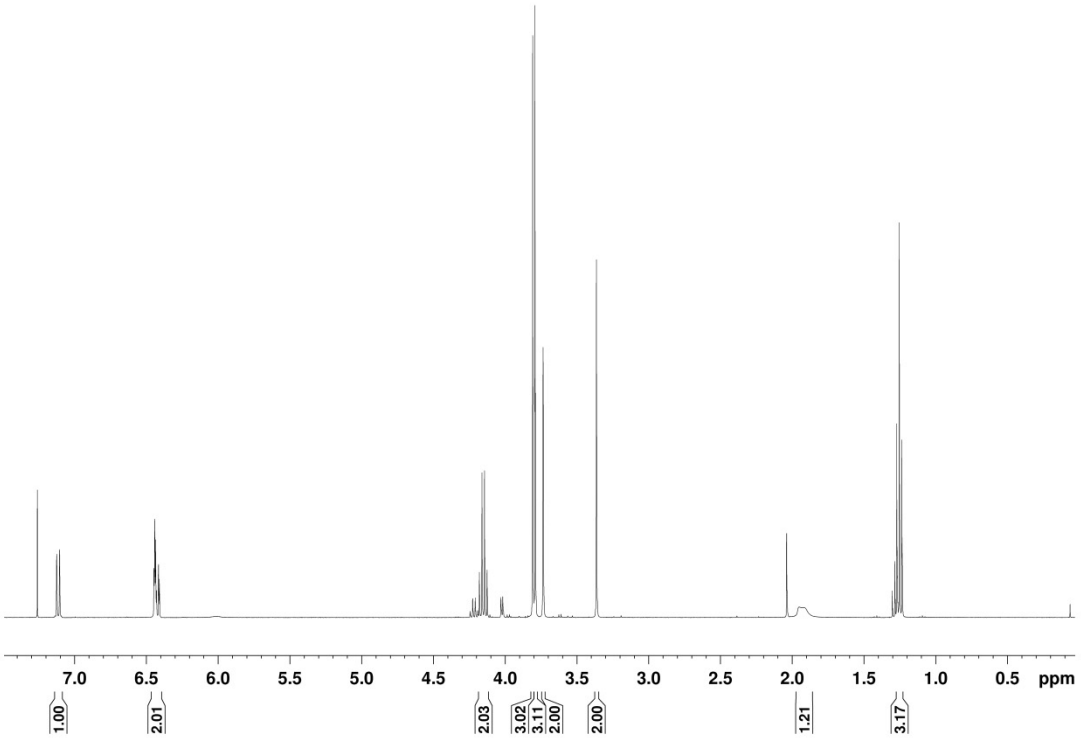
## 5.3.7. Tetramic Acid Building Block 43

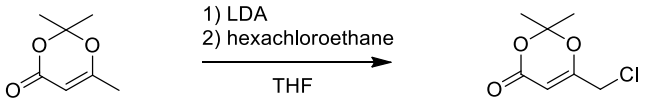



**203** **204** **205**

**Amine 205:** 2,4-dimethoxybenzaldehyde (**204**) (0.60 g, 3.61 mmol, 1.0 eq.) was dissolved in 20 ml dichloromethane and triethylamine (1.09 g, 10.83 mmol, 3.0 eq.) as well as glycine ethyl ester hydrochloride (**203**) (0.756 g, 5.41 mmol, 1.5 eq.) were added. The mixture was stirred for 10 minutes at rt. At rt $NaB(OAc)_3H$ (1.53 g, 7.26 mmol, 2.01 eq.) was added and the grey suspension was stirred for 17 hours at rt. Afterwards, the suspension was treated with 20 ml sat. $NaHCO_3$ solution. The aqueous phase was extracted 3 times with dichloromethane and the organic layer was dried over MgSO4 and concentrated under reduced pressure. The crude product was purified over 45 g SiO2 (ethyl acetate/dichloromethane: 4:1) to afford 810 mg (89%) of a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.11 (d, $J$ = 8.1 Hz, 1 H), 6.46-6.40 (m, 2 H), 5.15 (q, = 7.1 Hz, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.74 (s, 2 H), 3.64 (s, 2 H), 1.93 (br, 1 H), 1.25 (t, $J$ = 7.1 Hz, 3 H).

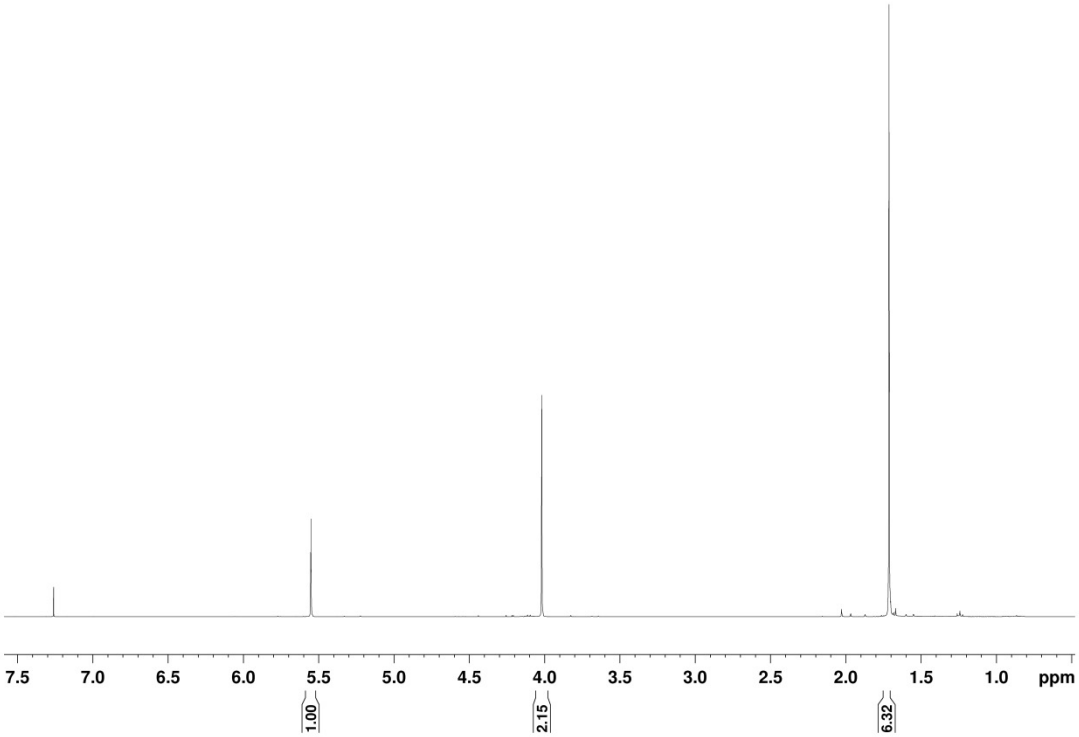





**206** **207**

**Chloride 207:** Diisopropyl amide (2.29 ml, 16.32 mmol, 1.45 eq.) was dissolved in 10 ml tetrahydrofuran and cooled to -78 °C. At this temperature n-BuLi (9.57 ml, 15.31 mmol, 1.36 eq.) was added dropwise over a period of 10 minutes and the mixture was stirred for another 10 minutes at -78 °C. The mixture was allowed to warm to RT and cooled again to -78 °C. 2,2,6-trimethyl-4H- 1,3-dioxin-4-one (**206**) (1.6 g, 11.26 mmol, 1.0 eq.) in 2.0 ml tetrahydrofuran was added dropwise over a period of 10 minutes. Afterwards, the reaction was stirred for 20 minutes and resulted in a yellow suspension. The yellow suspension was transferred with a syringe and was added dropwise over a period of 8 minutes to a solution of hexachloroethane (3.86 g, 16.32 mmol, 1.45 eq.) in 15 ml tetrahydrofuran at -52 °C. The solution changed its color from colorless over orange to a dark-red solution. The dark-red solution was stirred for 70 min and the temperature was allowed to warm slowly to -23 °C. The mixture was poured in 20 ml of 1M HCl and briefly shaken to discharge the red color. Afterwards, the organic layer had a yellow-green color. The aqueous layer was extracted two times with diethyl ether. The combined organic layers were washed with 10 ml sat. aq. $NaHCO_3$ solution and with 10 ml of brine, dried over $MgSO_4$ and concentrated under reduced pressure. A brown solid was isolated (3.42 g, crude). The crude product was purified over 70 g SiO2 (ethyl acetate/hexane: 1:4) to afford 999.6 mg (50.3%) of a colorless liquid.

$^1$H NMR: (400 MHz, $CDCl_3$) δ 5.56 (s, 1 H), 4.02 (s, 2 H), 1.72 (s, 6 H).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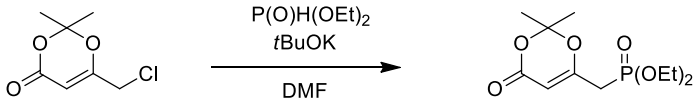
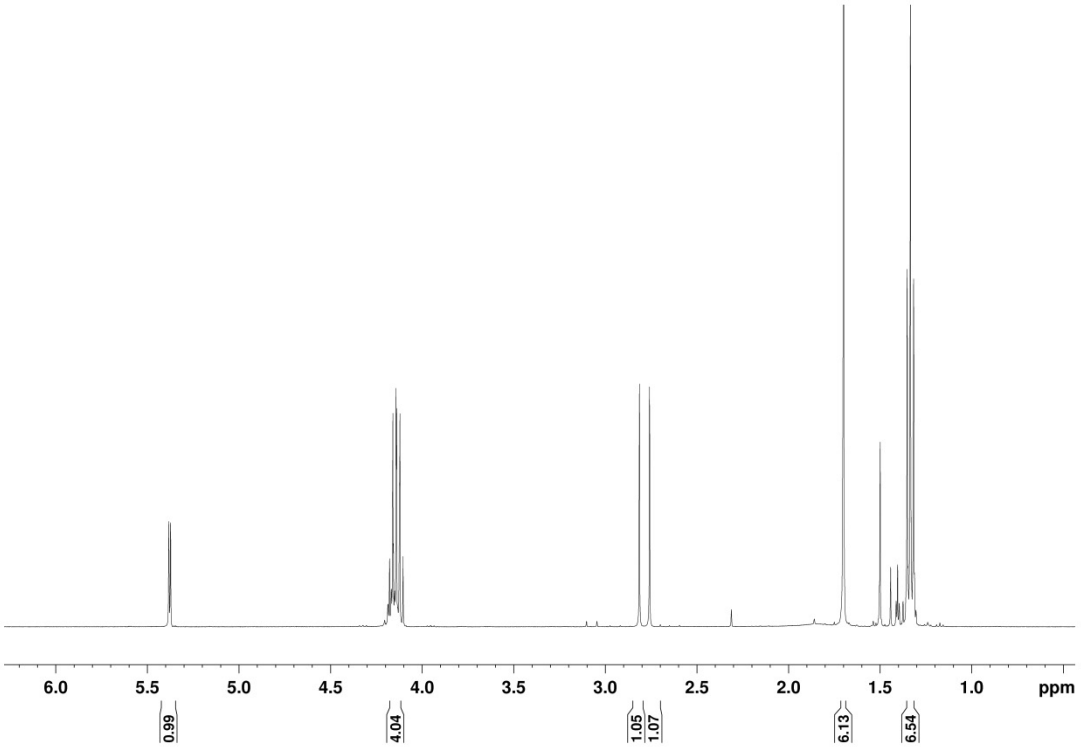
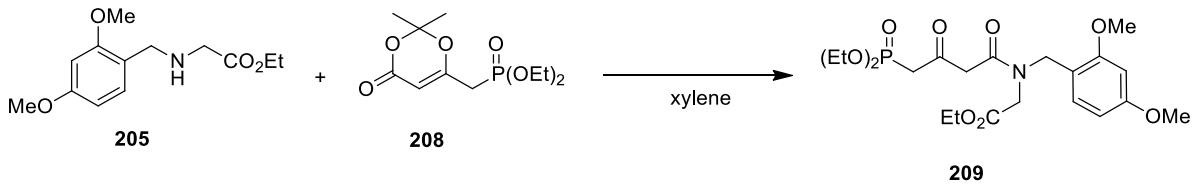



**207** **208**

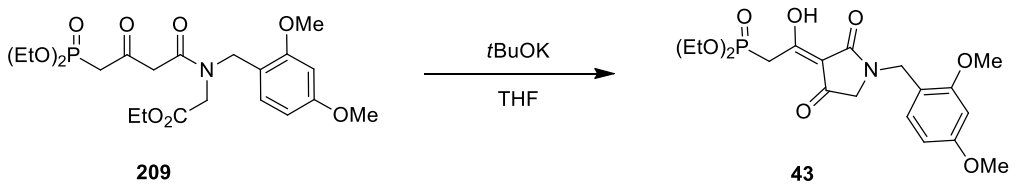
**Phosphonate 208:** *t*BuOK (0.488 g, 4.35 mmol, 4.8 eq.) was dissolved in 3.4 ml dimethyl formamide and the freshly distilled diethylphosphite (0.601 g, 4.35 mmol, 4.8 eq.) was added dropwise over a period of 4 minutes at 0 °C and the reaction was stirred for 35 minutes at 0 °C. **208** (0.16 g, 0.906 mmol, 1.0 eq.) dissolved in 0.9 ml dimethyl formamide was added dropwise over a period of 8 minutes, meanwhile the color of the mixture changed from clear to dark purple. The reaction was allowed to stir 45 minutes at 0 °C. 0.18 ml conc. HCl was added and the color changed immediately from dark purple to pale brown. The mixture was stirred for 10 minutes at 0 °C. Afterwards, the mixture was filtered over Celite and washed with 50 ml of diethyl ether. The organic layer was concentrated under reduced pressure, with the water bath at 38 °C. The resulting solution was distilled under HV. (Oil-bath max. 50 °C, Head-temp: 27 °C). After all dimethyl formamide and diethylphosphite was removed, the yellow solution was concentrated under reduced pressure and purified over SiO2 (ethyl acetate) to afford 103 mg (56%) of the product as a slightly yellow liquid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.38 (d, $J$ = 3.79 Hz, 1 H), 4.18-4.11 (m, 4 H), 2.81 (s, 1 H), 2.75 (s, 1H), 1.70 (s, 6 H), 1.34 (t, $J$ = 7.13 Hz, 3 H).



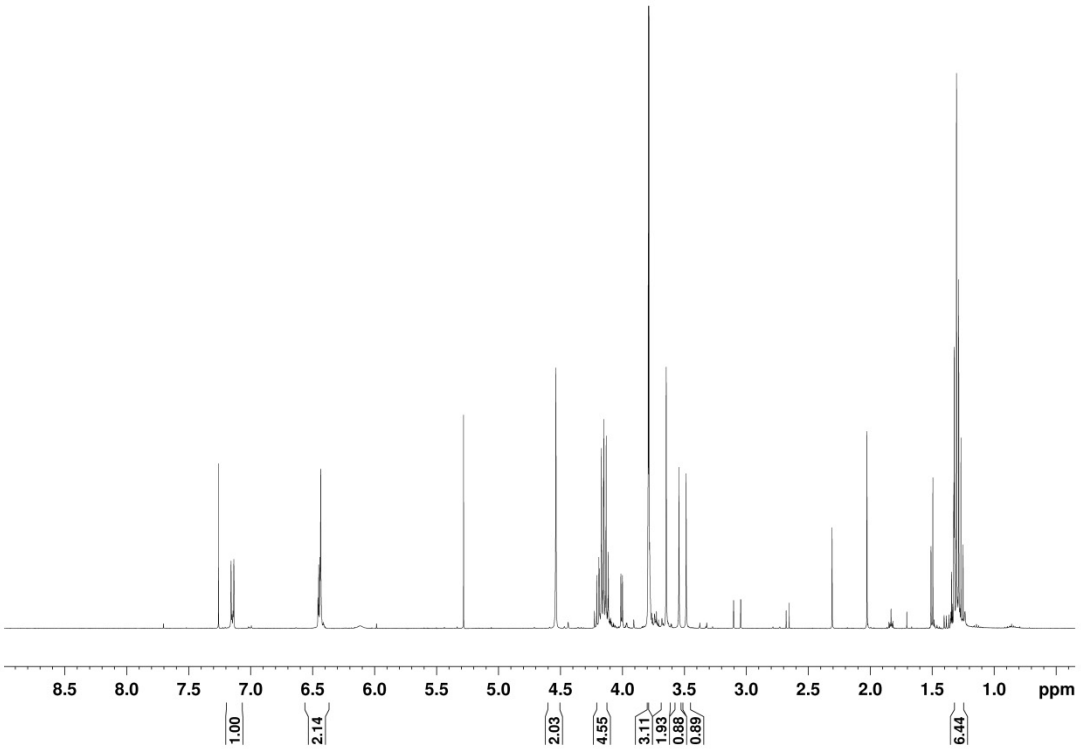



**Amide 209: 208** (504 mg, 1.812 mmol, 1.50 eq.) and **205** (306 mg, 1.2081 mmol, 1.0 eq.) were dissolved in 5.0 ml xylene and heated up to 150 °C oil-bath temp. After stirring for one hour at this temperature, the reaction was cooled to RT and xylene was removed under reduced pressure. The crude yellow product was purified over 5.4 g SiO2 (ethyl acetate) to afford 532 mg (93%) of the slightly yellow product. Crude product was used without further purification.




**Tetramic acid 43: 209** (0.050 g, 0.106 mmol, 1.0 eq.) was dissolved in 2.8 ml tetrahydrofuran and *t*BuOK (13.0 mg, 0.116 mmol, 1.1 eq.) dissolved in 1 ml tetrahydrofuran was added at RT. The reaction was stirred for 17.5 hours. Afterwards, the reaction was neutralized with sat. aq. ammonium chloride solution and the aqueous layer was extracted 3 times with 5 ml diethyl ether and washed 2 times with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford 35.5 mg (79%, unpure) of yellowish, viscous oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.19-7.13 (m, 1 H), 6.47-6.43 (m, 2 H), 4.55 (s, 2 H), 4.21-4.12 (m, 4 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.66 (s, 2 H), 3.54 (s, 1 H), 3.48 (s, 1 H), 1.31 (t, $J$ = 7.18 Hz, 6 H).



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